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In this issue a number of themes are revisited including woman and community issues in addition to basic research related to cancer and education. Al Husban, H et al, Assessed the Association between PR and Different Clinico-Pathologic Breast Cancer Features. The authors concluded that progesterone receptor status affects different clinico-pathologic breast cancer features. The exact role of PR and its impact on breast cancer progression should be assessed in larger study. Bani, S et al, looked at the level of social support for pregnant women and its relationship with neonatal anthropometric indices and postnatal depression in pregnant women. The authors concluded that social support during pregnancy can reduce occurrence of postnatal depression. As postnatal depression has many adverse consequences, providing social support for pregnant women should be emphasized.

Taavoni S et al, investigated the effect of pelvic special movements using birth ball, listening to nature sounds and honey syrup consumption on labour pain in nulliparous women. The results of this study showed that pelvic movements using birth ball could reduce labour pain in nulliparous women. Therefore, the use of this method during labour is suggested. Also, healthcare providers need to get familiar with this method in degree education and on the job training.

Semnani V et al, hypothesized that the impairment of quality of life following the appearance of Helicobacter pylori (H. Pylori)-induced chronic idiopathic urticaria (CIU) might be effectively prevented by eradicating this bacterium. The authors concluded

that eradicating H. Pylori bacterium in CIU patients not only is associated with better outcome of this chronic condition, it can improve the quality of life in treated patients. Whereas Khaled, A.R et al, investigated the impact of religion on social wellbeing among women. Fitness of theoretical model of research was confirmed with structural model analysis (path analysis) of structural equation modeling using Amos software.

Baharvand, P et al, examined using a cross sectional study the state of mental health in physicians and determined the factors associated with it. The authors concluded that it is necessary for the managers and the authorities of the health services organizations to provide counseling services in various fields and to adjust the factors affecting mental health in the workplace in order to improve the mental health of members of this group. Whereas Ghashghaie, K.Z et al, examined the relationship between individualism and mental health among the people of Kohgiluyeh and Boyer-Ahmad province. The result of the research showed that there is relationship between individualism and mental health, in other words, this relation is significant and negative, if the rate of individualism be more, the rate of the mental health be less and vice versa.

Helvacı, M.R et al, tried to understand whether or not there is an association between chronic obstructive pulmonary disease (COPD) and priapism in the SCDs. The authors concluded that SCDs are chronic catastrophic processes on endothelium particularly at the arteriolar and venular level, and terminate with accelerated vascular damage induced end-organ failures in early years of life. There are highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke that may show a role of chronic endothelial inflammation in priapism in the SCDs. Khoshfetrat M et al, conducted a study to compare the performance of laryngeal tube suction (LTS) and endotracheal tube (ETT) in terms of leak and peak pressures, intubation time, peripheral capillary oxygen saturation (SPO<sub>2</sub>), End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) and perioperative complications. The authors concluded that LTS and ETT are highly effective devices for airway management and protection. Although peak and leak pressures were significantly higher in the LTS

group, there was no significant difference between the two devices in terms of complications.

Pahlevan, D carried out a cross-sectional study in order to Classification and assessment of medication errors in the emergency ward of a hospital in Iran by SHERPA. The authors concluded that In both occupations, functional errors (with the most frequency) and reviewing errors should be considered as priorities for controlling the errors. Golmohamadi, S et al attempt to determine the prevalence of Non-alcoholic fatty liver disease (NAFLD) and related risk factors amongst hemodialysis patients. The authors concluded that ESRD patients should be investigated for the presence of NAFLD, as it was present in about one-fifth of the studied sample. Established risk factors for CVD were significantly more common in ESRD + NAFLD patients compared to ESRD cases without NAFLD. This emphasizes more aggressive treatment of the risk factors in NAFLD patients.

Dalimi H et al, looked at the validity of new device to improve sitting posture. The results of all studies proved the general consistency of the gained results through both methods at all levels and averages. Shafe, A et al, designed and used a laser-based device along with fluoroscopy imaging for locating a desired target, resulting in less fluoroscopy exposure time, in comparison to the conventional method. The device was able to locate the target using fluoroscopy imaging. Hashemi, M et al evaluated the efficacy of short-term play therapy for children in reducing the symptoms of ADHD. According to the results, short-term play therapy for children can be used as an appropriate intervention in reducing the symptoms of ADHD.

Tezerji, S et al, looked at the effect of resveratrol and quercetin in different steps of cancer. There are conflicting reports on effectiveness of resveratrol and quercetin in different steps of cancer and lack of existence of study on simultaneous effect of the two compounds on colon cancer in vivo, this study tends to evaluate their effect together, so that positive results obtained from this study can be generalized to human studies. Sarihi, S et al, looked at Quercetin, which is available in fruits and majority of vegetables and can be considered as an important cancer prevention compound. The cancer

preventive effects of the compound can be attributed to antioxidant activity of quercetin, inhibition of carcinogen activating enzymes, regulation of intercellular signal transfer paths and interaction of quercetin with receptors and other proteins. Rabiei, Z et al, investigated the antidepressant effects of oleuropein in mice by forced swim test (FST) and tail suspension test (TST). Oleuropein treatment for 3 days caused a significant decrease of immobility in FST, a significant increase in brain and serum antioxidant capacity, and a significant decrease of brain and serum MDA and NO levels ( $P < 0.05$ ).

Saeedinejad S et al, analyzed the relationship between academic innovation and organizational identity with higher-order thinking skills among students at Yasuj University of Medical Sciences. The results indicated that academic innovation had a significant relationship with higher order thinking skills and could be effective in improving these skills.

Pourahmad, M et al stressed that outbreaks of influenza in a country it seems that religious rituals have important role (such as Hajj) and regional rituals (such as Ashura mourning). The objective of the authors was to determine this relationship in Iran. The authors emphasized more preventing actions from 12th lunar month (Dhu al Hija) until 6 months later in Iran (and other Islamic countries) because in these months in religious rituals contact of the people will be happened more frequently.

Al-Shuaibi, S M et al; reviewed of all patients records who underwent tympanoplasty during the period 2013 – 2016. The total patients were 102. Males were (48%) and females (52%). Female to male ratio is 1.08:1, and the mean age was  $25.9 \pm 6.5$  years. The authors concluded that cartilage tympanoplasty is a reliable graft material for reconstruction of tympanic membrane perforations, give excellent hearing results, in unilateral and in bilateral tympanic membrane perforations.

Momeninejad, M et al, reviewed 25 studies dealing with the use of thyme. From 25 Verified study, 3 studies (12%) was conducted in clinical trial. In all cases the therapeutic efficacy of thyme

was equal or better than synthetic drugs. Aliakbari, F et al, evaluated the effectiveness of *Melissa officinalis* on sleep problem in patients with chronic heart failure. The time duration of waiting for falling into sleep in intervention group was significantly less than control group ( $p=0.001$ ). The hours during which the subjects were fully asleep were significantly more than control group ( $p<0.05$ ).

Pourahmad, M et al, looked at the Coincidence of the influenza epidemic attacks with special lunar months in Iran. The total count and the mean of frequency of patients in first till 6th lunar month (Muharram till Jumada al thani) were significantly more than the number of the patents in other 6 lunar months ( $P$  value = 0.003). We emphasize more preventing actions from 12th lunar month (Dhu al Hija) until 6 months later in Iran (and other Islamic countries) because in these months in religious rituals contact of the people will be happened more frequently.

Gholami1, S et al, evaluated the performance of hospitals affiliated to Qazvin University of Medical Sciences three years before and after implementation of the Health Reform Plan. In general, performance indicators of hospitals affiliated to Qazvin University of Medical Sciences are in desirable condition regarding standards. However, with the implementation of the Health Reform Plan and the reduction of out the pocket of patients in public hospitals, they have increased the number of patients referred to these hospitals and their transfer to the fourth zone. Therefore, measures should be taken to use the appropriate strategies for optimal and efficient use of resources for proper management.

Shobeiri, E, investigated the relationship between VR space dilatation on brain MRI and symptom of headache in migraine headaches. The author concluded that VR space dilatation seen on brain MRI is relatively a common radiologic finding on among patients with migraine headaches found to be more common than patients without headaches. This radiologic finding can be considered as an important finding in the assessment of patients with migraine headaches.

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# Chronic endothelial inflammation and priapism in sickle cell diseases

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## Abstract

**Background:** Sickle cell diseases (SCDs) are chronic destructive processes on endothelium, initiating at birth, all over the body. We tried to understand whether or not there is an association between chronic obstructive pulmonary disease (COPD) and priapism in the SCDs.

**Methods:** All patients with SCDs were taken into the study.

**Results:** The study included 411 patients with the SCDs (199 females). There were 60 patients with COPD (14.5%). Mean age of the patients was significantly higher in the COPD group (33.0 versus 29.5 years,  $P=0.005$ ). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%,  $P<0.001$ ). Smoking was also higher in the COPD group, significantly (36.6% versus 9.9%,  $P<0.001$ ). Parallel to the smoking, alcoholism was higher in the COPD group too (3.3% versus 0.8%,  $P<0.05$ ). On the other hand, transfused red blood cell units in their lives (69.1 versus 32.9,  $P=0.001$ ), priapism (10.0% versus 1.9%,  $P<0.001$ ), leg ulcers (26.6% versus 11.6%,  $P<0.001$ ), digital clubbing (25.0% versus 7.1%,  $P<0.001$ ),

coronary heart disease (26.6% versus 13.1%,  $P<0.01$ ), chronic renal disease (16.6% versus 7.1%,  $P<0.01$ ), and stroke (20.0% versus 7.9%,  $P<0.001$ ) were all higher in the COPD group, significantly.

**Conclusion:** SCDs are chronic catastrophic processes on endothelium particularly at the arteriolar and venular level, and terminate with accelerated vascular damage induced end-organ failures in early years of life. There are highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke that may show a role of chronic endothelial inflammation in priapism in the SCDs.

**Key words:** Sickle cell diseases, chronic endothelial inflammation, chronic obstructive pulmonary disease, priapism

## Introduction

Chronic endothelial damage induced atherosclerosis may be the major cause of aging by causing disseminated tissue hypoxia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic ischemia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in atherosclerosis. Some of the currently known accelerator factors of the inflammatory process are physical inactivity, overweight, smoking, and alcoholism for the development of irreversible end points including obesity, hypertension (HT), diabetes mellitus (DM), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the issue of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on endothelium particularly at the capillary level. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity instead of shape of RBCs is the major problem, since terminal sickling is very rare in the peripheral blood samples of the SCDs patients with associated thalassemia minors, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole lifespan, but exaggerated with increased metabolic rate of the body. The hard cells induced chronic endothelial inflammation, edema, and fibrosis mainly at the capillary level terminate with generalized tissue hypoxia all over the body in early years of life (3, 4). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is an association between COPD and priapism in the SCDs in the present study.

## Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and July 2015. All patients with the SCDs were studied. The SCDs are diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused RBC units in their lives, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. Cases with acute painful crises or any other inflammatory event were treated at first, and then the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram, both to evaluate cardiac walls and valves and to measure the systolic blood pressure (BP) of pulmonary artery, an

abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (5). Stroke is diagnosed by the computed tomography of brain. Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia in the patients (6). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention and discomfort, vomiting, obstipation, and lack of bowel movement. Ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity of the abdomen. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent period is accepted as pulmonary hypertension (8). CRD is diagnosed with a serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females during the silent period. Cirrhosis is diagnosed with liver function tests, ultrasonographic findings, and histologic procedure in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0 and with the presence of Schamroth's sign (9, 10). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Stress electrocardiography is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Ophthalmologic examination was performed according to the patients' complaints. Eventually, cases with COPD and without were collected into the two groups, and they were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 411 patients with the SCDs (199 females and 212 males). There were 60 patients with COPD (14.5%). Mean age of patients was significantly higher in the COPD group (33.0 versus 29.5 years,  $P=0.005$ ). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%,  $P<0.001$ ). Smoking was also higher in the COPD group, significantly (36.6% versus 9.9%,  $P<0.001$ ). Parallel to the smoking, alcoholism was higher in the COPD group, also (3.3% versus 0.8%,  $P<0.05$ ). Prevalences of associated thalassemia minors were similar in the COPD group and other (71.6% versus 66.6%, respectively,  $P>0.05$ ) (Table 1). On the other hand, transfused RBC units in their lives (69.1 versus 32.9,  $P=0.001$ ), priapism (10.0% versus 1.9%,  $P<0.001$ ), leg ulcers (26.6% versus 11.6%,  $P<0.001$ ), digital clubbing

**Table 1: Characteristic features of the study cases**

Variables	Cases with COPD*	P-value	Cases without COPD
Prevalence	14.5% (60)		85.4% (351)
<u>Male ratio</u>	<u>80.0% (48)</u>	<u>&lt;0.001</u>	<u>46.7% (164)</u>
<u>Mean age (year)</u>	<u>33.0 ± 10.0 (13-58)</u>	<u>0.005</u>	<u>29.5 ± 10.1 (5-59)</u>
Thalassemia minors	71.6% (43)	Ns†	66.6% (234)
<u>Smoking</u>	<u>36.6% (22)</u>	<u>&lt;0.001</u>	<u>9.9% (35)</u>
<u>Alcoholism</u>	<u>3.3% (2)</u>	<u>&lt;0.05</u>	<u>0.8% (3)</u>

\*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05)

**Table 2: Associated pathologies of the study cases**

Variables	Cases with COPD*	P-value	Cases without COPD
Painful crises per year	6.3 ± 8.7 (0-36)	Ns†	5.1 ± 8.4 (0-52)
<u>Transfused RBC‡ units</u>	<u>69.1 ± 89.1 (0-434)</u>	<u>0.001</u>	<u>32.9 ± 39.8 (0-250)</u>
<u>Priapism</u>	<u>10.0% (6)</u>	<u>&lt;0.001</u>	<u>1.9% (7)</u>
Ileus	5.0% (3)	Ns	3.4% (12)
Cirrhosis	6.6% (4)	Ns	3.7% (13)
<u>Leg ulcers</u>	<u>26.6% (16)</u>	<u>&lt;0.001</u>	<u>11.6% (41)</u>
Pulmonary hypertension	11.6% (7)	Ns	12.8% (45)
<u>Digital clubbing</u>	<u>25.0% (15)</u>	<u>&lt;0.001</u>	<u>7.1% (25)</u>
<u>CHD§</u>	<u>26.6% (16)</u>	<u>&lt;0.01</u>	<u>13.1% (46)</u>
<u>CRD¶</u>	<u>16.6% (10)</u>	<u>&lt;0.01</u>	<u>7.1% (25)</u>
Rheumatic heart disease	8.3% (5)	Ns	5.1% (18)
Avascular necrosis of bones	20.0% (12)	Ns	24.2% (85)
ACS**	1.6% (1)	Ns	3.9% (14)
<u>Stroke</u>	<u>20.0% (12)</u>	<u>&lt;0.001</u>	<u>7.9% (28)</u>
Mortality	8.3% (5)	Ns	5.9% (21)

\*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05) ‡Red blood cell §Coronary heart disease ¶Chronic renal disease \*\*Acute chest syndrome

**Table 3: Peripheral blood values of the study cases**

Variables	Cases with COPD*	P-value	Cases without COPD
Mean WBC† counts (/µL)	15.796 ± 6.374 (6.600-36.900)	Ns‡	14.879 ± 6.670 (1.580-48.500)
Mean Hct§ values (%)	22.8 ± 6.0 (10-35)	Ns	23.7 ± 5.0 (8-42)
Mean PLT¶ counts (/µL)	433.071 ± 177.283 (113.000-1.142.000)	Ns	457.538 ± 236.171 (48.800-1.827.000)

\*Chronic obstructive pulmonary disease †White blood cell ‡Nonsignificant (P>0.05) §Hematocrit ¶Platelet

(25.0% versus 7.1%, P<0.001), CHD (26.6% versus 13.1%, P<0.01), CRD (16.6% versus 7.1%, P<0.01), and stroke (20.0% versus 7.9%, P<0.001) were all higher in the COPD group, significantly (Table 2). The differences according to the mean white blood cell (WBC) counts, hematocrit (Hct) value, and platelet (PLT) counts of peripheral blood were nonsignificant between the two groups (P>0.05 for all) (Table 3). Beside these there were just three patients with sickle cell retinopathy in the group without COPD. There were 26 mortality cases during the nine-year follow up period, and 14 of them were males. The mean ages of mortality were 33.0 ± 9.6 (range 19-47) in females and 30.8 ± 8.9 years (range 19-50) in males (P>0.05). Additionally, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR). Although antiHCV was positive in

25 cases of the study (6.0%), HCV RNA was detected as positive just in four (0.9%) by PCR.

## Discussion

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of morbidity and mortality in the elderly. Probably whole afferent vasculature including capillaries are involved in the body. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vessels are probably protected to some extent. Secondary to the prolonged endothelial damage induced fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that can reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including

physical inactivity, excess weight, smoking, and alcoholism may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to their fibrotic nature (11).

SCDs are life-threatening genetic disorders nearly affecting 100,000 individuals in the United States (12). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium particularly at the capillary level (13), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages of the patients (14). As another difference from other causes of endothelial damage, the SCDs probably keep vascular endothelium both at the arteriolar and venular level due to the hard RBCs. In other words, SCDs are mainly chronic inflammatory disorders, and probably the major problem is endothelial inflammation, edema, and fibrosis induced occlusions in the vascular walls rather than the lumens both at the arteriolar and venular level. As a result, the lifespans of patients with the SCDs were 48 years in females and 42 years in males in the literature (15), whereas they were 33.0 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC supports in emergencies in our country.

COPD is an inflammatory disease that may mainly affect the pulmonary vasculature, and aging, excess weight, smoking, and alcoholism may be major underlying causes. The inflammatory process of endothelium is enhanced by release of various chemical factors by lymphocytes, and it terminates with fibrosis. Probably the accelerated atherosclerotic process is the main structural background of the functional changes characteristic of the disease. Although COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of an associated chronic endothelial inflammation all over the body (16, 17), and there may be close relationships between COPD, CHD, PAD, and stroke (18). In a multicenter study performed on 5,887 smokers aged between 35 and 60 years, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers, and CHD was the most common cardiovascular complication among them (19). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (19). In another study, 27% of all mortality cases were due to the cardiovascular causes in the moderate and severe COPD (20). Similarly, COPD may be one of the terminal consequences of the SCDs (21), and there were close relationships between COPD, priapism, leg ulcers, digital clubbing, and stroke in the SCDs in the present study.

Priapism is the painful erection of penis that does not return to its flaccid state within four hours in the absence of any stimulation (22). It is an emergency due to its potential

complications. Damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (22). It may be associated with hematological and neurologic disorders including SCDs, leukemia, thalassemia, Fabry's disease, spinal cord lesions, and spinal cord trauma (hanging victims) (23, 24). It may also be associated with glucose-6-phosphate dehydrogenase deficiency (G6PDD), which leads to decreased NADPH. NADPH is a co-factor involved in the formation of nitric oxide, thus G6PDD will lower nitric oxide levels, which may result in priapism. Ischemic (veno-occlusive, low flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high flow) are the three types of it (25). Ninety-five percent of clinically presented priapisms are the ischemic or low-flow disorders in which blood does not return adequately to the body from the penis as in the SCDs, and they are very painful (22, 25). The other 5% are nonischemic high-flow type usually caused by a blunt perineal trauma in which there is a short-circuit of the vascular system in the penis (22). Treatment of high-flow type is not as urgent as that of low-flow type since there is no risk of ischemia (22). For patients other than SCDs, oral pseudoephedrine or terbutaline may relax the stretched corporeal smooth muscles and increase permeability of erectile cavernous tissue that may permit easy flow of fluid from sinusoids into the venous system. If the drugs are not effective, aspiration of blood from the corpus cavernosum under local anesthesia is tried. If the aspiration also fails, distal shunts may cause the blood to leave the penis and return to circulation. Whereas in the SCDs, RBC support is the treatment of choice in the acute phase (26). RBC transfusions decrease sickle cell concentration in blood, suppress the bone marrow in production of abnormal RBCs, and eventually prevent further sickling induced damage to the penis. Whereas in the chronic phase, hydroxyurea should be the treatment of choice in priapism in the SCDs. It is the only drug that was approved by Food and Drug Administration for the treatment of SCDs (12). It is an oral, cheap, safe, and highly effective drug for the SCDs that blocks cell division by suppressing formation of deoxyribonucleotides which are building blocks of DNA (13). Its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs. Although presence of a continuous damage of hard RBCs on capillary endothelium, severity of the destructive process is probably exaggerated by the patients' own WBCs and PLTs as in the autoimmune disorders. Similarly, lower neutrophil counts were associated with lower crises rates, and if a tissue infarct occurs, lower neutrophil counts may decrease severity of pain and tissue damage (27). According to our experiences, hydroxyurea is an effective drug for prevention of attacks of priapism and its terminal consequences if it is initiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls later in life.

Digital clubbing is a deformity of the finger and fingernails that is characterized by loss of normal  $<165^\circ$  angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (28).

Schamroth's window test is a well-known test for the diagnosis (10). Some authors found clubbing in 0.9% of all patients admitted to the Department of Internal Medicine (9). Whereas the prevalences were much higher in the SCDs, and they were 13.2% in males and 6.0% in females ( $P<0.01$ ) in the present study. The exact underlying cause of digital clubbing is not known, but chronic tissue hypoxia, vasodilation, secretion of growth factors, and some other mechanisms were proposed (29-32). Beside that, significance of digital clubbing is not well established. According to some authors, only 40% of digital clubbing cases turned out to have significant underlying diseases, while 60% remained well over the subsequent years (9). Whereas according to our experiences, it is frequently associated with pulmonary, cardiac, and hepatic disorders that are featuring with chronic tissue hypoxia, since lungs, heart, and liver are closely related organs that affect their functions in a short period of time (11). Similarly, hematologic disorders that are featuring with chronic tissue hypoxia may also terminate with digital clubbing. Smoking may also have a major role, since it takes significant roles in systemic atherosclerotic processes such as COPD, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11, 33). Its atherosclerotic effects are the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels and capillaries, and it has never been reported in the absence of smoking. COPD may also be accepted as a localized Buerger's disease of the lungs. Similarly, there were highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke in SCDs cases in the present study ( $P<0.001$  in all), and digital clubbing may be an indicator of disseminated vascular damage particularly at the capillary level in the SCDs.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (34), and the ratio was 13.8% in the present study. The incidence increases with age and they are rare under the age of 10 years (34). They are also common in males and sickle cell anemia (HbSS) cases (34). Similarly, there were 57 cases with leg ulcers, and 41 of them were males (19.3% in males versus 8.0% in females,  $P<0.001$ ) in the present study. Additionally, mean age of the patients with leg ulcers was significantly higher than the others (34.8 versus 29.2 years,  $P<0.000$ ). Leg ulcers have an intractable nature, and around 97% of healed ulcers return in less than one year (35). The ulcers occur in distal areas with less collateral blood flow in the body (35). Chronic endothelial inflammation particularly at the capillary level due to the hard RBCs may be the major cause in the SCDs (34). Prolonged exposure to the causative factors due to the blood pooling in the lower extremities by the effect of gravity may also explain the leg but not arm ulcers in the SCDs. Probably the same mechanism is also true for the diabetic ulcers, Buerger's disease, varicose veins, and onychomycosis. Smoking may also have some additional effects on the ulcers (36), since both of them are much more common in males (34), and strong atherosclerotic effects of smoking are well-known (33). Venous insufficiency may also accelerate the process by causing pooling of causative hard RBCs in the

legs. According to our nine-year experiences, prolonged resolution of ulcers with hydroxyurea in early years of SCDs may also suggest that leg ulcers may actually be secondary to the increased WBC and PLT counts induced chronic endothelial inflammation rather than an irreversible damage. But later in life, it is difficult to heal completely due to the irreversible and fibrotic consequences of the prolonged endothelial inflammation.

Stroke is a common complication of the SCDs (37). Similar to the leg ulcers, stroke is also higher in the HbSS cases (38). Thromboembolism in the background of accelerated atherosclerosis is the most common cause of stroke in the normal population. Whereas in the SCDs, sickling induced disseminated endothelial injury, activations of WBC, PLT, and coagulation systems, and hemolysis may terminate with prolonged endothelial inflammation, edema, and fibrosis (39). Similarly, a higher WBC count is associated with a higher incidence of stroke (40). In other words, stroke may not have a macrovascular origin, instead disseminated and prolonged endothelial edema may be much more important in the SCDs. Infections, emotional stresses, trauma, and other inflammatory events may precipitate stroke, since increased metabolic rate may accelerate sickling and secondary endothelial edema. Similar to the number and severity of painful crises, priapism, and leg ulcers, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes are secondary to the increased WBC and PLT counts induced prolonged and disseminated endothelial edema in the SCDs (13, 41).

As a conclusion, SCDs are chronic catastrophic processes on endothelium particularly at the arteriolar and venular level, and terminate with accelerated vascular damage induced end-organ failure in early years of life. There are highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke that may show a role of chronic endothelial inflammation in priapism in the SCDs.

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# Comparing the performance of the laryngeal tube suction with cuffed endotracheal tube during general anesthesia with controlled ventilation in elective surgeries: A prospective, block-randomized, single-blinded, parallel group trial

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## Abstract

**Introduction:** Maintaining a safe airway in patients who are candidates for surgery and who are required to undergo general anesthesia is one of the most important duties of the anesthesiologist. This study was conducted to compare the performance of laryngeal tube suction (LTS) and endotracheal tube (ETT) in terms of leak and peak pressures, intubation time, peripheral capillary oxygen saturation (SPO<sub>2</sub>), End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) and perioperative complications.

**Methods:** The prospective, block-randomized, single-blinded, parallel group trial was conducted on the 100 patients with ASA class 1 and 2 who were scheduled for the elective surgery under general anesthesia and volume-controlled ventilation. The convenience sampling and then, blocked randomization, were used to randomly assign the patients to two groups of LTS and ETT. Outcomes variables were intubation rate, ventilation quality, leak and peak pressures and complications. Data were analyzed using independent sample t-test and Chi-square test by SPSS-19.

**Results:** The mean age of LTS and ETT group was 35.94±5.96 and 34.76±4.20 years, respectively, (P=0.25). The mean peak pressure in the LTS group (28.54±1.55 CmH<sub>2</sub>O) was significantly higher than in the ETT group (25.76±1.93 CmH<sub>2</sub>O), (P<0.001). The mean leak pressure in the LTS and ETT groups was 20.84±3.59 cmH<sub>2</sub>O and 18.16±2.5 CmH<sub>2</sub>O, respectively, (P<0.001). The time required for placement of LTS and ETT devices was 25.66±2.09 and 28.28±2.17 seconds (P<0.001). Both devices exhibited a good performance, and the difference between the two groups in terms of dysphonia and sore throat incidence rate was low and insignificant (P>0.05).

**Conclusion:** LTS and ETT are highly effective devices for airway management and protection. Although peak and leak pressures were significantly higher in the LTS group, there was no significant difference between the two devices in terms of complications.

**Key words:** Cuffed endotracheal tube, General anesthesia, laryngeal tube suction

## Discussion

Maintaining a safe airway in patients who are candidates for surgery and are required to undergo general anesthesia is one of the most important duties of the anesthesiologist. In emergency cases or when intubation is made difficult by patients' anatomic shape of the oral cavity, head and neck, apart from the cuffed endotracheal tube, supraglottic devices such as laryngeal tube suction can also be used for intubation (1).

LTS is an advanced version of the Laryngeal Tube (LT) that has an esophageal drainage tube, which facilitates the insertion of the gastric tube and gastric emptying. Therefore, this device plays a notable role in airway management during airway restoration and anesthesia, and is a suitable device for managing airway in pre-hospital emergencies (2).

Endotracheal tubes (ETT) are designed to provide a safe airway. Suitable cuff pressure prevents massive pulmonary aspiration (3).

In the last three decades, many anesthesia airway care units have become significantly safer. According to a report published by American Society of Anesthesiologists (A.S.A), the number of accidents related to airway management declined from 37% in 1910 to 14% in 1990. However, there has been a more than 2-fold increase in the contribution of characteristics attributable to difficult intubation, which is probably due to the excessive use of monitoring (4).

Prolonged intubation leads to complications such as hypoxia and hypercarbia, increased risk of aspiration, cardiovascular responses (hypertension, tachycardia, arrhythmia), respiratory responses (bronchospasm, laryngospasm) and cerebral complications (increased ICP) (5). On the other hand, post intubation complications include sore throat (with laryngeal or pharyngeal origin), or caused by the tube size (contact with the tracheal cuff), hoarseness, laryngeal edema, stridor caused by obstruction along with general wheezing, vocal cord edema and paralysis, dislocation of the vocal cord and vocal cord granulomas (6).

Tracheal intubation during anesthesia is considered as a standard and safe method used for airway management and lung ventilation. Also, the cuffed endotracheal tube can be used in people over 8 years of age (7, 8).

LT seems to be a good alternative for ETT in cases of difficult intubation or during cardiopulmonary resuscitation (CPR) because it is easier to place and the esophageal cuff can prevent aspiration of gastric contents (9). LT was licensed for use in cardiopulmonary resuscitation in Japan in 2002 and was approved by the U.S. Food and Drug Administration in 2003 (10).

Prescribed and non-prescribed use of LT is similar to the laryngeal mask, and it can be utilized for general anesthesia during minor surgeries (11). Doubled-lumen suction tube, which allows insertion of nasogastric tube, has more

advantages than the standard LT and is recommended as a first-line device for maintaining airway in emergency situations, especially when the direct laryngoscopy fails in newborns and infants (12).

In a study in Germany in 2009, Cavus et al. compared Easy Tube (EZT), ProSeal laryngeal mask airway (PLMA), LTS and ETT. They determined the overall intubation success rate, cuff pressure, and airway leak pressure. Overall, the intubation success rate of EZT, PLMA, LTS and ETT was 14 out of 22 patients (64%), 20 out of 22 patients (91%) and 21 out of 22 (96%), respectively. The time for first successful ventilation in EZT was significantly longer than PLMA, LTS, and ETT. (56, 25, 24 and 20 seconds respectively). The lowest and highest airway leak pressure was observed in EZT (19 cmH<sub>2</sub>O) and LTS (40 cmH<sub>2</sub>O). In contrast to EZT, both PLMA and LTS are considered as appropriate devices for airway management by anesthesiologists (13).

In a study in Germany, Russo et al. (2012) compared i-gel™, LMA-S and LTS-D in terms of their performance in airway management. The leak pressure was somehow the same (i-gel™: 25.9cmH<sub>2</sub>O, LTS-D: 27.1 cmH<sub>2</sub>O and LMA-S: 24 cmH<sub>2</sub>O). Moreover, the placement time was as follows: i-gel™: 10, LMA-S: 11 and LTS-D: 14 seconds. The leak pressure in LMA-S was significantly higher than LTS-D in low cuff pressures. The intubation success rate was significantly different (i-gel™ 95%, LMA-S 95%, LTS-D 70%). The highest and the lowest airway compliance was observed in i-gel™ and LTS-D, respectively. At the end, the performance of all devices in lung ventilation under anesthesia for surgery was described as adequate (14).

Considering that LTS is a new device that is still under study and given the conflicting results reported in the previous studies, the study was designed and carried out to compare the performance of laryngeal tube suction (LTS) and endotracheal tube (ETT) in terms of leak and peak pressures, intubation time, peripheral capillary oxygen saturation (SPO<sub>2</sub>), End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>), and perioperative complications during general anesthesia with controlled ventilation in elective surgeries as the researchers hypothesized the LTS has acceptable and better performance than ETT.

## Methods

A prospective, block-randomized, single-blinded, parallel group trial was conducted in Ali-Ibn-Abitalib hospital in Zahedan, Iran from January 2014 to December 2015 to compare the performance of the laryngeal tube suction with cuffed endotracheal tube during general anesthesia with controlled ventilation in elective surgeries. The hospital was a general, referral, and governmental hospital with 200 beds. The hospital had different wards, including medical, surgical, neurological, pediatric, and neonatal ICUs, with different general adult and pediatric medical and surgical wards.

All parts of the study were reviewed according to the consolidated Standards for reporting trials (CONSORT)

statement (Hopewell et al., 2008). In the first step, a convenience sampling method was used. All patients who met the inclusion criteria were recruited. The inclusion criteria were (1) patients aged 18 to 45 years, and (2) ASA I & II. The exclusion criteria were (1) an underlying systemic disease such as heart disease, lung disease, hypertension, neurological disease, diabetes; (2) patients with full stomach; (3) neck condition and diseases affecting upper part of the digestive tract; (4) patients with gastroesophageal reflux; (5) patients who had a difficult airway; (6) lack of consent to participate in the study; (7) body mass index less than 15 or greater than 30.

According to the formula and similar studies (15, 16), a sample size of 50 patients was selected for each group.

Considering a confidence level of 95% and a power of 80%, a required sample size of at least 45 cases was determined. In order to prevent patient attrition from affecting the results of the study, a total of 50 qualified patients were asked to participate. The major reason for patient attrition was failure to meet the inclusion criteria. Then, ASA I or II class patients who underwent elective surgery performed in the supine position, were randomized into two groups of 50 people. Random allocation was conducted using Random Allocation Software® to place 50 patients in the LTS group and 50 in the ETT group. For the allocation of the patients, a computer-generated list of random numbers was used. Patients were randomly assigned to one of two treatment groups following simple randomization procedures (computerized random numbers). Block randomization was done by a computer-generated random number list prepared by an expert statistician who had no clinical involvement in the trial.

The approval of the Institutional Review Board of the Research Committee of Zahedan University of Medical Sciences (Zahedan, Iran) was obtained with the code of ethics (IR.ZAUMS.REC.1392.6043), and the study was conducted according to the Declaration of Helsinki principles (Association, 2014). The ethical considerations of this study were related to the patients' autonomy, confidentiality, and anonymity during the study period and the study's publication. The purpose of the study was explained to all patients, and they were also informed that they were free to participate, decline participation, or withdraw from the study at any time. A written informed consent form to participate in the study was obtained from each patient's next of kin.

All standard pre-anesthetic monitoring was done for patients in both groups. The protective padding was used to maintain the patient's head and neck. Then, the patients first underwent pre-oxygenation and then 0.03 mg/kg midazolam, 1-2 µ/kg fentanyl and 2-2.5 mg/kg propofol were all injected intravenously in order to induce anesthesia. Also, 0.15 mg/kg of cis-atracurium was used to relax the muscles before airway manipulation. To maintain anesthesia, 5-8 mg/kg/h of propofol and N<sub>2</sub>O+ O<sub>2</sub> mixture (50% each) were used. After achieving effective airway, the intubated device LTS (VBM Medizin technik, sulus, GERMANY) (Figure 1) was used.

According to the manufacturer's recommendations with regard to the patient's height (size 3 for patient's height of 122-255 cm, size 4 for those height of 155-180 cm, and size 5 for patients taller than 180 cm and suitable ETT offered for the patient by two anesthesiologists) was attached to the respiratory system (Fabius, Drager, Lubek, Germany). The cuffs were inflated to the maximum allowable volume before starting ventilation.

The lungs were first ventilated at the tidal volume of 8 ml/kg, RR=12bpm and I/E= 1/2 in the volume mode. Five minutes after tightening the device and ensuring the airway safety, maximum airway pressure and SPO<sub>2</sub> and ETCO<sub>2</sub> were recorded (Siemens sc7000 Monitor made by China). The leak pressure was later recorded and measured by closing the exhalation valve of the respiratory circle and using constant flow of 3 lit/min and by considering the leak pressure (maximum 40 cm H<sub>2</sub>O).

The placement time of the device was measured and recorded from the time it was taken by hand to the time the cuff was filed.

Following the controlled ventilation with above specifications, if ETCO<sub>2</sub> remains constant at the normal level, there will be no need to change the device settings, but respiratory rate can be adjusted, if needed. In case of normal chest movements, attempts were made to ensure adequate oxygenation and Square waves on SPO<sub>2</sub> in the capnograph; moreover, lack of audible leaks and gastric expansion were considered as reasons indicating adequate ventilation.

Patients were followed up for 24 hours after the surgery, and their sore throat and dysphonia, if any, were recorded in their information forms. Also, the follow-up was done in the form of a phone call up to 24 hours later in case of patient discharge.

All analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL). Frequency (percent) and mean (standard deviation) were presented for qualitative and quantitative variables, respectively. The normality of the study variables was tested by the Kolmogorov-Smirnov one-sample test. Normality was confirmed for all variables. For comparing outcomes variables in the two groups, independent-sample t-test and chi-square test were used. P values < 0.05 were considered significant.

## Results

this study, a total of 100 patients who were hospitalized in Ali Ibn AbiTalib Hospital of Zahedan to undergo elective surgery, were randomly divided into two groups: LTS and ETT. The mean age of patients in the LTS and ETT groups was 35.94±5.96 and 34.76±4.20 years, respectively. There was no statistically significant difference between the two groups (P=0.25), Independent samples t-test).

There were a total of 49 male patients (49%) and 51 female patients (51%) in the study. There was no statistically significant difference between the two groups (Table 1).

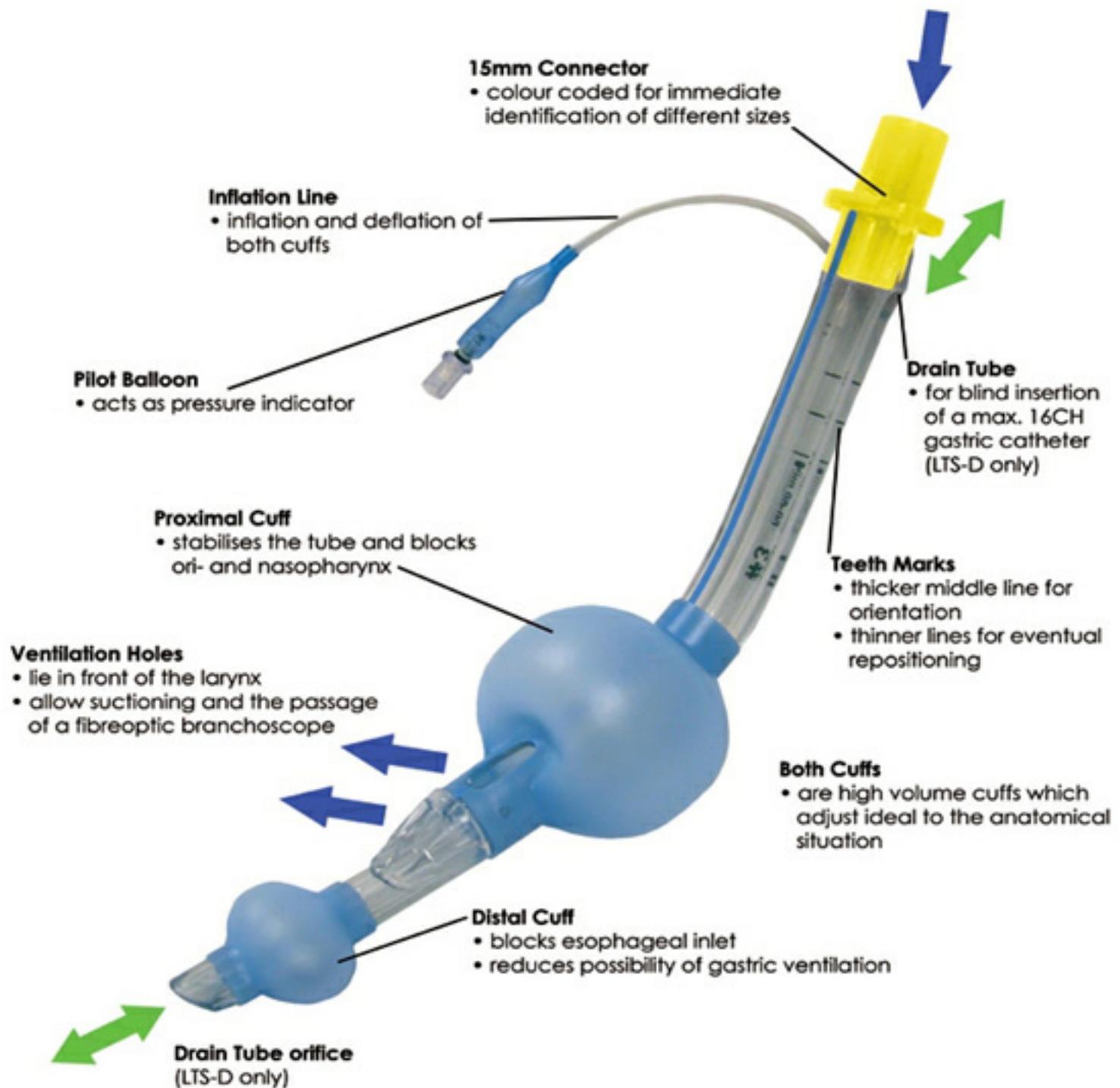


Figure 1: Laryngeal tube and its components (<http://medtree.co.UK/vbm-it-d-laryngeal-tube>)

Gender	LTS	ETT	P-Value
	Frequency (%)	Frequency (%)	
Male	22 (44%)	27 (54%)	0.42
Female	28 (56%)	23 (46%)	

Table 1: Frequency of patients in the two groups based on gender

After inserting the device, the leak pressure was measured in each group.

The mean leak pressure in the LTS group was significantly higher than that in the ETT group ( $P < 0.001$ ). The mean leak pressure in LTS and ETT groups was  $20.84 \pm 3.59$  and  $18.16 \pm 2.5$  mmHg, respectively, which was statistically significant ( $P < 0.001$ ) (Table 2).

**Table 2: Mean and peak pressures, ETCO<sub>2</sub>, PO<sub>2</sub>, and the intubation time in two groups**

Variables	LTS (Mean $\pm$ SD)	ETT (Mean $\pm$ SD)	t	df	P-Value*
Leak Pressure (CmH <sub>2</sub> O)	1.55 $\pm$ 28.54	0.93 $\pm$ 25.76	7.92	98	<0.001
Peak Pressure (CmH <sub>2</sub> O)	3.59 $\pm$ 20.84	2.5 $\pm$ 18.16	8.92	87.39	<0.001
ETCO <sub>2</sub> (CmH <sub>2</sub> O)	1.10 $\pm$ 39.08	1.16 $\pm$ 38.72	1.58	98	0.11
SPO <sub>2</sub> (%)	1.17 $\pm$ 98.04	1.34 $\pm$ 97.56	1.9	98	0.06
Required time for placement (s)	2.09 $\pm$ 25.66	2.17 $\pm$ 28.28	6.92	98	<0.001

\* Independent sample t-test

There was no statistically significant difference between the two groups in terms of ETCO<sub>2</sub>, the mean value of which in LTS and ETT groups was respectively  $39.08 \pm 1.10$  and  $38.72 \pm 1.16$  mmHg. Also, there was no significant difference between the two groups in terms of SPO<sub>2</sub>, the mean value of which was respectively  $98.04 \pm 1.17$  and  $97.56 \pm 1.34$  mmHg in LTS and ETT groups ( $P = 0.06$ ).

In order to evaluate the intubation rate in this study, the intubation time variable was used. The intubation time was equal to  $25.66 \pm 2.09$  seconds in the LTS which was significantly less than the same time for ETT ( $28.28 \pm 2.17$  seconds) ( $P < 0.001$ ).

These results reflect higher intubation rate for LTS (Table 2). There was no difference between the two groups in terms of incident rate of post-operative dysphonia and throat (Table 3).

**Table 3: Frequency of risk of dysphonia and sore throat in the two groups**

Variables	ETT Frequency (%)	LTS Frequency (%)	P-Value*
Dysphonia	6 (12%)	9 (18%)	0.57
Sore throat	15 (30%)	18 (36%)	0.67

\* Chi-square test

## Discussion

The results of this study showed that higher leak and peak pressures can be achieved using LTS. LTS was intubated more quickly than ETT, but there was no difference between the two devices in terms of side effects. Maintaining a safe airway in patients who are candidates for surgery and need to undergo general anesthesia is one of the most important duties of the anesthesiologist. Apart from the cuffed endotracheal tube, supraglottis devices such as laryngeal tube suction can be used in difficult intubation caused by patients' anatomic shape of the oral cavity, head and neck and in emergency cases (1).

LTS is a new type of LT, in which an additional channel for suction and emptying of the stomach and digestive system is embedded. LTS is also used in order to maintain the airway during general anesthesia. It is one of the supraglottic airway devices and can be inserted using blind intubation method (2).

In this study, 100 patients who underwent elective surgery in Ali Ibn Abi Talib Hospital in Zahedan, were randomly divided into two groups, including LTS and ETT. After the device was inserted, the leak pressure was measured in each group. The mean leak pressure in the LTS group was significantly higher than in the ETT group. The mean peak pressure in LTS was higher than the ETT group, which was not statistically significant.

Although there were no similar studies comparing the two devices, several studies have addressed the LTS, including Cavus's study (2009), the results of which are consistent with the results obtained in the present study (13). In a study, Russo (2012) also reported a leak pressure that was equal to the one obtained in the present study (14).

Yet in another study on LT and LMA, Cook (2003) reported that leak and peak pressures were respectively 71.12 and 44.45 CMH<sub>2</sub>O in the LT group which is consistent with the findings obtained in the present study (17).

In a study conducted by Esa et al. in Malaysia in 2011, 54 patients were randomly divided into two groups to receive LTS and PLMA.

Both devices provided a safe airway even when the intra-abdominal pressure was increased to 17 mm Hg. In this study, there was no difference between LTS and PLMA regarding their ease of placement, hemodynamic changes, airway quality, oxygenation and ventilation parameters and complications (18).

Scheller et al. (2010) published the results of their study on 8 patients who underwent surgery using LTS. The results showed that LTS was successfully intubated in all cases. The placement was performed at the first attempt, which was classified as "easy". The tracheotomy surgery was performed in 6 of 8 patients, while the LTS was used for oxygenation and ventilation. LTS enables rapid oxygenation in patients with emergency difficult airway (15).

In a prospective study conducted by Wiese et al. in 2008, 50 volunteers underwent the standard treatment for cardiac arrest simulated on a mannequin. The volunteers were assigned to two groups using LST and ETT. The duration of lack of air flow during the cardiac arrest in mannequins, was significantly reduced in the LST group, compared with the ETT group (109.3 vs. 190.4 sec). The LST can be inserted much faster than ETT (13 vs. 52 seconds). Also, its success intubation rate in the first attempt was 98% compared with 72% obtained for the ETT (19).

In a study, Thierbach et al also showed that LTS is a fast and reliable method to maintain an open airway and to achieve better ventilation results in the mannequin model. The success rate, time of placement and participants' views indicated that the LTS is an important alternative to ETT. LTS offers special benefits for less experienced users (20).

In a study of 2001 on CPR cases, Ganz Walker et al. concluded that the stomach expansion issue was observed in all alternatives to ETT, except for the LST. The maximum airway pressure in the ETT group was 28 CMH<sub>2</sub>O and reached 32 CMH<sub>2</sub>O when LST device was used during ventilation (21).

In another article by Ganz Walker et al., LST was introduced as an effective device during difficult intubation. The significant difference calculated between the airway resistance and dynamic compliance confirms the fact that the total airway resistance in the LT was higher than that of ETT and the dynamic compliance of the LT is lower than the ETT, which indicates that routine use of LTS in patients' high airway resistance, whether admitted to the intensive care unit or for anesthesia, seems inappropriate because its resistance is added to the airway resistance thereby leading to barotrauma (16).

The time required for LTS placement is 25.66±2.09 seconds, which is significantly less than the same time in ETT (28.28±2.17 seconds). These results reflect higher intubation rate for LTS.

In another study, Cook (2003) reported a peak pressure of 17.9 cmH<sub>2</sub>O and an intubation time of about 22 seconds for LT which is almost similar to the findings obtained in the current study (22). Another similar study was conducted by Wiese (2008) who reported a LT intubation rate that was consistent to the same intubation rate obtained in the present study (19).

With regard to the adequacy of ventilation between LTS and ETT, the mean SPO<sub>2</sub> and ETCO<sub>2</sub> was higher in the LTS group than the ETT group; but since this difference is not significant, all patients enjoyed the desirable and acceptable ventilation. In terms of complications, the incidence rate of postoperative dysphonia and sore throat in the LTS and ETT groups was 18%, 36% and 12%, and 30%, respectively, which of course was not statistically significant. So, none of these devices were preferred over the other from this point of view. Both LTS and ETT can be safely used in airway management in elective surgery.

Higher peak and leak pressures can be achieved using LTS. LTS can be inserted more quickly than ETT, but there was no significant difference between the two devices in terms of the side effects. Since the LTS is much easier to implement compared with ETT and does not require great skill, especially in difficult intubation cases, it can save a patient's life.

## Conclusion

Airway management provides gas exchange, protects the lungs from injury and permits treatment. This requires safe, effective and reliable use of equipment, often in combination. A management plan with backup plans is essential, but a sequence of logical plans forming an airway management strategy is better. Correct equipment use needs correct knowledge, skill and attitudes.

In the present study, despite the statistically significant results of this study and also considering that few studies have been conducted with the same purpose, it is recommended to conduct further studies to evaluate the efficacy of LTS in obese patients and patients with difficult airway and high risk for aspiration and patients with underlying lung disease.

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# Non-alcoholic fatty liver disease and associated risk factors among hemodialysis patients

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## Abstract

**Background:** Non-alcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD) have common pathogenic mechanisms and many important cardio-metabolic risk factors, thus diagnosis and treatment of NAFLD and related factors among CKD patients can potentially prevent CVD-related mortality, which is considered as the most common cause of death in CKD patients.

**Objective:** To determine the prevalence of NAFLD and related risk factors amongst hemodialysis patients.

**Methods:** 150 ESRD patients were included in this cross-sectional study in a 1-year period. Abdominal ultrasound was done to determine the presence of NAFLD. Risk factors and related variables including hypertension, abdominal obesity, dyslipidemia, anemia, diabetes mellitus, and qualitative C-reactive protein (CRP) were gathered.

**Results:** The prevalence of NAFLD was 20% (30 patients). The frequency of abdominal obesity was significantly higher in the NAFLD group (73.33%) compared to ESRD patients who did not have NAFLD (23.33%);  $P < 0.0001$ . Also, hypertension was more common in the NAFLD group (90%) than in the other group (69.16%);  $P = 0.021$ . Likewise, anemia, DM, abnormally high ALT (i.e.,  $> 20$  IU/L), dyslipidemia, and positive CRP test results all were significantly higher in the NAFLD group in comparison to the other group.

**Conclusion:** ESRD patients should be investigated for the presence of NAFLD, as it was present in about one-fifth of the studied sample. Established risk factors for CVD were significantly more common in ESRD + NAFLD patients compared to ESRD cases without NAFLD. This emphasizes more aggressive treatment of the risk factors in NAFLD patients.

**Key words:** Non-alcoholic fatty liver disease; chronic kidney disease; hemodialysis; risk factor

## Introduction

Chronic kidney disease (CKD) apparently is a global health issue and its prevalence is increasing. In a recent meta-analysis of more than 100 studies, the overall prevalence of 5 stages of CKD globally was determined as 11-13%, and stage 3 was the most prevalent type (1). An important consideration in CKD patients is increased rate of cardiovascular diseases (CVD) in a way that CKD is regarded as an independent risk factor for CVD. In addition, CVD is the most common cause of morbidity and mortality in this population (2). When CKD progresses to end-stage renal disease (ESRD), replacement therapy becomes inevitable. ESRD, as well, has faced an increasing trend in most countries and its health related costs are concerning for many health-care programs.

Considering the above mentioned facts about CKD, more knowledge is required to find contributing factors in the progression of CKD, in particular focusing on CVD occurrence. The risk factors for CKD and CVD are very similar. Accumulating evidence suggests that NAFLD is associated with an increased prevalence and incidence of CKD. Non-alcoholic fatty liver disease (NAFLD) is a common liver condition and is assumed as the most prevalent liver disease at least in Western societies (3). NAFLD is characterized by accumulation of fat in the liver (i.e., hepatic steatosis) with or without evidence of inflammation (i.e., non-alcoholic steatohepatitis [NASH]) in the absence of significant cause for this fat accumulation (for instance, significant alcohol taking history). Different radiologic and laboratory methods are used to define NAFLD and its prevalence is estimated as 25.4%, depending on the definitions used to diagnose NAFLD and geographical variation depicted by higher prevalence of NAFLD in the Middle East and South America (4). Patients with NAFLD usually have components of metabolic syndrome, namely obesity, high blood pressure, dyslipidemia, insulin resistance or DM. All these factors are the same as mentioned previously for CVD and CKD. Many experts believe that NAFLD is the hepatic manifestation of metabolic syndrome (3). As stated earlier, finding contributing factors in progression of CKD to ESRD is of paramount importance with focus on decreasing the rate of CVD among CKD patients. One of these culprits is NAFLD. In fact, in recent years, much research has been done in order to determine if any possible association exists between NAFLD and CKD as well as renal function (3, 5-9). These studies have also been done in hemodialysis and renal transplant received patients. For example, in a study including hemodialysis patients, NAFLD was diagnosed in about one-quarter of patients using transient elastography (8). Furthermore, NAFLD has been proposed as a meaningful risk factor for morbidity in renal transplant recipients (10).

The objective of this study was to explore the frequency of NAFLD in patients who were receiving hemodialysis and to investigate the relevant risk factors. The authors believe that findings of this study will add to the current knowledge about the interplay between NAFLD, ESRD, metabolic

syndrome and the previously known risk factors in an effort to diagnose contributing factors at earlier stages to improve the survival of ESRD patients.

## Materials and Methods

### Study population and research design

In this cross-sectional study conducted from March to February 2016 in two university hospitals, the study population consisted of all ESRD patients who were receiving hemodialysis. Exclusion criteria were history of alcohol intake, inherited liver diseases, and taking tamoxifen.

### Sample size

The sample size was calculated based on a former study which reported the prevalence of NAFLD among hemodialysis patients as 40% (9), at confidence level of 95% and power of 90%, the estimated sample size was calculated as 150 patients.

### Data collection

A checklist was designed to gather the required data. The demographic data gathered included age, gender, blood pressure (BP), and waist circumference. Hypertension was defined as systolic BP (SBP) of  $\geq 140$  mmHg and/or diastolic BP (DBP) of  $\geq 90$  mmHg. Abdominal obesity was defined as waist circumference of more than 102 cm in males and 88 cm in females.

Five CC venous blood sample was obtained from the brachial vein and sent to the laboratory. The laboratory markers assayed were lipid profile, CBC, qualitative C-reactive protein (CRP), random plasma glucose, and alanine aminotransferase (ALT). Dyslipidemia was defined as triglyceride  $> 150$  mg/dL, high-density lipoprotein (HDL)  $< 40$  mg/dL, and low-density lipoprotein (LDL)  $> 150$  mg/dL. DM was defined as random plasma glucose  $> 140$  mg/dL. The presence of CVD was assessed using medical records of the patients.

In order to determine the presence of NAFLD, abdominal ultrasound was done. Based on the observation of increased hepatic echogenicity, the diagnosis of NAFLD was made. The severity of steatosis was graded as grades I, II, and III (11).

### Statistical analyses

Descriptive indices such as frequency, percentage, mean, and its standard deviation (SD) were used to express data. In order to compare the frequency of the evaluated categorical variables between patients with NAFLD and those without NAFLD, the chi-squared test was applied. Age was compared using the Student t test. The data were gathered and entered into the SPSS software for Windows (version 21.0) (IBM Corp., Armonk, NY, USA). Significance level for all analyses was set at 0.05.

### Ethics

The study protocol was approved by the Ethics Committee of our medical university. The study objectives were explained for the patients before participation, and if agreed, written informed consent was obtained from them.

## Results

There were 94 male (62.7%) and 56 female (37.3%) patients. Mean ( $\pm$ SD) age of the sample was 63.68 ( $\pm$ 15.66) years.

Thirty patients (20%) had NAFLD. The severity of steatosis in 49 patients was determined. Grades I, II, and III NAFLD were recorded respectively in 15, 32, and 2 patients.

**Table 1: Comparison of gender, age, cardiovascular disease, hypertension, and abdominal obesity between end-stage renal disease (ESRD) patients with non-alcoholic fatty liver disease (NAFLD) and ESRD cases without NAFLD**

		NAFLD (N= 30)	No NAFLD (N= 120)	P value
Age, year		66.5 ( $\pm$ 11.36)	62.98 ( $\pm$ 16.52)	0.272
Gender	Male	15 (50%)	79 (65.83%)	0.109
	Female	15 (50%)	41 (34.17%)	
CVD		21 (70%)	70 (58.33%)	0.242
Hypertension		27 (90%)	83 (69.16%)	0.021
Abdominal obesity		22 (73.33%)	28 (23.33%)	< 0.0001

Table 1 presents comparison of gender, age, CVD, hypertension, and abdominal obesity between 30 ESRD patients with NAFLD and 120 ESRD cases without NAFLD. As observed, the frequency of abdominal obesity was significantly higher in the NAFLD group (73.33%) compared to ESRD patients who did not have NAFLD (23.33%);  $P < 0.0001$ . Also, hypertension was more common in the NAFLD group (90%) than in the other group (69.16%);  $P = 0.021$ .

Anemia, DM, abnormally high ALT (i.e.,  $> 20$  IU/L), dyslipidemia, and positive CRP test results all were significantly higher in the NAFLD group in comparison to the other group (Table 2).

**Table 2: Comparison of the frequency of anemia, diabetes mellitus, increased ALT, dyslipidemia, and CRP between end-stage renal disease (ESRD) patients with non-alcoholic fatty liver disease (NAFLD) and ESRD cases without NAFLD**

	NAFLD (N= 30)	No NAFLD (N= 120)	P value
Anemia	19 (63.33%)	33 (27.5%)	< 0.0001
DM	20 (66.66%)	49 (40.83%)	0.011
ALT $> 20$ IU/L	6 (20%)	7 (5.83%)	0.014
Dyslipidemia	20 (66.66%)	21 (17.5%)	< 0.0001
CRP, positive	25 (83.33%)	64 (53.33%)	0.003

## Discussion

There is a complex interplay between metabolic syndrome, NAFLD, CVD, and CKD. In fact, all these conditions share similar risk factors (12). In recent years, extensive studies have focused on the existence of a link between NAFLD, CKD and CVD. Epidemiologic findings show that in NAFLD patients, the prevalence of CKD and CVD is significantly higher than the general population (13). The prevalence of CKD among NAFLD patients has a wide range from 4% to 40% (12). Therefore, many experts suggest that it is useful to explore the presence of NAFLD in CKD patients. In fact, NAFLD which is the hepatic manifestation of metabolic syndrome promotes inflammation and via this mechanism may have a role in worsening CKD and reduced renal function. The severity of NAFLD has been shown to have association with CKD stage (14). This evidence supports the possible shared pathogenic mechanisms between CKD and NAFLD.

The prevalence we observed here (20%) is lower than a previous report which noted the prevalence of NAFLD in hemodialysis patients as 58% (7). However, the mentioned study included only elderly patients older than 65 years. Plus, the definition of NAFLD was based on controlled attenuation parameter (CAP) obtained by transient elastography. In the current study, we applied ultrasound to diagnose NAFLD. The previous studies have used both ultrasound and elevated hepatic transaminases in the diagnosis of NAFLD. However, more than half of NAFLD patients may have normal hepatic transaminases (3). The most definite method to diagnose NAFLD is liver biopsy. However, we did not find any study to use biopsy-confirmed NAFLD among CKD patients. Most former studies have followed NAFLD patients to discover what percentage develop decreased kidney function over time. For instance, diabetic patients with ultrasound-defined NAFLD had higher prevalence of CKD than patients without evidence of steatosis (13). Higher prevalence of

microalbuminuria has also been reported in patients with impaired glucose tolerance and NAFLD diagnosed by ultrasound (15).

One of the important issues regarding NAFLD is the inflammatory state present in such patients. As observed here, a significantly higher number of patients in the NAFLD group had positive CRP test results. Inflammation plays an important role in morbidity and mortality of CKD patients and several physiologic, metabolic, and immunologic components contribute to the development of inflammation (7). It has been proposed that in NAFLD patients, inflammatory biomarkers are released more frequently, although production of inflammatory cytokines is more pronounced in NASH (7, 16).

According to the obtained findings, hypertension, abdominal (central) obesity, dyslipidemia, DM, and anemia were more common in the NAFLD group. Hypertension and DM are the two most highly suspected culprits indicated in the high prevalence of both CKD and metabolic syndrome. In the Framingham study, the prevalence of hypertension was reported as 65% in NAFLD, 60% in metabolic syndrome, 50% among diabetics, and 40% in obese patients (17). Insulin resistance precedes overt DM and is the cornerstone of metabolic syndrome. It has been shown that insulin resistance has a direct role in progression of fatty liver to NASH (18). Abdominal obesity was also another important finding which was significantly more common in NAFLD patients. Both insulin resistance and visceral obesity are in particular common among NAFLD and CKD patients (5). Our results demonstrate that in the presence of NAFLD, in addition to CKD, the frequencies of these conditions increase more dramatically.

### Limitations

We faced some limitations in this study. Firstly, we used ultrasound to diagnose NAFLD and its severity. Ultrasound has been shown to be associated with considerable between and inter-observer variability to diagnose steatosis (19). Secondly, due to the nature of cross-sectional studies, it is not clear whether patients developed NAFLD after starting hemodialysis or not. We were not able to follow the patients to determine prognosis of patients with NAFLD and the role of abnormal laboratory derangements. Also, alcohol consumption was only determined subjectively and we did not have access to objective methods to determine alcohol intake by the studied patients.

### Conclusion

NAFLD was observed in about one-fifth of ESRD patients who were receiving hemodialysis. The frequency of hypertension, abdominal obesity, and metabolic derangements were more common in NAFLD patients. More studies are required to examine the therapeutic effects of available modalities in managing NAFLD and to explore the effect of such interventions in the prognosis of CKD patients.

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# Assessing the Association between PR and Different Clinico-Pathologic Breast Cancer Features

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## Abstract

**Background:** Breast cancer is the most common malignancy in females and characterized by high morbidity and mortality. A plethora of data supporting the role of hormone receptors in breast cancer, exist. The majority of these data has focused on the roles of estrogen receptor (ER) and epidermal growth factor receptor (Her2). Data regarding the role of progesterone receptor are not as prevalent as ER receptor. This study aims at assessing the association between PR and different clinico-pathologic breast cancer features.

**Methods:** Clinicopathologic and demographic data from a cohort of 298 patients who referred to King Hussein Medical City (KHMC) between 2007 and 2014 were retrieved and analyzed.

**Results:** The average age of the cohort under investigation was 51.2 years with most of the patients having intraductal tumors. Two hundred and three patients had PR positive tumors (68%). Patients with PR negative tumors were more likely to have lymphovascular invasion ( $\chi^2=4.6$ ,  $p=0.03$ ). Additionally, patients with PR positive tumors were more likely to have ER positive tumors ( $\chi^2=102.7$ ,  $p<0.0001$ ) and Her2 negative tumors ( $\chi^2=11.5$ ,  $p=0.001$ ). Interestingly patients with PR positive and negative tumors did not differ in age, tumor size or number of lymph nodes involved.

**Conclusion:** Progesterone receptor status affects different clinico-pathologic breast cancer features. The exact role of PR and its impact on breast cancer progression should be assessed in a larger study.

**Key words:** Breast cancer, progesterone receptor, lymphovascular invasion

## Introduction

Breast cancer is the most common type of cancer among females (1). Every year, about 246,660 females will be diagnosed with breast cancer (1). Breast cancer is considered the second leading cause of cancer related mortality in the United States accounting for about 40,450 deaths in 2016 (1).

Hormone receptor and Her2 status are well established prognostic factors in breast cancer patients (2-4). Additionally, they have an essential role in selecting treatment modality (2). The majority of data on the association between hormone receptor expression treatment modality and prognosis are derived from studies with a main focus on estrogen receptor (ER) (2-4). Data on the possible interaction between progesterone receptor and outcome is still limited. Nishimukai suggested a role of PR in prognosis in postmenopausal breast cancer patients (5). The role of PR as a possible prognostic factor and its interaction with different clinicopathologic data outside this age group is still unknown. Accordingly, we are aiming at assessing the association between PR and different clinicopathologic breast cancer features.

## Methods

Patients with an established diagnosis of invasive breast cancer who underwent surgery in the King Hussein Medical City (KHMC), Royal Medical Services, Jordan between the years 2007 and 2014 were recruited in this study. The diagnosis of invasive breast cancer was performed using tumor samples from the resected tumors in the pathology department in the KHMC. Tumor characteristics for breast cancer patients were extracted from relevant pathology reports issued by Pathology Department at RMS at time of diagnosis of disease. Reports included details of the clinicopathologic characteristics including tumor histologic type and size, ipsilateral axillary lymph node status, lymphovascular invasion, histologic grade, and detailed receptor status. Expression status of estrogen receptor (ER) and progesterone receptor (PR) was determined using immunohistochemical methods. Activity greater than 1% was considered positive for each hormone receptor. Evaluation of Human Epidermal Growth Factor Receptor 2 (HER2) was assessed by immunohistochemical analysis in which scores of 0 or +1 were considered negative while a score of +3 was considered positive for HER2 receptor overexpression. For unclear results of immunohistochemical analysis (+2), fluorescence in situ hybridization (FISH) analysis positive for gene amplification was considered to be positive for HER2 expression. The study was approved by the ethics committee in the Royal Medical Services (approval number: 2/2018/ (37)).

### Statistical Analysis:

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22.00 (SPSS Inc., Chicago, IL). Chi square test was used to assess significance between dichotomous data. Statistical difference between continuous variables was detected

using either student t-test or ANOVA as appropriate. A p value of less than 0.05 was considered significant

## Results

### Patients' demographics:

In this study we recruited 298 patients with invasive breast cancer. The average age of the cohort under investigation was 51.2 years (51.2±12.97). About half of the patients (163 patients) were 45-65 years of age at the time of presentation. Patients younger than 45 years of age accounted for about 34.4% (99 patients) of the study population. Almost half of the sample presented with intermediate grade tumors. Progesterone receptor was detected in 203 (68.1%) of the patients. On the other hand, estrogen receptor was detected in 215 (72.1%) patients. Table 1 (next page) provides full demographic data of the patients.

### Progesterone receptor presence was not related to the age at presentation, tumor size or number of lymph nodes involved:

Patients with different progesterone receptor status at the time of presentation were similar with regard to the age on presentation (Figure 1 A). The average age at presentation in patients with progesterone receptor positive tumors was about 50 years of age which was similar to what is observed in patients with progesterone receptor negative tumors. Similarly, the size of the tumor (3.9 vs. 4.2) as well as the number of involved lymph nodes (4 vs. 5) were similar between patients with progesterone receptor positive tumors and progesterone receptor negative tumors (Figure 1 B and C; respectively).

### Patients with PR negative tumors were more likely to have lymphovascular invasion

At the time of presentation, about 45% of the patients who had lymphovascular invasion had a PR negative tumor. In contrast patients who had PR positive tumors constituted more than 70% of the patients ( $\chi^2=4.6$ ,  $p=0.03$ ) (Figure 2A).

### PR negative tumors are more common in high grade tumors

The majority of patients (80%) who presented with either low or intermediate grade tumors had PR positive tumors (Figure 2 B). This percentage is dramatically reduced in patients with high grade tumors. About 50% of patients who had high grade tumor did not have PR expression ( $\chi^2=80.6.7$ ,  $p<0.0001$ ).

### PR negative tumors were more likely in patients with ER negative tumors

The expression of PR was more common (90%) in patients with ER positive tumors (Figure 3 A). At the same time, about 80% of patients who had ER negative tumors had a concomitant lack of PR ( $\chi^2=102.7$ ,  $p<0.0001$ ).

### PR negative tumors were more likely with Her2 negative tumors

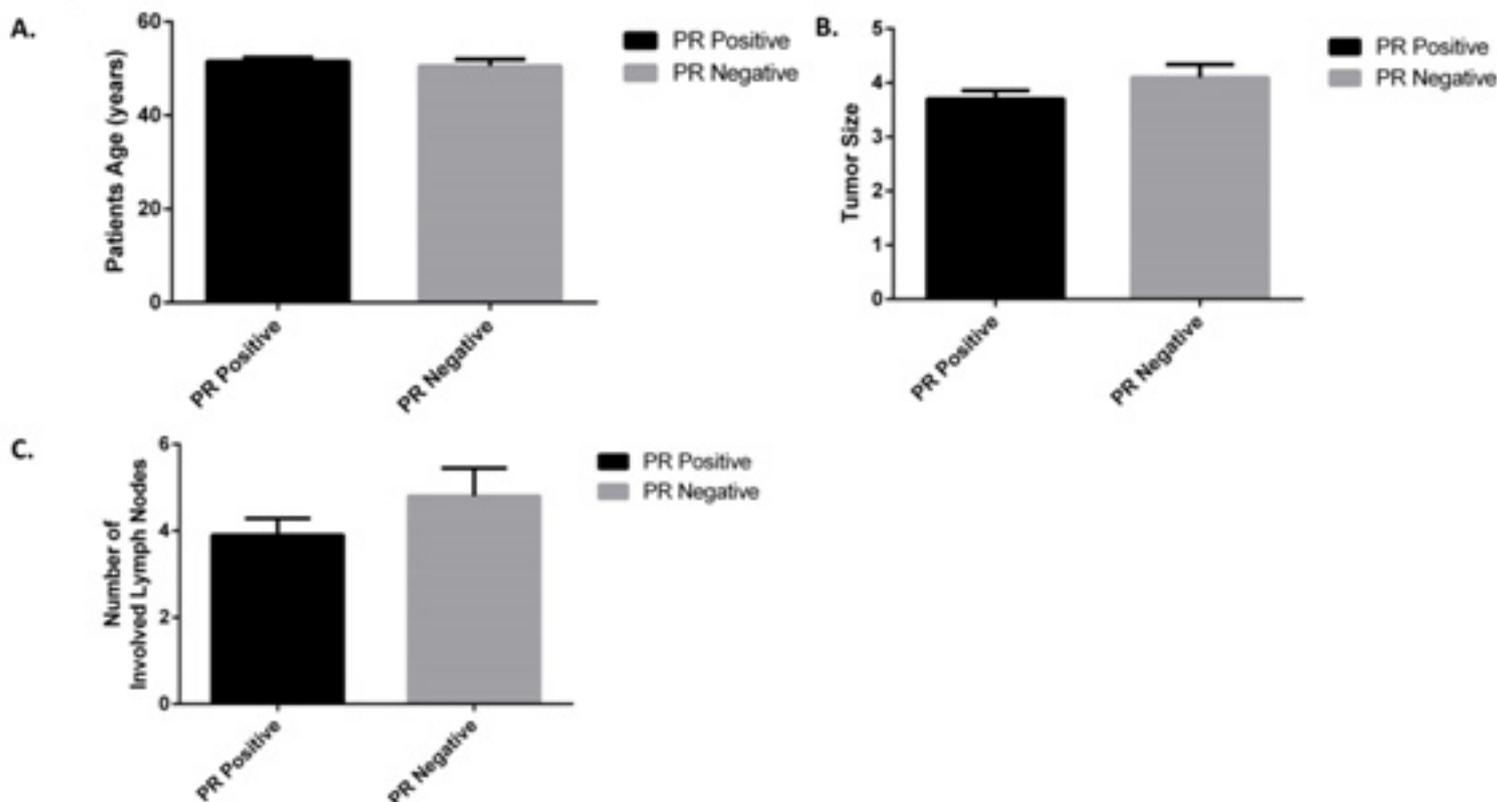
About half of the patients who had Her2 positive tumors had PR positive tumors (Figure 3 B). In contrast, the majority of patients (70%) who had her2 negative tumors did not have detectable concomitant PR expression ( $\chi^2=11.5$ ,  $p=0.001$ ).

**Table 1: Population Characteristics**

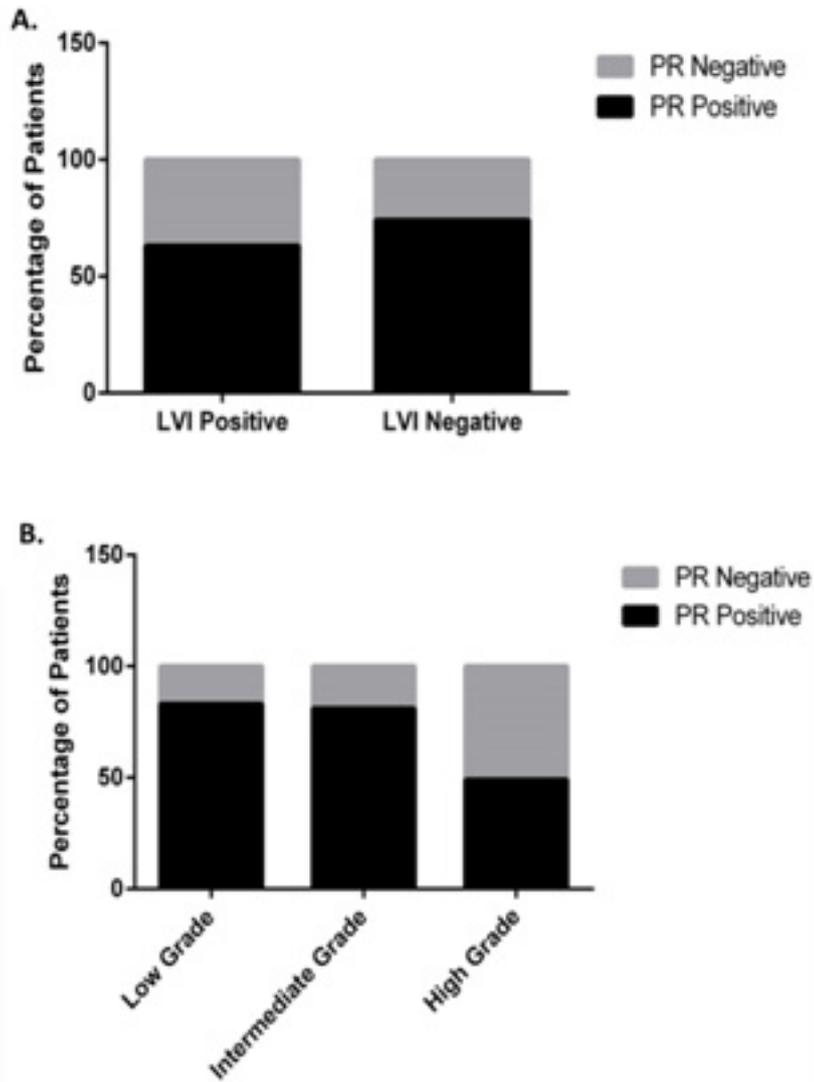
Characteristic	n (%)
<b>Age (years)</b>	
≤45	99 (34.49)
45-65	163 (47.39)
≥65	25 (18.12)
<b>LVI</b>	
Yes	158 (53)
No	140 (47)
<b>PNI</b>	
Yes	73 (24.5%)
No	224 (75.5%)
<b>Histologic grade</b>	
High	116 (41.6)
Intermediate	137 (49.1)
Low	23 (8.2)
<b>Number of involved lymph nodes</b>	
0	48 (28.2)
1-3	107 (35.9)
≥4	143 (64.9)
<b>Estrogen Receptor</b>	
Yes	215 (72.1)
No	83 (27.9)
<b>Progesterone Receptor</b>	
Yes	203 (68.1)
No	95 (31.9)
<b>Her2</b>	
Yes	65 (21.8)
No	233 (78.2)

**Figure 1: The association between different clinical parameters and progesterone receptor expression status.** Patients with different PR expression status had similar age at presentation (A), tumor size (B) and number of involved lymph nodes (C). data represent mean±SEM.

Figure 1

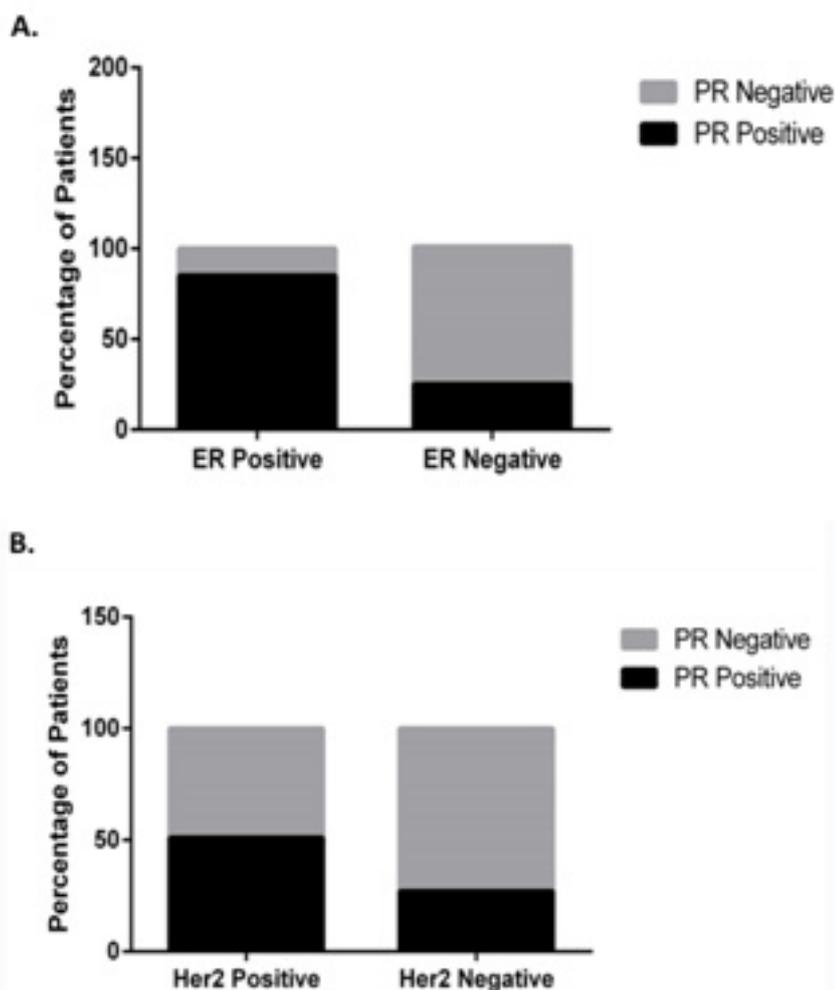


**Figure 2: The association of PR expression and pathologic parameters.** Patients with PR negative tumors were more likely to have lymphovascular invasion (A) and to present with high grade tumor (B). Data represent the percentage of the patients in each class.



**Figure 3: The association between PR expression status and ER and Her2 expression.**

Patients who had PR negative tumors were more likely to have ER (A) and Her2 negative tumors (B). Data represent the percentage of the patients in each class.



## Discussion

The aim of this study was assessing the association between PR and different clinico-pathologic breast cancer features in patients with invasive breast cancer. The expression of PR did not differ among patients with comparable tumor size, number of lymph nodes involved and age at presentation. In contrast patients who had PR negative tumors, were more likely to have lymphovascular invasion, tumors with higher grades, ER negative tumors, and Her2 negative tumors.

Our data did not detect a relationship between tumor size, number of involved lymph nodes, and the age at the time of presentation with the expression of PR. Similarly, Arpino et al. did not detect a relationship between tumor size and lymph node involvement in both patients with sporadic and familial breast cancer (6). In contrast, Nishimukai et al. reported that patients with PR negative tumors were more likely to have larger tumor sizes (5). This discrepancy might be related to the differences in the populations addressed in these two studies. The population assessed by Nishimukai et al., was postmenopausal breast cancer patients (5). In our study, we included patients without regard to their menopausal status and a good proportion of patients in our study were younger than the age of menopause.

The association between lymphovascular invasion and outcomes in patients with breast cancer is well established (2-4, 7-9). Patients who had lymphovascular invasion at the time of presentation are expected to have poor outcome as compared to patients without lymphovascular invasion (2-4, 7, 9). In this study, our results suggest an association between lymphovascular invasion and the lack of PR expression. Similarly, Marinho et al. reported a negative association between ER, PR status and LVI (10). On the other hand, Ugras et al. reported that lack of hormone receptors as well as Her2 receptors were associated with lower incidence of lymphovascular invasion (4). In their study, their focus was on patients with triple negative tumors, which constitutes a totally different type of breast cancer.

Data from our study suggest that patients with PR negative tumors are more likely to present with high grade tumors. In postmenopausal women, lack of PR expression was shown to be associated with poor outcome in terms of disease free survival (5). This association was not detected in premenopausal women with breast cancer. In this study we demonstrated that PR expression status may predict a more aggressive tumor type at the time of presentation.

Our results suggest a co-regulation of ER, HER2 and PR expression. Patients with PR negative tumors were more likely to be ER negative. Similarly, Nishimukai et al. reported that patients with low PR expression had lower ER expression (5). Moreover, Howlader et al. reported similar findings on the relationship between the expression of PR, ER and Her2 in data derived from a US based database (11).

In conclusion, our data suggest an association between PR expression and different breast cancer clinicopathologic data. Additionally, lack of PR expression was associated with predictors of poor prognosis and outcome. More studies are required to establish the favorable effect of progesterone receptor expression on prognosis and outcome among breast cancer patients.

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# Assessment of the Efficiency of hospitals before and after the implementation of the Health Reform Plan in Qazvin province based on the Pabon Lasso model (2011-2016)

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## Abstract

**Introduction:** In order to measure the efficiency of hospitals, various approaches have been proposed, which among them the Pabon Lasso model graphically evaluates the performance of hospitals. Therefore, the aim of this study was to evaluate the performance of hospitals affiliated to Qazvin University of Medical Sciences three years before and after implementation of the Health Reform Plan.

**Method:** This study was descriptive-analytic and evaluated the performance of 6 Public hospitals and 5 private hospitals of Qazvin University of Medical Sciences in the 3 years before (2011-2013) and 3 years after (2014-2016) the implementation of the Health Reform Plan with the Pabon Lasso model. In this model, three indicators (bed turnover, bed occupancy and average length of stay) were used simultaneously. Data was collected using a standard checklist. SPSS software was used to analyze the data.

**Results:** The results showed that the average of three indicators in public hospitals (bed turnover, bed occupancy rate and hospital stay) has changed from 59.61 to 77.63, 61.13 to 75.75 and 4.96 to 5.15, respectively, and in private hospitals, respectively, from 109.33 to 92.81, 63.23 to 54.73, 2.3 to 2.2.

**Conclusion:** In general, performance indicators of hospitals affiliated to Qazvin University of Medical Sciences are in a desirable condition regarding standards. However, with the implementation of the Health Reform Plan and the reduction of out of the pocket patients in public hospitals, they have increased the number of patients referred to these hospitals and their transfer to the fourth zone. Therefore, measures should be taken to use the appropriate strategies for optimal and efficient use of resources for proper management.

**Key words:** Hospital, Health Reform Plan, Pabon Lasso, Qazvin

## Introduction

The health care system in Iran is a combination of health care providers in the public and private sectors, of which the public sector, in particular, the Ministry of Health and Medical Education, has a greater role to play in this regard. According to statistics, of about 62% of medical institutions affiliated to medical universities, 16% of the total health care facilities are available to the private sector, 0.08% of social security hospitals, 0.06% of military hospitals, 0.03% of charity hospitals and 0.05 are available to other hospitals (1,2).

Hospitals are one of the most important and costly components of health care systems that have allocated themselves more than two-thirds of health costs (3). Considering the significant contribution of the state budget to the health sector, the need for assessing the hospital's performance has not previously been covered (4). One of the methods for assessing how hospitals use the high volume of resources allocated to them is to evaluate performance using performance indicators (5). Effectiveness refers to the conditions in which a maximum output is obtained using a given amount of resources (6). One of the major problems in health systems in developing countries are inefficiencies in the allocation and use of inefficient resources(7).

In order to measure the efficiency of hospitals, a variety of approaches have been proposed, in which the Pabon Lasso model graphically evaluates the performance of hospitals (8). The Pabon Lasso model to compare the performance of different hospitals or different parts of a hospital uses a combination of Three indicators; bed turnover (BTO), bed occupancy (BOR) and average length of stay (ALS) (10,9). The percentage of bed occupancy represents the percentage of occupied beds in a hospital over a given period.(11) The bed turnover indicator is the number of times a patient uses a hospital bed, which is obtained from the ratio of the number of discharges to the average active bed occupation in a given period (12). The average length of the patient's stay is calculated from the total number of occupied beds at a given time in the number of discharged and deceased patients in the same period (13). The Pabon Lasso model represents the average of performance indicators and hospital performance levels (15). The first zone represents hospitals with bed occupants and low bed turnover (number of offered hospital beds is more than what is demanded). The second zone indicates a high bed turnover and low bed occupancy (unnecessary hospitalization and extra beds especially in gynaecology and obstetrics blocks). The Third zone, is there are hospitals with high bed turnover and low bed occupancy (these hospitals have desirable efficiencies; they also use the least number of beds they have) and in the fourth zone, high bed occupancy and bed turnover are low (longer hospitalizations, using less outpatient facilities, high costs especially in Psychiatric and Nursing homes) (10).

Initiation of the Health Reform Plan from early 2014 with seven service packages to reduce hospitalized patients' share of payments in hospitals related to the Ministry of

Health and Medical Education, support the retention of physicians in deprived areas, specialized physicians' residency programs in hospitals related to the Ministry of Health and Medical Education, Instruction for improving the quality of services provided in hospitals related to the Ministry of Health and Medical Education, Instruction for improving the quality of hotel services in hospitals related to the Ministry of Health and Medical Education, Instruction for the provision of financial support for incurable patients, other specific patients, and needy patients, Instruction for promoting natural childbirth. It is obvious that this design can be viewed from a variety of dimensions, from the perspective of later therapies and reduction of payment from the pocket of patients, but certainly the educational system of health, research and even cultural universities are also implementing this scheme now and more importantly into the future(16). Of course, it is worth noting that the induced demand phenomenon leads to the growth of an intolerable cost index that will overwhelm the positive outcomes of the plan and will disrupt the efficiency of the allocation of national resources (17). In a study by Bastany and colleagues who reviewed The Performance Analysis of Teaching Hospitals Affiliated with Shiraz University of Medical Sciences Before and After Health System Reform Plan Using Pabon Lasso Model, they concluded that before the implementation of the health system reform plan in 2013, of the total 14 hospitals, 14% were in zone 1 (poor performance) and 28% of hospitals in zone 3 (good performance). In 2014, after the implementation of the health system reform plan, 21% of the hospitals were in zone 1 and 21% in zone 3 (18). In a study on the Assessment of the Efficiency of Hospitals before and after the Implementation of Health Sector Evolution Plan in Iran Based on Pabon Lasso Model, they concluded that hospital performance showed an increase in mean of bed occupancy and turnover ratio, which changed from 65.40% and 86.22 times/year during 12 months before to 69.97% and 90.98 times/year during 12 months after HSEP, respectively. In line with the Pabon Lasso model, before the implementation of HSEP, 27.27% and 36.36% of the hospitals were entirely efficient and inefficient, respectively, whilst after the implementation of HSEP, their condition changed to 18.18% and 27.27%, in order (19). Therefore, this study aimed to evaluate the performance of teaching hospitals affiliated to Qazvin University of Medical Sciences using Pabon Lasso graph in the 3 years before and 3 years after the implementation of the health reform plan.

## Method

This descriptive, cross-sectional study was carried out on hospitals affiliated to Qazvin University of Medical Sciences (7 public hospitals and 6 private hospitals) which were included in the study. The Takestan Shifa Hospital and the Mehregan Private Hospital were excluded because the criteria for entering the study were one year past from the start of the founding of the hospitals (since 2010).

The data were collected in a six-year period including two three-yearly time frames: before implementation of HRP (2011 and 2013) and after implementation of HRP (2014

and 2016). The selected performance indices included BOR, BTR, and ALS. Data were collected using monthly activity forms approved by the Ministry of Health and Medical Education (MHME). The data were analyzed in SPSS21 and drawing of the Pabon Lasso chart was analyzed.

## Results

In this study, we evaluated in the years before (2011-2013) and after (2014 -2016) the implementation of the health reform plan in public and private hospitals in Qazvin province. The results of evaluating the performance indicators of hospitals in these years showed that the number of active beds in public hospitals was an average of 126 beds, of which Bouali Sina hospital (average 244 beds) was the most and Amiralmoonin in Bouin Zahra Hospital (average of 49 beds) had the smallest number of beds. The lowest percentage of bed occupancy during these years (30.22%) belonged to Amiralmoonin Boyen Zahra Hospital and the highest (75.51%) was related to the 22 Bahman Hospital. The least bed turnover was related to the 22 Bahman Hospital with 18 times a year and the maximum bed turnover of 94 times a year was related to Kosar Hospitals. The highest and the least average length of stay before the implementation of the plan related to the 22 Bahman and Kosar hospitals, respectively. In the years after the implementation of the transformation plan, the average number of beds was 143 active beds, which Bouali Sina Hospital (average of 240 beds) had the highest and Amiralmoonin in Bouin Zahra hospital of Boein Zahra (average of 50 beds) had the least beds.

The least percentage of bed occupancy in the three years after the implementation of the transformation plan (42.61%) belonged to the Amiralmoonin in Bouin Zahra, and the highest (86.13%) was in Bouali Sina Hospital. The Lowest bed turnover after implementation of the plan for the 22 Bahman Hospital(18.22) was 48 times a year, and the maximum bed turnover of 12 times per year related to Kosar Hospital. The highest and least average duration of stay after the implementation of the plan was related to the 22 Bahman and Kosar hospitals respectively. (Table 1)

The results of evaluating the performance indicators of non-academic hospitals in the years before the implementation of the development plan showed that the number of active beds in hospitals was an average of 100 beds, of which Zakariya-e Razi Hospital in Qazvin (an average of 220 beds) was the highest and Valaisr Hospital (average of 46 beds) had the smallest bed numbers. The least percentage of bed occupancy during these years (46.64%) belonged to Rahimian charity Hospital in Alborz and the highest (90.01%) was Tamin Ejtemaei in Takestan. The least bed turnover 61 times a year was Vali asr in Ab-yek and the highest bed turnover of 185.42 times a year belonged to Deh khoda. The highest and the least average duration of stay before the implementation of the change plan related to Valie Asr and Dehkhoda hospitals respectively.

In the years after the implementation of the development plan in non-academic hospitals, the average number of

beds was 104 active beds, the highest in Zakariya-e Razi Hospital in Ghazvin (average 222 beds) and Valie Asr Hospital (average of 49 beds) was the least.

The lowest percentage of bed occupancy during these years (30.15%) belonged to Rahimian Hospital in Alborz and its highest (78.35%) belonged to Zakariya-e Razi Hospital in Ghazvin. The least bed turnover was about 62 times per year for the Valiasr in Ab-yek and the maximum bed turnover of 114.59 times per year related to Dehkhoda Hospital. And the highest and least average duration of stay before after the implementation of the change plan was attributed to Tamin Ejtemaei in Takistan and Pasteur hospitals (Table 2).

## Discussion

In the Pabon-Lasso model, three indicators of duration of stay, bed occupancy and bed turnover rates are used simultaneously to evaluate the performance of hospitals. According to the relationship between these three indicators, the simultaneous survey of these indicators can indicate the function of hospitals to use efficiently or inefficiently the existing resources in hospitals (21).

In the present study, three hospitals (43%) were in the efficient zone and two hospitals (29%) were in the ineffective zone but after the implementation of the Health Reform Plan, 1 hospital (14%) was in the zone of efficient and 0 hospitals (0%) in the inefficient zone. Among the 6 private hospitals, 2 hospitals (33%) were in the efficient zone and 2 hospitals (33%) were in the ineffective zone. After the implementation of Health Reform Plan, 2 hospitals (33%) were in the efficient zone and 2 hospitals (33%) in the inefficient zone.

In a study by Bastani and colleagues, the number of hospitals in the efficient zone decreased from 28% to 21% (18). Also, in the assessment of the 5-year performance of hospitals in Kermanshah (22) and the performance of hospitals in Isfahan, after health reform plan (23), the number in the first zone was reduced. Moving public hospitals from the inefficient zone to the other zone and increasing the number of private hospitals in the efficient zone indicates improvements in efficiency and favorable use of resources, and it points out that hospital managers, and policymakers in the university, monitor the performance of hospitals and identified the causes of inefficiencies and the use of interventions and management solutions to enhance the productivity and efficiency of resources in the following years.

In this study, in the years before and after the implementation of health reform plan in public hospitals, respectively (14%) and (28%) and in private hospitals were respectively (16%) and (33%) in the second zone.

In a study by Mottaghi et al, in 6 Kashan hospitals in 2010, 17% and in 2011, 34% were reported (24).

In the study of Alijanzadeh et al. who examined the performance of hospitals in Gilan, 23% of hospitals were in the second zone(25). Also in the study of Nekoeimoghadam

**Table 1: Data on the performance of inpatient wards in the studied hospitals before and after the implementation of Health Sector Evolution Plan**

Row	Hospital name	Active beds		Active day beds		Bed occupancy		Bed turnover		Average length of stay	
		Before	After	Before	After	Before	After	Before	After	Before	After
1	22 Bahman	57	60	20425	21900	76.26	85.58	18.28	18.22	14.58	17.17
2	Amiralmoonin in Bouin Zahra	49	50	17842	18250	30.49	42.6	55.05	95.66	2.22	1.62
3	Bouali Sina	244	402	86963	80830	74.67	86.13	64.11	63.76	4.13	4.55
4	Shahid rajaei	149	146	53535	50045	71.95	74.21	77.98	91.92	3.33	2.79
5	Qods	134	143	46971	47935	68.42	84.33	67.71	76.79	3.51	3.68
6	Kosar	143	142	52233	51830	59.13	80.75	94.60	127.5845	2.34	2.30
7	Velayat	106	221	47108	79822	47.09	76.63	39.53	69.48	4.64	3.98
Total		126	143	46440	50087	61.13	75.75	59.61	77.63	4.96	5.15

**Table 2: Data on the performance of inpatient wards in the studied hospitals before and after the implementation of Health Sector Evolution Plan**

	Hospital name	Active beds		Active day beds		Bed occupancy		Bed turnover		Average length of stay	
		Before	After	Before	After	Before	After	Before	After	Before	After
1	Valie Asr	46	49	17648	17529	48.81	46.16	60.61	61.77	3.16	2.67
2	Pasteur	108	106	37230	39209	55.26	44.69	114.70	111.34	1.68	1.47
3	Tamin Ejtmaei in Takistan	99	104	35507	40150	89.37	76.21	118.82	108.65	2.71	2.72
4	Rahimian Charity	59	70	20227	20743	42.14	30.15	78.28	48.67	1.86	1.83
5	Dehkhoda in Qazvin	68	70	24576	30164	71.08	52.82	185.42	114.59	1.48	1.96
6	Zakariya-e Razi	220	222	79729	80862	72.74	78.36	98.2	111.86	2.70	2.55
Total		100	104	35820	38110	63.23	54.73	109.33	92.81	2.3	2.2

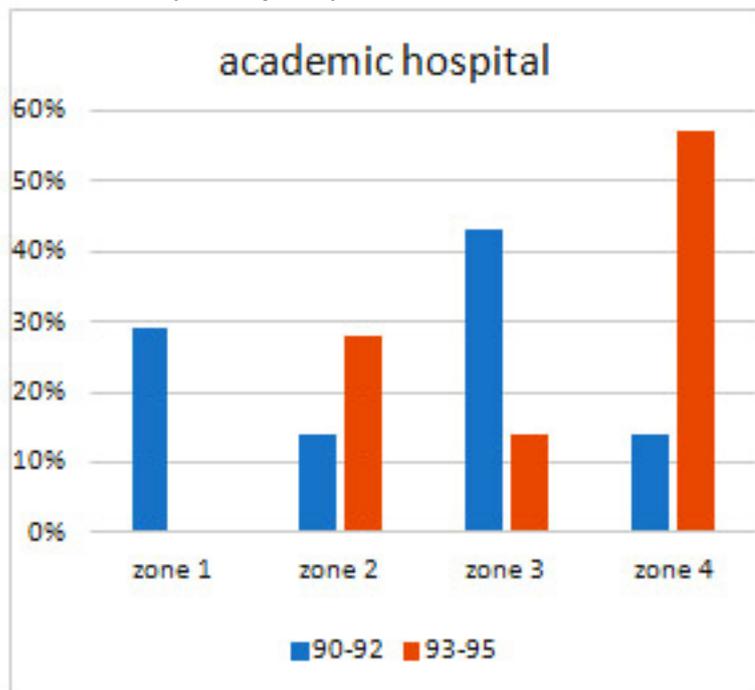
**Table 3: Hospital Performance Indicators According to the Ministry of Health (20)**

Indicator type	Favorable	Average	Unfavorable	Public hospitals		Private hospitals	
				Before	After	Before	After
bed occupancy	More than 70	60-70	Lower than 60	61.13	75.75	63.23	54.73
average length of stay	Lower than 3.5	3.5-4	More than 4	4.96	5.15	2.3	2.2
bed turnover	More than 24	17-24	Lower than 17	59.61	77.63	109.33	92.81

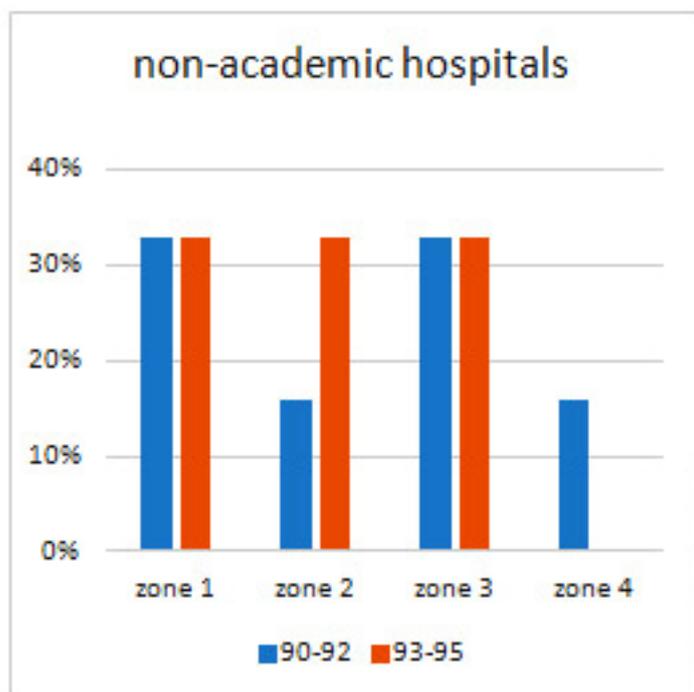
25 percent of hospitals were in the second zone which was similar to this study (26). In the study of Bahadori in Urmia, 4% of the hospitals were in the second zone, which was different from the results of the study (27). The second zone is more specific for large bed turnover hospitals, such as Obstetrics and Gynecology Hospitals and hospitals with a low average length of stay, and if a hospital with these features is in this zone it is indicative of the effectiveness of these centers. Finally, in the years before and after the implementation of health reform plan in public hospitals (14%) and (57%) and in private hospitals were (16%) and (0%) respectively in the fourth zone.

In Bastany's study, 42% of hospitals in 2013 and 35% of hospitals were in the fourth zone in 2014 (18). In a study by Kalhor et al, who studied 21 hospitals in Mashhad in a 4-year time period, they found that 28% of hospitals were located in this area during the study years (28). The fourth zone includes centers that have high bed occupancy rates, low bed turnover, low utilization of facilities and high costs (features of long-term hospitalization centers, such as psychiatric and seniors' centers). By comparing the performance indicators of the present study with similar studies, the reason for these differences can be due to the the implementation of health reform plan because, according to the provisions of this plan, the proportion of direct payments from the pocket of patients has decreased, as demand for services in public hospitals has increased.

**Diagram 1: Relative frequency of hospitals in Qazvin University of Medical Sciences in different areas of performance Pabon Lasso (13 hospitals)**

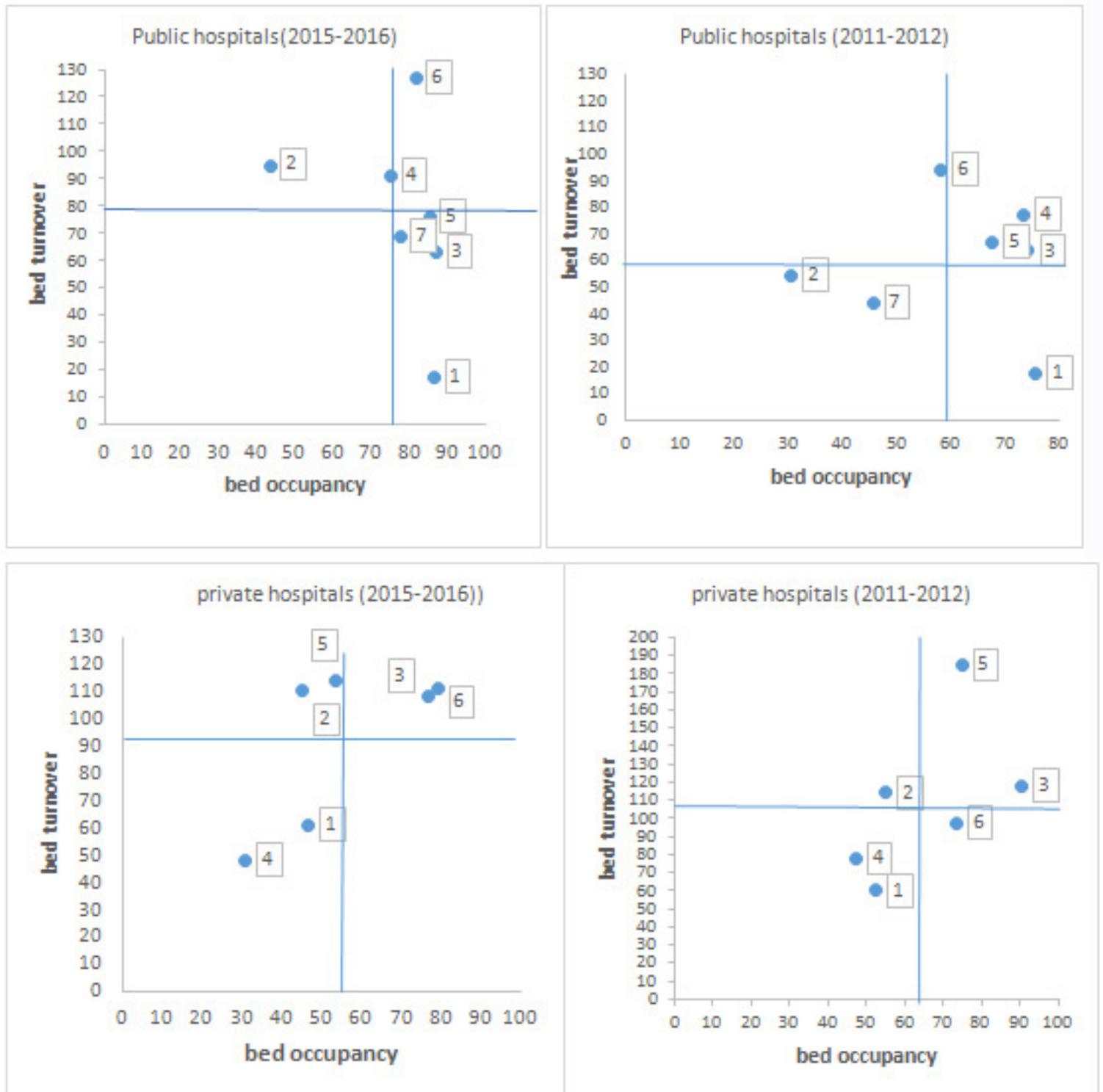


	90-92	93-95
<b>zone 1</b>	29%	0%
<b>zone 2</b>	14%	28%
<b>zone 3</b>	43%	14%
<b>zone 4</b>	14%	57%



	90-92	93-95
<b>zone 1</b>	33%	33%
<b>zone 2</b>	16%	33%
<b>zone 3</b>	33%	33%
<b>zone 4</b>	16%	0%

**Diagram 2: The status of the studied hospitals based on the Pabon Lasso Model before the implementation of Health Reform Plan**



## Conclusion

In general, performance indicators of hospitals affiliated to Qazvin University of Medical Sciences in regard to standards are in a favorable condition. However, with the implementation of the health reform plan and the reduction of the contribution of patients to hospitals affiliated with the Ministry of Health and Medical Education, the increase in the occupancy rate of public hospitals has been a natural occurrence, resulting in an increase in the percentage of flat occupancy and a simultaneous increase in the average. The increase in the average number

of admissions leads to long-term admissions and increases in costs (Chart 4), each of which, in turn, causes problems in hospitals and provides services to patients. Therefore, actions should be taken using appropriate strategies to make optimal and efficient use of resources for proper management.

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# Relationship between Virchow-Robin space dilatation on magnetic resonance imaging (MRI) and migraine headaches

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## Abstract

**Objective:** Virchow-Robin (VR) spaces are perivascular spaces that surround the perforating arteries of the brain. These spaces are usually microscopic, but when they dilate, they may be seen on magnetic resonance imaging (MRI). The aim of this study was to investigate the relationship between VR space dilatation on brain MRI and symptom of headache in migraine headaches.

**Methods:** In this cross-sectional study, two groups of patients with (30 patients) and without migraine headaches (30 patients) who referred to our academic radiology department to undergo MRI examination, were included. VR space dilatation was considered as a size of larger than 2 mm. Results: VR space dilatation was seen in 29 patients (48.3%). This was significantly more common among patients with migraine headaches (20 patients, 66.7%) than in patients without headaches (9 patients, 30%);  $P= 0.009$ .

**Conclusion:** VR space dilatation seen on brain MRI is a relatively common radiologic finding among patients with migraine headaches and found to be more common than in patients without headaches. This radiologic finding can be considered as an important finding in the assessment of patients with migraine headaches.

**Key words:** Virchow-Robin space; headache; migraine; magnetic resonance imaging; brain

## Introduction

Virchow-Robin (VR) spaces are small, perivascular spaces that surround the perforating arteries of the brain and expand from the subarachnoid space to the cerebral parenchyma (1). There is evidence about the function of these spaces, such as acting as a channel for the drainage of interstitial fluid as well as having immunological function (2). These spaces are usually microscopic, but when dilated, they may be seen on magnetic resonance imaging (MRI) of the brain. Typically, dilated spaces are seen as cystic dilatation with cerebrospinal fluid (CSF) signal (3). MRI is the sole imaging method capable of evaluating the anatomical details of VR spaces (4, 5).

The dilatation of VR spaces has been reported in some pathological conditions of the brain including vascular, inflammatory, neoplastic, metabolic and traumatic brain conditions (2, 6). One of the important conditions in this regard is migraine headache. Migraine is a relatively common debilitating disorder (about 14% in the United States), which is diagnosed using clinical criteria. In general, it is not necessary to perform imaging of the brain in patients with typical migraine symptoms. Neurological imaging has, however, been the focus of recent attention in some studies. Imaging studies have shown new evidence of changes in the brain of migraine patients and these findings can be effective in following and choosing therapies, although these are still at the research stage (8).

One of the imaging findings of the brain in migraine patients is VR space dilatation. There is controversy about VR dilatation in migraine headache. In some studies, it has been shown that the number of dilated VR spaces in these patients is clearly and significantly increased (9-12). Three studies have been conducted on children (10-12). In one study, the average age of the patients was 42 years (9). A case report presented an adult patient who had a migraine headache with a very large dilatation of VR space (3). Contrary to these results, in a recent study, there was no significant difference in the frequency of this finding between adult patients with migraine headache and those without headache (1).

The aim of this study was to determine the frequency of VR space dilatation in patients with migraine headache and compare it with patients without migraine headache. Considering the fact that VR space dilatation may be seen even in patients without headache, investigation as to whether the presence of VR dilatation in patients with migraine headache has a significant relationship with this disease is important. Therefore, if there is a meaningful relationship between VR dilatation and migraine headache, the importance of mentioning this finding in the interpretation of brain MRI in patients with headache complaints can be established. Given the fact that no specific criteria for imaging migraine has yet been identified, it may be possible to use this radiologic finding in developing more useful radiologic criteria for migraine headaches.

## Materials and Methods

### Study Design and Population

In this cross-sectional study, two groups were included. One group (case group) included patients with migraine headache symptoms and because of neurological disorders, according to a board-certified neurologist consultation, imaging with MRI was considered necessary. Migraine headache was diagnosed using the diagnostic criteria proposed by the International Headache Society (13). The second group (control group) included patients who did not have migraine headaches and were referred to the radiology department to undergo MRI examination for various reasons. The age range of 15-50 years old was considered for inclusion in the study. Exclusion criteria in the two groups were history of ischemic attacks or evidence of atherosclerosis, multiple sclerosis, previous history of white matter neurodegenerative diseases, history of granulomatous and rheumatic diseases such as systemic lupus erythematosus (SLE) and history of infectious diseases such as tuberculosis, and metabolic diseases. Also, patients who had a history of smoking were not included. In addition, observation of any incidental finding on brain MRI was considered as an exclusion criterion.

### Sample size

The sample size was estimated using the findings of a similar study (9) in which the frequency of VR space dilatation rates on brain MRI of patients with migraine headache and without headache symptoms were reported as 40% and 7%, respectively. Considering a confidence level of 95% and a power of 90%, the minimum sample size was calculated as 30 patients in each group.

### Data collection

The Data gathered included demographic characteristics (age, gender, body mass index), clinical signs and MRI data. The instrument used was a Philips MRI machine with a magnetic field intensity of 1 Tesla. Based on the MRI of the brain, the size of the VR space of more than 2 mm was considered dilated VR space (1). MRI images were interpreted by a radiologist who was unaware of the patients' characteristics.

### Data analysis

The mean, standard deviation (SD) and frequency were used to report the data. To compare the quantitative variables between the two groups, the independent t-test or Mann-Whitney U test were used. The U-Mann-Whitney test was used to compare the age distribution of patients with and without migraine headache symptoms. The Chi-square test was used to compare the qualitative variables. The significance level was considered as 0.05. The SPSS software (Ver. 22.0) was used for data analyses.

## Results

Mean ( $\pm$ SD) age of the patients was 37.28 ( $\pm$ 11.75) years (range, 18-60 years). There were 56 females (93.3%) and two males (6.7%). Mean ( $\pm$ SD) BMI was 4.32 ( $\pm$ 4.60) kg/m<sup>2</sup> (range, 19.53 to 34.37).

Sixteen patients (26.66%) had a medical condition including hypertension (4 patients, 6.7%), hypothyroidism (2 patients, 3.3%), cardiovascular disease (one patient, 1.7%), seizure (3 patients, 5%), epilepsy (3 patients, 5%), and brain astrocytomas (3 patients, 5%). The comparison of demographic variables between the two groups is shown in Table 1.

**Table 1. Comparison of demographic data between patients with and without migraine headaches**

	Migraine headache group (N= 30)	Control group (N= 30)	P value
Age, year	39.47 ( $\pm$ 12.18)	32.16 ( $\pm$ 9.05)	0.023
Gender, female	29 (96.7%)	27 (90%)	0.612
BMI, kg/m <sup>2</sup>	26.92 ( $\pm$ 4.36)	24.42 ( $\pm$ 4.03)	0.194
Medical condition	7 (23.3%)	9 (30%)	0.99

The dilatation of VR space was observed in 29 patients (48.3%). Anatomical location of the dilatation was basal ganglia (28 patients, 93.3%) and hemispheric white matter (2 patients, 6.7%). VR space dilatation was diagnosed in 20 patients of the migraine headache group (66.7%) which was significantly more prevalent than that observed in the control group (9 patients, 30%);  $P = 0.009$ .

Of 20 patients with migraine headache who had dilated VR spaces, the anatomical location of the lesion was in the basal ganglia in 19 patients (95%), and only one patient had VR dilatation in the hemispheric white matter. VR dilatation was diagnosed in the basal ganglia in all 9 patients of the control group. There was no significant difference in the anatomical location of the lesion between the two groups.

## Discussion

According to the results of this study, about two thirds of patients with migraine headache had dilated VR spaces on brain MRI. The prevalence of this finding was significantly higher in patients with migraine than in patients who did not have headaches. VR spaces with round, ovoid, or linear appearance have signal intensity similar to the CSF. In previous studies, the basic ganglia and hemispheric white matter have been reported as the most common anatomic locations for dilated VR spaces (1-3, 14, 15).

Few studies have compared the frequency of VR space dilatation of patients with migraine headache symptoms and those without migraine headache symptoms. A study by Schick et al., compatible with our findings, concluded that based on the findings of MRI, VR dilatation was observed in 61% of patients with migraine headache and in 22% of patients with tension headache. Therefore, recognizing the dilated VR space can be helpful in improving primary headache management in children (10). In another study in adult patients, in agreement with the presented results, the dilatation of VR space in the group of patients with migraine headache was 40% and in the group of patients without headache was only 7% (9). In a study by Biedroń et al., it was shown that among children with dilated VR space, 28.3% of the patients were diagnosed with headache. The most frequent anatomic location was in the subcortical area. There was no relationship between the location of dilated VR space and symptoms of the patients, except that a large dilated VR space could lead to pressure on the surrounding tissues (12). In a study by Husøy et al., the basal ganglia and hemispheric white matter were the most common reported locations for dilated VR spaces

(1). However, in contrast to the above mentioned findings, there was little difference in the frequency of perivascular space dilation of patients with migraine headache and those without migraine headache (1). However, patients with a migraine headache without aura had a smaller perivascular space than those without headache in the basal ganglia (1).

In a study by Rollins et al., it was shown that there was a relationship between neurological disorders such as headache in children and the existence of dilatation of VR space based on MRI findings (11). Relation between dilatation of VR space and physiological aging, hypertension and dementia has been reported. There is a clear correlation between the age and VR dilatation which indicates that this is another phenomenon that is related to the aging of the brain, similar to that which occurs in the subarachnoid space (1).

Pathogenesis of the headache is an ongoing topic with two main theories proposed. These are vasodilatation caused by vasodilatation and neurogenic process associated with secondary vasodilation associated with sterile neurogenic inflammation. But in a new theory about headache pathogenesis, factors such as defects in controlling estrogen-dependent microvascular integrity which leads to the extraction of plasma proteins, potential activation of perivascular space and neurons associated with connective tissue stroma related to pain and the release of inflammatory responses were discussed (16). VR spaces are potentially one of the most important pathways for soluble proteins like leukocytes to enter the central nervous system (16), which are associated with the transfer of soluble factors between the extracellular fluid of the brain and the CSF.

## Limitations

The current study had some limitations. We were not able to follow patients and find out the association between VR space dilatation with migraine headache attacks. Only migraine headache patients were enrolled and other types of headache such as tension-type headache and cluster headache were not included.

## Conclusion

The dilation of VR space was relatively common in migraine headache patients. This finding was significantly more common in the migraine group than in the control group. This radiologic finding can be considered as an important criterion in examining patients with migraine headaches.

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# Cartilage Tympanoplasty type 1: Surgical Outcome in Aden, Yemen

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## Abstract

**Background:** Tympanoplasty type 1 is surgical repair of the tympanic membrane (TM) perforation with assessment of ossicular mobility which is indicated to restore hearing ability as well as to prevent recurrent otorrhea.

**Methods:** A retrospective review of the records of all patients who underwent tympanoplasty during the period 2013 - 2016.

**Results:** The total patients were 102. Males were (48%) and females (52%).

Female to male ratio was 1.08:1, and the mean age was  $25.9 \pm 6.5$  years.

Bilateral were (36.7%), and unilateral (36.3%). Sites of tympanic membrane were (42.2%) central, (31.4%) posterior and (26.4%) anterior.

Perforation sizes were (52.9%) large, (25.5%) medium and (21.6%) small.

The preoperative A-B gap was higher 92(90.2%) in the hearing level of  $> 20$  decibels, while the post-operative A-B gap was higher in the gap group 0-10 decibels (51%) followed by gap group 11-20 decibels 45(44.1%); ( $p = 0.000$ ).

The mean preoperative A-B gap was  $32.16 \pm 6.84$  dB and postoperative A-B gap was  $12.11 \pm 8.19$  dB. The hearing gain was 20.05 dB ( $p = 0.000$ ).

The preoperative hearing threshold was  $52.16 \pm 6.84$  dB and postoperative hearing threshold was  $32.15 \pm 8.19$  dB. The hearing gain was also, 20.01 dB. ( $p < 0.05$ ). Only 7 (6.9%) patients had complications, and the graft success rate was 98.04%.

**Conclusion:** We concluded that cartilage tympanoplasty is a reliable graft material for reconstruction of tympanic membrane perforations, and gives excellent hearing results, in unilateral and in bilateral tympanic membrane perforations.

**Key words:** Cartilage Tympanoplasty, hearing outcome, complications

## Introduction

Surgical repair (tympanoplasty) of the perforated tympanic membrane (TM) is indicated to restore hearing ability as well as to prevent recurrent otorrhea (1). Tympanoplasty was introduced by Berthold and later developed and modified by Wullstein and Zollner (1,2,3,4). The various surgical approaches to tympanoplasty include endomeatal (per meatal), endaural, and post-auricular routes. These approaches have a different effect on surgical outcome, depending on the size and site of perforation (1). A surgical technique using either underlay or overlay of grafts over the perforated TM has been employed by various surgeons (1,5,6). The underlay is widely used and is relatively simple to perform, as the graft is placed entirely medial to the remaining drum and malleus (1,2,7).

## Objective

To evaluate the outcome of cartilage tympanoplasty: hearing results and complications

## Materials and method

The study was a retrospective study involving all patients who underwent Type I tympanoplasty done by the same surgeon (the author) at the Ear, Nose and Throat (ENT) department at Al-Gamhoria Teaching Hospital, and two private hospitals, in Aden, Yemen, between January 2013 and December 2016.

## Results

A total number of 102 patients, who were admitted in the ENT department in Al-Gamhoria Teaching Hospital and two other private hospitals during the study period, were included in this study. Table 1 and Figure 1 shows that forty nine (48%) were males and 53(52%) were females. The female to male ratio is 1.08:1, and the mean age was 25.9 ± 6.5 years (range 15 - 45 years). The predominant sides involved were bilateral 65 (36.7%), while the unilateral sides were 37(36.3%). The perforation locations of tympanic membrane were 43(42.2%) central, 32(31.4%) posterior and 27(26.4%) anterior. The predominant perforation sizes were 54 (52.9%) large, 26(25.5%) medium and 22(21.6%) small.

All patients were assessed pre-operatively by detailed history and clinical examination. The patients with tubotympanic disease and dry central perforations were selected.

Patients with a history of nasal allergy, other nasal diseases, throat problems or any systemic disease were appropriately treated before having ear surgery. Cases of cholesteatoma, ossicular pathology and wet tympanic membrane perforations were excluded from the study. The side, size and site of the perforations were recorded. The patency of Eustachian tube was assessed. Hearing assessment was initially performed clinically by tuning fork tests and then by Pure tones Audiometry. Ossicular chain integrity was speculated by preoperative A-B gap on audiometry and then it was checked per operatively when the tympanum was opened. CT scan of temporal bone was performed in all patients. All cases were operated through post aural approach using cartilage perichondrium graft from tragus by underlay technique under general anesthesia. Patients were followed at regular intervals for minimum 1 year post-operatively. Status of the graft, along with any evidence of complications was noted, assessment of hearing was done 1year postoperative by pure tones audiometry. A-B gap and air conduction threshold from speech frequencies (500,1000 ,2000HZ ) were recorded.

The collected data were tabulated and statistical analysis was done by estimating rates, means and standard deviations, paired sample t-test was used and p-value < 0.05 was considered as statistically significant. The statistical software package SPSS version 17 was used.

**Table 1: Distribution of variables**

Variables	No	%
<b>Sex:</b>		
Males	49	48.0
Females	53	52.0
<b>Female to male ratio:</b>	1.08:1	
<b>Mean age (years):</b>	25.9 (SD) ± 6.5	
<b>Age range (years):</b>	15-45	
<b>Side involved:</b>		
Unilateral	37	36.3
Bilateral	65	63.7
<b>Site of perforation:</b>		
Anterior	27	26.4
Central	43	42.2
Posterior	32	31.4
<b>Size of perforation:</b>		
Large	54	52.9
Medium	26	25.5
Small	22	21.6

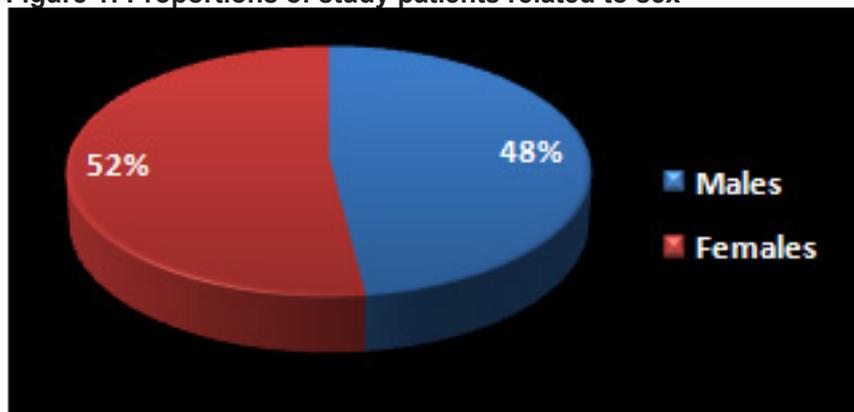
**Figure 1: Proportions of study patients related to sex**

Table 2 and Figure 2 show the pre-operative and postoperative hearing gap related to hearing levels in decibels. Preoperative gap in the air bone gap group 0 – 10 decibels were 0 (0.0%) and in the group 11 – 20 dBs were 10 (9.8%). The preoperative gap was higher 92(90.2%) in the hearing level of > 20 decibels,

while the postoperative gap was higher in the gap group 0-10 decibels 52(51%) followed by gap group 11-20 decibels 45(44.1%) and in the gap group more than 20 decibels were 5(4.9%). The difference between values is statistically significant ( $p = 0.000$ ).

**Table 2: Pre-operative and postoperative gap related to air bone gap group (n = 102)**

Air bone gap group (dB)	Preoperative gap		Postoperative gap	
	No	(%)	No	(%)
0–10	0	(0.0)	52	(51)
11–20	10	(9.8)	45	(44.1)
> 20	92	(90.2)	5	(4.9)

Chi-square = 152;  $p = 0.000$

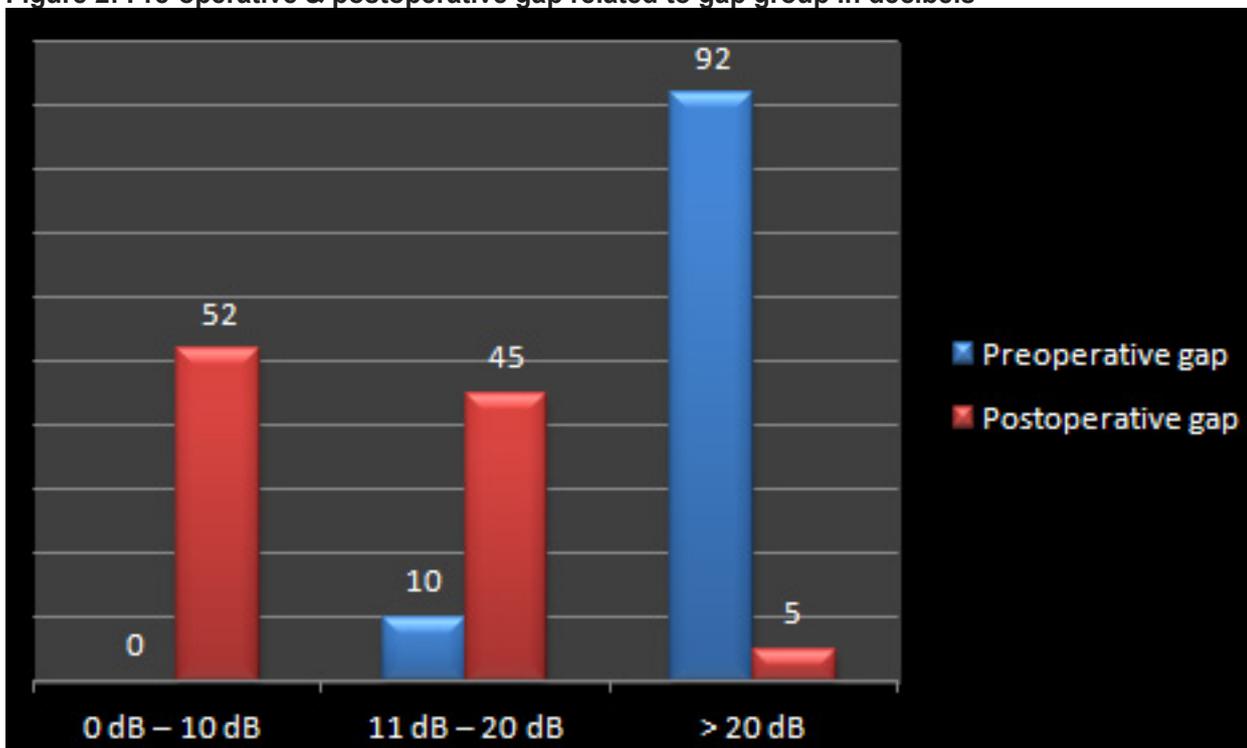
**Figure 2: Pre-operative & postoperative gap related to gap group in decibels**

Table 3 reveals that the mean of preoperative A-B gap is  $32.16 \pm 6.84$  dB and postoperative A-B gap is  $12.11 \pm 8.19$  dB. The hearing gain is 20.05 dB. The difference between means is statistically significant,  $p = 0.000$ ; [95% CL: 19.117 – 20.981].

**Table 3: Means of preoperative and postoperative A-B gap and hearing gain**

Items	Mean $\pm$ SD	P-value & paired test
Preoperative A_B gap	32.16 $\pm$ 6.84	p = 0.000; [95%, CL: 19.117-20.981]
Postoperative A_B gap	12.11 $\pm$ 8.19	
Hearing gain	20.05 dB	

The preoperative air conduction hearing threshold is 52.16  $\pm$  6.84 dB and postoperative air conduction hearing threshold is 32.15  $\pm$  8.19 dB. The hearing gain is also, 20.01 dB. Also, the difference between values is statistically significant, p = 0.000; [95% CL: 19.09 – 20.93] as shown in Table 4.

**Table 4: Means of preoperative and postoperative air conduction threshold and hearing gain**

Items	Mean $\pm$ SD	P-value & paired test
Preoperative threshold	52.16 $\pm$ 6.84	p = 0.000; [95%, CL: 19.09-20.93]
Postoperative threshold	32.15 $\pm$ 8.19	
Hearing gain	20.01 dB	

Complications were Otorrhea 3(2.9%) and a group of complications (adhesive graft, failed graft, serous otitis media, and wound infection) for each one 1(1.0%), as appears in Table 5.

**Table 5: Distribution of patients without & with postoperative complications**

Items	No	%
No complications	95	93.1
Adhesive graft	1	1.0
Failed graft	1	1.0
Otorrhea	3	2.9
Serous otitis media	1	1.0
Wound infection	1	1.0
<b>Total</b>	<b>102</b>	<b>100</b>

## Discussion

Perforations of the tympanic membrane are quite frequent, being caused by infections, trauma or by iatrogenic maneuvers. The size and localization of tympanic defects are variable, their correct evaluation being essential for a successful management of the pathology (8,9).

Cartilage or composite cartilage grafts are more resistant to infections, middle ear pressure, and lack of capillary feed (10,11).

Our study included 102 individuals who had examined, diagnosed and undergone tympanoplasty and were postoperatively evaluated for hearing bone air gap, hearing threshold and complications. The female patients were predominant 53(52%) while male patients were 49(48%). The female to male ratio was 1.08:1.

These findings are in accordance with the findings of Gierek et al (12), Kiakujori et al (13) and Prasad et al (14) who in their studies also had female predominance. In contrast to our study Homquist (15) had male predominance.

The mean age of the patients in our study was 25.9  $\pm$  6.5 years (range 15 - 45 years). This finding was similar to findings by others (13,14,16).

In the present study the predominant sides involved were bilateral 65 (36.7%), while the unilateral sides were 37(36.3%). We classified the tympanic membrane perforation size as large (subtotal), medium and small. The predominant perforation sizes were large (52.9%) followed by medium (25.5%) and small (21.6%). We found also, the perforation locations of tympanic membrane were central (42.2%), posterior (31.4%) and anterior (26.4%).

These findings were to some extent similar to the finding reported by Thakur et al (17) who found that site of perforation affects the degree of hearing loss. Big central and central malleolar perforation causes greater hearing loss than other perforation sites (18). Most authors also reported less success with the anterior perforation probably because the anterior portion of the tympanic membrane is the least vascular area. Longer duration of disease causes more damage to the middle ear mucosa (19).

We used underlay technique of graft placement in all patients of the present study. Similar technique of graft placement was used in the study of Gerber et al (20), Kotecha et al (21) and Dornhoffer (22).

In the present study, 92(90.2%) patients had preoperative hearing loss (air-bone gap) more than 20 decibels. While in the group of 11 – 20 dBs there were only 10 (9.8%) patients, whereas no patient had an air bone gap 0 - 10 dB prior to surgery.

This was similar to the finding reported by Dabhekar et al (23) that 91% (60/65) patients had preoperative hearing loss (air-bone gap) between 20-40 dB.

Other authors such as Dornhoffer (22) found (45%), Gerber et al (20) found (59.9%) and reported much less preoperative hearing loss, between 20-40 decibels.

In a study from Egypt by Fatthy et al (24), they reported that in preoperative hearing loss (air-bone gap) there was no patient in group of A-B gap 0 to 10 dBs. This finding is comparable to our finding.

Our results differ in the number of patients in the group of A-B gap 10 - 20 decibels as well as in the group above 20 decibels.

Our explanation of the higher preoperative hearing loss in the present study is similar to that mentioned before by Dabhekar et al (23) that it is probably due to more reluctance of patients towards their health, resulting in late referral to an otologist.

In the present study, mean preoperative air bone gap was  $32.16 \pm 6.84$  dB. A similar finding was reported by Dabhekar (23) et al ( $30.14 \pm 6$  dB) and Aidonis (25) et al ( $32.4 \pm 14.1$  dB).

Mean postoperative air-bone gap in this study, was  $12.11 \pm 8.19$  dB while in the study by Dornhoffer (22) it was  $14.1 \pm 9.5$  dB and in the study of Mayaleh et al (26) it was  $12.2 \pm 7.3$  dB.

The hearing gain in this study was 20.05 dB which was in accordance with a previous study by Dornhoffer (27) wherein mean hearing gain was 19 dB and a study finding of Dabhekar (23) where it was 18.6 dB.

Onal et al (28) reported in their study that hearing outcomes for all patients ABG was  $29.59 \pm 9.88$  dB pre-operatively and  $16.56 \pm 9.30$  dB post-operatively and the association between values was statistically significant ( $p = 0.001$ ).

We found in our study the preoperative air conduction hearing threshold was  $52.16 \pm 6.84$  dB and postoperative hearing threshold was  $32.15 \pm 8.19$  dB. The hearing gain was also, 20.01 dB. Also, the difference between values is statistically significant,  $p = 0.000$ ; [95% CL: 19.09 – 20.93]. Our finding is to some extent similar to the findings reported by Onal et al (28) that preoperative air conduction threshold was  $40.69 \pm 9.11$  decibels and the postoperative threshold was  $22.97 \pm 8.37$  decibels.

Also, in our study the hearing gain in air conduction threshold was 20.01 dB which is comparable to that reported by Ben Gamra et al (29) in which they mentioned in their study that the postoperative mean of air conduction gain was  $21 \pm 11$  dB.

In the current study we found that out of 102 patients only 7(6.9%) patients had complications. The complications were Otorrhea 3(2.9%) [due to mild otitis externa which was treated by antibiotics] and a group of complications

(adhesive graft, failed graft, serous otitis media, and wound infection) for each one 1(1.0%). Serous otitis media developed in an allergic rhinitis patient and was improved by anti-allergic treatment.

If we consider that adhesive graft 1(1%) and failed graft 1(1%) the lack of success in the tympanoplasty surgery was in 2 patients and the success of tympanoplasty in 100 patients, so the graft success rate was 98.04%. Our finding was comparable with the study result of Khan et al (30) in which they reported the success rate was 98.20%.

## Conclusion

- Cartilage tympanoplasty gives excellent hearing results whatever the site or size of perforation, with rare postoperative complications;
- Cartilage is a reliable graft material for repairing the tympanic membrane perforations;
- Cartilage tympanoplasty gives better hearing results in bilateral tympanic membrane perforations where the dysfunction is of the Eustachian tube.

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# The effectiveness of *Melissa officinalis* on sleep problems in Patients with Chronic Heart Failure

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## Abstract

**Background:** Numerous studies have documented high prevalence rate of major depression in patients with heart failure.

**Aim:** The aim of the present study was to evaluate the effectiveness of *Melissa officinalis* on sleep problems in patients with chronic heart failure.

**Methods:** In a randomized, controlled trial study eighty patients (40 in each group) with chronic heart failure and experiencing insomnia were allocated randomly into intervention and control groups. The patients in the intervention group, received 12 ml *M. officinalis* syrup in addition to conventional treatment one hour before going to bed for 4 weeks. A demographic questionnaire and the Pittsburgh Sleep Quality Index were used to collect data. Questionnaires were completed by all subjects before and after the intervention.

**Results:** The time duration of waiting for falling asleep in the intervention group was significantly less than the control group ( $p=0.001$ ). The hours during which the subjects were fully asleep was significantly more than the control group ( $p<0.05$ ).

**Conclusion:** *M. officinalis* may improve the quality of sleep in patients with chronic heart failure who experience insomnia.

**Key words:** Heart failure, *Melissa officinalis*, Sleep

## Introduction

Sleep problem is a common problem in patients with chronic heart failure (CHF) [1], and is a significant contributing factor to fatigue and poor quality of life. The pathophysiology of CHF often leads to fatigue, due to nocturnal symptoms causing sleep disruption, including cough, orthopnea, paroxysmal nocturnal dyspnea, and nocturia [2].

The presence of insomnia symptoms, despite the stable condition in patients who suffered from heart failure and received evidence-based management, suggests that this management alone is not sufficient to decrease insomnia symptoms [3]. Only about 10% of these patients receive adequate treatment [2].

Conventional approaches to the treatment of chronic insomnia usually involve either pharmacotherapy or psychological interventions. Pharmaceutical hypnotics are the primary first-line pharmacotherapy used to treat chronic insomnia [4].

Benzodiazepines are the most effective and utilized drugs used to combat insomnia [5]. The consumption of these drugs, especially in prolonged use, has the potential of serious adverse effects [6] such as dependence, rebound insomnia, bad sleep quality, negative consequences for cognitive functions [7], and decreased effectiveness [2], which has led to the search for safe alternative treatments among herbal products.

Complementary and alternative medicine (CAM) may be useful for management of insomnia in older adults. The 2003 National Sleep Disorders Research Plan recognized as a priority the importance of studies evaluating CAM therapies for sleep problems [8].

Interest in the use of alternative therapies and products for insomnia has grown over the past two decades due to a range of motivational factors [9].

Many patients prefer "Natural remedies" for the treatment of their diseases because they think that remedies have low adverse effects and interactions, and do not require a medical prescription [10].

Despite evidence of widespread interest, research evidence is lacking on the efficacy of many plant-based therapies, especially in older adults [10]. One of the herbal medicines with sedative effect is *M. officinalis* that has been recognized since the 18th century in Europe and has since been used for sleep disorders [11].

Medicinal plants including *M. officinalis* are effective in a wide variety of diseases [12-15]. Recent evidence suggests that *M. officinalis* extract, which contains rosmarinic acid and the triterpenoids oleanolic acid and ursolic acid, inhibits gamma-aminobutyric acid transaminase (GABA-T) activity [16].

Sleep problems are a common problem in patients with CHF, but there are few studies investigating the effects of herbal medicines on sleep disorders in these patients. Thus, it is necessary to conduct more research in this field. The aim of the present study was to evaluate the effects of *M. officinalis* on sleep problems in patients with CHF.

## Materials and methods

This was a parallel group, placebo controlled trial study that was conducted in the Cardiovascular Disease Clinic of Shahrekord, Iran, from March 2010 till November 2010. Overall coordination of the trial was conducted by Medical Plants Research Center of the Shahrekord University of Medical Sciences. Participants in the study were male and female outpatients aged older than 40 years. The study participants were patients with CHF who were conscious and communicable, and had agreed to participate in the study. All participants were examined by a cardiologist, who took a patient history and performed a clinical examination. Doppler echocardiographic examinations were performed to assess left ventricular ejection fraction (LVEF). Prior to formal inclusion in the study, participants underwent a screening interview to determine the nature and history of sleep difficulty. In addition, the researcher completed PSQI questionnaires in order to select the people with a score of at least 6.

Patients were excluded if they were unwilling to continue participating or had allergy or physical problems to medicines during the study.

The protocol and informed consent were reviewed and approved by the Ethics Committee of the Shahrekord University of Medical Sciences. The protocol was registered in the Iranian Registry of Clinical Trials (no.: IRCT 201204042289N2).

The participants were informed about the study method and assured of confidentiality and anonymity. They

gave written consent and it was made clear that they could withdraw from the study at any time. Regarding statistical calculations, the number of population was 40 for each group; totally 87 cases were selected for pursuing investigation. In the first step, purposeful sampling was adopted. However, patients were randomly divided into 2 study groups. At the end of each sampling day, each patient with inclusion criteria was characterized by 1 or 2 to be included in groups one or two, respectively. The patients in the intervention group received conventional CHF treatment while taking 12 ml, *Melissa officinalis* syrup (produced by Mina-Pharmaceutical and Cosmetics Laboratory, Tehran, Iran), an hour before going to bed every night for one month. The control group received conventional CHF treatment and Alprazolam as a hypnotic drug. Data were collected through a questionnaire comprising two sections of demography and sleep quality questionnaire.

The questions specified for sleep appraisal included Petersburg Sleep Quality Investigation (PSQI) questionnaire, with 89.6 percent sensitivity and 86.5 percent specification. The questionnaire was developed for investigating patient's attitude toward sleep quality within 4 weeks and has 7 scales of general description of sleep quality by individuals, delay in falling asleep, useful sleep duration, sleep adequacy (ratio of useful sleep duration to the total time spent in bed), sleep disorders (nightly getting up), the amount of soporific medicine taken and finally daily performance (i.e. the difficulties due to insomnia experienced by an individual during the day).

The review of the literature indicates an acceptable consistency between the questionnaire's results and laboratory sleep investigation by means of polysomnography. The score for each scale is 0-3, representing natural condition, moderate to mean and severe difficulties, respectively. The summation of 7-fold scales comprises total score, ranging from 0 to 21. The total score of 6 or more was considered as sleep quality unacceptability [17].

Questionnaires were completed by all subjects before and after intervention. Data were analyzed by SPSS software 16 and x2, paired and independent t tests and one way ANOVA.  $p < 0.05$  was considered significant.

## Results and Discussion

In this study, 87 patients were recruited in a cardiovascular disease center in Shahrekord. However, seven people were subsequently excluded, one because of death, three due to unwillingness to take medicine, and three patients did not perform any baseline visit and thus were not eligible for evaluation. Finally, 80 patients were allocated into two groups. There were 60 (38.2%) male patients while the rest (61.8%) were female ( $p > 0.05$ ) with the mean age of  $62.4 \pm 9.65$  years. The mean time to fall asleep was  $1.2 \pm 0.96$  hours before intervention, and  $0.74 \pm 0.41$  hours after intervention. Furthermore, the time duration in which an individual was fully asleep during the night was 0-10 hours,  $4.54 \pm 1.74$  on average,

**Table 1: Comparison of total score sleep quality in the two groups**

	Before	After	Sig
Intervention	24.10 ± 7.44	5.75 ± 3.93	(p=0.001)
Control	29.9±6.01	21.27±7.9	(p=0.278)

and 2-8 hours,  $5.38 \pm 1.05$  on average before and after intervention, respectively ( $P < 0.05$ ). The results obtained before intervention indicated that there were no significant differences regarding the time of falling asleep, time duration of waiting to fall asleep, and the number of hours during which the subjects were fully asleep, as well as sex and age distribution ( $p > 0.05$ ). Besides that, the samples were normally distributed between the two groups.

The time duration for waiting to fall asleep was significantly less in the intervention group ( $p = 0.001$ ). In addition, the hours during which the subjects were fully asleep were significantly more than those in the control group ( $p < 0.05$ ).

In the present study, before intervention there was no significant difference between the two groups in total score of quality of sleep ( $p = 0.239$ ). However, after intervention, the control group had a lower score in comparison to the intervention group (Table 1).

The most notable finding of the current study was that *M. officinalis* is effective in causing significant improvements in important sleep parameters in patients with CHF. Findings showed improvement of sleep quality in the intervention group compared to the control group. Scientific evidence related to the efficacy of *M. officinalis* is inconclusive. The current study is one of the few randomized placebo controlled trials evaluating treatment of insomnia using medicinal plants among CHF patients. Some systematic reviews on the efficacy of *M. officinalis* on insomnia have been performed, but they reach different conclusions [18].

In a previous study, Wheatly et al. found that stress decreased significantly after daily taking of 600 mg over 6 months. Besides, the patient's insomnia was considerably improved [19]. In another study, Donath and colleagues found that the patient's sleep improved significantly after taking valerian for several days [20]. Moreover, there was a significant decrease in sleep latency time in the intervention group in a recent study. The same result was achieved in Leathwood and colleagues who demonstrated the group taking valerian achieved an improvement in sleep quality compared to the placebo group. In addition, the sleep latency time, as well as nightly getting up frequency was decreased [21].

The use of 450 mg valerian, at bedtime in improving sleep in patients who are undergoing treatment for cancer in study by Barton could not improve sleep as measured by the PSQI [22].

Morin in a clinical trial study assessed Valerian-hops combination and diphenhydramine for treating insomnia.

The result showed that Valerian produced slightly greater, though non-significant, reductions of sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and greater reductions than placebo at the end of 28 days of treatment [23].

Recently, Shinomiya et al. reported that a significant shortening in sleep latency without any significant effects on the total duration of wakefulness was observed with valerian extract [24]. Although GABA is present in *M. officinalis* extracts, its brain bioavailability via oral administration is uncertain. The action of *M. officinalis* on the CNS might be due in part to GABA involvement through a number of mechanisms, including inhibition of GABA uptake into synaptosomes. *M. officinalis* constituents inhibit the enzymatic breakdown of GABA and enhance benzodiazepine binding [25].

## Conclusion

The results of this study support the hypothesis that *M. officinalis* can improve sleep quality in patients with CHF. Because of fewer side effects of herbal medicines, these products can be taken as a safe substitute for synthetic medicines.

## Acknowledgments

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# Coincidence of the Influenza Epidemic Attacks with Special Lunar Months in Iran

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## Abstract

**Introduction:** In outbreaks of influenza in a country it seems that religious rituals play an important role (such as Hajj) and regional rituals (such as Ashura mourning). The objective of this study was to determine this relationship in Iran.

**Methods:** In this cross sectional study we evaluated the frequency of admission of patients with diagnosis of influenza in a central hospital in Isfahan, Iran; in different lunar months, from January 2010 to January 2016. At the end we analyzed our data by SPSS-22.

**Results:** In this study 873 admitted patients were studied. The total count and the mean of frequency of patients in first till the 6th lunar month (Muharram till Jumada al thani) were significantly more than the number of the patients in the other 6 lunar months ( $P = 0.003$ ).

**Conclusion:** We emphasize more preventive actions from 12th lunar month (Dhu al Hija) until 6 months later in Iran (and other Islamic countries) because in these months in religious rituals contact between people will happen more frequently.

**Key words:** Influenza, Lunar months, Outbreak, Iran

## Introduction

Influenza epidemics are one of the most important medical events, in various regions of the world. Every year the World Health Organization (WHO) asks all the member states to prepare their plan for a pandemic attack by influenza. This strategy should be a holistic plan to provide education of health care workers at all levels, and institute awareness plans and public health measures (1, 2).

If an influenza epidemic occurs in a country, it will be a difficult and costly event, for that country. Great expenditure will be undertaken from health budgets; such as purchasing antiviral and antibacterial drugs, vaccinations, hospitalizations, etc.

It should be kept in mind that at all times prevention is cheaper than treatment. Therefore, finding ways for prevention is very important as if we can limit the distribution of the disease over the population it will be very worthwhile.

In influenza epidemic attacks in a country it seems there are two important. The first is the entrance of the virus in the country and the second is the distribution of the virus over the population. With attention to these two items, coherence of international and regional ceremonies, may be substantial for entrance and distribution of viral infections (such as influenza) in a country. Religious rituals are very important especially in Islamic countries. Hajj Tamattu ceremony happens every year in the 12th month of the lunar year "Dhu al Hijjah", in which many people from Muslim countries go to Mecca (Saudi Arabia) all together for this religious ceremony. On the other hand, some of the people travel to Mecca in other lunar months and not at this time, which is named Hajj Omrah.

Every year, more than 5 million pilgrims go to Hajj from 184 Islamic countries (3). Two million of these pilgrims are from Iran (4). These pilgrims gather at the same time in a large number in a small area to perform the Hajj rituals (5).

This Islamic ritual consists of several religious actions which begin before the pilgrims reach the boundary of Mecca. They should circumambulate the Kaabah seven times, in masses of pilgrims. After that they should move to the Mina and Muzdalifa. At the end of this ritual; Hajji should shoot the stones at the metaphorical devil and sacrifice a animal such as sheep or goat at designated abattoirs. All of these rituals happen in organized groups of pilgrims (6).

In a mass gathering there is health hazard to the attendees. This hazard is through the transmission of infectious diseases via contaminated water and food, person to person contact and respiratory transmission. We can see a true mass gathering in Hajj which is associated with significant international travel (7).

In addition to this big Islamic ritual; on the other hand, in some of these Islamic countries some regional ceremonies also occur when the pilgrims come back to their countries.

In Iran most people are Shia (a branch of Islam). They believe that Tassua and Ashura are two days of great sorrow due to the tragic events of Karbala. This ritual is in the first lunar month; Muharram; that is the immediate month after the last lunar month; Dhu al Hijjah; in the lunar calendar (when the Hajj ceremony is ended and all of the Hajjis come back to their country). In addition, in Iraq a great meeting occurs in the second lunar month; Safar; in recent years in which many people come together. Therefore, in these religious rituals many people including "Hajjis" come together to respect this event, in streets and mosques all over the cities in these countries. These rituals take place for at least 10 days. In these days it seems that contacts between the patients with influenza (that may come back from Mecca: ie Hajji) with other people can distribute the disease between the people who are involved in the ritual.

Due to these events the epidemics of some infectious diseases (such as influenza) may happen in relation to the lunar months in Islamic countries and not the solar almanac.

In this study we wanted to evaluate the coincidence of the influenza epidemic attacks with the lunar months (especially the lunar months after Dhu al Hijjah (such as Muharram and Safar) so we evaluated the frequency of hospitalization of the patients with diagnosis of influenza in the days of these sacraments in Iran.

## Materials and methods

This was a cross sectional study; in which we evaluated all the patients who were admitted in a central hospital by diagnosis of influenza between January 2010 to January 2016. This study was in Isfahan in a multicenter hospital (Al-Zahra Hospital) in which the infectious ward is a central ward in this state.

We referred to the patients records who had been admitted by diagnosis of influenza and the numbers of the patients in each month. After that we referred to the lunar months in the calendar and the frequency of admitted patients in every lunar month.

At the end, we compared the frequencies and the mean, of admitted patients with influenza; in attention to the lunar months.

Because of the shorter duration of lunar years than Gregorian years, in 2011 we had two Moharram months (one in January and the other in December); so we summed the frequencies and calculated for the same year (2011).

Finally the data were analyzed by SPSS version 22 software. For comparing the means between two groups t- test was used; and one-way ANOVA used for comparing the means between more than 2 groups.

## Results

In this study 873 patients with diagnosis of influenza were enrolled.

The frequencies of the patients who attended to the hospital by the diagnosis of influenza from January 2010 to January 2016 are in Table 1. We evaluated the number of the patients in the lunar months.

The difference of the means of patients count in every year from 2010 till 2016 was not significant ( $P$  value = 0.370), but the numbers of the patients between the first and second 6 consecutive lunar months of every year was significant ( $P$  value = 0.003).

It seems that the total count of patients in Muharram till Jumada al thani were more than the number of the patients in other 6 months. On the other hand, the mean of the frequencies is also higher in these months.

More evaluation showed that the mean of the numbers of the patients in every 2 months was decreasing from the first months till the last months of every year (Table 2).

## Discussion

This study showed that the prevalence of influenza is concentrated in about 5 consecutive lunar months in Iran; in which some Islamic religious rituals occur. The first lunar month is Muharram and the fifth month is Jumada al Awwal. These 5 months are after Dhu al Hijjah in which the Hajj pilgrims move to Saudi Arabia for Hajj ritual. This ritual is one of the greatest mass gatherings with about 5 million people from all over the world (7). These pilgrims gather every year in Mecca in Dhu al Hijjah (3, 8), and are exposed to various infectious agents (9).

After the end of this ritual the pilgrims come back to their countries and they bring home various infectious agents in addition to souvenirs (9).

Pellerin et al. reported that influenza is an infectious disease that may be seen to be associated with religious rituals; he reported that this is in addition to other infectious diseases such as meningococcal meningitis, vibrio cholera diarrhea and tuberculosis in Hajj/Umrah mulim ritual (10).

Table 1: The frequency of the patients with influenza in different lunar months from Jan 2010 to Jan 2016

Lunar months \ Year	Muharram	Safar	Rabi al Awwal	Rabi al Thani	Jumada al Awwal	Jumada al Thani	Rajab	Shaban	Ramadan	Shawwal	Dhu al Qi'dah	Dhu al Hijjah	Total
2010	40	40	16	10	7	1	0	1	2	1	0	1	119
2011	10	19	21	22	11	1	0	0	0	0	0	2	86
2012	6	22	17	2	2	6	0	2	0	0	0	0	57
2013	0	14	11	10	0	0	1	0	1	0	1	1	39
2014	1	11	5	3	4	0	8	13	7	2	0	5	59
2015	4	2	10	14	16	9	0	0	2	1	0	4	62
2016	7	71	201	108	53	6	5	0	1	2	1	1	451
Total	68	179	281	169	93	23	14	16	12	4	1	13	873
Mean/month	9.7	25.5	40.1	24.1	13.3	3.3	2	2.3	2	0.7	0.2	2.17	10.91

Table 2: Means of the number of the patients with influenza in every 2 consecutive lunar months in 7 years' evaluation

2 months (first to 6 <sup>th</sup> )	Means of the number of the patients
First (Muharram, Safar)	17.6
Second (Rabi al Awwal, Rabi al thani)	31.4
Third (Jumada al Awwal, Jumada al thani)	8.2
Fourth (Rajab, Shaban)	2.1
Fifth ( Ramadan, Shawwal)	1.3
Sixth (Dhu al qidah, Dhu al Hijjah)	1.1

$P$  value = 0.009

Hashim et al showed that the prevalence of respiratory diseases was 93.4% in 468 Malaysian pilgrims in 2013 (11) and Razavi et al reported that the most prevalent disease is the common cold in these pilgrims in Iran (4) and therefore; one of the most infectious agents is influenza virus. Our study shows that this agent will enter our country in Du al Hijjah and then will exist for five consecutive months between the people.

WHO have some plans to ensure the wellbeing of pilgrims in Saudi Arabia (12) but we recommend that these efforts should be continued into the countries to reinforce global health security. These global health initiatives should be converged with all the Islamic countries.

We know that when the pilgrims return home, they celebrate their come back and invite their relatives and friends. In this celebration they embrace and kiss their friends and relatives and this provides further opportunities for the spread of infectious agents.

After this opportunity for infection, Muharram will begin and Shia rituals will start. In this ritual that may continue for at least 2 months we have mass gathering in mosques and other religious sites. This facilitates more distribution of infectious agents.

It should be said that the lunar calendar is the base for Islamic rituals such as Fasting and Hajj; and we know that the months of the lunar calendar are not accordant with the solar calendar. On the lunar calendar each month is 11 days less than the solar calendar; therefore, each lunar month may happen in different times to the solar calendar in different years. For example, in 2011 Muharram was in January but in 2015 it was in November.

In Iran also the Shia rituals are based on the lunar calendar. One of the most important of these rituals is Ashura mourning; in which during 10 days all the people who believe the tragic events of Karbala come together in mosques and the other mourning sites to do their weeping ritual.

Although, Ashura mourning happens in the first 10 days of the first lunar month; Muharam, but it will be continued for 2 to 3 months with milder intensity. Muharram, is after the 12th lunar month; Dhu al-Hijjah in which Hajj ceremony occurs. Therefore, many of the people who have referred from Mecca will contribute in these mornings and can transmit their viral infection to healthy people; and after that everyone who has the virus can transmit it to their family and friends. Therefore, an international and after that a regional transmission of the virus occurs.

Our results emphasize these events and therefore we should have programs for this transmission of virus.

Ibrahim et al showed in their study that, the pilgrims who didn't receive health educational advice before Hajj are more prone to infectious diseases. They recommended that health education activities should be intensified before the Hajj to raise awareness of pilgrims about health-related behaviors (8). With attention to our study

we should intensify our efforts for health before Hajj but it should be continued for a further five months.

Non-pharmaceutical measures such as wearing face masks, hand wrapping and keeping away from symptomatic patients are effective to reduce the spread of infectious agents from person to person (13). These actions should be our recommendations to everybody in religious rituals such as Hajj and Ashura mourning.

Although vaccination and antiviral drugs are the mainstay of influenza; Hashim et al. showed that risk of respiratory illness is significantly low in Malaysian Hajj pilgrims with regard to good hand hygiene (11). This item is easily applicable in Muslims because they should have ablution before every prayer (five times a day) (11). In addition, Imani et al. concluded from their study that vaccination against influenza should stop and it is better to save it for the people of high-risk condition such as children, immunocompromised individuals and elderly. They emphasize on the relevance of implementing hygienic precautions (14).

Other authors recommend honey for preventing common cold and influenza (15). Sulaiman et al. suggested that pilgrims begin taking honey a few weeks before journey to have the maximum preventive effect (16).

We should pay special attention toward the elderly in these religious rituals because they almost all have strong belief and participate in these rituals and they are more prone to infections. Khan et al. revealed in their study that most patients were elderly with chronic medical disorders (17).

With attention to the above we emphasize preventive measures before moving to Mecca for all Hajj pilgrims and it is more important to continue these measures after returning to their county and in ceremonies that will happen after that; especially returning celebrations and Ashura carnivals.

## Conclusions

Overall this study showed that frequency of influenza will be increased in specific times which coincide with ritual ceremonies in Muslim countries. Therefore, our recommendations are attention to preventive measures before these ritual ceremonies and we emphasize that these preventive actions should continue for at least 6 months after Dhu al-Hijja in lunar calendar.

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# Improvement of the quality of life following the eradication of *Helicobacter pylori* infection in patients with chronic idiopathic urticaria

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## Abstract

**Background:** The current study hypothesized that the impairment of quality of life following the appearance of *Helicobacter pylori* (*H. Pylori*)-induced chronic idiopathic urticaria (CIU) might be effectively prevented by eradicating this bacterium.

**Methods:** Sixty patients (11 men and 49 women; mean age, 34.2 years) affected by diagnosed CIU came from a series of consecutive patients referred to the Dermatology private clinics. The patients were examined for the presence of IgG antibody to *H. pylori* using ELISA method. Those with seropositive results were scheduled for this clinical trial and received the eradication treatment consisting of bismuth subcitrate 120 mg plus metronidazole 250 mg plus tetracycline 250 mg qid plus omeprazole 20 mg bid (OBMT) at the time of diagnosis for 10-14 days and then assigned to the treated and the untreated groups. The quality of life of the two groups was assessed using the Dermatology Life Quality Index (DLQI).

**Results:** The mean of DLQI was unchanged in patients who were treated with *H. pylori* eradication treatment (from  $28.67 \pm 6.79$  to  $28.70 \pm 7.90$ ,  $p = 0.965$ ), but this score was significantly increased in the patients without the evidence of *H. pylori* eradication (from  $27.50 \pm 7.22$  to  $33.20 \pm 8.14$ ,  $p < 0.001$ ). Multivariable linear regression analysis showed that the positive response to anti- *H. Pylori* regimen could prevent unfavorable changes in life quality in the treated patients.

**Conclusions:** Eradicating *H. Pylori* bacterium in CIU patients is not only associated with better outcome of this chronic condition, it can improve the quality of life in treated patients.

**Key words:** chronic idiopathic urticaria, *Helicobacter pylori* infection, quality of life.

## Introduction

Chronic life threatening gastric disorders induced by helicobacter pylori (*H. Pylori*) infection such as chronic active gastritis, B-cell gastric lymphoma, and gastric cancer might potentially result in unfavorable outcomes in these patients [1]. The relationship between *H. Pylori* infection with other extra-digestive conditions such as cardiovascular, immunological or skin diseases such as urticaria has been also revealed [2]. Moreover, in recent research, it has been hypothesized that some antibodies induced by *H. pylori* infection can be involved in the development of autoimmune diseases [3]. Chronic urticaria is a long-lasting skin disease with a complex pathophysiological feature and in a large number of patients with unknown etiology, which is called chronic idiopathic urticaria (CIU). In the recent decade, the role of *H. Pylori* infection as a main causal factor for CIU has been suggested and a higher prevalence of *H. Pylori* infection in patients with CIU compared to the general population has been proved [4]. Current summarizing of available studies that evaluated the course of chronic urticaria after proven *H. Pylori* eradication demonstrates a statistically significant benefit compared to untreated patients or *H. Pylori*-negative controls without urticaria [5-7]. In some research, antibiotic eradication of *H. Pylori* led to regression of CIU in up to 100 % of cases [8-10]. Therefore, it seems that the treatment of *H. Pylori* infection in those with CIU not only can be associated with better outcome of this chronic condition, but can positively influence the patient's life quality and even increase life expectancy. On the other hand, impairment of the psychological status as well as quality of life following the appearance of *H. Pylori*-induced chronic disorders, including CIU might be effectively prevented by eradicating this bacterium. Although several studies determined the prevalence of *H. Pylori* in CIU patients as well as considered the relationship between this infection and clinical features of CIU, few published studies are available regarding influence of *H. Pylori* eradication on patient's quality of life. Given this consideration and in an attempt to clarify the possible role of *H. Pylori* eradication treatment schedule in improvement of life quality in patients with CIU, a clinical trial was performed to assess changes in quality of life in CIU patients following routine anti- *H. Pylori* regimen in a sample of Iranians.

## Material and Methods

Between August and December 2016, 60 patients (11 men and 49 women; mean age, 34.2 years) affected by diagnosed CIU were enrolled in this study. The study patients came from a series of consecutive patients referred to the Dermatology private clinics in Semnan city. The subjects who had received antibiotics within two months prior to the examination were excluded. Patients were also excluded if they were on chronic steroid treatment, were receiving any immunosuppressive medication, and had physical urticaria, cholinergic urticaria, exercise-induced urticaria, a history of atopic diseases and food allergy, or current or recent other serious diseases. On enrollment, each patient completed a standard questionnaire, which

included information about demographic factors such as sex, age, educational level, and occupation; and medical history, with particular reference to symptoms of upper gastrointestinal diseases. This study was approved by the research and ethics Committees of Semnan University and all subjects provided their written informed consent before entering the study.

Serum samples were collected from all the patients to examine for the presence of IgG antibody to *H. pylori* using ELISA method and patients with seropositive results were then scheduled for our clinical trial. The patients received the eradication treatment consisting of bismuth subcitrate 120 mg plus metronidazole 250 mg plus tetracycline 250 mg qid plus omeprazole 20 mg bid (OBMT) at the time of diagnosis for 10-14 days and were then assigned to the treated group (with the negative results of urea breath test (UBT) immediately after the treatment) and the untreated group. In all subjects, quality of life was assessed using the Dermatology Life Quality Index (DLQI). This questionnaire that was first developed in 1994 is a simple 10-question validated questionnaire which has been used in 33 different skin conditions. It consists of 10-questions. Scores range from 0 to 30 and a score of 10 or more indicates quality of life impairment. The patients' life quality score was determined by DLQI questionnaire immediately before and also after the finishing of treatment protocol to examine treatment effects on patients' quality of life in the treated and untreated groups.

Data were expressed as mean  $\pm$  standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables between the treated and untreated groups were compared using t test or non-parametric Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. Categorical variables across the two groups were compared using the Chi-square test or Fisher's exact test if required. The changes in the DLQI scale in the two groups following treatment schedule were compared using paired t test. To determine the relationship between the changes of DLQI score and response to *H. pylori* eradication treatment regimen, multivariable linear regression analysis was used adjusting for probable cofounders such as demographic characteristics, education level and medical history. Results of this model were presented as Odds Ratio (OR) and 95% confidence intervals (95% CIs) for OR. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

## Results

Eradication of *H. pylori* was achieved in 30 patients by the quadruple therapy. Baseline characteristics and medical history of treated and untreated patients are presented as Table 1. The two groups were similar in terms of sex ratio, mean age, education level as well as family history of urticaria or allergy. Although the mean of DLQI was unchanged in patients who were treated with *H. pylori*

Table 1: Baseline characteristics and medical history of study patients

Characteristics	Treated group (n = 30)	Untreated group (n = 30)	p-value
Female gender	24 (80.0)	25 (83.3)	0.739
Age (year)	34.63 ± 11.56	34.33 ± 13.16	0.926
<b>Education level</b>			
Illiterate	2 (6.7)	0 (0.0)	0.959
Primary level	4 (13.3)	5 (16.7)	
Secondary level	16 (53.3)	16 (53.3)	
Academic degree	8 (26.7)	9 (30.0)	
Family history of urticaria	13 (43.3)	12 (40.0)	0.793
Family history of allergy	12 (40.0)	9 (30.0)	0.417

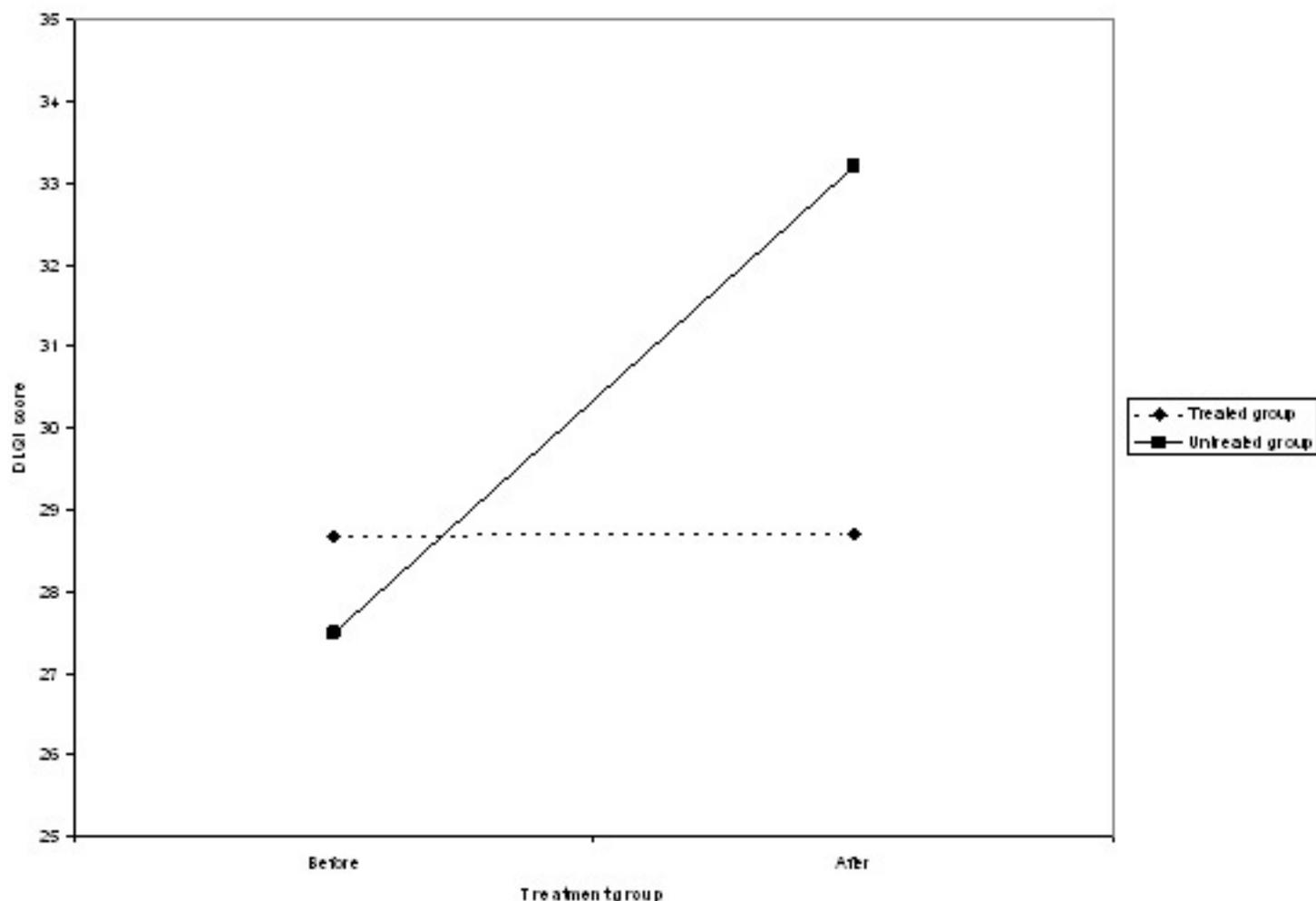
Data are presented as mean ± SD or number (%)

Table 2: Multivariate analysis of the relationship between the changes in quality of life score and anti- H. Pylori treatment result

Variable	Beta	Standard Error	p-value
Untreated vs. treated group	2.418	1.164	0.041
Female vs. male	2.173	1.394	0.123
Advanced age	0.066	0.053	0.215
Education level	0.489	0.816	0.550
Family history of urticaria	0.078	1.036	0.940
Family history of allergy	0.202	4.728	0.966

R square = 0.147

Figure 1: Changes of DLQI quality of life score in treated and untreated group with anti- H. Pylori treatment schedule



eradication treatment (from  $28.67 \pm 6.79$  to  $28.70 \pm 7.90$ ,  $p = 0.965$ ), this score was significantly increased in the patients without any evidence of *H. pylori* eradication (from  $27.50 \pm 7.22$  to  $33.20 \pm 8.14$ ,  $p < 0.001$ ) (Figure 1). There was also no significant difference in the mean of DLQI score between the treated and untreated group before the treatment protocol ( $p = 522$ ), whereas this score was significantly higher in the untreated subjects after the treatment ( $p = 0.034$ ). Multivariable linear regression analysis showed that the negative response to *H. pylori* eradication regimen in patients with chronic idiopathic urticaria had a relationship with quality of life impairment, whereas positive response to this regimen could prevent unfavorable changes in life quality in these patients (Table 2).

## Discussion

Based on the current evidence for a relationship between *H. pylori* infection and chronic extra-digestive disorders, the European Helicobacter Study Group consensus 2007 recommended the eradication of this infection in affected patients. Lastly, one or few published reports have documented associations between *H. pylori* infection and autoimmune or inflammatory disorders, but these are only descriptive in nature [11]. In the present study, we conducted a clinical trial that examined changes in quality of life of patients with seropositive results of *H. Pylori* infection and who received anti- *H. Pylori* regimen and compared it between treated and untreated patients. Our study first showed a partially low success rate of clinical remissions of CIU after eradication therapy in patients with *H. Pylori* infection and half of the patients were categorized in the untreated group after the two-week anti-*H. Pylori* treatment. Although some early studies had shown a high success rate of clinical remissions of CIU following *H. Pylori* eradication regimens [12-15], some other recent studies failed to support the therapeutic effects of *H. Pylori* eradication for CIU [16-19]. In a study by Yadav et al. *H. Pylori* associated gastritis was present in 70.58% of CIU patients, out of whom 81.25% responded to eradication therapy and thus the response of *H. Pylori* eradication therapy in infected patients was significant [20]. In another study by Pliego et al. in the group with CIU, there were 52.8% of patients infected with *H. Pylori*, and in the control group only 11.1% [21]. Differences in eradication regimens may be associated with the various types of administered antibiotics, the dose of antibiotics and/or the duration of the treatment. It seems that the eradicating *H. Pylori* infection in CIU subjects with our studied routine, quadruple therapy for two weeks is not a standard regimen among our population with unacceptable response rate. It may be related not only to the virulence and resistance of the organism, but also on host and environmental factors [22,23]. Moreover, because in each population, especial drug regimens may be approved by the health insurance system for the eradication of *H. Pylori* [24,25], those approved regimens can be useful for eradicating *H. Pylori* in that population.

One of the issues, which was not addressed in previous studies, was the improvement of quality of life in patients who were treated with *H. Pylori* treatment schedule compared to those who remained untreated. In fact, *H. Pylori* eradication in our trial was in parallel to improvement of patient's life quality, but may not be dependent on the rate of *H. Pylori* eradication. It has been previously confirmed that the chronic forms of urticaria often adversely impact on quality of life. In a study by Poon et al [26], the patients with CIU without concurrent physical urticaria suffered moderate quality of life impairment whereas, the patients with CIU with concurrent delayed pressure urticaria suffered significantly higher quality of life impairment. In their study, disability in the CIU group based on the indices of DLQI questionnaire was greatest in the dimensions of work/study, symptoms/feelings and leisure. Thus, we think that although *H. Pylori* eradication using quadruple regimen for two-weeks may not be accompanied with low response rate, its high positive influence on improving different aspects of quality of life, especially on physical function and work status in treated patients is expected. However, for confirming the beneficial effects of *H. Pylori* eradication regimens on quality of life in CIU patients, more trials with the use of especial validated quality of life questionnaires on larger sample sizes is recommended. Also, according to the critical role of *H. Pylori* infection in impairment of quality of life affected subjects; regular diagnostic workup of patients with CIU should be considered.

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# A novel device to improve sitting posture

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## Abstract

Change to the body position leads to consequent changes in a certain part of the body in relation to other parts and change to the gravity center in relation to the leaning level. These changes, in turn, can cause pain and poor posture. There are different methods of curing kyphosis including surgery, braces, exercises and feedback. One of the methods for improving and controlling posture is to improve the awareness of the patient or to provide them with the benefit of feedback. The device that the researcher used is a kind of biofeedback, which can be placed around the neck like a necklace and is equipped with an accelerometer and a button to control the level of sensitivity and can display error rate, angle and the amount of time the device has been used.

The aim of our study was to determine the validity of the device. Thus the movement analyzer device was used as the standard to which the device activity was compared; the angle displayed on the device was compared with the angle offered by the movement analyzer device in two stages also. In the first stage all data obtained from the angle displayed on the device was compared with the angle offered by the movement analyzer device and the Intra Class Correlation (ICC) and their correlation coefficients were compared. At the next stage, the data was classified into three categories: flexion, extension and hyper-extension; and the ICC and correlation coefficients were studied at all three postures and with a 14-data average. Investigation of both models reviewed showed that generally ICC of the device is

0.995 (0.994, 0.995) and the correlation coefficients is 0.999. The results of all studies proved the general consistency of the gained results through both methods, at all levels and averages.

**Key words:** kyphosis, validity, necklace, feedback, biofeedback, posture

## Introduction

Nowadays people are very often using computers. Prolonged sitting with the same slouch posture, especially in office workers, makes them susceptible to back pain or injury. This kyphotic posture will result in discomfort, pain, and changes in thoracic alignment and it will contribute to changes in other parts of the body. Musculoskeletal problems and postural mal-alignments are usually the result of lack of muscle coordination. Weakness on one side can cause tightness in the other muscle (Watkins, 2009). Medical and ergonomic studies indicate that poor sitting and standing postures will contribute to pain in muscles and connective tissues of tendon, ligaments and joint capsule. Some evidence has shown that these symptoms will lead to chronic diseases like rheumatic disorders (Grandjean, 1997). Slump sitting posture will result in relaxation of the spinal stabilizing muscles, which will cause increase in intervertebral disc pressure and increases in the connective tissue loading (O'Sullivan, 2006). One of the postural mal-alignments at thoracic spine is Hyper-kyphosis and one of its causes is poor posture (Lou, 2012). Hyper kyphosis will cause tightness and shortness of muscles at the anterior side of the thorax and it can contribute to rounded shoulders. In contrast, posterior trunk muscles will be weakened by continuous stretching (Scanel, 2003). The thorax has an important role in all thoracic spine movements, including flexion, extension, lateral bending and rotation (Watkins, 2005). Biomechanics of the thoracic spine are different from neck and lumbar spine due to thorax and sternum and these structures help stability and movement control of the thoracic spine (Horton, 2005). Thoracic movements in sagittal plane are being affected by spines, sternum and ribs (Horton 2005). Wedge fracture of thoracic spines will indirectly result in fracture of the sternum (Lund 2001).

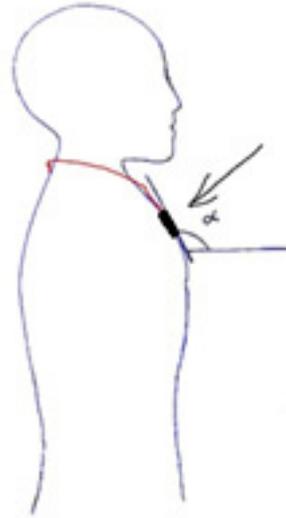
There are several methods to manage poor posture such as surgery, bracing, exercise and feedback. Surgical correction of kyphosis is an extensive method and can cause complications (R de Amoreira Gepp, 2013). Braces are not often comfortable and reduce spinal movement (Osman, O., 2015).

Thoracic hyper kyphosis can be corrected by voluntary extension of the thoracic spine (Lovel, 2006). Our necklace like device is an alert system which has an accelerometer and a button to adjust the intensity and shows the rate of error, angle and the amount of time using the device and has a reliability of 0.99% with the movement analysis device and it will help correction of posture by voluntary extension of spinal muscles.

## Method

### Feedback necklace

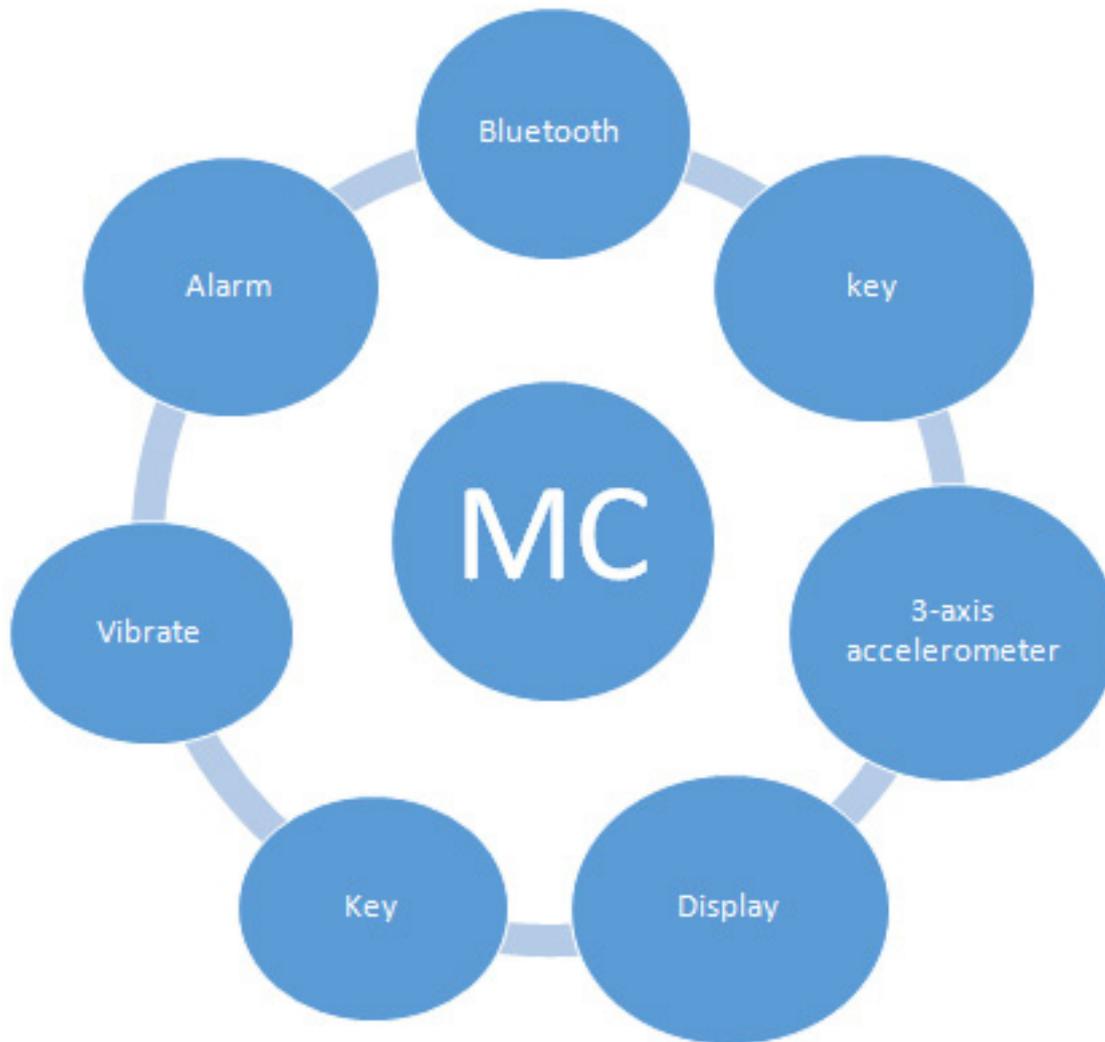
The device we made is a feedback device which can be used like a necklace or by sticking it to the body.



**Image1: Place of installation on the body**

It contains 3-axis analog accelerometer, processor, display, vibration, and battery and a few buttons. It is easy to use and the main function of the device is performed with a key; at one pressure it will be started and by longer pressure it will be stopped. The device will react to pressure by "vibration" or "beeps". The very low energy consumption of the device will help it to continue its activities for a long time (over a month).

For measuring the body angle a three-axis analog accelerometer sensor is used. The output of the sensor can be positioned by internal processor. The output of the device is in voice or vibrate type and the user can choose between them by the two buttons on its sides. The activity of the device is only possible when the person is not moving or walking so it is recommended to use it in an upright or sitting posture, especially when using the computer; in case of a movement, the process will stop. (If you use two devices simultaneously, it will continue its activities, even when moving). Although the device can be set up to correct movement of one plane, such as flexion and extension of the upper trunk and it will not show error while moving from the pelvic girdle forward or backward because it will not change the device's angle is to the ground. To start using the device, it should be set by the physiotherapist in the correct sitting posture; the device will keep the angle to its memory. Each time the user keeps a bad posture for a long time (time can be set by the therapist) the device will alert the user to correct their. In addition, the changes of the angle are also stored. All of the information will be stored on the device, including angles, number of bad postures, the amount of time the device has been used etc. and it can interface with computer software or mobile phone. The therapist can use this information to check and compare the amount of progressions and help the user to further improvements.

**Image 2: Internal components of the device**

The stored information includes:

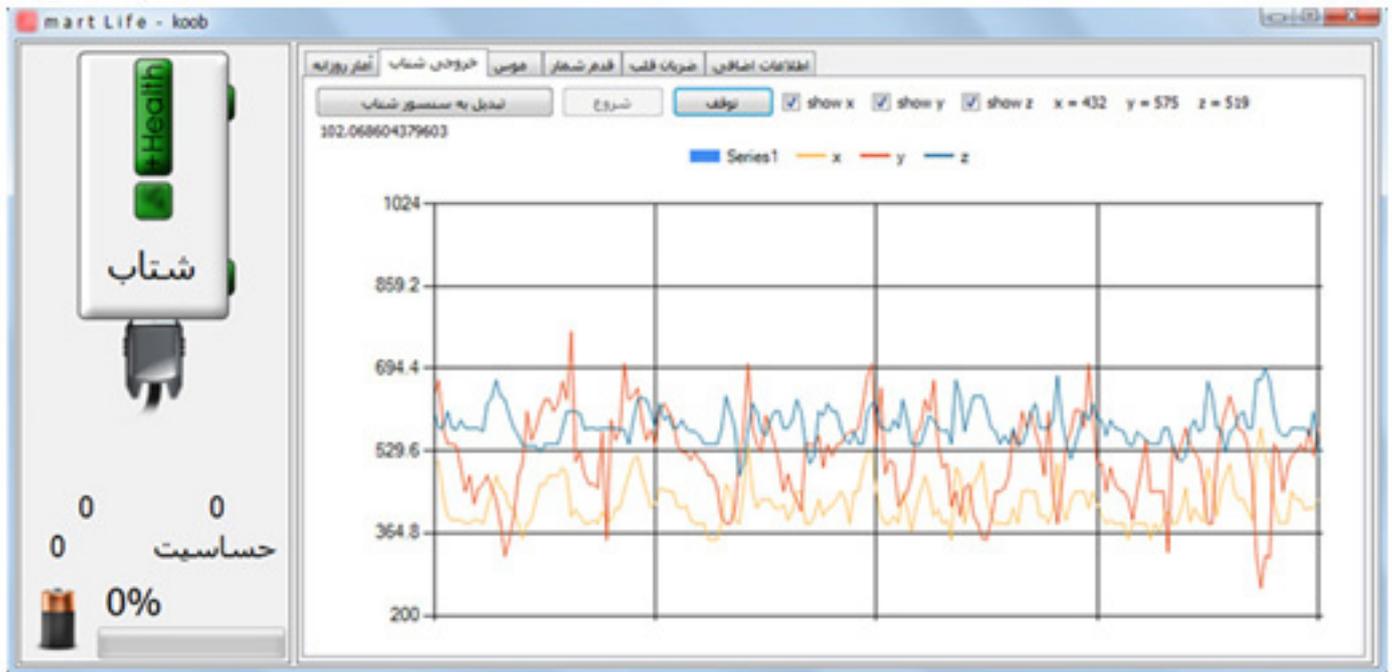
1. The angular moment of any individual when using the device
2. Showing the difference between the original angle and the individual's angle in the form of graphs and the angles
3. The amount of time the device is turned on and being used
4. The amount of individual errors in form of chart
5. The ready to work time
6. The number of second-order errors
7. The number of times the device has continuously been active for more than 10 minutes (or any other optional number).

In addition to monitoring and showing the time of use and the person's errors it will show the angles and the difference of angles as well as errors in the form of numbers and graphs with special software for the user and therapist.

In addition, it is fully customizable and since it has been designed in necklace shape the user can use it easily at any time of the day without causing pain, pressure or drawing any attention that is normally created by a vest or brace and it can be turned off whenever it is not needed.

Regarding the point that the sternum is related to spinal fracture and its stability, it can have an important role in spinal deformities and correction of severe injuries in the sagittal plane. (Horton 2005). Since Tormene and colleagues used their assessment device on the anterior side of the body (Tormene 2012) and because of the sternum role in thoracic movements we used our device in necklace form.

In addition, it is fully customizable and since it has been designed in necklace shape the user can use it easily at any time of the day without causing pain, pressure or drawing any attention that is normally created by a vest or brace and it can be turned off whenever it is not needed.

**Image 3: The device's software**

Regarding the point that the sternum is related to spinal fracture and its stability, it can have an important role in spinal deformities and correction of severe injuries in the sagittal plane. (Horton 2005). Since Tormene and colleagues used their assessment device on the anterior side of the body (Tormene 2012) and because of the sternum role in thoracic movements we used our device in necklace form.

#### Reliability assessment

At first the device's software was set to measure the angle in a circular pattern. Then to compare the accuracy of device's measurement with an index, we used a Video motion analysis system called Simi Aktisys. The error rate of this device was reported less than 1/6% of the manufacturing company in addition several lots of research have also been carried out with the use of this device. (<http://www.simi.com/en/references/publications.html>)

After filling out the informed consent form by the sample volunteer, he was asked to take off his clothes and the markers were placed on his sternum by the physiotherapist; the red marker was placed at the apex of the bone and the green marker was placed at the top of the xyphoid process. (Image 4)

**Image 4: Sensor places**

These markers can be identified by the camera and the software and the angle they make to the ground will be identified. Then the device was set on the body of the volunteer, and he sat on a table. First the correct flexion and extension movement was practiced by the volunteer and then he was asked to start doing the movements as required. Then the results and the graphs were compared. To ensure, and increasing the error rate, the measurements were repeated three

## Results

To ensure that the angle measurement and the results of the device have reliability the Video motion analysis system, and the data were investigated generally and in the 3 groups, flexion, extension and hyper extension group.

In general there is a correlation coefficient of 0.99 when comparing the two methods; it shows that the device has a very good reliability index.

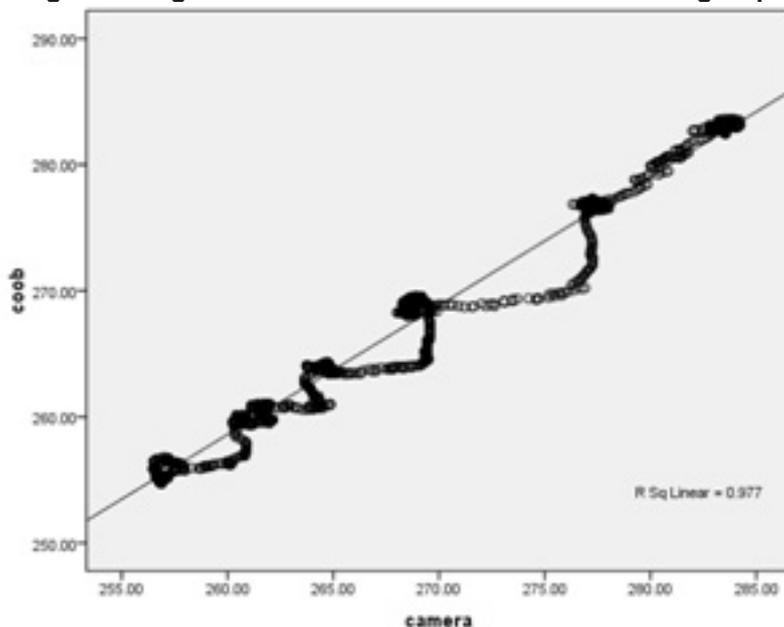
Statistics	r (p-value)	ICC(0/95CI)
Data		
General Data	0/99 (0/00)	0/99 ( 0/99 .0/99)

For data smoothing and prevention of possible adverse disturbances of both methods, they were divided into 3 groups, flexion, extension and hyper extension, then the data of each group was divided into 14 classes.

At each stage, the data were classified into two groups of complete and smooth category. For statistical consistency of the methods, ICC was used and to identify the correlation coefficient, the Pierson correlation coefficient was used. To normalize the data the Kolmogorov–Smirnov test (K–S test or KS test) was used.

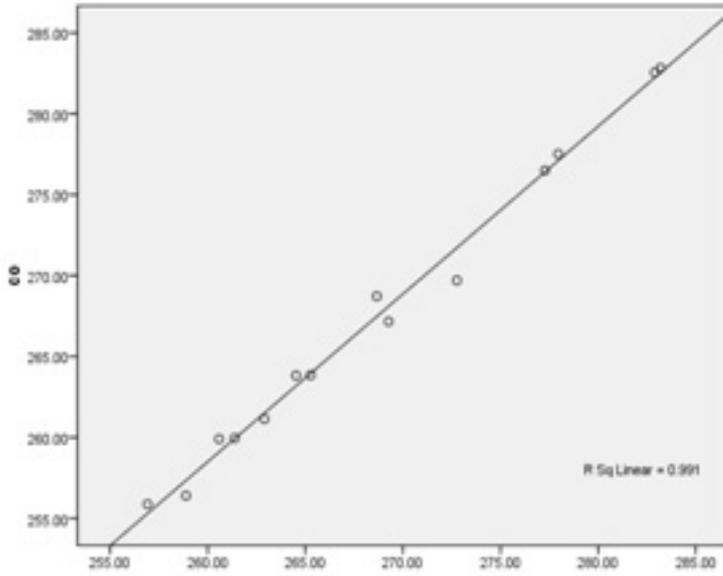
The coefficient correlation between the total data in the flexion group was 0.994 (0.994, 0.993) and the coefficient correlation of Pearson showed 0.998, the amount of ICC was (0.999, 0.992) 0.997 and the coefficient correlation showed that 0.996, represents a perfect match of measuring device and movement analysis device. K-S also being the normal distribution of the data is well paved. Image 5 shows the general the distribution of the data at flexion group and image 6 shows homogeneous data distribution in forward flexion.

**Image 5: The general distribution of the data at flexion group**

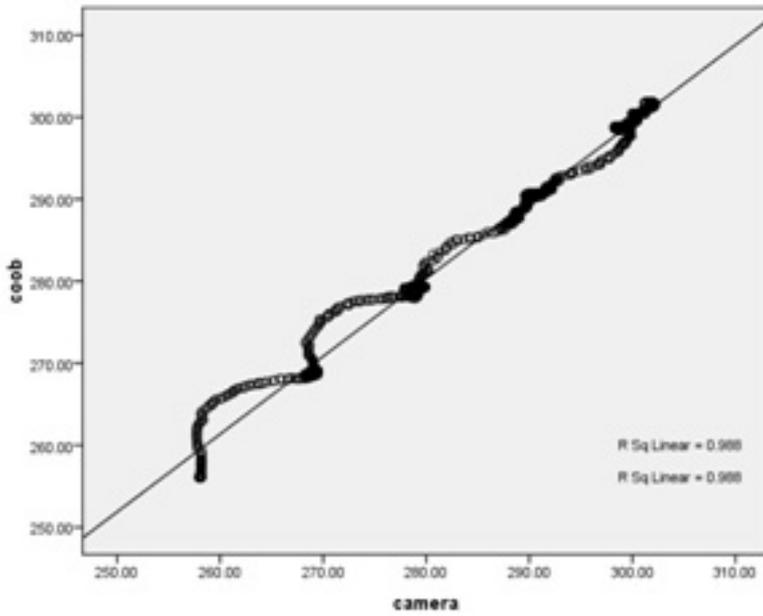


The second group is the extension group, which means extension from flexion movement; the coefficient correlation between the total data in the extension group was 0.997 and the coefficient correlation of Pearson showed 0.994, the amount of ICC was 0.999 and the coefficient correlation showed that as 0. Image 7 shows the general distribution of the data at extension group and image 8 shows homogeneous data distribution in extension.

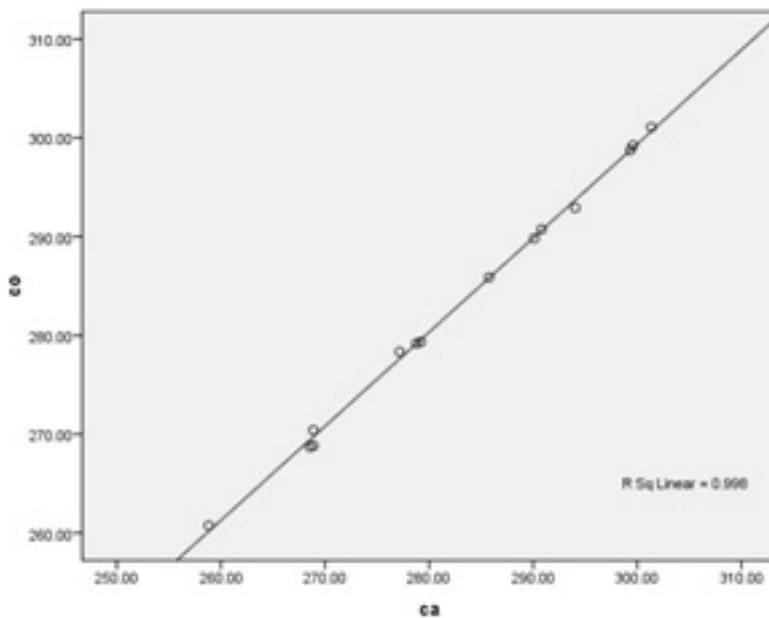
**Image 6: The homogeneous data distribution in flexion**



**Image 7: The general the distribution of the data at extension group**

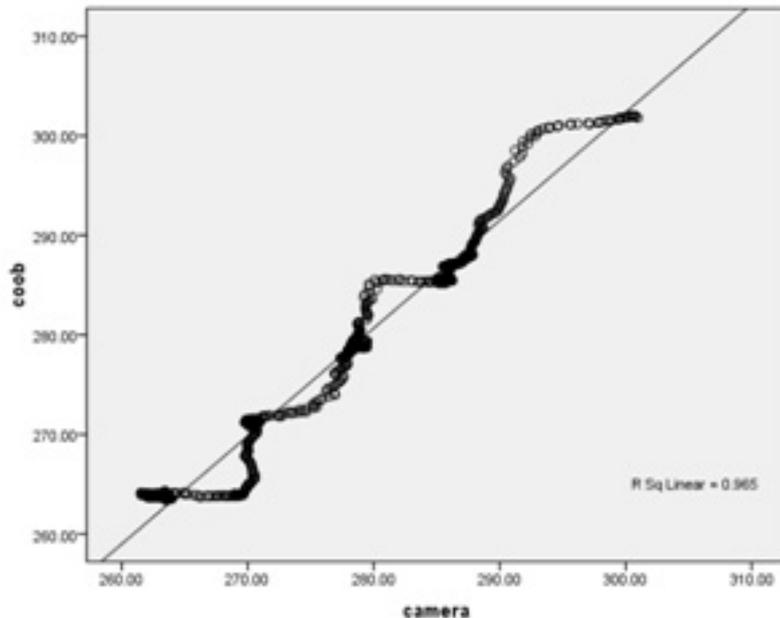


**Image 8: The homogeneous data distribution in flexion**

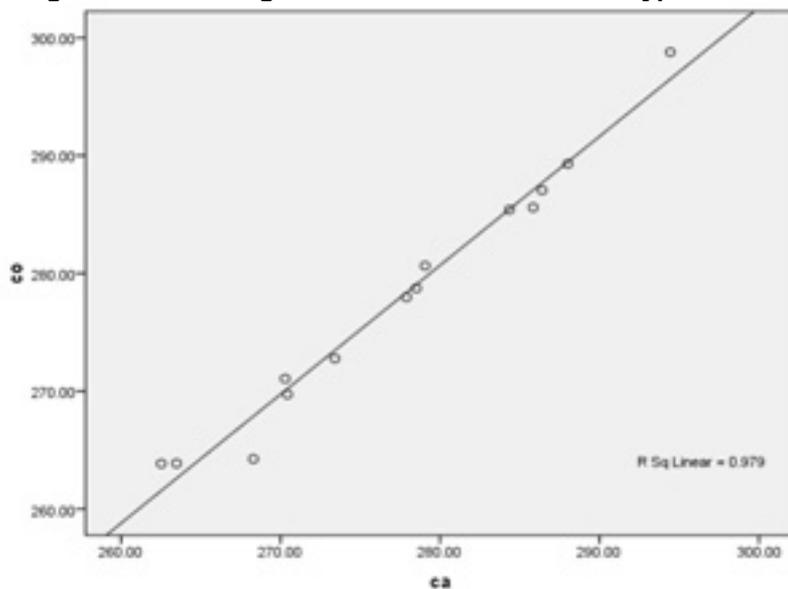


At the last period, the hyper-extension movement was tested and these results were identified. The coefficient correlation between the total data in the hyper extension group was 0.989 and the coefficient correlation of Pearson showed 0.992; the amount of ICC was 0.992 and the coefficient correlation showed that as 0. Image 9 shows the general distribution of the data at hyper- extension group and image 10 shows homogeneous data distribution in hyper- extension.

**Image 9: The general distribution of the data at hyper- extension group**



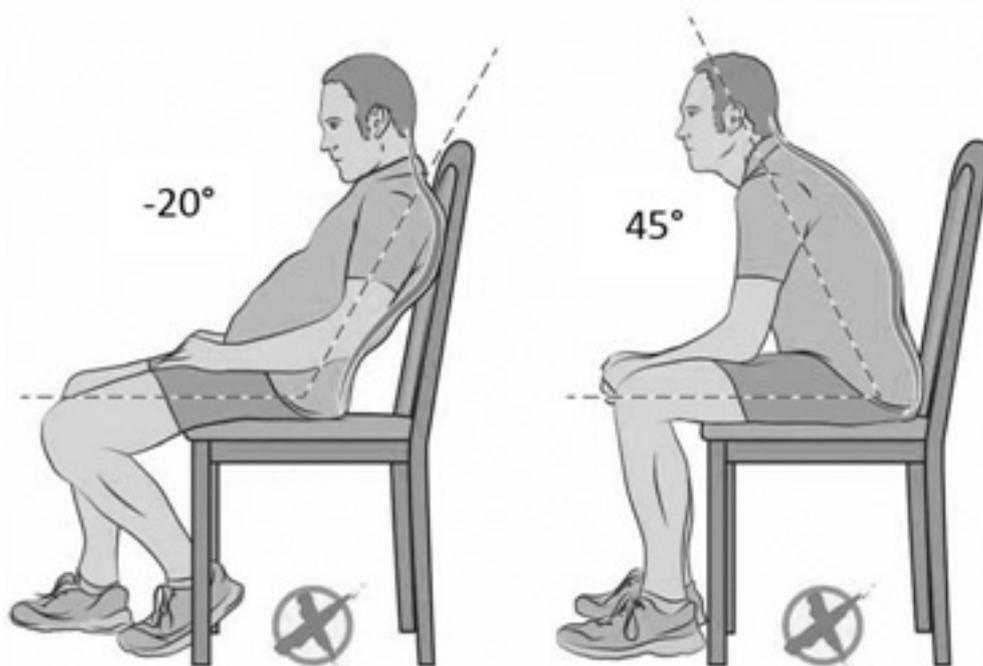
**Image 10: The homogeneous data distribution in hyper- extension**



The overall result shows the exact correlation in both methods and it seems that both devices show the same values and it shows the validity of the device in a motion analysis system and it can be used to assess and correct. When the subject sits in the perfect position that the physiotherapist has chosen the device shows no error, as Image 11 (next page).

**Image 11: The perfect sitting posture by physiotherapist**

If the subject sits in different posture, shown in image 12, the device indicates the bad posture and will vibrate.

**Image 12: Poor posture degrees**

## Discussion

The thorax has an important role in all thoracic movements, including flexion, extension, lateral bending and rotation (Watkins, 2005). As we know the biomechanics of the thoracic spine are different from the lumbar and cervical spine because of the rib cage and sternum and these structures help the stability and movement control of the thoracic spine (Horton, 2005). Horton et al. show that the sagittal plane movements of the thoracic spine are influenced by the sternum and ribs (Horton, 2005). Sternum and Sterno-costal joints have a vital role in the respiration mechanics, but we should not ignore their biomechanical role in thoracic spine fractures and correction of thoracic

spine deformities (Horton, 2005). For example, in 2001 Lund showed that wedge fracture of the thoracic spine will indirectly result in a Sternal fracture (Lund, 2001). Horton et al in 2005 showed that the second effective treatment for kyphosis after removing the disc and its contents is a combination of removing part of the sternum and releasing the sternocostal joints (Horton, 2005). It seems that it can be possible to use sensors in front of the body to assess or correct the kyphotic posture as Tormene et al used sensors in front of the body to measure the thoracic extension (Tormene, 2012) and in Bazarelli et al's research the kyphosis was not measured directly but also changing the angle of the thoracic and lumbar region comparing to neutral position was evaluated (Bazarelli,

2003). Therefore, in this study to determine proper posture we used the sternal angle.

To do this research, first the required software was designed to measure angles. The measured angle is the angle sternum makes radially to make a circle.

To compare the performance and reliability of the device a reference is required. To do this Simi Actisys 1.3 model motion analysis system was used which is a quick and simple way of conducting dynamic movement analyses with the fully automatic tracking of colored LED markers. To perform the test with 95% and 80% statistical power, 14 angles were required. To eliminate the error due to the large number of samples, data were analyzed separately in each part of the graph.

Kolmogorov-Smirnov statistical method was used to determine the distribution of the same data and the same correlation coefficient to determine the function of both methods. The results revealed 99% correlation between the motion analysis system and device and the results were consistent with the results of other investigations. For example, to demonstrate the validity of biofeedback made by Luo and colleagues in 2006 the accelerometer was used. The results of their device were compared with the laboratory accelerometer and the results showed that the innovative device demonstrates 2 degrees of error at any angle of 180 degrees and the mean angle was 6.1 after 3 measurements (Lou, 2006). The designed device looks like a brace which includes three accelerometers and a small micro-computer in one's pocket; the brace size and the location of the sensors was determined by X-rays or a doctor. The cause of 2 degree differentiate may be because of the placing the accelerometers in 3 different places. Our designed device doesn't need particular placement by the doctor or X-rays and everyone can use it easily. The results of another study by Wong et al. in 2008 showed that the laboratory tests of their smart jackets represent the accuracy of 1 to 1.5 degrees with the motion analysis system and the Pearson correlation coefficient obtained by this method was 0.99. The device consists of three sensors, which each consist of accelerometers and gyroscopes and to check the validity of it an accelerometer and motion analysis system was used (Wong, 2008). But their experiment with the motion analysis system was not accomplished on a human subject, but on a moving robotic basis and of course their results are similar to ours. The advantage of our system is its smaller size and more accurate measurement compared to Wong et al.

In another study in the same year Wong et al. noted that built-in sensors can measure body movements and these results are comparable to the motion analysis system and this time they used a large number of sensors in various parts of the body showing their innovative device has 4.3 degrees in the sagittal plane, 6.3 degrees in the coronal plane, and less than 0.829 degrees in flexion and lateral flexion movement difference with the motion analysis system and ICC was 0.999 (Wong, 2008) which seems to be the same with our device.

In 2012, Lou et al.'s device shows  $2 \pm 2$  degrees difference while measuring body angles without movement,  $2 \pm 3$  degrees difference with slow movements and  $4 \pm 4$  degrees difference with fast movement comparing with a motion analysis system and Pearson correlation coefficient obtained in this way was 0.999 (Lou,2012). The device consists of a cable that is placed over the thoracic spine and is connected to the body in the lumbar and shoulder by a long leg brace. They also used human samples in their experiment. The difference made by Lu and colleagues in 2006 and 2012 is that the designed device in 2006 was for children while the new device has no age limit. In addition, 3 accelerometer sensors were used in the construction of the older device, but the new device uses accelerometer and gyroscope at the same time and wearing this new device is easier than the older one and doesn't need a specialist or X-rays.

With the progress of the investigation, one of the most important characteristics is the ease of use and the less visibility of the device to permit easier acceptance by the patient and the treatment to be effective. Advances include: minimizing size, low power consumption, low weight and comfort wearing compared to the means. (Bazzarelli, 2003) All of this, including low weight, its non-visibility while using, low power consumption and the method of its application is easy. The device is a small necklace with very low battery consumption and the user does not feel the weight on the neck. The method of its application is easy and it doesn't need a specialist or x-rays and the information it provides is beneficial and can be useful for the user and the therapist.

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# Social support during pregnancy and its relationship with anthropometric indices at birth and postnatal depression in Iranian women

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## Abstract

**Background:** Pregnancy is a critical stage of a woman's life. Considering the dramatic increase of the need for social support during pregnancy, the present study aimed to determine the level of social support for pregnant women and its relationship with neonatal anthropometric indices and postnatal depression in pregnant women who referred to health centers of Tabriz, Iran in 2013.

**Methods:** In this study, 450 women were selected using cluster sampling. We assessed socio-demographic characteristics and social support status (using interpersonal support evaluation list) ISEL)) at 26-36 weeks of pregnancy. Neonatal height and weight were measured immediately after birth. Maternal depression was assessed six weeks after delivery using the Edinburgh postnatal depression scale (EPDS). Pearson's correlation was used for determining the relation between the social support score with anthropometric indices and depression score.

**Results:** The mean (standard deviation) score of social support was 69.6 (14.6) out of 90. Overall, 12% of the pregnant women had poor social support (score less than 45). Increasing social support score was correlated with decreasing depression score ( $P < 0.001$ ,  $r = 0.421$ ). There were no statistically significant relationships between social support and birth weight ( $p = 0.055†$ ) and height ( $p = 0.132$ ).

**Conclusion:** Social support during pregnancy can reduce occurrence of postnatal depression. As postnatal depression has many adverse consequences, providing social support for pregnant women should be emphasized.

**Key words:** Social support, anthropometric indices at birth, postnatal depression

## Introduction

Pregnancy and the postnatal period are the most critical stages of a woman's life requiring equal physical, psychological, and social attention. Pregnant women need to be supported by their family and friends.[1] According to the conceptual framework published by the World Health Organization (WHO), psychological stressors, anxiety, depression, and social support are among the social determinants of health.[2]

Social support has recently attracted considerable attention. Myler pictured social support as an important predictor of health status.[3] It is believed that social support can directly boost self-confidence, increase resistance to infections, and contribute to a healthier lifestyle. Moreover, it may indirectly lead to social adjustment, relevant reaction to stressors, decreased stress, and thus enhanced physical and mental health.[2,4,5]

Neonatal mortality rate is a significant, multifactorial indicator of health in any society.[6] The prevalence of low birth weight infants in Iran has been reported as 8%. Low birth weight can be a result of various factors such as low socioeconomic level and inadequate maternal social support[7,8].

Mahmoudi et al. (2013) suggested demographic factors to have the greatest effects on birth weight [9]. On the other hand, inadequate social support will affect not only fetal health, but also mothers' health, either during pregnancy or after delivery [10-12].

While a study described increased risk of postnatal depression as a result of poor social support during pregnancy [10], some other studies have indicated the absence of relationships between depression and various biological and psychological factors and poor social support [13,14].

Considering the contradictory results of previous studies and the effects of sociocultural differences on social support provision, we conducted this research to determine the level of social support for pregnant women and its relationship with birth weight and height and postnatal depression in Tabriz, Iran in 2013.

## Materials and Methods

This study was done from October 2012 to May 2013 on pregnant women referring to health centers of Tabriz, Iran. Using Stata (StataCorp, USA, version 9.2) and considering 1.0 for difference in mean depression score between the groups and  $sd=1.4$  (based on results of a study done by Mohammadi et al.[15]),  $\beta=0.20$ ,  $\alpha=0.05$ , sample loss of = 15%; and design effect = 1.5 for cluster sampling, the sample size was calculated to be 450[15].

### Selection of participants

In this study, 26- to 36-week pregnant women who had a record at the selected health centers in Tabriz were included if they were aged 18-35 years, had singleton

pregnancy, were literate and generally healthy (as stated by the subjects), and scored less than 30 on the Perceived Stress Scale. Women who were smoking and had substance abuse habits, history of divorce/separation, jobs involving night shifts, history of infertility, and obstetric problems, were not included. Moreover, the presence of fetal abnormalities and intrauterine growth retardation prevented women from entering the study. After obtaining permission from Tabriz University of Medical Sciences (Tabriz, Iran), cluster sampling was carried out. First, 10 health centers in Tabriz were randomly selected and then convenience sampling was used to select subjects based on the number of visitors per center. Eligible women were invited to participate in the study and asked to provide written informed consent.

### Study tools

Four questionnaires were used for data collection.

#### **Sociodemographic and obstetric characteristics**

Sociodemographic and obstetric characteristics were collected using a 19-item researcher-made questionnaire including age, the woman and her spouse's job and education level, number of pregnancies, gestational age, fetal sex, and obstetric risks. The questionnaire was validated for content and face validity.

#### **Social support**

The standard Interpersonal Support Evaluation List (ISEL) was used to rate the social support mothers received from their family, friends, and community members. The questionnaire contained 30 questions which could be answered as definitely false, probably false, probably true, and definitely true (with the first and last options having the minimum and maximum scores, respectively). The total social support score was achieved by summing the scores of all items [16]. Since no cut off point has been previously determined for the ISEL, we categorized subjects with scores below and above 50% (45 out of a total of 90) to have received (unfavorable and Favorable) social support, respectively.

#### **Anthropometric assessment**

Height/length: Standard techniques measurement was applied; A form including anthropometric indices, as well as gender, was also completed shortly after birth.

#### **Postnatal depression**

Finally, the Edinburgh Postnatal Depression Scale (EPDS), developed by Cox et al (1978) and revised in 1994, was used to measure perinatal and postnatal depression. EPDS consists of 10 multiple choice questions. Each question is scored between zero and three, the total score of the scale ranges between zero and thirty. Mothers select the options that describe their feelings during the last week. Score 12 or higher represents postnatal depression.

All the questionnaires were completed through interview. While the sociodemographic questionnaire and ISEL were filled out during pregnancy, anthropometric indices form after birth and the EPDS was completed six weeks after delivery.

To determine the validity of the questionnaire, face and content validity were used. Moreover, with test and re-test on 30 people, reliability of the two aspects of repeatability (ICC = Intra Class Correlation) and internal consistency (Cronbach's alpha coefficient) was determined. ICC (95% Confidence Interval) and Cronbach's alpha for social support were (0.71-0.94) and 0.86 respectively.

Data analysis was performed using SPSS version 18. Skewness and kurtosis tests for normality of quantitative data showed that depression did not have normal distribution. Therefore, logarithmic transformation was performed. Reassessment of normality with skewness and kurtosis tests suggested the normal distribution of depression.

### Statistical analysis

Descriptive statistics including frequency, mean, standard deviation, and median (percentile 25 to percentile 75) were used to describe social support, sociodemographic characteristics, anthropometric indices, and depression. The relationships between maternal social support and the infants' birth height and weight were evaluated with Pearson's correlation analysis. The Pearson correlation was used to examine the relationship between depression and social support.

## Results

### Characteristics of the study population

Although 450 pregnant women were initially included, 60 participants were excluded since they could not be followed up after delivery due to changed residence (22 participants) or unwillingness to participate (38 participants). Hence, data of a total of 390 women was ultimately analyzed.

### Sociodemographic and obstetric characteristics

Mean (SD) of the mothers' age, birth spacing and gestational age at the recruitment time was 26.5 (5.1) years, 5.7 (3.2) years and 31.1 (3.9) weeks, respectively. Birth spacing was more than five years in over 76%. The mean body mass index (BMI) of the participants was 25.6 (SD= 4.7) kg/m<sup>2</sup> and half of them had normal BMI. The majority (92.8%) of the subjects were housewives. About two-thirds of the participants' spouses had Primary school or Middle High school education and 54.6% of them were self-employed. The majority (97%) of the women reported no pregnancy problems (Table 1).

**Table 1: Sociodemographic characteristics in pregnant women referred to health centers of Tabriz city**

Variable	Number (percent)	Variable	Number (percent)
<b>Number of pregnancies</b>		<b>Age (years)</b>	
1	237 (52.7)	Less than 25	165(36.6)
2	145 (32.2)	25-29	138 ( 30.6)
3 and more	68 (15.1)	29 or more	147 ( 32.8)
mean (SD)	1.7 (0.9)	mean (SD)	26.5 (5.1)
<b>Occupation</b>		<b>Education</b>	
housewife	418 (92.8)	Primary school	157 (34.9)
working at home	21 (4.7)	Middle High school	139 (30.9)
work outside the home	11 (2.5)	High school	128 (28.4)
		College	26 (5.8)
<b>Spouse occupation</b>		<b>Spouse Education</b>	
Unemployed	16 (3.5)	Primary school	141 (31.3)
Labor	131(29.1)	Middle High school	140 (31.1)
employees	58(12.8)	High school	125 (27.8)
self-employed	245(54.6)	College	44 (9.8)
<b>birth spacing (years)</b>		<b>BMI (kg / m<sup>2</sup>) *</b>	
less than 3	28(6.2)	Underweight	36 (8)
3 to 5	88(19.6)	Normal	227 (50.4)
More than 5	334(74.2)	Overweight	84 (18)
mean (SD )	5.7(3.2)	Obese	103 (23.6)
<b>Pregnancy problems **</b>		mean (SD)	25.6 (4.7)
yes	13(2.9)		
no	437(97.1)		

BMI (kg / m<sup>2</sup>) were measured on weight and height and BMI were classified into 4 groups, underweight (less than 19.8), normal (19.8-26), overweight 26-29 and obese (greater than or equal to 29).

\*\* Pregnancy Problems include bleeding, high blood pressure, gestational diabetes etc.

### Social support and anthropometric indices

The subjects' mean score of social support was 69.5 (SD 14.6) out of 90 and 50 mothers (12%) had received poor social support. The Mean (SD) birth weight and height were 3206 (552) and 49.7 (2.5), respectively. The lowest and highest birth weights among the neonates were 1590 and 5700 grams, respectively. A total of 85 infants (18.9%) had birth weight below 2500 grams (LBW). There was no significant relationship between social support and birth height ( $p=0.132$ ) and weight ( $p=0.055$ ) (Table 2).

**Table 2: Relationship between social support in pregnant women and neonatal anthropometric parameters**

Neonatal anthropometric parameters	Number (percent)	Social Support score	Test results for the relations	
		Mean (SD)	p	r
<b>Height (cm)</b>				
51 or more	124 (27.6)	69.8 (14.9)	0.851*	
Less than 50	326 (72.4)	69.5 (14.6)	0.132*	0.071
<b>Weight (grams)</b>				
2500 and more	365 (81.1)	70.3 (14.3)	0.024*	
Less than 2500	85 (18.9)	66.3 (15.8)	0.055*	0.099
All	450	69.6 (14.6)		

\* results of independent t-test

† results of Pearson correlation

### Social support and postnatal depression

The median (percentile 25 to percentile 75) postnatal depression scores in mothers with unfavorable and favorable social support were 8.5 (1.7-13.2) and 2.0 (1.0-6.0), respectively.

There was a statistically significant relationship between maternal social support and postnatal depression score ( $p<0.001$ ) (Table 3).

**Table 3: Status of social support during pregnancy, postnatal depression and its relationship**

Social support status	Number	Depression score		Test result for the relation
		Mean (SD)	Median (p 25 to p75)*	P<0.001† r=0.421
Favorable	340	3.9 (3.9)	2.0 (1.0 to 6.0)	
Unfavorable	50	8.9 (6.6)	8.5 (1.7 to 13.2)	
Total	390	4.5 (4.6)	3 (1 to 7)	

\* (Percentile 25 to Percentile 75), † results of Spearman's rho

We found most of our participants to have enjoyed a relatively good level of social support as only 12% of the studied women had received poor social support, similar to Collins et al. [1] In the present study, there was no significant relationship between mean social support score of pregnant mothers and birth weight and height. Similarly, in a clinical trial, Hodnett et al (2005) pointed out the slight effects of social support on low birth weight.[17] However, the findings of Feldman et al (2000) and Collins et al (1993) were in contrast to ours.[1,18] Lynch et al (1997) stated that a woman with poor support in the family would have a child with lower birth weight.[19] Such inconsistency

can be attributed to differences in sample size and culture and lifestyle of the study population. Furthermore, in this study most of our participants had a good level of social support.

Our findings indicated a significant relationship between social support during pregnancy and postnatal depression. Lau et al (2008) reported higher prevalence of perinatal and postnatal depression in women with less social support. [20,21] According to Logsdon et al (1994), adequate maternal social support, primarily by the spouse and then by the society, could reduce the risk of postnatal depression by 40%.[22] Likewise, Chen et al (2007) highlighted the relationship between social support and postnatal depression[23]. They emphasized

on the significance of sufficient social support in improving pregnancy outcomes both for the fetus and the mother. These results are consistent with ours.

Since we could not establish a significant relationship between social support for pregnant women and postnatal depression, special attention has to be paid to social support before and during pregnancy. Moreover, health care providers are required to explain the value of comprehensive social support during pregnancy to the women's family. Preventive measures, e.g. classes and educational pamphlets, should also be taken on the irreversible consequences of poor social support during pregnancy for the parents and the community.

One of the limitations of the present study was its cross-sectional nature in which the observed relationships were not exactly indicative of a causal nature. Hence, in order to obtain more precise results regarding the relationship between social support and anthropometric indices and postnatal depression, further studies have to evaluate maternal social support throughout the pregnancy and even before its initiation.

## Conclusion

Social support is effective on the incidence of postnatal depression. Therefore, enhancing social support from the family appears to be essential for improving the mental health of mothers. As the probability of mental disorders and adverse outcomes of pregnancy may increase in mothers with poor social support, promoting interpersonal communication skills among adults can increase access to the required social resources for maintaining mental health and coping with stressful life events.

Moreover, establishment of a support system (with the pregnant woman's spouse and family) might have a prominent effect on reducing the prevalence of mental disorders during pregnancy.

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# The efficacy of short-term play therapy for children in reducing symptoms of ADHD

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## Abstract

**Objective:** The purpose of this study was to evaluate the efficacy of short-term play therapy for children in reducing the symptoms of ADHD.

**Method:** This is a single-subject study in a base single-line method. Six children of 7-10 years old with ADHD were selected through purposive sampling. Participants received short-term play therapy. Every participant received 10 sessions of intervention and the follow-up phase was run after three months. Conners Parent Questionnaire and CBCL were used as the research instrument.

**Results:** The results showed that short-term play therapy for children is effective in decreasing symptoms of ADHD.

**Conclusion:** According to the results, short-term play therapy for children can be used as an appropriate intervention in reducing the symptoms of ADHD.

**Key words:** Short-term play therapy for children, ADHD

## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurobehavioral disorders diagnosed in children (Barkley, 2012). It is deemed as the most commonly diagnosed mental disorder in children, and about 3% - 5% of children suffer from it around the world (Franck-Briggs, 2013). It usually begins from preschool age and often continues until adulthood (Halperin & Healey, 2011). Although psychiatric drugs are still the common treatment, the use of it to treat ADHD has decreased dramatically so that referring to a psychiatrist has dropped from 15% in 2003 to 6% in 2010 and attention is continuously moving away from psychiatric treatment in order to manage the disorder (Kaduson, 2014).

Many studies have been conducted on the effectiveness of various treatments for ADHD, such as behavioral or cognitive-behavioral therapy. A number of experts also have called for an answer to the question whether therapeutic play could act as an effective intervention for ADHD. Over the past 20 years, the efficiency of play therapy for children with ADHD has been tested clinically and experimentally and is increasingly recognized as a useful treatment tool (Barzegari & Zamini, 2011; Braton et al. 2013; Ray, Schottelkarb & Tsai, 2007). Alternative play therapy is a suitable psychological treatment for a wide range of psychological problems in children and adolescents aged between 3-16 years (Harris & Landreth, 1997). Play therapy is a method that psychologists and researchers have used for decades to treat a wide range of disorders and problems and have demonstrated its effectiveness (Halperin et al. 2013; Barton, Bankart and Davis, 2005). Play therapy potential such as problem solving, self-regulation, and direct and indirect education (Schafer, 2014) can help children with ADHD to diagnose their problems and to communicate with them through

playing and full participation in treatment (Kaduson, 2014).

To treat ADHD requires involvement of many specialists, including doctors, psychologists, educational experts, social workers and play therapists. For years, each of these specialists treated ADHD by themselves and had their own definitions and ideas for evaluation and treatment. The short-term play therapy is a combination of different clinical strategies tested with a multi-dimensional approach that is used for children of ADHD to help treat them more efficiently. This multidimensional perspective requires parents to be educated on the nature and diagnosis of the disorder as weekly parental training, education on medication therapy if necessary, classroom interventions, social skills training, and individual play therapy (Kaduson, 2006). Therefore, this treatment seems to help lessen the symptoms of ADHD. The present study aims to investigate the effectiveness of short-term play therapy for children in reducing ADHD.

## Method

A single subject or single case and A-B design were used to carry out the research. Achenbach Child Behavior checklist (CBCL) was applied three times to determine the baseline before the intervention. Standard questionnaires and parent interviews before the intervention were also used to collect data. In the process of the interventions, Conners parent questionnaire was filled out by the mother every session and CBCL was completed by her at the first, fifth and tenth sessions.

In this research, with the help of public and private schools as well as consultation centers associated with the Ministry of Education, the subjects were selected by purposive sampling out of the children with ADHD between 7- 12 years old. They were selected according to Conners parent rating scale, the DSM- 5 diagnostic criteria and the results of the interview. Exclusion criteria included other psychiatric disorders. The children participated in the therapeutic-research program after receiving family consent. The research sample consisted of 6 subjects.

Individual characteristics questionnaire: This questionnaire was made by the researcher and included personal information.

**Conners Parent Rating Scale (CPRS) (Revised):** This is the popular scale of ADHD from the parental perspective (Goldstein & Goldstein, 1998). The questionnaire has 26 questions and has a 4-point Likert scale of never, to very high, completed by mothers. It also consists of 4 sub-scales of attention deficits, hyperactivity / impulsivity and oppositional defiant disorder (ODD). The content validity of the scale has been confirmed (Goldstein & Goldstein, 1998). The construct validity of the Conners form has been obtained using factor analysis methods and the differential validity of the questionnaire's ability to differentiate between the normal and clinical groups with ADHD has been strongly confirmed (Zargarinejad & Yazdan Doost, 2008).

**Child Behavior Checklist (CBCL):** The Child Behavior Checklist is a series of the Achenbach System of Empirically Based Assessment (ASEBA) addressing the problems of children and adolescents based on 8 factors: anxiety / depression, isolation / depression, physical complications, social problems, thinking problems, attention problems, ignoring the rules and aggressive behavior. Two factors of ignoring the rules and aggressive behavior constitute the second-order factor of exogenous problems. The questionnaire assesses emotional-behavioral problems as well as the educational and social competencies of 6-18 years old children from the parents' perspective. It is filled out in 20 to 25 minutes (Minaei, 2005). This checklist is completed by the parents, the person who cares for the child or anyone who treats the child in a family-like environment and fully understands him or her. The respondent first answers questions that measure the child's competencies while s/he responds to open-answer questions that relate to the child's illness, disability, and the main concerns of the respondent about the child and his/her attitudes to the best characteristics of the child. The form is followed by questions on the child's emotional, behavioral, and social problems. The questionnaire consists of 115 questions about the types of behavioral patterns of children. The questions are responded to as a 3-point Likert scale ranging from 0 to 2. The point 0 is assigned to items that are never observed in the child's behavior; the point "1" is given to the states and behaviors that are sometimes observed and the score "2" is given to cases that usually or always are observed in the child's behavior. The overall validity coefficients of CBCLs have been reported as 0.97 via Cronbach's alpha and 0.94 via a retest. Content validity (selection of questions logic and use of first-class analysis of questions), criterion validity (using a psychiatric interview with the child, and correlation with CSI-4 scale) and construct validity (internal relations of scales and group differentiation) of the checklists have been reported desirable (Minaei, 2006).

**Short-term play therapy for children derived from Kaduson (2006):** A short-term play therapy for children is based on ADHD primary components including attention (focus range), hyperactivity (restlessness, squirm in their seats) and impulsivity (acting without thinking, poor planning ability, low tolerance, etc.). Treatment goals are focused on creating the child's self-concept in various areas of deficit, increasing their ability to stay focused on assignments, encouraging them to express self-control, and educating the child to pay attention to the results of their actions. This treatment plan is a 10-week program that uses new strategies to achieve more success. The protocol includes a 15-minute visit with parents separately and then with the child individually in the play therapy room for 35 to 50 minutes. This program directly trains both parents and children in the ways of managing ADHD.

## Findings

To evaluate the effectiveness of short-term play therapy for children in reducing the symptoms of ADHD, participants were weekly measured by the Conners Parent Questionnaire. In this research, a single-subject B-A design was used; A refers to the baseline and B refers to the intervention. Results of each subject are summarized in the following tables.

**Table 1: Within/between-condition visual analysis of ADHD variables for Participant No. 1, Amir Mohammad**

Variable	Baseline	Within-condition Intervention Line
Sequence of conditions	A	B
Length of conditions	3	8
Median of conditions	3.00	2.73
The range of changes	1.03	1.54
Stability bar	2.40-3.60	2.18-3.27
The percentage of data in the stability bar	100%- Stable	50% - Unstable
First half median	3.06	3.33
Second half median	3.29	2.60
Relative level change	-0.23	0.73
First value of data	2.55	2.84
Last value of data	3.00	2.15
Absolute level change	0.45	0.69
Trend direction	Ascending	Descending
Percentage of points inside the stability range	100%- Stable	100%- Stable

Variable	Between-condition After the intervention (B to A)
Comparison of the conditions	B to A
The number of variables changed between the conditions A and B	1
Changing the trend between the conditions A and B	Descending to ascending
Targeted effect	Positive
Changes in the stability of the process	Stable to stable
Relative level change	(3.33 to 3.29) -0.04
Absolute level change	(2.84 to 3.00) 0.16
Change in the median level	(2.73 to 3.00) 0.27
Change in the average level	(2.77 to 3.04) 0.27
Percentage of non-overlapping data (PND)	25%
Percentage of overlapping data (POD)	75%

**Table 2: Within/between-condition visual analysis of ADHD variables for Participant No 2, Zeynab**

Variable	Baseline	Within-condition Intervention line
Sequence of conditions	A	B
Length of conditions	3	9
Median of conditions	3.35	1.85
The range of changes	0.27	1.88
Stability bar	2.68-4.02	1.26-1.89
The percentage of data in the stability bar	100%- Stable	56%- Unstable
First half median	3.27	2.50
Second half median	3.23	1.35
Relative level change	-0.06	1.15
First value of data	3.35	3.23
Last value of data	3.46	1.35
Absolute level change	-0.12	1.88
Trend direction	Ascending	Descending
Percentage of points inside the stability range	100%- Stable	67%- Unstable

Variable	Between-condition After the intervention (B to A)
Comparison of the conditions	B to A
The number of variables changed between the conditions A and B	1
Changing the trend between the conditions A and B	Descending to ascending
Targeted effect	Positive
Changes in the stability of the process	Unstable to stable
Relative level change	( 2.50 to 3.33) 0.83
Absolute level change	(3.32 to 3.46 ) 0.23
Change in the median level	(1.58 to 3.35) 1.77
Change in the average level	(1.98 to 3.33) 1.35
Percentage of non-overlapping data (PND)	89%
Percentage of overlapping data (POD)	11%

**Table 3: Within/between-condition visual analysis of ADHD variables for Participant No 3, Amir Abbas**

Variable	Baseline	Within-condition Intervention line
Sequence of conditions	A	B
Length of conditions	3	9
Median of conditions	2.96	2.42
The range of changes	0.42	1.15
Stability bar	2.37- 3.55	1.94-2.91
The percentage of data in the stability bar	100%- Stable	67%- Unstable
First half median	2.94	2.58
Second half median	3.06	2.00
Relative level change	-0.12	0.58
First value of data	2.73	2.88
Last value of data	2.96	1.77
Absolute level change	-0.23	1.12
Trend direction	Ascending	Descending
Percentage of points inside the stability range	100%- Stable	89%-Stable

Variable	Between-conditions After the intervention (B to A)
Comparison of the conditions	B to A
The number of variables changed between the conditions A and B	1
Changing the trend between the conditions A and B	Descending to ascending
Targeted effect	Positive
Changes in the stability of the process	Stable to stable
Relative level change	(2.56 to 3.06) 0.48
Absolute level change	( 2.88 to 2.96) 0.08
Change in the median level	( 2.42 to 2.96) 0.54
Change in the average level	( 2.27 to 2.95) 0.68
Percentage of non-overlapping data (PND)	89%
Percentage of overlapping data (POD)	11%

Table 4: Within/between-condition visual analysis of ADHD variables for Participant No 4, Mani

Variable	Baseline	Within-condition Intervention line
Sequence of conditions	A	B
Length of conditions	3	9
Median of conditions	3.42	2.15
The range of changes	0.77	1.00
Stability bar	2.74-4.11	1.72-2.58
The percentage of data in the stability bar	100%- Stable	89%- Stable
First half median	3.19	2.31
Second half median	3.35	2.12
Relative level change	-0.15	0.19
First value of data	3.42	2.96
Last value of data	3.73	1.96
Absolute level change	-0.31	1.00
Trend direction	صعودي	نزولي
Percentage of points inside the stability range	100%- Stable	100%- Stable

Variable	Between-condition After the intervention (B to A)
Comparison of the conditions	B to A
The number of variables changed between the conditions A and B	1
Changing the trend between the conditions A and B	Descending to ascending
Targeted effect	Positive
Changes in the stability of the process	Stable to stable
Relative level change	(2.31 to 3.35) 1.04
Absolute level change	(2.96 to 3.73) 0.77
Change in the median level	(2.15 to 3.42) 1.27
Change in the average level	(2.26 to 3.37) 1.11
Percentage of non-overlapping data (PND)	100%
Percentage of overlapping data (POD)	0%

**Table 5: Within/between-condition visual analysis of ADHD variables for Participant No 5, Ali**

Variable	Baseline	Within-condition Intervention line
Sequence of conditions	A	B
Length of conditions	3	9
Median of conditions	3.04	1.92
The range of changes	0.38	1.50
Stability bar	2.43-3.65	1.54- 2.31
The percentage of data in the stability bar	100%- Stable	33%- Unstable
First half median	2.94	2.42
Second half median	3.13	1.42
Relative level change	-0.19	1.00
First value of data	2.85	2.77
Last value of data	3.23	1.27
Absolute level change	-0.38	1.50
Trend direction	Ascending	Descending
Percentage of points inside the stability range	100%- Stable	100%- Stable

Variable	Between-condition After the intervention (B to A)
Comparison of the conditions	B to A
The number of variables changed between the conditions A and B	1
Changing the trend between the conditions A and B	Descending to ascending
Targeted effect	Positive
Changes in the stability of the process	Stable to stable
Relative level change	(2.42 to 3.13) 0.71
Absolute level change	(2.77 to 3.23) 0.46
Change in the median level	(1.92 to 3.04) 1.12
Change in the average level	(1.95 to 3.04) 1.09
Percentage of non-overlapping data (PND)	100%
Percentage of overlapping data (POD)	0%

Table 6: Within/between-condition visual analysis of ADHD variables for Participant No 6, Mohammad Hossein

Variable	Baseline	Within-condition Intervention line
Sequence of conditions	A	B
Length of conditions	3	9
Median of conditions	2.81	2.23
The range of changes	0.42	1.42
Stability bar	2.25- 3.37	1.78-2.68
The percentage of data in the stability bar	100%- Stable	56%- Unstable
First half median	2.94	2.62
Second half median	2.87	1.77
Relative level change	-0.19	1.00
First value of data	2.81	2.88
Last value of data	2.65	1.46
Absolute level change	0.15	1.42
Trend direction	Stable	Descending
Percentage of points inside the stability range	100%-Stable	100%- Stable

Variable	Between-condition After the intervention (B to A)
Comparison of the conditions	B to A
The number of variables changed between the conditions A and B	1
Changing the trend between the conditions A and B	Descending to stable
Targeted effect	Positive
Changes in the stability of the process	Stable to stable
Relative level change	(2.62 to 2.87) 0.25
Absolute level change	(2.88 to 2.65) -0.23
Change in the median level	(2.23 to 2.81) 0.58
Change in the average level	(2.20 to 2.85) 0.65
Percentage of non-overlapping data (PND)	89%
Percentage of overlapping data (POD)	11%

As shown by Tables 1 to 6, short-term play therapy for children is effective in reducing ADHD.

## Discussion and Conclusion

The results of the study indicated that short-term play therapy for children is effective in reducing attention deficit hyperactivity disorder. To explain this result we can say that through playing, children naturally express their inner self. Therefore, the treatment that uses play for children provides a good growth environment for communication and excellence (Landerth, 2002). In addition, parental involvement in play therapy extends the therapeutic effects (Bratton, Ray, Rhine & Jones, 2005). In the short-term play therapy, parental involvement is a fundamental principle in the treatment process. During each session, parents should make specific activities during the week, i.e., they play an active role in the child's treatment process. Parental involvement and their active participation in the treatment process will increase the fortifications received by the child, and the proper behaviors of the child with ADHD will be further affected by receiving these fortifications.

To train parenting practices of parents of ADHD children is another important factor in short-term play therapy. The results of research on intervention programs for parents of ADHD children suggest that the symptoms of ADHD have reduced among 45% of these children. Furthermore, the intervention program has had a positive impact on improving the parents' mental health and qualification as well as on parent-child interactions (Daley & O'Brien, 2013). In a short-term play therapy for children, the therapist provides parents with the necessary training regarding the criticisms and comments of other people who are not aware of the situation and gives them advice on dealing with such situations (Kaduson, 2006). Such training, by itself, leads to decrease in the parents' stress; as a result, the therapeutic effects will clearly appear. Moreover, this treatment is multifaceted so that the treatment and education given to parents can bring about effective outcomes. Therefore, short-term play therapy can be used as an effective treatment to reduce symptoms of ADHD.

As a limitation, it can be noted that the treatment used in this study was designed for the western population of the country and despite the reforms, there may be problems in using it for all of the Iranian population. Therefore, other studies on the effectiveness of short term play therapy for other mental disorders should be conducted using other statistical methods to analyze the research data.

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# Mental Health and Related Factors in Physicians Working in Hospitals: A Study in Western Iran in 2016

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## Abstract

**Background and Objective:** Attention to mental health is important in all areas of life, including personal, social, and occupational life. One of the factors affecting the mental health of physicians is occupational stress. This study examined the state of mental health in physicians and determined the factors associated with it.

**Methods:** This cross-sectional study was designed in 2016. The sampling method used was a census method and all the general practitioners working in hospitals affiliated to the Lorestan University of Medical Sciences were studied. The data was collected by the GHQ-28 questionnaire and a checklist containing the demographic characteristics and occupational status of the physicians was provided. The data was analyzed with descriptive and analytical statistics.

**Results:** Among 120 doctors included in the study, 36 (30%) had a mental disorder. The highest disorder was for anxiety ( $20 \pm 5.7$ ) and the lowest was a social disorder at  $11.5 \pm 5.5$ . The mental health disorder of the physicians was significantly correlated with work experience, the number of shifts worked, income, overtime, marital status, employment status and status of shifts ( $p$  value  $<0.05$ ).

**Conclusion:** With regard to the results of this study and considering the importance of mental health for the physicians, it is necessary for the managers and the authorities of the health services organizations to provide counseling services in various fields and to adjust the factors affecting mental health in the workplace in order to improve the mental health of members of this group.

**Key words:** Mental Health, physicians, disorder

## Introduction

One of the components of health is the mental dimension of health. Maintaining mental health is as important as bodily health. There may be some measures in this regard, but mental health services are mainly allocated to a small group of people who have serious and obvious problems [1].

Mental health is a knowledge or art that helps people adapt to their environment by establishing sound psychological and emotional methods and which enables them to choose the best solutions to their problems [2].

Problems in the field of mental health have existed since the advent of humanity; no particular economic or social class is immune to them [3].

According to the available evidence, mental disorders are one of the most common components of diseases and by 2020, the share of mental disorders is expected to increase by about 50% of the total burden of disease [4]. Information from epidemiological research in this country implies that the prevalence of these problems in this country is not lower than in other countries. Regarding the prevalence of psychiatric illnesses in people aged 15 years and older in Iran, an epidemiological study in the country has found that altogether 21% of the subjects in the country suffer from mental disorders and about 10–12 million adults require mental health services. In addition, about 0.6% of the patients suffer from psychiatric disorders [5].

Mental health issues are one of the major problems that add to financial burden. The cost of dealing with psychiatric problems in Europe and North America in 1999 was \$ 120 billion [6].

Attention to mental health is important in all areas of life, including personal and social life and occupation. Occupation is one of the areas where mental health is of significance. The US National Occupational Safety and Health Administration (NSA) has introduced medicine at the top of 40 professions with a high prevalence of stress-related diseases [7]. In the medical profession, there are many stressful occupational factors like working in the shift system, workload, conflict with colleagues, frequent contact with suffering and death of patients, a lack of supporting resources, and a lack of time to address the patients' emotional needs and their own professional responsibilities.

Disruptions in the health of physicians may lead to poor performance and insufficient quality of care for patients: hence, attention to mental health of this stratum is important [7].

Few studies have been conducted on the level of mental health in doctors and related factors. Considering the inevitability of some factors affecting mental health and the need to prevent their psychological effects, the use of specific measures to improve the working environment can be helpful. This study was designed to determine the

level of mental health and the identification of the relevant factors in physicians.

## Methods

### Study setting and sample

This cross-sectional study was designed for general practitioners working in teaching hospitals affiliated to the Lorestan University of Medical Sciences in 2016. Census sampling was done and all physicians working in educational hospitals were studied.

### Measurement and device

The data collection tools were a GHQ-28 questionnaire and a checklist containing the demographic characteristics and the physicians' occupational status (age, gender, marital status, work record, employment status, overtime, job condition, and income level). The GHQ questionnaire was first designed by Goldberg (1972) to identify and differentiate people with mental disorders. In this study, a 28-question form was used. This questionnaire has four dimensions—A, B, C, and D—and each scale has seven questions, with four categories of disorders including anxiety, physical problems, social function disorder and depression disorders.

The validity and reliability of this questionnaire has already been confirmed in previous studies [8–10]. In this study, Cronbach's alpha value for the physical symptoms was 0.84, for anxiety was 0.85, for social function was 0.79, for depression was 0.81, and for the total questionnaire was 0.91, which indicates the acceptable internal consistency of this questionnaire. The replies were encoded as a Likert Score (0-1-2-3). The cut-off point in this study was that individuals with a score of less than 23 were in the healthy group and those with a score of 23 and above were categorized in the group with mental disorder [11, 12]. In the case of subscales, the cut-off point was also considered. This means that six and fewer signs indicated a lack of disorder and higher than six signs was considered as a disorder in the sub-scale [11, 12].

### Statistical methods

After collecting the questionnaires, the data was entered into the software SPSS Version 22 and using descriptive statistics (mean, standard deviation, and frequency), t-test analysis statistics, one-way ANOVA (groups were compared with Tukey's post hoc test), and multiple logistic regression (for controlling confounding and predicting factors related to mental health), the data has been described and analyzed. A significance level of  $P < 0.05$  was considered.

## Results

In this study, 120 subjects were interviewed and, of them, 37.5% were female and 62.5% were male. The mean age of the participants was  $38.9 \pm 9.8$  years. The youngest participant was 27 years old and the oldest was 55 years old. Of the total number of participants, 72.5% were married, 56.6% had a record of work experience less than 10 years, 20.1% had an official record, 57.5% worked

overtime, 53.4% had more than 20 shifts in a month and 34.2% had an income of more than six million.

Of the 120 physicians, 36 (30%) had mental disorders and 84 (70%) had no mental health disorder. In examining the dimensions of the mental health questionnaire administered to the physicians, the highest disorder was for anxiety ( $25 \pm 5.7$ ) and the least was for social function at  $11 \pm 5.5$ . In the other two dimensions, mental health, that is, the physical dimension and mean depression, the frequencies were  $20 \pm 5.9$  and  $15 \pm 4.9$  respectively.

Logistic regression analysis was used to modify the effect of the confounders and the results are shown in Table 1. In the single group, the probability for mental health disorder was 1.3 [OR: 1.3 95% CI (1.2–4.9)]. In the group with more than 20 shifts, the probability of mental health disorder was 2.4, [OR: 2.7 95% CI (1.5–3.6)]. In the night shift group, the probability of mental health disorder was 1.8 [OR: 1.8 95% CI (1.4–5.7)]. In the group with income of less than 4 million, the probability of mental health disorder was 2.1 [OR: 2.1 95% CI (1.7–6.5)]. In the group with contract employment status, the probability of mental health disorder was 3.2 [OR: 3.2 95% CI (2.5–6.6)]. In the group with less than 10 years of work experience, the probability of mental health disorder was 2.4 [OR: 2.4 95% CI (1.5–5.1)]. Overtime increased the probability of mental health disorder by 3.6% [OR: 3.6 95% CI (2.2–6.5)].

**Table 1: The frequency of job and demographic variables in the groups with or without mental health disorder**

Variable	Mental Health Disorder (%)	Lack of Mental Health Disorder (%)	P value
Age = <30	5 (31.2)	11 (68.8)	0.45
31–40	10 (32.2)	21 (67.8)	
41–50	13 (26.6)	32 (73.4)	
51–60	8 (28.5)	20 (71.5)	
Male	28 (37.4)	47 (62.6)	0.12
Female	8 (17.7)	37 (82.3)	
Marriage Status			0.03
Single	8 (32)	17 (68)	
Married	25(28.8)	62(71.2)	
Divorced	3(37.3)	5(62.7)	
Work experience less than 10 years	25(36.8)	43(63.2)	0.01
Work experience of 10 to 20 years	10(31.3)	22(68.7)	
Work experience of 21–30	1(5)	19 (95)	
Employment Status = Contractual	24(41.4)	34(58.6)	0.002
Employment Status = Contract	9(23.7)	29(76.3)	
Employment Status = Official	3(12.5)	21(87.5)	
Shift time			0.001
Morning	5(27.7)	13(72.3)	
Afternoon	4(23.5)	13(76.5)	
Night	22(35.4)	40(64.6)	
Rotational	5(21.7)	18(78.3)	
Overtime = Yes	30(43.5)	39(56.5)	0.001
No	6(11.8)	45(88.2)	
Number of shifts			0.04
Less than 10 shifts	5(27.7)	13(72.3)	
10–20 shifts	9(23.6)	29(76.4)	
More than 20 shifts	22(34.3)	42(65.7)	
Income of less than 4 million	17(36.9)	29(63.1)	0.001
Income of 4–6 million	9(27.2)	24(72.8)	
Income of more than 6 million	10(24.3)	31(75.7)	

## Discussion

The present study was designed to investigate the state of mental health in physicians and to investigate the factors affecting it. The findings of this study showed that (30%) of the subjects had mental health disorders. The results of this study are similar to other studies conducted in this regard. Claplan stated that in the UK the level of stress, anxiety, and depression among hospital staff was more than expected [13]. In a study by Flaherty & Richman mental illness in the US was reported by 23% of the doctors [14]. In a study conducted by Firth-Cozens, 20% of the physicians had some kind of mental health disorder [15].

Another finding of this study was the relationship between mental health disorders and marital status. The results of Masoomeh Saberian's study showed that those who do not live with their partners or reasons such as death, divorce or other causes are more affected by mental illness [16]. In a study by Firoozabadi, the relationship between mental health disorders and marital status is also mentioned [17]. With regard to these results, it can be said that married people are in a better position in terms of social and psychological performance than single or divorced physicians and this can be due to factors such as the difference caused by communicative and participatory skills.

The results of our study showed that there is a significant relationship between the employment status and overall mental health score. Similar results were obtained in the study of Mustafa Brezidah [18]. Naturally, the more people feel they are at risk in terms of job security, the more they ruminate mentally, looking for the right solution to leave the current job, and focusing on finding a better and more permanent job. In such a situation, the likelihood of psychological harm increases. In this study, there was a significant relationship between work experience and mental health disorder in the physicians. Similar results were obtained in the study of Mollart [19]. In a study by Tattersall the relationship between mental health disorders and work experience is also mentioned. [20]. This can be attributed to increased experience and adaptation to the stressors as well as better skills.

Another finding of this study was the direct relationship between the number of work shifts and mental health disorder in physicians. In Firth-Cozens' study, there was a significant relationship between the number of shifts and mental health status of the physicians and as the number of shifts increased, psychiatric disorders increased [15]. In the same vein, Poissonnet also reported a significant relationship between the number of shifts and mental health—and the findings are consistent with the results of our study [21]. Long and unpredictable work hours are directly linked to increased stress and psychosocial illnesses.

In this study, there was a significant inverse relationship between income and mental health disorder. This result is not consistent with the results of the study conducted by Lambert et al. [22]. Khaghanizadeh observed a significant

relationship between the economic status and mental health of nurses in their study and it was consistent with our results [23]. Considering the unevenness of income in the subjects of this study, these results are justifiable. Insufficient wages lead to long hours of work and full-time activities which endanger employee health.

In our study, there was a significant relationship between shift status and mental health in the physicians. The group that had night shifts was more affected by mental health problems. This finding is consistent with the results of the study by Mustafa Brezideh et al. and the research by Firth-Cozens [15]. It seems that work in the night shift affects the sleep cycle, causing insufficient rest. Personnel working in night shifts need to sleep during the day, which often does not allow full and undisturbed sleep. Owing to the ambient noise during the day, the quality of sleep is impaired. On the other hand, such professionals tend to sleep for shorter durations so that they can spend some time with family and friends. Also, some of these people may have to do other jobs during the hours of the day for additional income, which causes eventual burnout.

The findings of this study showed a significant relationship between working overtime and the overall mental health score in the physicians. This relationship with overwork was also observed in sub-scales like anxiety and physical dimension. In a study conducted by Morteza Khaghanizadeh on 200 nurses working in teaching hospitals affiliated to the Tehran University of Medical Sciences, there was a significant relationship between the overwork variable and mental health, which was a higher level of psychiatric disorders in overworked people [24]. Also, in a study conducted by Suzuki on the hospital nurses in Japan, there was a significant relationship between mental health and overwork and overworked nurses suffered from more psychiatric disorders [24].

Of the factors that cause mental health disorders in overworked people, it is possible to point out the stressful nature of their professions, workload, exposure to unexpected situations, work shifts, organizational factors as well as individual factors. On the other hand, these stressors also disrupt physical health.

Considering the high prevalence of mental disorders in the physicians and the importance of mental health and wellbeing for healthcare professionals, it is necessary to attract the attention of the doctors to this issue. Meanwhile, the managers and the authorities in the field of healthcare are also required to take action in order to modify some of the psychological pressures on this group, including establishing a balance between the state of shifts, creating job security, and raising wages and salaries in relation to inflation. Another suggestion is that in this country there are many studies on mental health status of nurses working in hospitals but less attention is paid to the mental health status of the doctors. Therefore, more such studies are recommended so that by identifying the factors associated with mental health disorders, the managers in the healthcare sector can plan to prevent and respond to these problems.

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# Role of Religion in Women's Social Health in Iran

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## Abstract

The article investigates the impact of religion on social wellbeing among women. According to related theories, impact of being religious, interpersonal networks and relations and social support were analyzed. The research uses survey methods. Research census is women in the city of Kashan. Predictors of interpersonal networks and relations (e.g. religion) explains 7/6 percent of its variance; predictors of social support (e.g. religion and interpersonal networks) explain 89 percent of its variance; and predictors of social wellbeing (e.g. religion, interpersonal networks and social support) explain 13/79 percent of its variance. Fitness of theoretical model of research was confirmed with structural model analysis (path analysis) of structural equation modeling using Amos software.

**Key words:** Social wellbeing;  
 Religiousness;  
 Interpersonal networks and relations;  
 Social support.

## Introduction

In recent centuries, Iranian society has moved from a traditional society towards a society with new structures. This movement, along with many other changes, has brought women to the public domain, but has not yet replaced structures to provide a secure public environment for their activity. The barriers and problems that have limited the opportunities for women's participation in various aspects of social life and development, and the inadequate functioning of economic, political and social institutions has also led to problems in society which indicate vulnerable conditions. On the other hand, study on problems and injuries and health have different aspects, and women as half of the population have more barriers and more vulnerability than men in facing social problems. These problems for women have many dimensions, and without considering them they cannot be properly understood, their inequitable and subordinate conditions in social situations against social participation, education and socialization, and the predefined situations, makes them less susceptible to social health and so many data confirm this analysis in this country. Women in society are less involved in social activities, and one of the most active cases that can create an interpersonal and social network in society is religious ceremonies. The research intends to answer the question: Does participation in religious ceremonies and in general religiosity have an impact on the level of social health of women or not? What is this effect? Which other variables affect this relationship? In 1995, McArthur conducted a study to evaluate the epidemiology of social health in the United States. The aim of this study was to achieve the prevalence of high and low level social health and the distribution of social health in the population with regard to variables such

as age, sex, marital status and occupational status. The results showed that almost 40% of adults aged from 25 to 74 years old had high scores in three social health scales. But 60% of adults had not achieved a high score on any of the social health scales. Also, 10% of the people in three or more of the three social health scales allocated a high score to themselves. The data showed that the majority of adults in the United States have a medium to high level of social health. But a significant proportion of the population had a very low social health, which, in terms of social indicators, could be considered as socially unhealthy.

Idler (2014) conducted research entitled Religion as a social determinant of public health. He points out in this research that religious institutions and public health institutions are trying to improve the health of the community. He tries to connect these two social institutions for the first time. He states that while social researchers have studied factors such as education, income inequality and discrimination experience in social health, they are less aware of the great influence of religion on health. He attempts to demonstrate with interdisciplinary approach that religiousness has a great impact as a social factor on the health of individual; the effect that has so far being regarded as a negligible social factor in health.

Marks (2005) has conducted research on the impact of religion on health. In this work, he attempts to link three dimensions of religious experiences, including religious practices, spiritual beliefs, and faith with three dimensions of health, namely biological, psychological, and social, by a conceptual model of the research. He considers this model as a framework for studying findings in relation to religion and health and provides a wider survey in this regard.

Historically, the right to be healthy is one of the oldest rights that has been stated in the constitution of many countries of the world. Internationally, Article 25 of the Universal Declaration of Human Rights has resolutely stated that "everyone has the right to have adequate living standards in terms of health and welfare for himself and his family ...". In the introduction to the constitution of the World Health Organization, it has confirmed that health is one of the basic rights of every human being to enjoy the highest accessible standard of health (Park & Park, 1997: 26). The concept of social health is a concept that has been considered alongside physical and mental health aspects. Belloc and Breslow in 1972 first addressed the concept of social health. They synonymized the concept of social health with the "degree of society members' performance" and built the social health index. They tried to reach the level of activity and function of the individual through a variety of questions about physical, psychological and social health of the individual (Belloc and Breslow, 1971). This concept was raised a few years later by McDowell et al in 1978 and they argued that health is beyond the reporting of disease symptoms or disease amount, and future functional capabilities. They believed that individual welfare and comfort is a distinct thing in physical and mental health. Based on their perception, social health is, in fact, part of the health status pillar and can also be a function of it. Measuring social health content since the

beginning was measured by focusing on the "individual" and on interpersonal interactions (for example, meeting friends) and social participation (such as membership in groups), and in measuring it, the objective elements (for example, the number of friends) and the subjective (such as the quality of friendly relationships) were all considered in the definition.

Larson (1992) in his study equates social health and social healthy and points out that there is no conceptual difference between these two in the literature discussed. McDowell & Newell point out that social health and healthy are less familiar to us than physical or mental health. Social health refers to society as a whole and its factors, such as the distribution of wealth or the social health of individuals; they define social health in individuals as follows: "that dimension of health of individuals, that involves how to communicate with others, how to respond to other people and how the person interacts with the social institutions and customs of the community." Durkheim (1951) states that among the potential benefits of plural life, social solidarity and coherence, feeling of belonging and interdependence, feeling of plural awareness and shared destiny. Keyes (1998) states that these benefits of plural life, are fundamental and basic for the definition of social health and defines social health as a status of the quality and function of an individual in society. The social health field, from 1995 onwards, in addition to a general and public attitude on the quality of health among all people, in industrialized countries began a specific tendency in the two dimensions of mental health and social health.

Kingsley Davis in his book Human Sociology presents the positive functions of religion and considers religion as the cohesion factor in society. He categorizes the meta-experimental activities into three modes of subjective (calm), high goals (immortality) and creatures and great beings (God), by distinguishing between the holy and unholy issue., He believes that individuals make intangible phenomena in the form of rules that are necessary for social order. In fact, the realities of the meta-experimental for achieving social cohesion link the group's goals with one's actions. He also adds that individuals increase their affiliation to group goals through participation in religious ceremonies, in this way; the unity of the people of the community is strengthened together (Hamilton, 1998: 210). Researchers who study the relationship between religion and health may agree on a number of points. First, most studies have found a positive relationship between participation in religious affairs and health of individuals. Witter and colleagues (1985) conducted a meta-analysis of 28 studies and concluded that in most of these studies, religion was positively correlated with health. Recent research studies emphasize on these findings (Ellison and Levin, 1998). Secondly, other research concluded that there is a significant relationship between religion and health (Inglehart, 2010; Myers, 2000; Witter et al., 1985). Witter et al. (1985) have estimated that the net cause of religious participation in health is between 2% and 6%. Lim Putnam (2010) stated that compared to some other factors, religion has less effect on health and loneliness, but its effect is equal to or greater than the factors of

education, marital status, social activity, age, gender, and race. Ellison, Gay, and Glass (1989) also point out that religious participation has an equal or greater effect on income. Ferriss (2002) explains that the number attending religious ceremonies is most closely related to health and social health; although some studies have found that the internal or spiritual dimensions of religion are related to health (Ellison, 1991; Greeley and Hout, 2006, Krause 2003).

Despite this general consensus, some of issues should be further evaluated. Firstly, most evidence about the religiousness effect on health comes from cross-sectional studies. While these studies control the critical factors affecting health, some people may be questioned casually about the interrelationship between religion and health (Regnerus and Smith, 2005). A slight or unobservable difference between religiousness and non-religiousness could explain this relationship. Self-choice is another important issue: healthy people choose religion to raise their spiritual health. On the other hand, those who find happiness in religion are more likely to be more religious than others. This is the self-imposed obstacle between people who come to a religion and those who are religious.

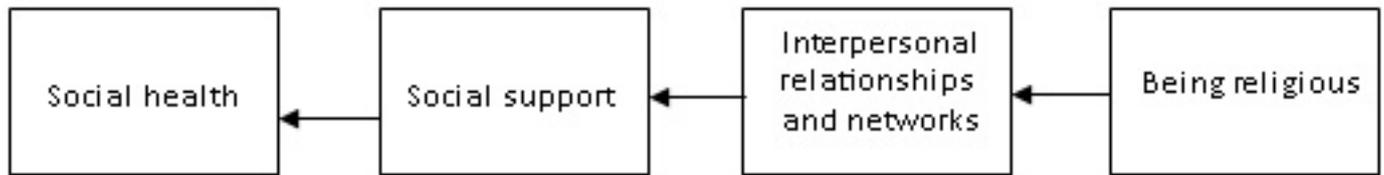
Although most religious studies and health studies use cross-sectional data, a number of longitudinal studies have also evaluated the causal effect of religiousness very carefully. Levin and Taylor (1998), using panel data collected from the National sample of African Americans, found that the general aspect and the private aspect of religiousness that had been measured at the first wave of their evaluation has significant relationship by health that had been evaluated in the second wave. Cross (2006) in a study on elderly Christians concluded that people who have been more skeptical about their religious beliefs show lower levels of health. Krueger et al. (2009), using a representative national sample, concluded that when people engage in religious activities, they experience higher levels of positive emotions. Many studies have been conducted to answer the question of why people who claim to be religious and regularly attend religious ceremonies are socially healthy and, ultimately, more satisfied with life. An important explanation for this question is that religion provides individuals with personal and social networks that result in social support for the individual. This is referring to classical sociologists such as Durkheim and Simmel, who considered the social dimension of religion as the foundation and essence of religion (Durkheim, 1951; Simmel 1997; also Cross, 2008). According to this discussion, religious participation increases social health because religious organizations create opportunities for social interaction between like-minded people and create friendships and social connections.

Although this interpretation is acceptable, many studies failed to find empirical evidence to support it. In the meantime, some studies found that the relationship between religious participation and health is positive and strong, and is shaped by social resources, such as the frequency

of social activities and the size of the friendship network. Most research focuses on social networks and forms of support without distinction between religious and secular social resources. This is based on the assumption that social resources that exist in religious organizations are no different from those found in secular societies. However, if social resources provided by religious organizations have qualities that do not provide secular social networks, then the measurements used on social resources by this research cannot show the impact of religious social networks. In fact, some studies show that religious social resources have distinct qualities. For example, Ellison and George (1994) state that those who go to church have a better sense of comfort with those who are of their religion, because they have similar beliefs about the ways and means of helping another. Psychology literature on social identity and social support provides a similar path to the debate; these studies show that social support is more intentional in thought, understanding and interpretation, when it comes from one person with whom he or she shares a sense of social identity, (Haslam et al., 2009: 11). In addition, Cross and Wulff (2005) suggested that church-centered friendship can create a sense of belonging and increase this mental and physical health. In another study, Cross (2008) found a positive relationship between social participation and friendship with a person in a church with social health.

Lim and Putnam (2010) state social resources are related to religious participation and social health. They state that religious social resources have an independent impact on public social resources and social networks of religious increase attendance at religious activities and events, and social health. Some other research, rather than focusing on public and participatory religious aspects, focus on the mental and private dimensions of religion as potential intermediaries, which relate to religious meaning and intention rather than religious affiliation. Some researchers argue that religious beliefs increase health by providing a conceptual framework for interpreting world events that lead to rise in cosmopolitan assurance, and a sense of meaning and purpose in life (in an inoperable world) (Emmons et al., 1998; Inglehart, 2010). Other research also suggest that strong religious beliefs and personal spiritual experiences can enhance health by enhancing self-esteem and self-efficacy (Ellison, 1991).

Other researches emphasize feelings of closeness and convergence with God instead of emphasizing personal spiritual experiences and religious practices in the influence of religion on health and satisfaction with life. For example, Greeley and Hut (2006) combine sensation of closeness with God with other criteria of religious sensation (such as the feeling of love for God and the feeling of deep harmony and inner peace) and concluded that there is a positive relationship between them and happiness. Pullner (1989) uses similar criteria to construct a mark that is positively correlated with health and then compares the relationship between holy relationship with God and social relationships with others and the impact of these relationships on health.

**Figure 1: Theoretical Research Model**

## Methodology

The methodology is survey and the data collection tool is a questionnaire. The statistical population of this study is women and girls aged between 19 and 39 years old in Kashan city. Based on the results of the census of the general population and housing population in 2011, their number is about 33,740. According to Cochran formula, 380 women were evaluated.

**Religiousness:** Lim and Putnam (2010) use several factor groups and dimension to measure religiousness amount. These dimensions include doing religious practices such as worshipping and reading the Holy book, the significance of self-declaration of religion in various dimensions of life, spiritual and religious experiences, such as the feeling of the presence and love of God throughout life and religious beliefs such as religious conservatism. (Like without lapse and error). The present study uses these dimensions to measure religiousness. According to the different dimensions of religious activities, the religiously significant self-importance of various aspects of spiritual, religious, and divine beliefs with 5, 4, 3, and 4 items are considered. Cronbach's Alpha followed by religious practices of 0.85, the significance of self-declaration of religion in various aspects of life equal to 0.86, spiritual and religious experiences equal to 0.85 and dimension of religious beliefs and divine values has been obtained equal to 0.86.

**Interpersonal relationships and networks:** In accordance with Garthoeffner, Henry & Robinson (1993), this variable in five dimensions of Self-disclosure (with four terms), the dimension of Genuineness (with four terms), Empathy dimension (with four terms), Comfort dimension (with six items) and communication dimension (with three items) was measured. Cronbach's alpha of dimension of Self-disclosure equal to 0.84, the Genuineness equal to 0.85, the dimension of Empathy equal to 0.85, the comfort dimension equal to 0.83 and the communication dimension is equal to 0.85.

**Social support:** Zimet, Dahlem, Zimet & Farley (1988) divide this variable into three dimensions: Family social support, social support for friends and significant other. They have used each of the 4 items to measure. The research, in accordance with them, considers the perceived social support in 3 dimensions and each dimension with 4 items. Cronbach's alpha for social support dimension of the family equal to 0.85, social support of friends equal to 0.84 and significant other dimension was obtained equal to 0.85.

**Social health:** These five dimensions were measured according to Keyes's scale (1998). Dimensions of social cohesion, social acceptance, social realization, social support, and social conjunction are each measured with 3 items. Cronbach's alpha of social cohesion dimension equal to 0.78, social acceptance equal to 0.77, social realization equal to 0.77, social support equal to 0.78, and social conjunction has been obtained equal to 0.75.

## Findings

Table 1 (next page) shows the average dimensions of each of the variables based on the scale of 0 to 100. As it is seen, the dimension of significance of the self-declaration of religion has the highest average (94.8) and dimension of the social conjunction has the lowest average (466.45).

As shown in Table 2, the three theoretical paths of the theoretical model of research are significant at the level of  $p < 0.001$ . Also, the interpersonal relationships, social support, and social health increase by 0.66%, 50.9%, and 0.254% unit, respectively when religion, interpersonal relationships, and social support increase by one unit.

Table 3 shows the standardized effects of the entire causal paths. The interpersonal network, social support and social health increase by 0.276, 0.261, and 0.96 standard deviation unit when religion is increased 1 standard deviation unit, respectively. When interpersonal relationships increase by 1 standard deviation unit, social support and social health increase by 0.494 and 0.350 standard deviation units, respectively. When social support increases by 1 unit of standard deviation, social health increases by 37.1% of standard deviation unit.

In Table 4, multiple square correlations have been calculated. The predictor of the variable between interpersonal relationships, that is, the religious variable, has explained about 6.7% of its variance; in other words, the variance of the variable error of interpersonal relationship is approximately equal to 92.35% of the variance of interpersonal relationships. Variable predictors of social support (religion and interpersonal relationships) explain the 167/89% of its variance, which is significant, the variance of social support error is 10.833% of the social support variance. Variable predictors of social health (i.e. religion, interpersonal relationships, and social support) explain the 79.13% of its variance; the variance of social health error is equal to 203.86% of the social health variance.

## Theoretical analysis of the research

In this section, the results of the fitting path analysis (Structural Modeling in Structural Equation Modeling), the theoretical model of the research, are evaluated by different



**Table 4: Multidimensional square correlations**

	Estimation
Interpersonal relationships	0.076
Social support	0.891
Social health	0.137

tests (using the Amos software). The value of CMIN / DF (Chi-square divided by the degrees of freedom) is equal to 1.553, because it is between 1 and 2, so we conclude that in terms of this indicator, the matching of experimental data with the theoretical model is confirmed in the sample (Cramines & Mclver, 1981); the value of p is also equal to 0.198; however, it can be concluded that the model has acceptable adaptation in terms of both the amount of Chi-square and its surface covered. On the other hand, Browne, M.W, Cudeck, and R (1993) point out that if the RMSEA value is equal to or less than 0.05, the model has a good fit; the RMSEA test value is equal to 0.073. In the case of CFI, it should be noted that one can vote for the conceptual model of research, which is higher than 0.9 (McDonald, R.P & Marsh, H.W, 1990); this value is 0.998 in this research. If the TLI index is higher than 0.9, then it can be concluded that the model is fit (Bentler, P.M & Bonnet, D.G., 1980); the test value is equal to 0.996. Joreskog & Sorbom (1984) state that the GFI value is equal to and less than 1, and if this value is greater than 0.90, the fit of the model is appropriate; the value of this index is equal to 0.994. The values which are close to one represent the suitability of the model in the AGFI index (Tanaka, J.S & Huba, G.J, 1985); this value in this research is equal to 0.980. Bentler and Bonnet (1980) also explain that if the NFI value is more than 90%, the model has a good fit; the value of this test is more than 0.90 and equal to 0.995. Bollen (1989) suggests that the suitability of IFI and RFI tests is close to 1; the values of these tests are 0.998 and 0.990, respectively, which indicates that the model is acceptable in these two tests. As you can see, all of these indicators have high fitting in the sample of this study and show that the theoretical model of research has a high degree of resilience among the statistical population of the research.

## Conclusion

This article seeks to evaluate the impact of religion on women's social health. Social health refers to the degree of participation and activity in affairs and relationships in society. One of the things about attending the community and participating in social networks and the formation of interpersonal relationships is to attend religious ceremonies; this is more important regarding women. Women in a traditional and people-centered society have fewer opportunities to participate in social activities. The purpose of this article was to evaluate the religiousness effect of women in their social health.

After evaluating different theories and designing the

theoretical model, statistical tests showed that the religion and religious beliefs of women have a significant effect on their social health. This result is also shaped by the effect of two other variables, means, interpersonal relationships and networks, and social support and the creation of a mechanism. For women who do not have many opportunities to create interpersonal relationships and social networking one of the best options for them is to attend religious ceremonies. Also, religiousness is also effective in creating health; more people associate with those who are equal in terms of intellectual and mental features. These findings are consistent with other studies, in particular by Lim and Putnam (2010).

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# Effect of Pelvic Movements using Birth Ball and Listening to Nature sounds and Honey Syrup Consumption on Labor Pain in Nulliparous Women: A Randomized Clinical Trial

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## Abstract

**Background & Aim:** Childbirth is a stressful event in women's lives. Therefore, the management of labour pain is an important goal of perinatal care. The aim of this study was to investigate the effect of pelvic special movements using a birth ball, listening to nature sounds and honey syrup consumption on labour pain in nulliparous women.

**Material and Methods:** In this randomized clinical trial, 66 nulliparous pregnant women admitted to a teaching hospital were recruited. Samples were divided randomly into intervention and control groups. The intervention group, on starting labour contractions, performed pelvic tilt movements such as tilting forward and backward, left and right using a birth ball, listened to nature sounds and consumed honey syrup. It was continued during the active phase from cervical dilation 4-5 cm to the transitional phase (cervical dilatation 8 cm). The control group received routine care. Pain was measured using the visual analog pain score scale every 30 minutes. Data was analyzed using statistical software SPSS v.16.

**Results:** The mean score of pain showed a significant difference between the groups at the end of the intervention ( $p < 0/001$ ).

**Conclusion:** The results of this study showed that pelvic movements using a birth ball could reduce labour pain in nulliparous women. Therefore, the use of this method during labour is suggested. Also, healthcare providers need to get familiar with this method in degree education and on the job training.

**Key words:** Honey syrup, pain management, active phase of labour, birth ball.

## Introduction

Pregnancy, childbirth and parenting are crucial events in women's life. They influence aspects of mothers' lives (1). In most cases, women have many concerns about pregnancy conditions and labour pain (2). Therefore, the management of labor for pregnant mothers has a special importance (3), and needs the recognition and offering (?) of methods that can manage different phases of labor to achieve the ultimate goals of midwifery and health promotion (4). Therefore, many non-pharmacological approaches are used to reduce pain in labor and childbirth (5, 6). Pharmaceutical methods of pain management including opioids or epidural anesthesia are used, and may produce negative consequences for the mother and child. In developed countries the use of non-pharmacological methods for pain relief have increased. Non-pharmacologic methods reduce pain, prevent suffering during labor and childbirth and facilitate childbirth. They include relaxation, acupuncture, hydrotherapy, cryotherapy, herbal medicine (7), heat therapy (8), music therapy (9), aromatherapy (10), electrical nerve stimulation (11, 12), massage therapy and reflexology (11, 13), birth ball (14, 15) and hypnosis (16, 17). Some of these methods are more acceptable to mothers including pelvis movements using birth ball (14, 15), nature sounds (18), music therapy (9), use of oral liquid (19) including honey and palm syrups (20), and heat therapy (8). According to the results of research conducted in 2003-2007, the use a combination of methods in labor and childbirth is suggested (21, 22). It is suggested that the use of certain methods in combination with other pain relief methods can help with managing pain in labor and childbirth (23). The results of a meta-analysis on the use of complementary medicine methods to reduce pain, and suffering in labor and childbirth indicated that during pain management, complementary medicine in combination

with other methods helped achieve greater effectiveness and increased mothers' compliance during labor and childbirth (7). On the other hand, a very limited combination of non-pharmacologic methods to manage pain in labor and childbirth is available. Also, most methods of complementary medicine on pain during the active phase of labor cannot be used in the first 30 minutes (10, 18, 22). Since a goal of healthcare is to reduce mothers' suffering during labor and childbirth (24), a combination of several methods to provide more favorable conditions for pregnant women is required. The effectiveness of pain relief after the first 30 minutes is related to creating psychological favorable conditions, reducing pain of labor, improving and creating a sense of confidence during labour. There are the guidelines recommended by the Ministry of Health and Medical Education (7) for the combination of interventions. Accordingly, a combination of low-cost and safe interventions such as listening to nature sounds, honey syrup for taking energy and exercise that helps improve childbirth was used in this study. Also, pelvic movements with or without the use of birth ball along with other methods was used to achieve maximum pain management. The aim of this study was to investigate the effect of pelvic special movements using a birth ball, listening to nature sounds and honey syrup consumption on labour pain in nulliparous women.

## Methods

After the approval of the Ethics Committee affiliated with Iran University of Medical Sciences, 66 pregnant women were selected using a convenient sampling method from a teaching hospital in an urban area of Iran. Given confidence interval 95%, power 80% and taking into account the possibility of a 10% dropout in samples, the sample size was determined at 33 patients in each group using the following sampling formula:

$$\frac{1}{1-f} \times \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 S^2}{(\mu_1 - \mu_2)^2}$$

$$\mu_1 - \mu_2 = d = 2$$

$$Z - \beta = 0.84$$

$$Z - \frac{\alpha}{2} = 1.96 \quad \longrightarrow \quad \% 95 \text{ Given the level of confidence}$$

$$N = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times S^2}{(\mu_1 - \mu_2)^2} \quad N = \frac{2(1.96 + 0.84)^2 \times (2.7)^2}{(2.0)^2} = 28.57 \approx 30$$

Inclusion criteria for sampling were age 35-20 years, gestational age 38-42 weeks, cephalic presentation, physical and mental health, no history of infertility, vaginal childbirth, cervix opening at a rate of 5 inches length for less than six hours, no history of allergy to honey, no fear of listening to nature sounds such as sea waves etc. Exclusion criteria included lack of desire to continue with the study, leaving the natural course of labor due to maternal factors, administration of oxytocin during labor, honey syrup consumption for less than 150 cc and performing the intervention for less than 30 minutes.

In this study, all women admitted to the labor and childbirth center were randomly assigned to intervention and control groups. The data collection tool consisted of questions about demographic factors (age, place of birth, occupation, education, abortion etc), registration controls in labor (during and between contractions of the uterus) and vaginal examinations (dilation, effacement ...) using the pain intensity score scale from 0-10 (0 = no pain, 3-1 = mild pain, 6-4 = moderate pain, 7-10 = severe pain). Vaginal examinations were carried out according to the protocols suggested by the Ministry of Health (8-25).

All participants were assessed in terms of the inclusion criteria on arrival. Also, the heartbeat of the fetus, severity of the mother's pain, contractions of uterus and pelvic examination by researchers were performed. The heartbeat of the fetus, intervals and duration of uterine contractions and pain were assessed and recorded every 30 minutes. The amount of dilation, effacement and fetal station after the vaginal examination according to the protocol of the Ministry of Health were recorded every 2 hours. All efforts to reach the dilatation of 8 inches were continued. The control group received only routine care throughout the study by the researcher. To prevent bias, a research assistant assessed and recorded pain. Also, to maintain ethical standards, the mental stress due to leaving the mother prior to the birth was reduced through provision of support. For the intervention group, the researcher had required knowledge and skills, provided necessary education to the women, helped with pelvic movements in terms of tilting and rotation of the front and back, left and right movements on birth ball. Also, 2.5 teaspoons of honey syrup and 150 cc water each 60-30 minutes were given to supply energy. Nature sounds were also listened to by the women. Nature sounds including sea waves, rain, soothing birds were presented through a headphone to prevent environmental sounds. The women could adjust the sounds based on their desire. The women in the control group received care in the same environment. Also, they were free to take water or other liquids if they were willing. Data was analyzed using descriptive and inferential statistics via the SPSS software v.16. The chi-square test, analysis of variance, Scheffe post hoc test, covariance analysis, nonparametric Kruskal-Wallis test and descriptive statistics were used for presenting findings.

## Results

The demographic descriptions of the women are presented in Table 1 (next page). The majority of the women in the intervention and control groups, were aged between 30-20 years old, had higher than high school education and 64% were housewives.

The severity of pain at the beginning of the study indicated that the two groups had a statistically significant difference in the mean score of pain ( $p = 0.001$ ). The pain intensity before and after the intervention was compared (Table 2). The severity of pain in the intervention group was less than the control group at the first 30 minutes to 120 minutes after the intervention. The analysis of variance showed that the intensity of pain was significantly different in intervention and control groups every 30 minutes. The pain severity in the control group had an increasing trend (Table 3). The mean of the pain intensity in the intervention group was  $7.61 \pm 1.17$  and in the control group was  $9 \pm 0.0$  (Table 4).

## Discussion

According to the recent policies of the Ministry of Health aimed at increasing the number of natural childbirths, this study aimed to determine the impact of pelvic movements using birth ball and nature sounds and the honey syrup on the severity of pain in nulliparous pregnant women. The use of special pelvic movements using birth ball and nature sounds and oral administration honey syrup reduces perception of labor pain in nulliparous women. According to the results of a study by Leung et al. (2012) on the effect of exercise using birth ball on labor pain on 203 nulliparous and multiparous women with gestational age 41-37 weeks in China, birth ball reduced labor pain, anxiety and promoted relaxation (10). The study Najmi (2015) to assess the effect of natural sounds on the first stage of labour pain and anxiety in nulliparous women revealed that 3.3% had mild pain, 12.2 moderate pain, and 2.62% severe pain. Statistically significant difference in pain between the groups was reported ( $p=0.01$ ), which was similar to the results the current study indicating the effect of nature sounds on labour pain.

In this study the collective effect of birth ball, nature sounds and honey syrup was assessed on labour pain. However, in another study by Taavoni et al. (2013), the effect of thermotherapy 60 minutes after the intervention was assessed. The study by Taavoni et al. (2015) assessed the effect of nature sounds in the active phase of labour. Converse to the present study, pain in the first 30 minutes after nature sounds was assessed, had statistically significant differences with the control group. Argvi et al. (2007) in Turkey investigated the effect of oral administration of liquid nutrients on the length of labor and pain in 110 nulliparous women with low-risk pregnancy. They showed that pain in the group receiving grape juice with the control group had no significant difference (20). Since the labor environment in terms of noises may have different effects on the process of managing labor pain, the same environment was used in one hospital for both groups.

## CONSORT 2010 FLOW DIAGRAM

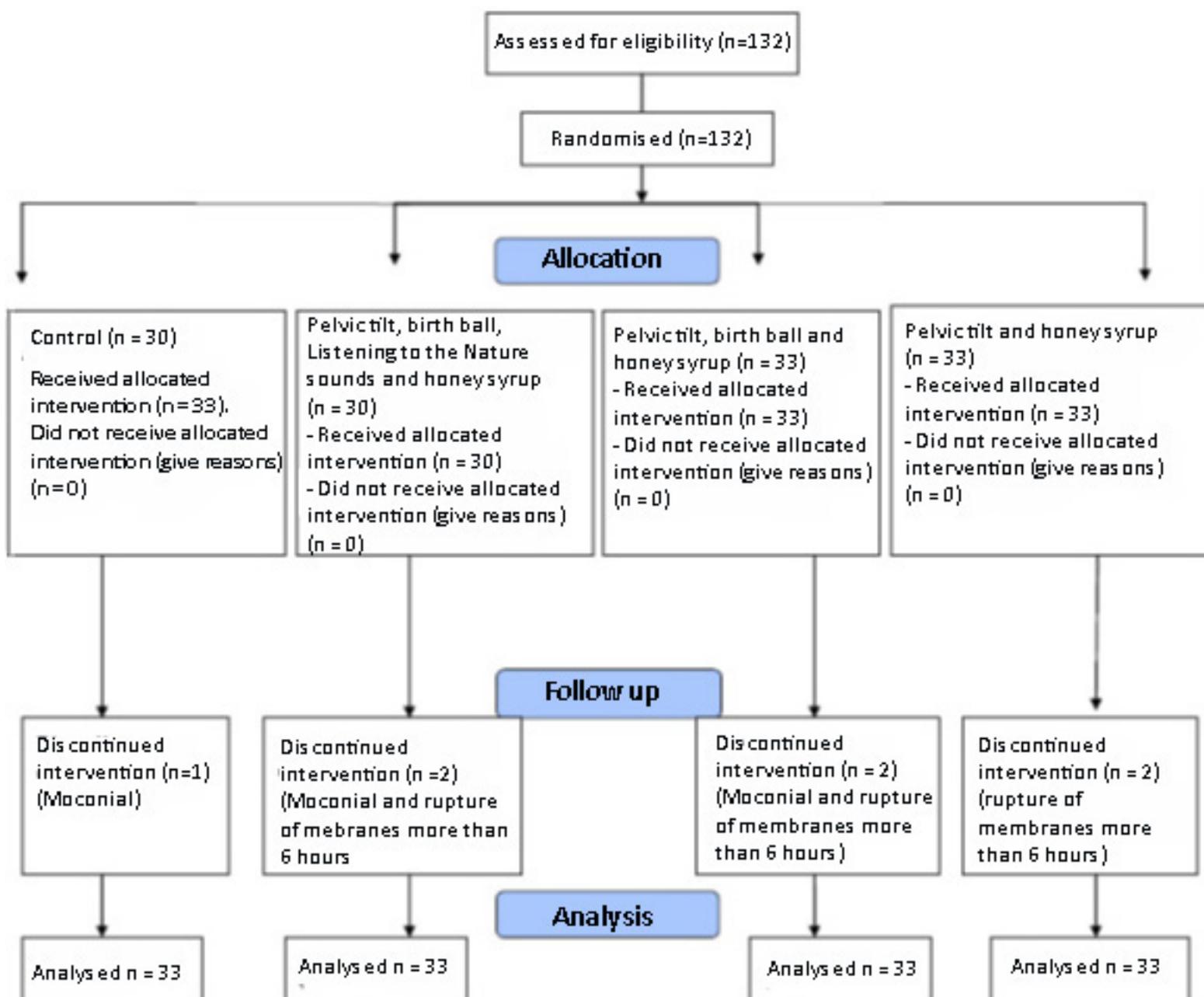


Table 1. The demographic characteristics of the women in the groups

Demographic characteristics	Control	Intervention
Age	20-30 years (51.5%)	20-30 years (33.3%)
Education level	Diploma (39.4%)	Diploma (51.5%)
Employment status	Housewife (72.7%)	Housewife (72.7%)
Pregnancy tendency	Agree (87.9%)	Agree (87.9%)
Gestational age	39.1±24.06	38.91±0.84
Abortion history	(75.8%) Absence	(66.7%) Absence

Table 2: The pain intensity in the groups

Group	After the intervention		Before the intervention	
	Control group	Intervention group	Control group	Intervention group
Pain intensity	Mean± Standard deviation	Mean± Standard deviation	Mean± Standard deviation	Mean ± Standard deviation
Mean± Standard deviation	9±0.0	7.61±1.17	7.76±0.75	7.91±0.94
The analysis of variance	$F = 44.243$ $P < 0.001$		$T = 0.720$ $df=64$ $P=0.474$	

Table 3. The comparison of changes in the pain intensity (every 30 minutes) in the groups

Group	Analysis of variance	Control groups	Intervention group
Pain intensity		Mean± Standard deviation	Mean ± Standard deviation
30 minutes	$P < 0.001$	7.85±0.75	6.03±1.01
60 minutes	$P < 0.001$	8/12 ± 0/69 8.12±0.69	5.55±0.9
90 minutes	$P < 0.001$	8.42±0.66	5.63±0.92
120 minutes	$P < 0.001$	8.68±0.47	6.15±1.28
150 minutes	$P < 0.001$	8.92±0.27	6.40±0.94
180 minutes	$P < 0.001$	9±0.0	7.05±1.27
210 minutes	$P < 0.001$	9±0.0	7.25±1.12

Table 4: The comparison of the pain severity in the groups before and after the intervention

Group	Control group	Intervention group
	Mean ± Standard deviation	Mean ± Standard deviation
Pain intensity changes	1.24±0.75	-0.30±0.92
Analysis of variance	$P < 0.001$	

## Conclusion

The results of this study showed that pelvic movements on a birth ball and nature sounds and honey syrup reduced labor pain in nulliparous women. Therefore, it is recommended to be used along with other complementary methods of pain relief in labor centers across the country. This study only assessed pain in the dilatation of 8-5 cm in the active phase of labor. Therefore, more studies on the effectiveness of these interventions in combination with other methods of labor pain reduction are needed.

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# Individualism And Mental Health (A study of people of Kohgiluyeh and Boyer-Ahmad province, Iran)

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## Abstract

**Introduction:** Mental health is one of the axes of health assessment of different communities and plays an important role in ensuring the dynamics and efficiency of each community. Mental health is the balanced and coherent behavior of the community, the recognition and acceptance of social reality and the ability to adapt to it, and the flourishing of intrinsic talents.

**Objective:** The goal of the researcher in this study was to examine the relationship between individualism and mental health among the people of Kohgiluyeh and Boyer-Ahmad province. This research was done in 2017.

**Method of research:** Survey method was used in this research. The questionnaire was applied as the method of data collection. On the basis of population; sample size was 616 people, who were selected by multi stage random sampling.

**Conclusion:** The result of the research showed that there is relationship between individualism and mental health, in other words, this relation is significant and negative, if the rate of individualism is more, the rate of mental health is less in Kohgiluyeh and Boyer-Ahmad province, Iran, and vice versa.

**Key words:** mental health, individualism, Kohgiluyeh, Boyer-Ahmad.

## Introduction

Mental health is one of the axes of health assessment of different communities and plays an important role in ensuring the dynamics and efficiency of each community. The World health Organization defines health as complete physical, mental and social well-being, and not just the absence of illness and disability. Mental health is the balanced and coherent behavior of the community, the recognition and acceptance of social reality and the ability to adapt to it, and the flourishing of intrinsic talents. Promoting mental health in society can improve the quality of life (1). Mental health is considered as one of the determinants of the general health of individuals, which means the sense of goodness and self-efficacy, self-reliance, competitive ability, interdependence, and self-actualization of potential intellectual, emotional and psychological well-being.... Mental health plays an important role in ensuring the dynamism and efficiency of each community. According to the World Health Organization (WHO), in the next two decades, the world will see major changes in the epidemiology of diseases and health needs of people, so that non-communicable diseases such as mental illness will quickly replace infectious and contagious diseases and are at the forefront of the causes of disability and early death. Currently, around 450 million people worldwide suffer from mental, neurotic and behavioral problems, and mental disorders account for more than 1% of deaths (2). As human thoughts influence behavior, they can be effective in mental health. A major challenge over the third world is the influx of foreign culture and appearance of alienation that has caused decline of authentic culture and identity. Today, the west's modernity influences all areas of third world countries, and has affected behaviors and tendencies of individuals; western modernity has changed

people's thinking and the ideas of the new generation and has caused the ideas of the new generation to be different from their forebears (3). In recent years, the ideas of modernity have penetrated the people of Kohgiluyeh and Boyer-Ahmad in different ways (especially through mass media) and have transformed the traditional and organic life of the people. The positive functions of modernity cannot be ignored, but its negative consequences have affected the general morale and public health and challenged people's lives.

Giddens considers modernity to be a way of life or a particular social organization that has evolved since the 18th century in Europe, and its influence gradually became global. (4) The effects of modernity have so happened in the recent decades that society has undergone major changes and it has had serious repercussions for some people. In turn, these changes and economic and social changes have led to significant changes among young people, insofar as they talk about the globalization of culture (5). One of the effects of modernity is the spread of individualism in society. What should be considered in the explanation and analysis of individualism is the consideration of its various dimensions. Positive individualism is considered one of the most important indicators of development and at the same time the development implications of "self-esteem", "self-development", "accountability", "Individual autonomy", etc., and negative individualism, is the way to comprehensive development (6). Negative individualism is selfishness and self-orientation, in which the individual sacrifices everything and, by giving their total focus to self-interest, seeks everything to gain personal advantage, which, according to Tocqueville's belief, "it dries the seed of each virtue" (7).

Negative individualism may cause a lot of damage. For example, in the family, it may weaken a family institution. Children place less importance on parents' views, new values are emerging, and leisurely forms of expression appear to be in conflict with family considerations in some cases (8). Thomas and Zananiki are among the people who have studied familial disorganization and they believe the cause of it, is individualistic attitudes against collectivism. They believe that the unstructured family should be seen in light of some of the new values of pleasure, new self-focused values, new types of individualism, and new forms of sexual attraction (9). Hoffstad believes that in collectivist cultures people feel deeply attached to their group and community. In these communities, group decisions are preferred to individual decisions, and individuals' behavior is checked against the rules, goals and values of the group. However, in some individualist cultures, personality and desires and emotions are more important (10).

Lensky is among those who saw the process of individualism and the emphasis on individual rights in the light of democratic world views. According to him, the process of political and educational institutions in the modern society has had a direct impact on the structure of the family. It believes, one of the important causes of the fall of traditional family authority can be related to the democratic worldviews of the new societies, which tend to emphasize

individual rights rather than group responsibilities. The process of democracy, as it transformed the traditional roles of political, economic, and educational institutions, also changed the role of the family. The last factor in this process is the emergence of more diverse options and choices now available to people. According to Jokar (1393), in a study entitled "Modernity, Lifestyle Change, and Reducing Population in Iran," believes that the arrival of modernity (the tendency towards secularism, modern rationalism, humanism, individualism, materialism, etc.) reduces the population. Belief, promotion of consumerism, increasing age of marriage and divorce, and general problems in Iran (12). Mahmoudi and Mombeyni (1392) in a study entitled "Investigating Some Factors Affecting Individualist Practices" believe that current individualism reduces public participation and disruptions in society and among the general public (13). Vosoughi and Mirzai (2008) in a research entitled "Individualism, Reflection on Dimensions and Indicators" has shown that individualism is synonymous with isolation, narcissism and selfishness, and its manifestation is found in selfish individualism, which is the basis of the disorder of social order and development (14). Accordingly, the goal of the researcher in this study is to examine this hypothesis; "There is a meaningful relationship between individualism and mental health among the people of Kohgiluyeh and Boyer-Ahmad province", in other words, the researcher wants to know is there any relationship between the tendency to individualism and mental health between the People in Kohgiluyeh and Boyer-Ahmad province or not?

## Material and Methods

According to the subject, the research method was survey. The multistage sampling method used in this study, was through the Cochran formula. 616 samples were selected according to the sampling structure. The tool of data collection in this research was questionnaire; the researcher used GHQ standardized questionnaire of 28 questions of Goldberg and Hiller. The reliability of the questionnaire was evaluated by three methods: Cronbach's alpha, Cronbach's, was, 70%, 90% and 93% respectively. The validity of this questionnaire was correlated with the total score and factor analysis. And the researcher used 9 self-made questionnaires of individualism for measuring the rate of individualism. The Validity of the variable of individualism was obtained through content method. The researcher, by referring to experts and other advisers, to examine the questions and the issues and eliminated the shortcomings, and the individualism's reliability was obtained through the use of Cronbach's alpha. The researcher first compiled 50 questionnaires distributed among the respondents, and then analyzed them by SPSS software. Cronbach's alpha was 70%, which indicates that the questionnaire has a high reliability.

**Data analysis:** According to the nature of the information, in the data analysis, descriptive statistics such as frequency, percent, and inferential statistics including Pearson correlation coefficient test, were used.

**Table 1: Cronbach's alpha for GHQ (Mental Health) and Individualism Questionnaires**

n	variables	Cronbach's alpha	The number of questions
1	GHQ Questionnaire	93%	28
2	Individualism Questionnaire	70%	9

## Findings

**Table 2: Descriptive statistics for individualism and mental health between the samples**

	N	Minimum	Maximum	Mean	Std. Deviation
Individualism	616	1.80	9.00	4.54	1.41
Mental health	616	9.25	27.75	18.76	3.26

On the basis of the above table, mean of the score for the individualism is 4.54, and Std. deviation is 1.41, while these values for mental health are 18.76 and 3.26.

**Table 3: The Pearson correlation test for relationship between mental health and individualism**

Test	N	Value	Sig.
Pearson correlation	616	-0/164	0.001

The above table shows that the significance level (sig.) in the test is 0,001, N is 616 and the intensity of this relationship is equal to -0/164. Considering that the significance level (sig.) is less than 0.05 ( $P < 0.05$ ), there is a significant relationship between tendency towards individualism and mental health. Therefore, the above hypothesis, "there is a significant relationship between the tendency toward individualism and the mental health of the people of the province". The relationship between tendency towards individualism and mental health is reversed: the greater the individualism among the people means the lower the mental health in Kohgiluyeh and Boyer-Ahmad province, Iran, and vice versa, the less individualism means the more mental health of the population, and on the basis of the intensity of the relationship between these two variables (-0/164) it can be said that intensity of this relationship is weak.

## Discussion and Conclusion

On the basis of the results of testing this hypothesis, it has been proved that there is an inverse and significant relation between individualism and mental health in Kohgiluyeh and Boyer-Ahmad province, Iran. In other words, the more individualism is among the people means the lower the mental health and vice versa, if the rate of individualism be less, the mental health of the people be more. The result of this test is consistent with Mahmoudi and Mamangi (2013), Sabouri and Moeed Far (2010) and Vosoughi and Mirzai (2008). Although positive individualism leads to development, which focuses on self-belief, self-actualization, self-confidence, individual autonomy, all of which have a positive value burden, but on the other hand, the development of individualism, the relationship between children and parents, and the reduction of the sense of belonging to Family norms are shaped in person. That is, the children will be inferior to the parents in different areas, such as leisure time, husband's choice, aspirations and personal and privacy goals, and the relationship and structure of the relationship between children and parents will be changed, thereby weakening these relationships and reducing the relationships of children. With parents and others, leads to individual isolation and ultimately hurts the mental health of the person.

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# Classification and assessment of medication errors in the emergency unit of a hospital in Iran by SHERPA

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## Abstract

**Background:** Human errors are of the most important causes of accidents in the medical profession and impose exorbitant costs on societies. Therefore, the present research was carried out in order to classify and assess medication errors in the emergency ward of a hospital in Iran by SHERPA.

**Method:** In a cross-sectional study, first the aims and procedures were instructed to physicians and then with their cooperation and presence in the unit and by viewing the activities, the errors were identified and analyzed using standard and authentic technique SHERPA.

**Results:** According to results, 60 errors were identified including 23 errors (38%) related to physicians' tasks and 37 errors (62%) related to nurses' tasks. In both groups, the functional errors had the highest percentage. In the nurse group, both functional errors (69%) and reviewing errors (40.5%) were higher than the doctors (respectively 49% and 17.3%). Moreover, in both groups, acceptable errors with modification were higher and unfavorable errors were secondary.

**Conclusion:** In both occupations, functional errors (with the most frequency) and reviewing errors should be considered as priorities for controlling such errors.

**Key words:** Emergency ward, SHERPA technique, health care staff

## Introduction

Since human resources are the most important asset of any system, omitting human roles, especially in complex and service systems such as medical jobs is not possible. On the other hand, according to the inherent fallibility of humans and also considering some limiting characteristics such as limited memory for recalling information, loss of judgment and decision-making in stressful and sensitive situations, it seems the only option available to prevent and reduce human errors is to minimize the vulnerability of the system and processes relative to human errors, and the implementation of appropriate methods for the detection and prediction of possible human errors and providing appropriate control methods. It should be said the best and most practical option, is the application of appropriate techniques to predict and identify the types of human errors, analyze their root causes and detect appropriate methods for controlling them (1,2).

In 2004, a cognitive taxonomy of medical errors was presented by Zhang and colleagues in which the classification scheme of medical errors in people and their interaction with technology, the use of cognitive theories of human errors and human performance were investigated in order to develop theoretical principles of classification and the building of classification structures, instruction in classification structures, localizing the classification by examples of medical errors, identifying cognitive mechanisms for each group of human errors in and their application in such problems (1).

Many of the major medical error studies have highlighted medication errors as a cause of adverse events suffered by patients (Bates et al., 1995; Leape et al., 1995; Brennan et al., 1991; Kohn et al., 1999). Ferner and Aronson (2000) defined a medication error as 'a failure in a drug treatment process that leads to, or has the potential to lead to, harm to the patient'.

Wolf (1993) pointed out that nurses make medication errors regardless of their specialty and that errors occurred on medical and surgical floors, postpartum units, emergency units and intensive care units.

There are several different methods of classifying medication errors; two are given here.

The first is based on psychological theory and divides errors into four types: knowledge-based errors, rule based errors, action-based errors and memory-based errors (3, 4). This classification gives insights into potential methods of prevention.

The second is the classification proposed by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP, Table 1), according to the intensity of the resulting harm (6, 7).

Inter-rater agreement when using the NCC MERP system has been determined in a study in which 550 users of the MEDMARX system were asked to categorize 27 medication

scenarios using the NCC MERP index and were randomly assigned to one of three tools (the index alone, a paper-based algorithm, or a computer-based algorithm) to assist in categorization. Of 119 positive responses, 101 completed surveys were returned. Overall inter-rater agreement for the participants, regardless of group assignment, was 0.61 and there was no difference among the kappa values of the three study groups and the tools used to aid in medication error classification. (8)

According to American Institute of Medicine (USAIM) in 2008, more than 225 million deaths occurred only due to medical errors. Of these, 7,000 deaths were caused by medicine prescription errors and over 106,000 of them were caused by side effects of medicines (9).

The results of consistent studies done by USAIM show that medication errors affect at least 1.5 million people yearly in which 400 thousand errors are preventable and 800 thousand are related to prescription drugs for long-term admission patients and 350 thousand are related to outpatient medicine-related needs (10).

Since study of medical errors, and in particular investigating medication errors by standard techniques, are very scarce and given the importance of identifying and preventing these errors on patients' health and reducing the length of treatment as well as reducing the cost of treatment, this study was done.

## Materials and Methods

This study was cross-sectional and was designed in order to identify, classify and evaluate medication errors and provide control approaches in the emergency unit. This study was performed using standard and authentic technique "SHERPA" (Systematic Human Error Reduction and Prediction Approach). One of the important reasons for choosing this method was that various studies were conducted worldwide using this method and its popularity is confirmed by researchers. We refer to a few examples: Lyons et al. (2004), mentioned this technique as one of the seven techniques used for assessing health workers. (Chance analysis, FMEA, HAZOP, SHERPA, EVENT TREE, FTA and effect diagram) (11)

In 2005, Novil using SHERPA technique, evaluated hospital errors. This study stated that the versatility of this method to all health processes is one of SHERPA's strengths (1). In 2005, Stanton and Harrison presented an article titled "Using Hierarchical Analysis Method for Medicine Management Errors". This study investigated patients' medication errors management in hospital. As medicine management is a complex and dangerous task and many frequent errors can occur in this process, SHERPA was used to identify them(5)

Bhuvanesh and colleagues (2008) used SHERPA for the process of medicines prescription in a cardiac telemetry unit and concluded that the method adopted is useful for hospital managers to plan and use the primary different technologies useful to improve the medicine prescription process (12).

## Implementation of SHERPA:

There are 8 steps for implementation of this method:

### 1. Hierarchical task analysis (HTA)

The process begins by analyzing administrative activities. In reality, analyzing begins by considering the ultimate goal and dividing it into smaller components. Then the final component which cannot be divided into smaller components is used by SHERPA Method.

### 2. Task Classification

Every stage of the work at the lowest level of analysis for error classification can be considered as follows:

- (A) Action: for example, opening a door
- (B) Recovery (error detection and diagnosis): receiving information through regulations, guidelines, circulars, monitor and....
- (C) Checking (review): leading and managing an investigation process
- (D) Selection: Choosing a different approach with respect to the higher official recommendation.
- (E) Information Exchange: Communicating with other sectors or groups

### 3. Human error identification:

At this stage, the types of human errors tabled in the SHERPA method (Appendix B) is used (13).

### 4. Consequence analysis

The investigation of each error on system is the next vital step and has applicable results for critical errors. It is necessary for analyst to provide a full description of the results, as well as error detection.

### 5. Error detection analysis (Recovery analysis)

At this point, the analyst should specify the possibility or impossibility of identified errors potential detection.

### 6. Analysis of the risk of error (Ordinal probability analysis)

At this stage, errors are usually classified into low, medium and high groups. If the error did not occur, it is classified in the low group. In the case it occurred sometimes in the past, it is classified in the medium group and if it has occurred repeatedly, places it in the high group.

### 7. Analysis of criticality or severity of error (Criticality analysis)

If the results were considered extreme or critical or led to unacceptable events, it must be considered. When an error is classified as a critical error it has led to a severe incident that results in damages for the structure of organization, industry, product and personnel (13). In medical jobs, risk level related to human errors can be easily determined regarding the symptoms, and consequences of each error in

terms of intensity, likelihood and frequency. Similar studies have been presented in the pattern of this work. In this study, in order to have a better and more comprehensive evaluation and analysis of errors and determination of their risk level for steps 6 and 7, the MIL-STD 88213 standard was used. In this standard, the error classification was put into four groups based on severity: Catastrophic (1), Critical (2), Borderline (3) Details (4). The errors were classified into four groups based on the possibility: Frequent (A) Likely (B), Occasionally (C) Very few (rare) (D) Unlikely (E). Finally with the combination of probability and severity of errors, the potential hazards are divided into four groups: unacceptable, unfavorable, acceptable with modification and acceptable without modification (safe) and necessary decisions are taken to prevent errors. (14).

### 8. Analysis modifying or providing control methods (Remedy analysis)

At this stage, error education approaches are presented. These approaches are in the form of changing suggestions in the work system which is provided to prevent errors. The guidelines are divided into 4 groups:

- (A) Equipment: Redesign or modifications in equipment
- (B) Education: Education or a change in education trend or process
- (C) Guidelines: Presenting new guidelines or revising them
- (D) Organization: Making changes in organization policy (13)

All identified errors and the obtained data are recorded in the techniques worksheet. For this purpose, first we formed a team of doctors and nurses working in this unit and then trained them regarding the objectives and methods. Then, with their cooperation and presence in the unit and viewing the activities and tasks and use of instructions and circulars, we identified and analyzed the errors. After that, we registered them in the relevant worksheet. Finally, in order to ensure the accuracy of data, we consulted with experts and other people.

## Results

A total of 60 errors relating to the tasks of doctors and nurses were identified. 38% (23 errors) were related to the task of doctors and 62% (37 errors) of errors related to nurses' duties. As can be seen nurses' errors rate were higher than doctors. In both groups, the functional errors were in first place and reviewing errors were in second place and other errors were in the following ranks. In the nurses' group, both functional errors (69%) and reviewing errors (40.5%) were more than doctors. (Respectively 49% and 17.3%) (Table 1)

**Table 1. The frequency, percentage and types of doctors and nurses' errors**

Error type Occupation	Action N (%)	Checking N (%)	Retrieval N (%)	Communication N (%)	Selection N (%)	Total N (%)
Physician	11 (48)	4 (17.4)	2 (8.6)	3 (13)	3 (13)	23 (38.4)
Nurse	24 (65)	5 (13.5)	2 (5.5)	3 (8)	3 (8)	37 (61.6)
Total	35 (58.4)	9 (15)	4 (6.6)	6 (10)	6 (10)	60 (100)

**Table 2: The frequency, percentage and types of doctors and nurses' error risk levels**

Error type Occupation	Unacceptable N (%)	Unfavorable N (%)	Acceptable, with modifications N (%)	Acceptable, without modifications N (%)	Total N (%)
Physician	0 (0%)	6 (26)	17 (74)	0 (0)	23 (38.4)
Nurse	0 (0%)	19 (51.3)	17 (46)	1 (2.7)	37 (61.6)
Total	0 (0%)	25 (41.7)	34 (56.7)	1 (1.6)	60 (100)

According to risk level of errors, in both groups, acceptable errors with modification took the first place and unfavorable errors took the second place but unacceptable errors were not seen. Acceptable errors with modification in doctors' group (74%) were more than nurses' group (60%) but unfavorable errors in nurses' group (3.51%) were more compared to doctors' (26%) (Table 2).

## Discussion

Due to the nature of the job and responsibilities of nurses and doctors, the results seem real because the nurse in charge of implementing medical directives (pharmaceuticals) and patient care, and the diversity and amount of activities and responsibilities of nurses are more than doctors.

According to investigations conducted, similar studies with this method or other standard methods have not been done to allow results to be compared with them.

In this study, the most important identified medication errors included errors in the name of medicine, errors in the choice of medicines, errors in medicine prescriptions, errors in medicine injection, error in reading the expiry date, medicine dose error, forgetting the medicine use or not timely use.

According to research done, medication errors are mostly due to excessive work pressure, interventions in nursing tasks, unfit shift patterns, poor communication, hard work at home, lack of information and skills in calculating the medicine dose, insufficient experience, aging, job complexity, hastiness and stress and unfolding emergency care (5 and 15).

Other causes of these errors can also be mentioned, such as resemblance in naming, similarity in medicine appearance, illegibility of medication orders, lack of control and information check list and information registration, lack of detailed records and history investigation, lack of information on medicine, wrong medicine calculation (9 and 16) etc.

In this regard, several studies have been done and we mention some of them:

Kelly Gonzales evaluated medicine prescriptions and management errors for aged people through systematic research and found that factors involved in occurrence of errors in the field are prescription of different doses of a medicine, prescription of wrong dose, non-prescription of standard dose, organ largeness (17).

Zane Robinson Wolf and colleagues, examined medicine prescriptions errors in nursing students in a descriptive study using the NCC MERP index (classification of medicines errors index) according to the prescriptions reports in MEDMARX system (Pharmacology database on patient safety program in the US). In this study, of 1305 students, about 3% had errors leading to patient injury. Most of these errors were errors of omission as a result of a mistake in students' performance (18).

Patricia van den Bemt et al, investigated medication errors in nursing homes that distributed medicines using an automated system by a retrospective observational study in New Zealand and found that most errors were related to wrong method of using medicines (inappropriate medicine crushing and lack of supervision on using medicines) and using medicine at the wrong time (19).

In a survey done on Canadian anesthesiologists, from 687 people who responded to questionnaires, 85 % reported at least one mistake during their practice but 98% of these cases did not have very serious consequences but 4 deaths were also reported. The most common error was the injection of muscle relaxants instead of conscious anesthesia drugs and the most common cause was syringe displacing (70.4%) and label false identification (% 46.8). 97.9% of professionals reported that they usually read the label but also label color is a very important factor (20).

In another study in Canada, anesthesia errors resulting in complaints cases recorded from 1998 to 2002 were investigated in which medication errors are put in the first place. The study, which looked at 232 cases of medication errors included: delay in medicine prescription, wrong prescription, wrong dose and mistake in patients' monitoring which accounted for 120 of the 232 cases (21).

In 2006, Kopp and colleagues, in a study based on direct observations, determined the incidence of medicine errors, and identified three reasons in this regard including 1- lack of medicine information, 2- having problem in memorization 3- medicine recognition (22).

## Conclusion

The important thing that should be mentioned is that control of functional and reviewing errors and errors with unfavorable risk review should be prioritized.

In this regard, the most important control measures based on the research are reported.

The authors gave numerous recommendations for actions to prevent errors, including the following:

- use of a pediatric formulary;
- use of a uniform system of weight-related dosing (e.g. mg / kg);
- inclusion in the prescription of the child 's weight, the dose, and the volume to be given;
- provision of checks and balances;
- avoidance of abbreviations;
- use of leading zeros to the left of the decimal point (eg 0.1 mg rather than .1 mg);
- avoidance of terminal zeros to the right of the decimal point (e.g. 5 mg rather than 5.0 mg);
- watching for look-alike and sound-alike medications and storing such medicines apart;
- knowing the antidote to each medication and ensuring that it is immediately available in the right dose;
- improved communication between physicians, pharmacists and nurses;
- Acknowledgement and reporting of medication errors in a blame-free environment. (23)

Also, USAIM has noted the following points for the removal and reduction of medication errors:

1. Food and Medicine Ministry cooperates with customers and manufacturers to redesign packaging and the contents to be easily readable.
2. Medications must be labeled according to standards.
3. The names of medicines that have a different use should not be similar.
4. The tablets need to be constructed in such a way that avoids confusion, especially those that have different purposes.
5. All doctors and pharmacists should become familiar with electronic prescribing systems that can reduce medication errors in writing and can automatically detect hidden medicine interactions.
6. Customers should have the necessary information for their medication (24).

In one study it was shown that computerized medical systems can reduce medication errors by 80% and, more importantly, reduce the damage to 55% of patients (25).

In another study it was shown that the standard loading system of medicine distribution system may reduce medication errors by 25% (26).

Points such as access to up to date resources like valid pharmacology books, adequate training of nurses, careful attention to the expiration date by customers and nurses, avoidance of no use of acronyms and paying attention to the effects of similar medicines, spelling out the exact name of medicines, careful attention to tags and labels, Medicine susceptibility- testing; -training - of - patients, - providing appropriate equipment and facilities for the preparation of medicines such as adequate lighting, and medicine delivery by a skilled technical director, management and supervision on the method of distribution of medicines, reduce medication errors (27).

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# Summary of studies on thyme in Iran: an integrated analysis study

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## Abstract

**Introduction:** Thymus Vulgaris is one of the Breed of mint herbs of lime trees that grows in the form of bushy trees on dry slopes and between the boulders of various Mediterranean regions, including in France, Portugal, Spain, Italy and Greece and the Middle East. Thyme is an herb that is used in the food industry, pharmaceutical, health and beauty industries. This plant is used in the treatment of cough, intestinal parasites, bacterial and fungal diseases, spasms, shortness of breath, bloating and indigestion, whooping cough, bronchitis, lung infections, colds, flu and muscle cramps. The goal of this study was to summarize published studies on the thyme.

**Methods:** After validation studies published in the thyme were selected by a team of experts. To find these studies, the various search engines and keywords of thyme and medication were used. The Period of time to search for the studies was from the beginning to the end of 2016. Data from the study in the form of recorded data was compiled. Information was collected and reported in the form of descriptive analysis.

**Results:** From 25 Verified study, 3 studies (12%) was conducted in clinical trial. In all cases the therapeutic efficacy of thyme was equal or better than synthetic drugs. 4 studies (16%), were related to animal studies. The majority of studies, 18 (72%) were laboratory studies. 17 studies of this type check the effects of antimicrobial, antibacterial and antifungal properties where in most cases, thyme or its combinations had acceptable effectiveness. Only one study was conducted to evaluate the anticancer effects of thyme.

**Conclusions:** The use of thyme in many cases had equal or better efficacy with fewer side effects than chemical drugs. It is necessary to conducted trials and studies in review of this plant.

**Key words:** Thyme, medicines, Iran, pluralization

## Introduction

*Thymus Vulgaris* is one of the breed of mint herbs of lime trees that grows in the form of bushy trees on dry and slopes and between the boulders of various Mediterranean regions, including in France, Portugal, Spain, Italy and Greece and the Middle East (1). In Iran, 14 different species of this genus are naturally occurring in different parts of the country, including 4 species of *Thyme carmanicus*, *Thyme Daenensis* (with two subspecies *Thyme daenensis* subsp. *Daenensis* and *Thyme daenensis* subsp. *Lancifolius*), *Thyme trautvetteri* and *Thyme Persicus* are Iran's exclusive genuses(2). Various species of it are found in the mountainous regions of Iran, especially in the mountains of Euclid city, where it is called *Zataria multiflora*.) Avishan Shirazi (3). In recent years, the use of herbal medicines for medical treatment has been increasing due to low side effects, or no side effects (4).

Among these plants, thyme is widely used in the treatment of bacterial, fungal and parasitic diseases. It is both fresh and dry as an anti-worm, anti-contraction, bronchodilator, stomach acid and digestive enhancer, as well as in the treatment of rheumatic pains, insect bites, wound disinfection, and skin diseases. Used (5). Antibacterial, antifungal and anti-corrosive properties are due to the presence of phenolic substances such as thymol and carvacrol, which are the main components of essential oil of thyme. Thymol has antioxidant effects and inhibits the production of superoxide anions in the xanthine-xanthine oxidase system (4). This plant has high antioxidant properties. What has been considered by researchers over the last two decades is its anti-cancer and anti-carcinogenic properties. The branches of this plant contain essential oils, tannins, bitter basic substances, saponins and infectious agents. Thyme essential oil is one of the ten essential oils that has anti-bacterial and anti-fungal properties, antioxidants, natural food preservatives, and delayed mammalian aging, and has a special place in global trade (6). Akbarinia and colleagues (7) identified 24 compounds in the *Thymus vulgaris*, which included thymol, parasmene, gammatripinen, carvacrol methyl ether, cineol, boraneol, and carvacrol. Brazandeh et al. (8) reported 27 compounds in thyme oil, that five of its major components were thymol, paracymene, gamma-tropinone, carvacrol and beta-caryophylline.

Thyme oil has properties such as antispasmodic, anti flatulence, antifungal, disinfectant, anti-corrosive, anti-rheumatism and sputum production (1). Its liquid extract is used in anti-pertussis preparations and as a conditioning agent (9). According to the Congress of the German Drug Commission, this plant has a positive therapeutic status, and it is ranked first in a single copy by the European Commission of Medicinal Plants Commission and the World Health Organization (WHO) Commission. Considering the economic importance of *Thymus vulgaris* plants, its proper recognition and determination of phytochemical properties and their applications is important in pharmaceutical, industrial and horticultural considerations (10). Therefore, this study was conducted to summarize the published studies on thyme and its drug use in various fields.

## Materials and Methods

This study was a meta-analysis study in which articles were searched through the Google Scholar database, the Scientific Information Database (SID), and the Scientific Information Database (Civilica) with the keywords "Thyme "and" medicinal "were obtained. The criteria for entry of articles were the relevance of the subject matter to the thesis, the validity or indexation of the publication in acceptable indexes, the study was done in Iran, the article has scientific writing conditions and is in Persian. All articles in these resources were considered from the beginning until the end of the first half of 2016. Articles that had the above input criteria were reviewed and were originally numbered 45 articles. The findings from these databanks were compared with each other, and repeated cases, as well as articles that, according to experts, did not qualify and did not qualify, were excluded. Finally, after reviewing the titles and studying the abstracts of the articles, 25 related articles were selected for final examination. Structure, Properties, Uses and Effects of thyme were classified into three categories of human intervention, animal intervention and laboratory studies. The collected data were analyzed using descriptive and analytic methods using SPSS software. The specific statistical methods related to Integrated analysis (21 and 20) were used for data analysis.

The use of thyme in the treatment of indigestion, digestive diseases, acute and dry cough, pain and inflammation and relaxation, has had equal or better efficacy with less complications than chemical (non-herbal) drugs. Antimicrobial, antimicrobial and anti-fungal effects include those related to: *Giardia Staphylococcus aureus* cyst, *Streptococcus mutans*, *Listeria* and *E coli*, *Enterococcus faecalis* *Candida albicans*, and *Aflatoxin*. The effects of its anti-cancer cells have been positive only in the laboratory studies. It is suggested that more trials be conducted on the therapeutic topics discussed.

Of the 25 approved studies, 3 (12%) studies were performed as a clinical trial. The subject of treatment of these trials included functional dyspepsia, digestive diseases, dry and acute cough. In all cases, the therapeutic efficacy of thyme was better or equal to chemical drugs. Four studies (16%) were from animal studies. They included two studies of anti-inflammatory, anti-inflammatory and anti-anxiety effects of thyme, a study on gastric ulcer induced in rats and a study on blood factors and hormones. The majority of the articles studied were 18 cases (72%) in laboratory studies. 17 studies of them were on antimicrobial and antifungal effects, including *Giardia* cysts, *Staphylococcus aureus*, *Streptococcus mutans*, *Listeria* and *E coli*, *Enterococcus faecalis* and *Candida albicans* have examined aflatoxin, and which in most cases had thymic acid or its compounds had an acceptable efficacy. In these studies, sodium chloride and chlorhexidine hypochlorite controllers were compared with 0.2% chlorhexidine, 100 mg / ml *Zataria* (Shirazi) *multiflora* or 0.1% chlorhexidine and 50 mg / ml peppermint essential oil. The diameter of non-growth halo in the Thyroid groups was significantly higher than other groups. Only one study of this type examined the anti-

cancer effects of thyme. In all of these studies, the positive results of the use of thyme in comparison with the used drugs were less complicated.

## Discussion

Considering the economic importance of *Thymus vulgaris* plants, its proper recognition and determination of phytochemical properties and their applications in terms of medicine, industry and gardening is important. In this study, the structure, properties, use and effects of thyme were evaluated in three groups of human intervention, animal intervention and laboratory studies.

### Human intervention.

Three studies were found as a clinical trial. Studies have shown that thymic spray drooping, soup spray, thyme mixing, and the combination of dopaminergic rhenitidine and clopramide have reduced the symptoms of 75 percent or more in patients. The final result was that medications containing thyme oil were better than the other medications in the treatment of pain. It was found that the most effective drug is 2% Thyme essential oil. The findings are in keeping with the study of Mohammad Ali Zadeh and his colleagues in Hamadan (11). Hydro-alcoholic extract of garden leaves and flower buds of thyme can increase the cytotoxicity of taxol. Therefore, it can be effective in the treatment of breast cancer and may cause the death of cells by inducing apoptosis. The findings are consistent with the study by Hamta et al., who examined the cytotoxic effects of garden thymus on the breast cancer cell line (6). Comparison of the therapeutic effect of thyme and dextromethorphan essential oil in treating patients with acute and severe cough showed that thyme essential oil in acute cough inhibition has an acceptable therapeutic effect similar to dextromethorphan. Combined syrup of ivy and thyme leaf; used in the treatment of acute bronchitis, showed the mean cough was reduced in 7-9 days after treatment with this compound compared with cough reduction in placebo treatment. This difference was statistically significant and showed the effect of thyme against placebo. The study by Ranjbar et al., also confirmed these results (12). The effect of this medicinal plant on the treatment of gastrointestinal disorders, such as irritable bowel syndrome, and the relief of gastrointestinal symptoms such as abdominal pain, bloating, heartburn, and changes in bowel habits has been shown. Microscopic, macroscopic and biochemical studies showed that Thyme had a good effect on the improvement of colitis in mice. Thyme can even have an effect equivalent to prednisolone versus acetic acid colitis. In a study on the effect of Shariatian thyme on gastrointestinal symptoms of nurses in intensive care units, it was shown that there was a decrease in symptoms score in the Shirazi multiflora group, which was significantly different, so that *Zataria multiflora* could reduce gastrointestinal symptoms (13).

Investigation of Thyroid aerial parts on mice showed that the thyme alcoholic extract at a dose of 800 mg / kg had anti-inflammatory effects. The antinociceptive effects of the thyme juice extract are probably due to the combination of para-cayman, beta-caryophylline, carvacrol and especially thymol (14). In the study of Mohammad Amini et al., who studied the effect of medicinal plants of turmeric, *Thymus*

and Cinnamon on ascites related parameters in broiler chicks of Arian strain, the results showed that medicinal plants had an effect on feed intake, conversion ratio, mean body weight and they did not have a lasting percentage. On the other hand, medicinal plants have a significant effect on the percentage of hematocrit, T4 hormone, T3 ratio to T4 and RV / T hormone. So, the use of medicinal plants tested improved blood parameters such as hematocrit, thyroid hormone levels and ascites heart rate (15). In the study of Narkai et al., which investigated the effect of diet containing the thyme leaf on the anxiety behavior in rats, the findings showed that a diet containing 10% of Shirazi plumage, the duration and number of animals present in the open arms of the Maze Ratio Increased significantly in the control group and cortisol hormone decreased compared to control group (16). Evaluation of the effect of hydroalcoholic extract of thyme on prevention of ethanol-induced stomach ulcer in rats showed decreasing of Index and increasing the percentage of wound inhibition and protective effect of plant extract in dose-dependent groups. (17).

### Laboratory intervention.

Investigating the efficacy of *Thymus vulgaris* on *Giardia* cyst in vitro compared to metronidazole showed that this plant has the highest lethal effect. Therefore, Zyman essential oil can be used as a suitable substitute for metronidazole, which should be designed for proper clinical trials to prove this. Findings of the study by Fresheng and colleagues also confirmed this (4). In the essence of distillation with water and steam, 44 and 57 compounds were identified, respectively. The results showed significant antimicrobial activity of these essential oils and fractions against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and Methicillin Resistant *Staphylococcus aureus* strains. The study of anti-bacterial and antifungal properties of essential oils of three species of thyme and two coccata ecotypes and Bakhtiari *Saviblia* species showed that the diameter of the growth halo of Bakhtiari Savory essential oil on the bacteria and fungi tested was significantly lower than those of other herbs. Be Thyme essential oil, *Zataria thyme* and *Mazandaran multiflorum* have the most effects on inhibiting the growth of bacteria and fungi, depending on the essence and type of bacteria or fungi, the severity of the effects is different. The essential oil of *Mazandaran* and *Kakotti Shirazi* cacti plants showed the least effect on the different species of bacteria and fungi tested in comparison with other essential oils. Evaluation of antioxidant properties, color and antibacterial effects of Chitosan oral film containing *Zataria multiflora* essential oil against *Listeria monocytogenes* showed that the film containing antimicrobial agents is an active type of packaging that is used to control microbial contamination in foodstuffs. Essential oils also significantly increase the anti-listeria properties of chitosan films, and the active film of chitosan can be prepared using the essential oil of *Zataria multiflora*. The addition of essential oils improved the functional and anti-bacterial properties of the film. The comparison of iron chelating properties, radicalization and anti-thyrosinase of *Thymus vulgaris* essential oil with commercial *Thymus* and *Thymol* showed that the nutritional

value of these plants was to prevent the formation of toxic reactive products, and Thymus can act as a good antioxidant. The study of the biological properties of Thyme essential oil shows that they have good potential for its application in the food and medicine industry (3, 18, 19 and 20). In the real study that evaluated antifungal activity of thyme, parsley, cumin and cumin essential oils on *Candida albicans* compared to fluconazole, it was shown that the essential oils of thyme, parsley, cumin and cumin Antifungal works against the standard strain of *Candida albicans*. As a result, the plant essential oils after completing studies can be suitable alternatives for chemical drugs for the treatment of candidal infections, especially mucosal candidiasis (21). Evaluation of antioxidant properties of hydroalcoholic extract of Shiitami thyme and their antimicrobial effect on *Staphylococcus aureus* in hamburger showed the effect of different concentrations of extract on *Staphylococcus aureus* growth during certain storage period. The extract of Shiraz's vetiver, in glacial conditions, inhibited the growth of *Staphylococcus aureus* bacteria in hamburger. Peppermint extract has antibacterial effect and can be recommended as an antibacterial preservative in burgers and other meat products (22). Analysis of antibacterial properties of chlorhexidine essential oil of thyme and mouth on streptococcus mutans elastic orthodontic rings in external conditions showed a statistically significant difference between the mean number of live bacteria isolated from contaminated rings before and after disinfection with thyme solution and Chlorhexidine 0.2 is present. This decline was not significant for distilled water. There was no statistically significant difference between the two mouthwashes of thyme and chlorhexidine in microbial plaque control. Antibacterial properties of zein film containing essential oil of Shirazi thyme and Monolourin in comparison with *Listeria monocytogenes* and *E-coli* in vitro showed that zein films containing essential oil and monolourin significantly increase the antibacterial activity compared to the control group. All films, except the blank film, showed anti-Bacterium effects against *Listeria monocytogenes*, while only films containing essential oil showed antibacterial effects against *E. coli*. In terms of effectiveness, the zein film containing 3% essential oil had the best antibacterial effect against both bacteria. Also, in all of the films studied, there was no bacterial colony in the film and agar contact area. The antibacterial effect of food coating, which included the combination of Baxi-methyl cellulose containing essential oil of Shirazi thyme and grape seed extract, showed that the coating containing essential oil of Shirjani and grape seed extract properly reduced the growth of microorganisms causing corruption and also increased durability. Antimicrobial and physical activity of oral film based on chickpea protein isolate containing Thyme essential oil by response surface method showed that chickpea protein has the ability to form a film. Also, optimization of the final formulation showed that for maximum antimicrobial activity of the oral film, minimum penetration of water vapor and maximum solubility should be used from 4 grams of chickpea protein, 44.4% glycerol and 1% essential oil. The use of different levels of thyme extract or nitrate did not affect the level

of glucose, cholesterol and triglyceride and also the level of aspartate aminotransferase enzymes in broiler chicks. Nitrate consumption significantly increased HDL levels compared to control treatment. Consumption is also used in independent comparisons

## Conclusion

The use of thyme in the treatment of indigestion, digestive diseases, acute and dry cough, pain and inflammation and relaxation, has had equal or better efficacy with less complications than chemical drugs. Antimicrobial, antimicrobial and anti-fungal effects include effects on *Giardia Staphylococcus aureus* cyst, *Streptococcus mutans*, *Listeria* and *E coli*, *Enterococcus faecalis* *Candida albicans*, and Aflatoxin. The effects of its anti-cancer cells have been positive only in the laboratory study. It is suggested that more trials be conducted on the therapeutic topics discussed.

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# Designing a Laser-based System for Locating Kidney Stones in Surgeries through Percutaneous Nephrolithotomy (PCNL)

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## Abstract

**Background:** The number of kidney stone surgeries is increasing worldwide. One of the most effective methods of removing kidney stones is percutaneous nephrolithotomy (PCNL) surgery. The PCNL surgery is a minimally-invasive procedure for extracting kidney stones through a small puncture made on the skin. This technique is most suitable for removing stones that are present near the pelvic region. Every standard PCNL operation requires 60 to 70 seconds of fluoroscopy imaging during which both the surgeon and the patient are exposed to X-ray radiation. This amount of radiation can be dangerous as surgeons may have several surgeries per week.

**Objective:** To design and use a laser-based device along with fluoroscopy imaging for locating a desired target, resulting in less fluoroscopy exposure time, in comparison to the conventional method.

**Methods:** A piece of lead wire is used as the target. The laser-based device is placed under the surgical bed. Steel was used as the major material for different parts of this device. Two linear lasers are used to point at the target. This device uses two step motors to aim the lasers towards the target.

**Results:** A small piece of lead was used as the target. Using the proposed method, 10 experiments were conducted. The mean  $\pm$ SD for radiation exposure time of the fluoroscopy device in 10 experiments was  $2.4 \pm 0.49$  (range 1.8 - 3) seconds and the mean  $\pm$ SD of the total error in locating the target was  $13.2 \pm 4$  (range 7.8 - 22) mm.

**Conclusion:** The device was able to locate the target using fluoroscopy imaging. By building a more accurate structure and using step motors with more resolution, better results can be achieved. This approach reduces the radiation exposure time in PCNL surgery.

**Key words:** Kidney stone, Fluoroscopy device, Laser, Locate

## Introduction

Kidney stone is a solid and crystalline material which is usually formed inside the renal pelvis due to the accumulation of a high amount of specific minerals. These stones are sometimes called renal calculi (1). About 80 percent of these stones are made of oxalate and calcium phosphate (2). The diameter of renal stones is usually less than one centimeter (3). In several countries, the average global prevalence was reported as 3.25% in the 1980s and 5.64% in the 1990s (4). In research done in 2005, it was concluded that in the United States of America, about 5 percent of women and 12 percent of men will suffer from kidney stone disease at some time in their life (2).

Four common treatments that are used on kidney stones are as follows.

- When the stone is very large or the anatomy of the patient's body is so complicated or unusual, open surgery will be recommended. Less than 1 percent of patients will need to use this method in which the skin is split to the extent that the surgeon can access the entire kidney tissue (5).
- If the stone is in the urethral duct, ureteroscopy will be used for accessing the ureter. In this method, a ureteroscope is passed through the bladder and then reaches the ureter. The surgeon may use laser energy or other tools for fragmenting and then removing the kidney stones (6).
- In another method, the physician or surgeon breaks the stone using high frequency ultrasound waves. These shock waves break the stones to smaller pieces so that they can pass through the urinary tract (7).
- When the kidney stone is in the renal pelvis, a technique called Percutaneous NephroLithotomy (PCNL) is preferred (8). The first PCNL operation was done in 1976 (9). This technique is most suitable for removing stones that are present near the pelvic region (8). Also, it is a minimally-invasive procedure for extracting kidney stones through a small puncture made on the skin. In the first step, by using fluoroscopy imaging, the location of the stone will be mapped. Then the surgeon inserts the tip of the needle into the patient's body in such a way that the needle direction, extends beyond the renal pelvis. In order to find out the distance between the needle tip and the renal pelvis, the surgeon readjusts the angle of the fluoroscopy C-arm in a different angle and places the needle into the drainage system of the kidney close to the stone being treated. During the whole procedure fluoroscopy imaging will be used. If the surgeon fails to access the renal pelvis, the whole procedure will be repeated (10).

In comparison to open surgery, PCNL surgery is a more effective procedure for extracting relatively large kidney stones (9). After the operation, the patient may only need one or two days of rest (11).

A standard PCNL operation requires about 60 to 70 seconds of fluoroscopy imaging during which both the surgeon and the patient are exposed to radiation (12). In a recent study, while PCNL surgery was effective for extracting relatively large stones, yet in 17% of patients,

some stones were not extracted during the first operation (13). In this case, another surgery was carried out. In each surgery, fluoroscopy imaging will be used, resulting in more radiation exposure (13). In another research conducted on 178 patients who had kidney stone, only in 60% of the patients, kidney stone was completely removed (14). But, others had to do another PCNL surgery which led to more radiation exposure time (14).

In order to minimize the exposure time in PCNL surgery, several methods have been suggested as follows.

- In 2012, Rassweiler et al, by application of augmented reality technique for kidney stone surgery, could observe anatomical details such as the location of adjacent bones and kidney arteries. In this procedure, iPad is used as a camera which takes images from the patient's skin; after which they are compressed and sent to a server placed in the control room via Wi-Fi. The server applies a pre-written algorithm on these images so that they are registered with previously taken CT images. Afterwards the created images are sent back to the iPad in real time. These images allow the surgeon to simultaneously observe the kidney and surrounding tissues during the surgery (15).
- In 2006, in another research done by Kagadis et al, combining MRI and CT imaging leads to more accurate results in locating the renal pelvis, however, in comparison to PCNL surgery, this technique does not decrease the absorbed dose of radiation (16).

While these two techniques provide better details about the surrounding tissues of the kidney, they are not preferred over the conventional PCNL surgery as they require CT imaging prior to the surgery and increase the cost of the operation as well as the radiation dose absorbed by patients.

The rate of received dosage by personnel while working with fluoroscopy device, depends on several factors such as the surgeon's talent and the X-ray exposure time. With the increasing demand for PCNL surgery, reducing the exposure time in PCNL surgery becomes more essential (17).

Our goal in this paper is to find an approach that can decrease the radiation exposure time in conventional PCNL surgery, with enough accuracy in locating the renal pelvis. In the proposed method, with the help of a low cost laser-based device and the fluoroscopy, we are able to locate a desired target.

## Materials and Methods

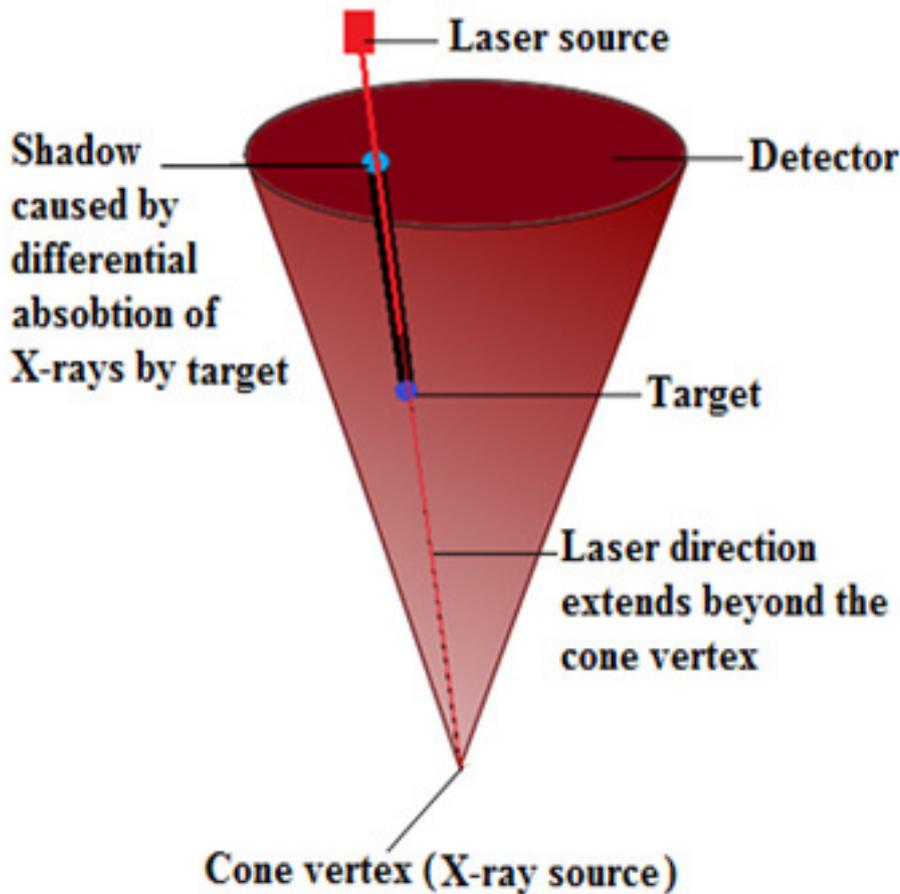
The aim of the conventional PCNL surgery is to access some part of the renal pelvis. For this purpose, a device was designed in such a way that it is able to show the best location and angle for insertion of a surgical needle into the patient's body, so that the renal pelvis could be reached by inserting the needle in the specified direction. In this paper we propose a method for reducing the fluoroscopy radiation exposure time, in PCNL surgery.

The fluoroscopy lamp and the detector are placed below and above the surgical bed, respectively. The X-ray beams are emitted from anode and, until they reach the detector, they travel on a cone-shaped path in the space between the lamp and the detector. The vertex of the aforementioned cone is under the surgical bed and inside the fluoroscopy lamp and the base of the cone is the detector.

Here, a small piece of lead, which was placed on the surgical bed, was used as target. When the X-ray beams collided with the target, they cast a shadow on the detector.

If we radiate a laser beam along the shadow of the target, so that the length of the laser beam extended beyond the vertex of the cone, then the length of the beam will also extend through the target (Figure 1). So, if we move a surgical needle in the direction of the laser beam and toward the target, the tip of the needle eventually reaches the target.

**Figure 1: Radiating a laser along the shadow of the kidney stone**



The coordinates of the shadow, relative to the center of the detector, could be obtained by means of two rulers with lead grading that are perpendicular to each other, and are attached below the surface of the detector, so that the centers of the rulers are located at the center of the detector (Figure 2 - opposite page).

Using the fluoroscopic image, we could obtain Cartesian coordinates of the shadow of the target relative to the center of the image (Figure 3).

When the coordinates of the target are specified, we can align the laser beam along the shadow of the target. For this purpose, we can align the interface of two laser planes, which is a line, with the shadow of the target, to locate the target through the use of the laser beam.

Using two step motors as follows, we could point the luminous planes of the lasers toward the target. Each laser was mounted on a C-shaped arm. The other end of each arm was attached to a step motor that was in turn mounted to a supporting box under the bed (Figure 4).

The rotation axes of the stepper motors are perpendicular to each other (Figure 5). The fluoroscopy lamp was placed in the box in such a way that the rotation axes of the stepper motors passed through the vertex of the cone. Also, the interface between these two luminous planes, which is a line in space, always crossed the vertex of the cone. Now, according to the Cartesian coordinates of the target, by rotating each of the arms with the help of the stepper motor, we could point at the target. Figure 5 illustrates how one of the lasers is mounted on its corresponding arm (Figure 5).

Figure 2. Connecting the Rulers to the Detector

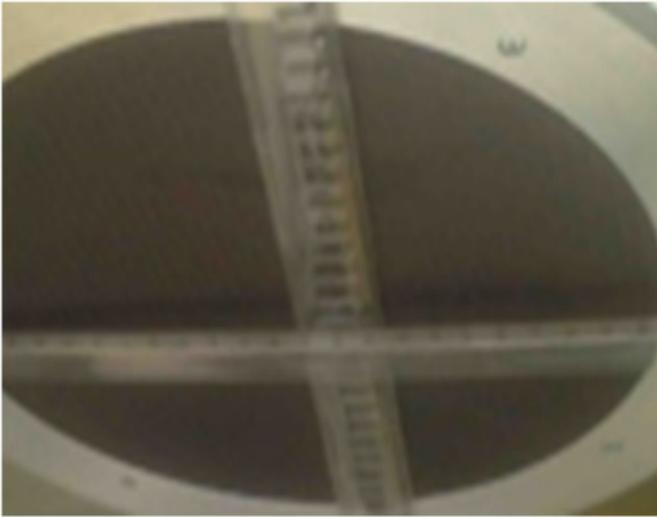


Figure 3. Specification of the lead wire's coordinates

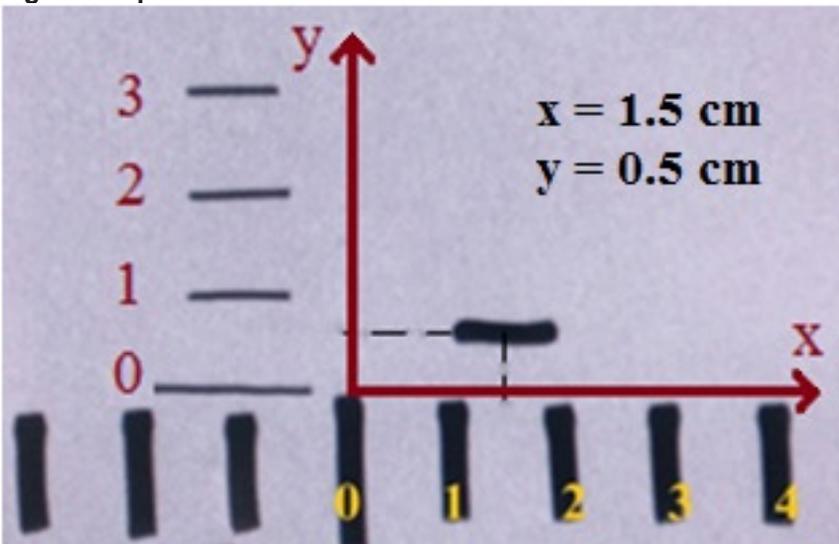
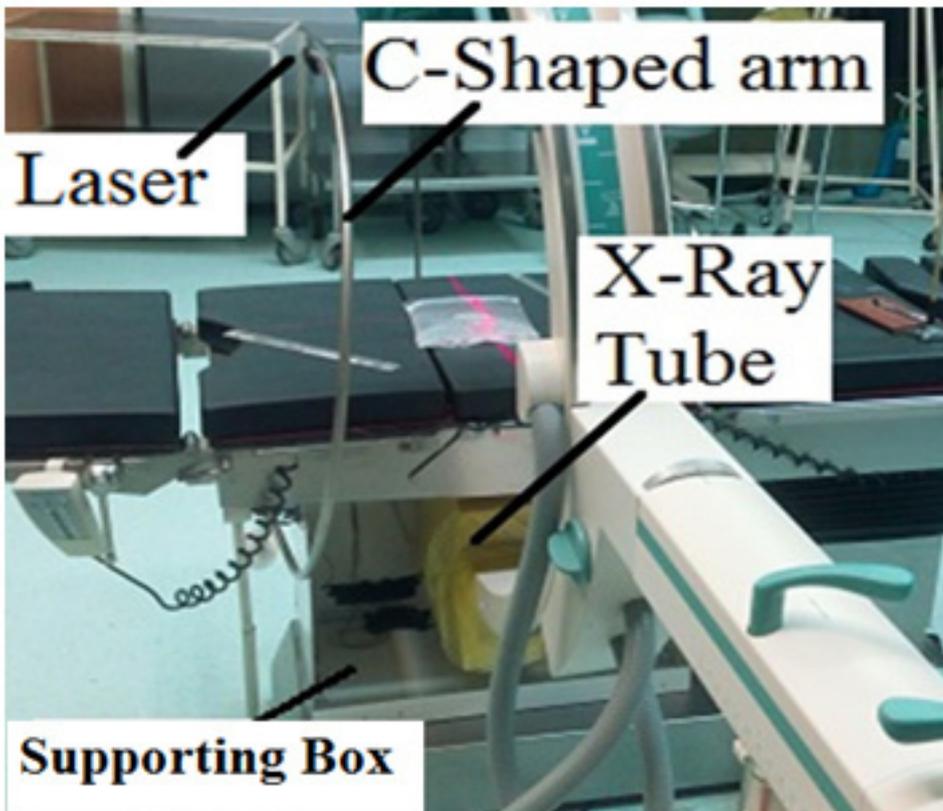
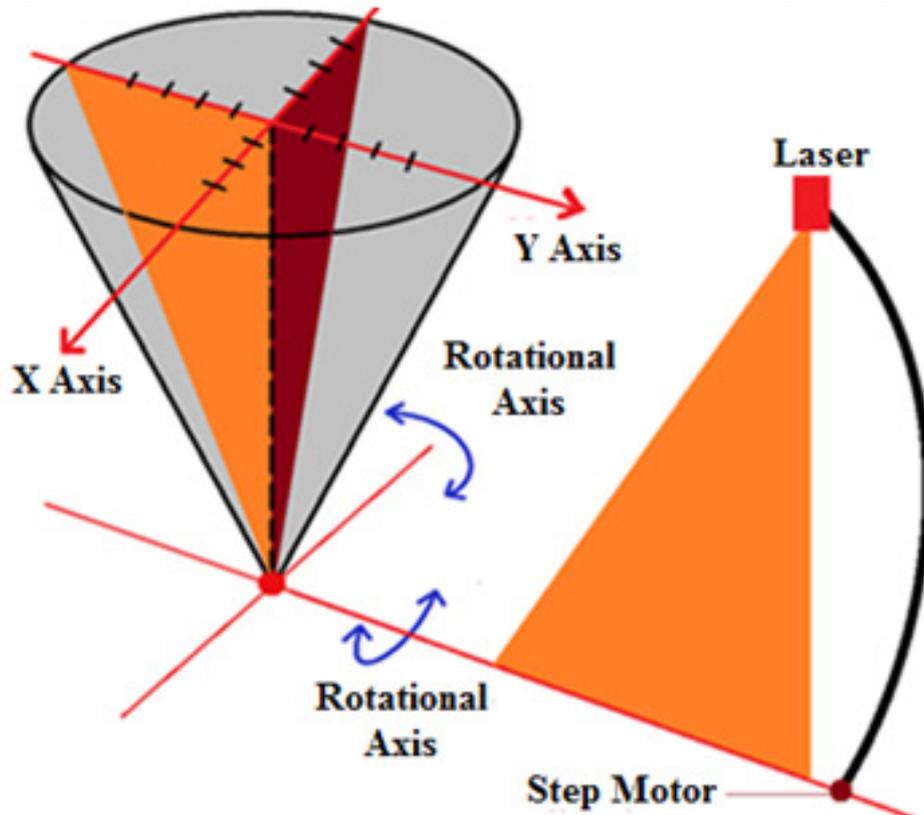


Figure 4. Placing the x-ray tube inside the box

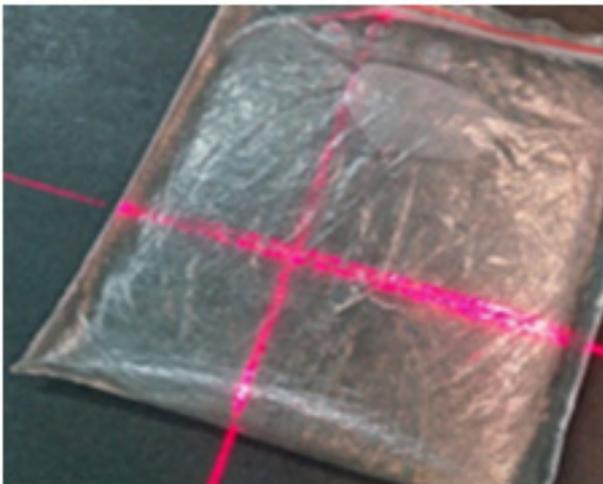


**Figure 5. The interface of the luminous planes of a line passing through the X-rays**



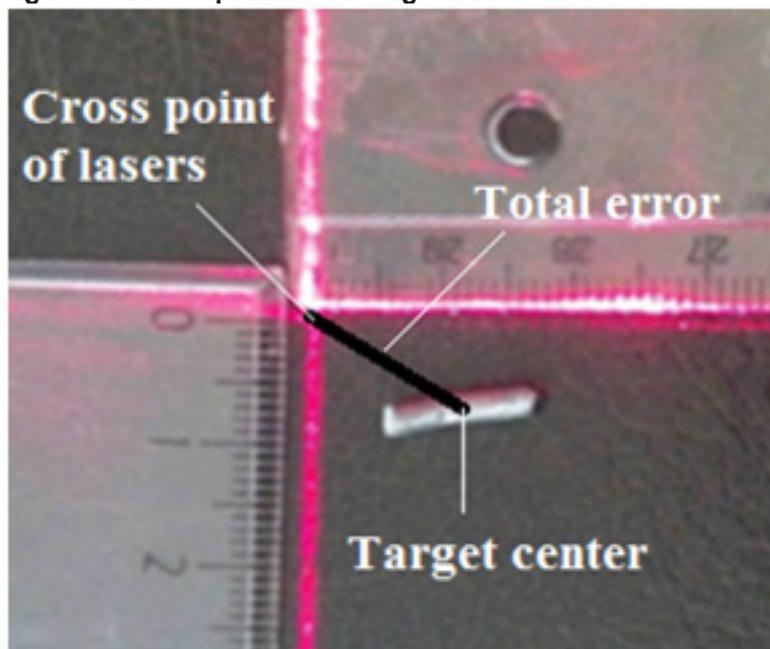
Each laser produce a luminous line on the surgical bed. The step motors rotate 1.2 degrees per step. With each step, every line was displaced about 10 mm on the surgical bed. In order to find out how accurately these luminous lines have pointed at a desired target, two rulers are needed to measure the distance between the target and each line. Placing the target inside an animal complicates this procedure, therefore, animal experiments were not preferred. A total of 10 experiments were carried out using the stated technique. In each experiment, by placing the target under a liquid-filled bag, and using the X-ray image of the target, the coordinates of the target were determined (Figure 6).

**Figure 6. Placing the liquid-filled bag on the target**



In accordance with the obtained Cartesian coordinates (x and y), the arms are rotated to the extent that the luminous lines be placed in the intended coordinates.

Then, by removing the bag, the error is measured in millimeters using two rulers. The distances between the target center and the vertical and horizontal lines show the value of error along X and Y axis respectively. The total error is the distance between the target center and the cross point of lasers (Figure 7).

**Figure 7: Lasers pointed the target with some error**

## Results

Using the proposed method, 10 experiments were carried out. The average fluoroscopy X-ray radiation exposure time was 2.4 seconds with a standard deviation of 0.49 seconds. The mean total error in pointing at the target was also measured 13.2 mm with a standard deviation of 4 mm.

The results table is as follows:

**Table 1: Results Table**

Experiment	1	2	3	4	5	6	7	8	9	10	Mean	Standard Deviation
Absolute value of Error Along X in millimeters	5	11	12	10	7	3	11	13	4	17	9.3	4.4
Absolute value of Error Along Y in millimeters	6	8	5	12	4	11	7	6	15	14	8.8	3.9
Total Error (mm)	7.8	13.6	13	15.6	8.1	11.4	13	14.3	15.5	22	13.4	4
X-ray Exposure time in seconds	3	3	3	2.4	2.4	1.8	2.4	1.8	1.8	2.4	2.4	0.49

## Discussion and Conclusion

Although there was some error in pointing at the target, the device was able to approximately find the location of the lead wire by using an X-ray image. Most of the errors that appeared were due to the accuracy of the stepper motors' angular rotation. The used stepper motors, rotated 1.2 degrees per step. Using stepper motors with smaller steps and higher resolution, could lead to better results.

The proposed method is simple and low cost, and compared to the conventional PCNL surgery, the x-ray radiation exposure time is relatively short, which will reduce the amount of received doses.

Combined methods in which other equipment, in addition to fluoroscopy, are used, will usually increase the received radiation dose and the expense for the patient.

In an article, in order to access the kidney, a Uro Dyna\_CT of a phantom was performed for 8 seconds. Based on the data from the 3D imaging of the Uro Dyna\_CT, iGuid laser guidance system installed on the device, was used to position the needle on the phantom's surface. Fluoroscopy imaging is then used to insert the needle towards the kidney (Figure 8) (14).

**Figure 8: Using Uro Dyna\_CT to position the needle**

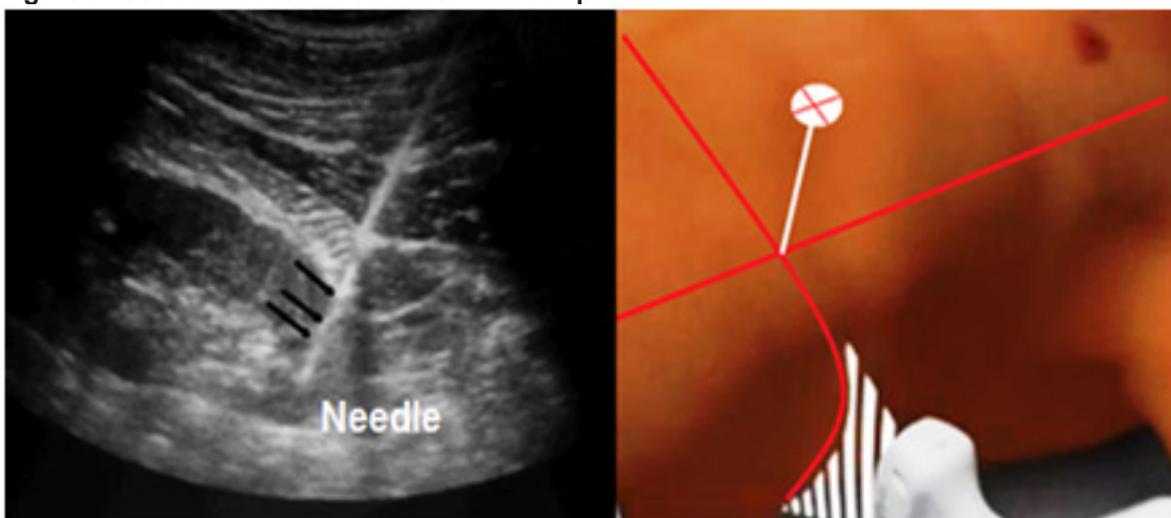


On average, the fluoroscopy is used for  $27 \pm 17$  seconds, which adds to the radiation exposure caused by the Uro Dyna\_CT device. While this technique is very useful for complicated cases, the amount of exposure and the cost of operation is much higher than the conventional method. This method is only recommended for patients with complicated and unusual anatomy (14).

By developing the proposed technique in this paper, a surgeon may insert the needle based on the luminous planes so that the tip and the end of the needle are placed where the lines meet each other, on the patient's skin.

Also, an ultrasound device may be used to simultaneously observe the depth of the needle and the kidney tissue. The ultrasound device can show the boundary of the kidney tissue (Figure 9).

**Figure 9. Use of ultrasound to observe the depth of the needle**



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# Investigating the relationship between academic innovation and organizational identity with higher-order thinking skills among students at Yasuj University of Medical Sciences

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## Abstract

The purpose of this study was to analyze the relationship between academic innovation and organizational identity with higher-order thinking skills among students at Yasuj University of Medical Sciences. This research is applied in terms of purpose and descriptive-survey in terms of collecting data. The population included the students at Yasuj University of Medical Sciences in (n=1404). Using Cochran's formula and stratified random sampling, a sample of 302 students were selected. The instrument used was a standard questionnaire, the validity of which was confirmed using content and construct validation and its reliability was confirmed through Cronbach's alpha and composite reliability. In this study, structural equation modeling and Amos and SPSS software were used for data analysis. The research results were obtained for three hypotheses, which were tested at 95% confidence level. The results indicated that academic innovation had a significant relationship with higher order thinking skills and could be effective in improving these skills. Also, the results indicated that academic innovation had a significant relationship with organizational identity and organizational identity had a positive and significant relationship with higher order thinking skills.

### Key words:

Academic Innovation, organizational identity, higher order thinking skills.

## Introduction

Today's man faces a huge body of knowledge and experiences, the scope and dominion of which is spreading on a daily basis. Despite the fact that access to this treasure of information is easily achieved from multiple sources, selecting the right and timely information from this body of knowledge has become a daunting task and requires high intellectual and mental skills (Duron et al., 2009). One of the most important needs of the present age is to educate people who can be active and logical in different fields of society. This requires attention to higher order thinking skills that consist of creative thinking and critical thinking skills. Higher order thinking skills are thinking beyond remembering facts or telling things exactly in the way you are told (Yazdi, 2009). Creative thinking refers to the ability to extract past thoughts and experiences, and combine them into novel ways. In other words, creative thinking requires divergent thinking, which stresses fluidity, flexibility, originality and expansion. Critical thinking is a blend of knowledge, attitude and skill to determine and diagnose, select the right information, solve problems, detect faults, make appropriate hypotheses, choose solutions, test results, and make judgments. In other words, it is the rational and systematic process of conceptualizing, implementing, analyzing, and expertly integrating and evaluating the collected information, which is used to orient ideas and actions (Adel, 2012). Hence, the acquisition of thinking skills in today's world has become an indisputable must in the labor market for confronting material and spiritual questions, assessing views and policies of individuals and organizations, and ultimately, facing social problems (Falch and Mang, 2015). One of the benefits of mastering higher order thinking skills is helping individuals identify their surroundings, and in particular the organizational environment in which they work. Therefore, organizational identity plays a central role in regulating the behavioral norms of an organization's members. Managers can use symbolic mechanisms in order to promote and consolidate a distinguished identity, which help create self-regulation for individuals in order to achieve performance goals, capture and maintain talents, gain reputation, create mental security in the organization, and help people to deal with ambiguous situations (Hosseini and Shahba, 2015). Since most research has focused on the organizational identity from a business perspective, little attention has been paid to the aspects related to the identity of non-profitable organizations such as universities.

The current environment of increasing competitiveness along with increasing limitation of public resources for university education, as well as the social debate over the need for universities to increase their ability to generate income has made image and identity an essential part of the modern strategic management in these institutions (Martinez & Garcia, 2011). Colleges and universities vary not only in terms of size, type of monitoring, choices, and goals, but also in terms of characteristics of their students and faculty members, as well as their mental and social environments. This diversity of higher education creates multiple identities. Educational motivations and ideas that help some organizations grow up are a kind of extra-

curricular life, which dominates the faculty identity (Kheiri et al., 2012). In studies on long-term economic growth, it has been suggested that technological change has been identified as the most important change that can improve growth and productivity. Innovation creates new products and methods of production, and ultimately improves economic growth. Educational systems at universities should be able to train students who are well versed in the concept of innovation in their work performance. Universities, therefore, refer to innovation as the most important factor in their education system (Falch and Mang, 2015). Identifying the factors effective on the acceptance and application of innovations and their impact on increasing the capacity of the educational system of universities, and adopting policies in line with the university goals is very important, because the widespread use of innovations has led to quantitative and qualitative changes in some activities (Ebadollahi et al., 2014). One of the recent innovations in the university education system is computer technology, which, thanks to its unique features, has had direct and indirect impacts on the educational system of universities and schools (Kahn et al. 2013). Higher education is considered to be an authority that generates and disseminates knowledge, which is itself considered as wealth. Higher education is also recognized as a tool for personal development of people for a better quality of life and as a means of production and economic growth; therefore, it leads to the economic prosperity of society and individuals. The traditional functions of producing and disseminating knowledge are at risk. In terms of social knowledge, the tendency towards a "knowledge-based economy" has made knowledge valuable and exposed to commercial transactions. Marketing in education is growing publicly. One of the strategies adopted by countries is the internationalization of higher education (Knight .2003). Creating a positive image for universities is very important; therefore, universities are nowadays doing a lot of work to promote their services, so that they can get a positive image of themselves for their students. Universities, which are serious about business and competitive environments, move towards educational innovations and related factors. This method has been controversial in gaining a competitive edge in the current environment (Poole et al. 2000). In the field of academic innovation, some skills predict more success in learning knowledge and technology-oriented skills. Integration of innovation in the university has transformed the teaching styles, learning approaches, and access to information. Academic innovation accelerates the process of enriching and deepening skills and motivating learners in relation to their experiences in the educational environment. Innovation at the university can make teaching and learning diverse, multi-dimensional and purposeful, engage and motivate learners, and develop collaborative activities and creativity in learning. In addition, it enables the individual to work well in different parts of the community (Demokānin, 2009).

Given the changes in, and attention to, the nature of science, new approaches have been proposed in determining educational objectives and processes. One of the most prominent approaches is to focus on higher

order skills in the education process. Training students who are thinkers, and creative and have scientific insights is not just achieved by the transfer of information to their minds, but requires the implementation of content and methods in university education systems through which they can learn how to learn through intellectual order and use what they acquire in their everyday lives. On the other hand, we live in an epoch of knowledge and information, and unbelievable acceleration of technology and creativity. With the popularity of fast access to computers and information technology and advanced media, no country can handle the 21st century economy without the 21st century electronic infrastructure. During the last decades, the speed and scope of environmental challenges have made competition more intense and has forced organizations to strategically coordinate their tools and technologies, and their required knowledge, skills and abilities in order to be as competitive as possible. One of the important factors in this regard is deciding on the level of focus on innovation in the educational system. Having accurate and timely information will speed up decision making and prevent many wrong decisions. Given the features of modern technology that cannot be controlled, we must strengthen the ideological foundations and beliefs of people and focus on internalization of values. Since educational environments are considered to be the second society, informing the educational systems of the correct use of the innovations at the level of education will help us better benefit from learning methods and their impact on the level of learning. Therefore, the purpose of this study was to investigate the relationship between academic innovation and organizational identity with the higher order thinking skills in students at Yasuj University of Medical Sciences.

## Methods

The present study is applied in terms of purpose and descriptive-survey in terms of implementing research. The population included the students at Yasuj University of Medical Sciences in (n=1404). Using Cochran's formula a sample of 302 students was selected. The sampling method in this study was stratified random sampling. The data collection instruments included Facione's (2011) 18-item Critical Thinking Questionnaire with components of curiosity, open-mindedness, truth-seeking, analyticity and maturity in judgment. Kanter's Creative Thinking Questionnaire (2009) consisting of detecting differences, finding the deleted symbol, and finding the relationship between the diagrams with 9 items was used to measure the higher order thinking skills. A 15-item researcher-made questionnaire based on Khosravi and Arman (2015) including comparative advantage, visibility, compatibility and ease was used to measure the academic innovation variable. Cheney's (1983) Organizational Identification Questionnaire (OIQ) including membership, loyalty and similarity was used for measuring organizational identity. All questionnaires used a 5-point Likert scale. In the inferential statistics section, AMOS software was used to analyze and test hypotheses. This software uses a component-based approach, which can measure reliability, validity and relationships between constructs. Analysis was conducted in two steps. The first step involved the analysis of reliability and convergent and divergent validity of the model and questionnaire. The second step involves testing all hypotheses of the study via the software. Path coefficients as well as the significance coefficient of T (T-VALUE) were used for general fitness of the model and testing the hypotheses and correlation. The results of the convergence and validity of the questionnaire are summarized in Table 1.

**Table 1: Summary of fitness for measurement models**

Construct	Cronbach's alpha	Composite reliability coefficient CR ≥ 0.7	Mean extraction variance AVE ≥ 0.5	CR ≥ AVE
Academic innovation	0.78	0.704	0.561	✓
Organizational Identity	0.82	0.710	0.505	✓
Thinking Skill	0.73	0.786	0.578	✓

## Results

In this research, descriptive results included analysis of the sample's demographic characteristics and the Kaiser-Meyer-Olkin (KMO) Test (for Sampling adequacy). Examining gender data shows that 203 participants were women (67%) and 99 were male (33%). Also, in the selected sample, 196 participants (65%) were under 30 years; 91 participants (30%) were between 31 and 40 years old; and 41 participants (5%) were over 41 years old. It is worth mentioning that the numerical value of KMO was 0.897, which is above 0.7 indicating the adequacy of using factor analysis. Pearson correlation test was used

to investigate the relationships between the research variables, the results of which are shown in Table 2.

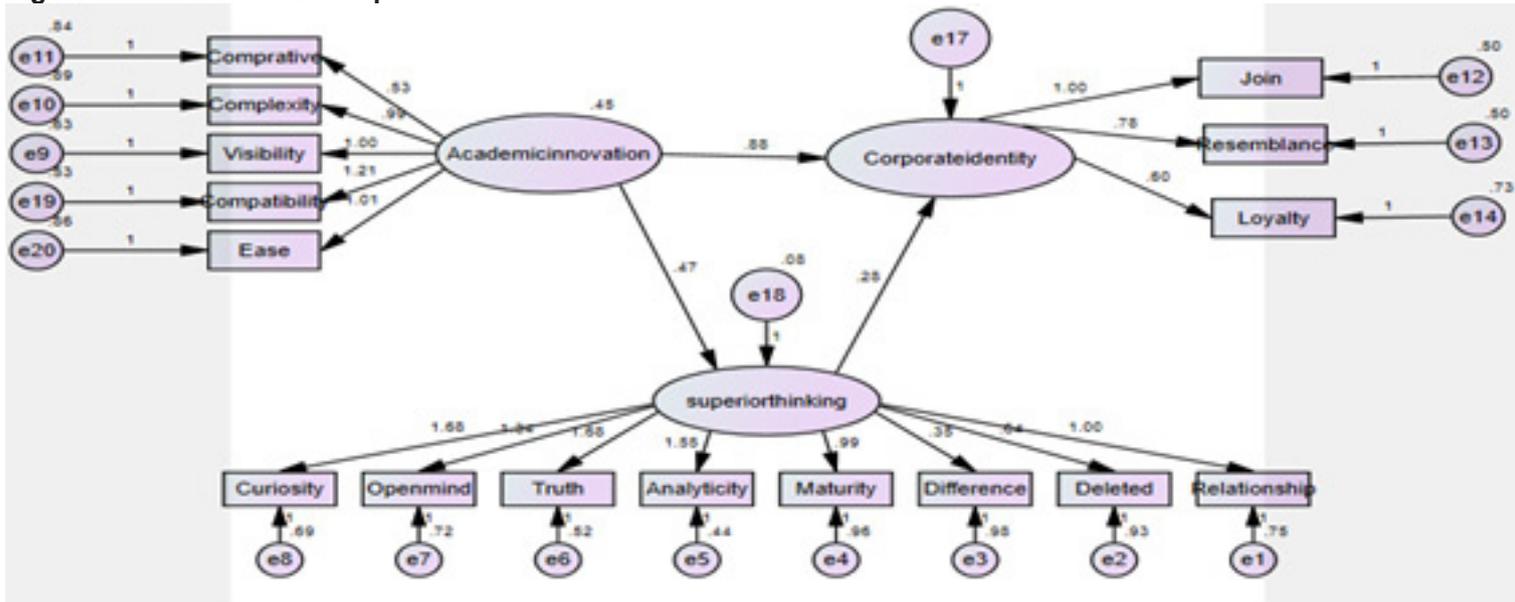
The results in Table 2 indicate that at the 95% confidence interval, the variable of academic innovation has a positive and significant relationship with organizational identity with a correlation coefficient of 0.540 and with higher order thinking skill with a correlation coefficient of 0.448. On the other hand, the organizational identity variable had a positive and significant relationship with higher order thinking skills with a correlation coefficient of 0.471.

**Table 2: Pearson correlation results indicating relationships among research variables**

Variables	Academic innovation	Organizational identity	Higher order thinking
Academic innovation	1	0.540	0.482
Organizational identity		1	0.417
Higher order thinking			1

In this study, two critical indicators of CR and P were used for the purpose of verifying the significance of the hypotheses tests. At the significance level of 0.05, the critical value should be more than 1.96 and the parameter values less than 1.96 were not considered significant. Similarly, values less than 0.05 for the P value indicate a significant difference between the calculated values for regression weights with zero value at the 0.95 level. To test the research hypotheses, structural equations and Amos22 software were used. The output of the software is presented in Figure 1.

**Figure 1: AMOS software output**



AMOS software was used to test the fitness of the above model indicating the general indicators as shown in Table3.

**Table 3: Conceptual Model Fitness**

RMSE	NFI	GFI	P	CIMN/ DF	CIMN
0.013	0.944	0.902	0.000	2.321	167.33

According to Table 4, it can be seen that the model has an acceptable fitness. Considering the results of the model analysis, the research hypotheses were tested as shown in Table 4.

**Table 4: Regression coefficient and partial index values related to the hypotheses**

Hypotheses	Regression coefficient	Critical value	P	Result
H1: University innovation at Yasuj University of Medical Sciences has a positive and significant effect on organizational identity.	0.88	5.86	0.000	Supported
H1: University innovation at Yasuj University of Medical Sciences has a positive and significant effect on higher order thinking skill.	0.47	6.64	0.000	Supported
H1: Organizational identity at Yasuj University of Medical Sciences has a positive and significant effect on higher order thinking skill.	0.27	2.31	0.002	Supported

According to Table 4 and tests of the main research hypotheses, the main research hypotheses were confirmed at 95% confidence level. Given the critical value (CR), which was greater than 1.96 for all hypotheses and the value (P), which was less than the 0.05 error level, the main research hypotheses are confirmed at 95% confidence level. Therefore, according to

Table 4, it can be concluded that at Yasuj University of Medical Sciences, academic innovation had a positive and significant effect on organizational identity and higher order thinking skills at 95% confidence level. Also, the results indicate that at Yasuj University of Medical Sciences, organizational identity had a positive and significant impact on higher order thinking skills.

## Discussion and Conclusion

The importance of universities in comprehensive, integrated, and balanced development of countries, and their various sectors in all economic, social and cultural areas has been investigated and emphasized by most scholars. Like any other organization, universities need efficient instruments and models to adapt to environmental conditions, use technological advances, and meet the diverse and broad needs of their target groups. This study aimed at examining the relationship between academic innovation and organizational identity with higher order thinking skills among students at Yasuj University of Medical Sciences. The results showed a significant relationship between educational innovations and higher order thinking skills. From this conclusion it can be inferred that today, educational organizations are seeking to identify people who are creator and thinker and attempt to identify students' aptitude with the help of innovations. The recognition of the students' thinking skills is necessary, because many differences in the performance of individuals can be attributed to their thinking skills rather than their abilities. On the other hand, identifying and understanding thinking skills helps an individual to better understand why some activities are suitable for him, but others are not. Therefore, if people properly use innovation in their educational environments, they can improve their skills. In a study on high school students, Abdullah Zadeh (2009) found that the amount of utilization of IT tools promoted the acquisition of thinking skills. In a study conducted on students, Emamipor (2003) found that creativity and progress had a positive and significant effect on thinking skills. Sternberg (2001) found a significant relationship between information technology and thinking skills. The results of this study indicate a significant relationship between academic innovation and organizational identity. Therefore, it can be concluded that people who are more loyal to their organization, and feel more dependent on and associated and satisfied with the organization, i.e. have a greater commitment to their organization and deem themselves as part of it, have a higher possibility of innovation in the organization. It can therefore be inferred that if the organization is designed in such a way that attracts people and increases their loyalty to the organization, they will seek to innovate and increase its competitive advantage. Therefore, the organizational identity of individuals represents the organization's good faith and increases the trust of individuals in the organization. Likewise, in order to strengthen the trust of individuals in the organization and increase innovation, we need to adopt a coherent approach. Seyyed Jawadin and Rezaee (2015) found a significant relationship between innovation and organizational identity of employees. Moayedi (2012) found out that teachers' creativity has a

significant relationship with organizational identity. On the other hand, according to the current results, organizational identity had a significant relationship with higher order thinking skills. Organizations try to increase loyalty of individuals to their organization and the style of thinking is very important in this regard. However, they should note that there is no best thinking skill as these skills vary based on decision-making positions and occupations, and it is the art of individuals to use the appropriate skill for each position. Therefore, organizations can create the appropriate grounds for strengthening their thinking skills in the organization. Madankar (2015) found a meaningful relationship between identity and thinking style. Hejazi and Borajali (2009) found that the level of individuals' commitment to and identification with the organization has a significant relationship with their thinking. According to theoretical literature, the following recommendations are made to create and improve the status of innovation and organizational identity in acquiring higher order thinking skills at higher education institutions:

- Before creating an image for the university, all external and internal aspects of the university must be clearly understood and interpreted so that there is no ambiguity.
- In order to understand the type of student thinking, higher education centers can present certain forms to students and their families upon enrollment or interview so that they can continuously recognize the dimensions and characteristics of students' thinking style.
- Today, given the growing need for innovation in higher education institutions in both public and private sectors, these institutions have recognized the effect of innovation on student satisfaction. That is a way positive and negative emotions towards the university may form in the minds of students. Hence, higher education institutions should provide new and innovative services to all students as well as apply innovations to the university's educational system in order to satisfy their students.

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# Antidepressant effects of oleuropein in male mice by forced swim test and tail suspension test

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## Abstract

**Objectives:** With increasing prevalence of depression in communities and public concern regarding the side effects of synthetic drugs, special attention has recently been paid to identifying natural compounds with antidepressant effects. Oleuropein is an antioxidant polyphenol that is present in the leaves and fruits of different variants of olive. The aim of the present study was to investigate the antidepressant effects of oleuropein in mice by forced swim test (FST) and tail suspension test (TST).

**Methods:** In this experimental study, 50 mice were randomly divided into 5 groups of 10. Group 1 received normal saline; group 2 intraperitoneally received reserpine at 5 mg/kg 18 hours before behavioral testing; group 3, in addition to reserpine, intraperitoneally received oleuropein at 10 mg/kg 15 minutes before behavioral testing; group 4, in addition to reserpine, received fluoxetine at 20 mg/kg; and group 5 received oleuropein at 10 mg/kg for 3 days and then reserpine 18 hours before behavioral testing.

Behavioral tests were FST and TST. Finally, the antioxidant capacity and malondialdehyde (MDA) and nitric oxide (NO) levels in the serum and brain of the mice were measured.

**Results:** Reserpine significantly increased the duration of immobility in FST and TST and significantly decreased serum and brain antioxidant capacity, significantly increased MDA levels in the brain and serum, and significantly increased serum NO level ( $P < 0.05$ ). Oleuropein treatment for 3 days caused a significant decrease of immobility in FST, a significant increase in brain and serum antioxidant capacity, and a significant decrease of brain and serum MDA and NO levels ( $P < 0.05$ ).

**Conclusion:** Oleuropein was found to exhibit significant antidepressant effects in mice, probably due to its antioxidant activity.

**Key words:** Oleuropein, depression, reserpine

## Introduction

Depression is one of the common psychiatric disorders that can decline function in all areas of life, including occupation, social relationships, and family crises. Two thirds of depressed patients develop suicidal thoughts and the suicide rate ranges from 10% to 15%. Fifty percent of depressed patients are 25-26 years old, and an increase in the prevalence of depression has been observed in the age group of under 20 years [1].

Studies have shown that most symptoms of depression are due to decreased function of certain transmitters such as norepinephrine, serotonin or 5-hydroxytryptamine, dopamine, glutamate, and GABA. Therefore, drugs that increase these neurotransmitters in the brain exert antidepressant effects [2].

Antidepressant treatments can be generally divided into two categories of pharmacological and non-pharmacological treatments. The available antidepressant drugs include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, and several new drugs such as nefazodone and bupropion. In severe cases, the use of antidepressants has been found to be the best choice. These drugs have quantitatively and qualitatively grown remarkably in recent decades, but due to their long-term use, many adverse side effects may occur [3].

The research on olive has shown that the main reason for bitter taste of olives is oleuropein. Oleuropein is one of the active compounds in the olive tree (*Olea europaea*). Oleuropein is found in high concentrations in unprocessed fruit and leaf of *O. europaea*. During the ripening of *O. europaea* fruit or processing of olive (e.g. oil production), certain chemical and enzymatic reactions occur, which decreases the concentration of oleuropein and increases the concentration of hydroxytyrosol, which is the main cause of the decomposition of oleuropein. The oleuropein molecule has three structural subunits consisting of a polyphenol called hydroxytyrosol (4-(2-hydroxyethyl)benzene-1,2-diol), a secoiridoid called oleic acid, and a glucose molecule [4].

The use of oleuropein plays a significant role in health. It has been reported that oleuropein and its antioxidant compounds, such as tyrosol, verbascoside, and dimethyl oleuropein, reduce the risk of coronary heart disease (arteriosclerosis) [5].

Studies have shown that oleuropein lowers the growth of colon cancer cells. Oleuropein may result in tumor reversal and prevention of proliferation of intestinal cancer cells by causing cell-cycle arrest at the G2-M phase. Oleuropein also increases apoptosis in intestinal cancer cells [6].

The antioxidant and hypotensive effects due to oleuropein have been shown in rabbits with alloxan-induced diabetes [7]. The analgesic and anti-inflammatory effects of oleuropein have also been shown to affect the pain and carrageenan-induced foot edema [8].

Therefore, our aim was to investigate the effects of one of the natural benefits, oleuropein, isolated from leaf and fruit of *O. europaea*, on depression, a chronic, costly, and complicated disease.

## Materials and methods

### Measuring oleuropein antioxidant effect

Oleuropein antioxidant effect was measured by the 2, 2-diphenyl-1-picryl Hydrazyl (DPPH) assay and the trolox equivalent antioxidant capacity (TEAC) assay.

### The DPPH assay

Oleuropein (3.5, 6.25, 12.5, 25, 50 and 100µg/ml) was first prepared and equal amount of the DPPH solution (1mg/ml) was added to oleuropein at all concentrations. The resulting solution was kept in the dark at room temperature for 15 minutes, the absorbance values measured at 517nm using a spectrophotometer and then the activity of the DPPH radical inhibition calculated [9].

### IC<sub>50</sub> (%) = (A<sub>control</sub>-A<sub>sample</sub>)/A<sub>control</sub>×100

IC<sub>50</sub> is the concentration of the solution in which 50% of the DPPH radical was scavenged.

### The TEAC assay

To prepare azino-bis 3-ethylbenzothiazoline-6-sulfonic acid (ABTS), an aqueous solution of ABTS (7mM) was prepared. Potassium persulfate was added to this ABTS solution to a final concentration of 2.45mM and the resulting solution left in the dark at room temperature for 16 hours. Meanwhile, ABTS was converted to its radical cation by addition of potassium persulfate. Then, oleuropein at 75, 125, 250 and 500µg/ml was prepared and 20µg/ml of each concentration of the sample mixed with 2ml of ABTS<sup>•+</sup> and the absorbance read at 734nm. The results were expressed as TEAC value (the ability to inhibit ABTS radical by the Trolox standard) [10].

### Metal chelating assay

Briefly, oleuropein (30, 50 and 100mg/ml) was mixed with FeCl<sub>2</sub> (0.5mM, 2mM) and ferrozine (0.2 mL, 5 mM) and shaken. After 10 minutes, the absorbance was read using a spectrophotometer at 562nm. EDTA was used to plot the standard curve. The percentage of the ferrous ion-chelating capacity was measured by the equation below:

$$(\text{Absorbance of control} - \text{Ab of sample}) / \text{Ab of control} \times 100$$

[11].

### Reducing power assay

Reducing power of a compound represents its electron-donating ability. Oleuropein (1mM) at 25, 50, 100, 200 and 300µg/ml was mixed with phosphate buffer (0.2M, pH=6.6) and 1% potassium ferricyanide (K<sub>3</sub>Fe(CN)<sub>6</sub>) and the resulting solution left to incubate at 50°C for 2 minutes. Chloro-acetic acid was added to stop the reaction. The mixture was centrifuged at 3000rpm for 10 minutes, the supernatant mixed with H<sub>2</sub>O<sub>2</sub> and ferric chloride 1% and the absorbance measured at 700nm [12].

### Hydroxyl radical scavenging assay

First, 1,10-phenanthroline (1ml, 1.865mM) was mixed with 2ml of oleuropein (25, 50, and 100µg/ml), and FeSO<sub>4</sub> (1ml, 1.865mM) then added to the resulting mixture. The reaction was started by the addition of H<sub>2</sub>O<sub>2</sub> (0.03%). The resulting solution was incubated in water bath at 37°C for 60 minutes and the absorbance read at 536nm. The scavenging activity of hydroxyl radical was measured by the equation below:

$$\text{HRSA (\%)} = \frac{[(\text{Absorbance of sample} - \text{Ab of A negative control}) / (\text{Ab of blank} - \text{Ab of negative control})] \times 100}{1} \quad [13].$$

### Laboratory animals and grouping

In this experimental study, 50 male mice (weighing 25 to 30 g) were divided into 5 groups of 10. Animals were kept in separate cages at 20-25°C with a 12:12-hour light: dark cycle. During this time, the mice were provided with sufficient water and food, and all experiments were carried out during lighting (9-1700 hours). The protocol of this study was in compliance with the Guide for the Care and Use of Laboratory Animals and the regulations of Shahrekord University of Medical Sciences.

Group 1 received normal saline; group 2 received reserpine at 5 mg/kg intraperitoneally 18 hours before behavioral testing; group 3 first received reserpine and then oleuropein at 10 mg/kg intraperitoneally 15 minutes before behavioral testing; group 4 first received reserpine and then fluoxetine at 20 mg/kg intraperitoneally; and group 5 (treatment group) first received oleuropein at 10 mg/kg intraperitoneally for 3 consecutive days and then reserpine at 5 mg/kg 18 h before the behavioral testing. Fifteen minutes after drug administration, behavioral testing consisting of forced swimming test (FST) and tail suspension test (TST) was performed. After behavioral testing, the rats had a deep anesthesia and their brain was removed. Blood samples were centrifuged at 3000 rpm and the serum was isolated. Serum and brain samples were stored at -30°C for biochemical tests.

### TST

To carry out the TST, metal bases with a height of 70 cm were used, with a 50 cm string stretching between the two metal bases longitudinally. The tail of the mouse was fastened with a string so that it is suspended by the tail. At the beginning, the mouse starts to move, and then becomes totally motionless and inactive, which indicates immobility [14].

### FST

The FST is one of the most reliable and most commonly used assays for the study of depression. In this test briefly, a glass container, 25 cm length, 12 cm width, and 15 cm height, is filled with water at 25°C and the animal is placed at a height of 20 cm from the water surface and then is gently immersed in water. Discontinuation of the movement of hind/forelimbs indicates immobility. The FST lasts 10 minutes with the first 2 minutes for acclimation. During the acclimation period, the duration of immobility is not recorded, but it is recorded for the following 8 minutes [15].

### Measuring the antioxidant capacity of the serum and the brain

To measure antioxidant capacity, three solutions were used consisting of (1) buffer (1.55 ml of sodium acetate and 8 ml of concentrated acetic acid diluted to a final volume of 500 ml with distilled water), (2) iron chloride solution [270 mg of iron chloride (III) diluted to a final volume of 50 ml with distilled water], and (3) triazine (47 mg of triazine dissolved in 40 ml of 40 mM hydrochloric acid). To prepare the stock solution, 10 ml of solution 1 was dissolved in 1 ml of solution 2 and 1 ml of solution 3. Twenty five µl of serum sample or brain homogenate was added to 1.5 ml of the stock solution and the resulting solution was left at 37 °C for 10 minutes. Then optical absorbance was recorded at a wavelength of 593 nm [16].

### Measuring serum malondialdehyde (MDA) levels

Briefly, 0.5 g of thiobarbituric acid was dissolved in 80 ml of acetic acid 20% and the pH of the resulting solution was adjusted to 5.3 by adding sodium hydroxide, and its final volume was increased to 100 ml by adding acetic acid 20%. One hundred µl of the serum sample was dissolved in 100 µl of SDS 1.8% solution and 2.5 ml of the stock solution. The samples were placed in boiling water for one hour, and then were cooled and centrifuged at 4000 rpm. Optical absorbance of the supernatant was measured at a wavelength of 523 nm [16].

### Measuring the level of malondialdehyde (MDA) in the brain

One g of the brain tissue was homogenized in 2.5% potassium chloride (10% w/w) and incubated at (37±1) °C in a metabolic shaker for 60 minutes. After one hour of incubation, 1 ml of 5% tetrachloroacetic acid and 1 ml of 67% thiobarbituric acid were added to the homogenate and the resulting mixture was finely mixed after each step. The content of each vial was transferred to a centrifuge tube and centrifuged at 2000 rpm for 15 minutes. Next, the supernatant was transferred to another tube and placed in a boiling water bath; after 10 minutes the test tubes were cooled and the absorbance was measured at a wavelength of 535 nm [16].

### Measuring the levels of nitric oxide (NO)

NO levels were measured by measuring the levels of its products, i.e. nitrate and nitrite, in serum using a calorimetric kit. First, nitrate was converted to nitrite by nitrate reductase and then the NO levels were measured by measuring nitrite with the Griess reagent at a wavelength of 570 nm [15].

### Analysis statistic:

Statistical analysis was performed using the SPSS version 16. First, distribution normality of the data was tested by using Kolmogorov-Smirnov test and then homogeneity of variances was investigated by using Levene's test. Then, one-way ANOVA was used to determine the significant difference between treatments and Tukey's test was used to compare the mean values. Data were expressed as mean (± standard error) and P < 0.05 was considered significance level.

## Results

### Oleuropein antioxidant property

#### DPPH levels

The results demonstrated that the anti-radical activity of oleuropein increased with increasing its concentration. In addition, the EC<sub>50</sub> of oleuropein was derived at 11.7 $\mu$ g/ml. EC<sub>50</sub> was directly correlated with oleuropein antioxidant activity.

#### TEAC assay

##### Metal chelating assay

The ferrous ion-chelating capacity of oleuropein increased with increasing its concentration. Ferrous ion-reducing power (%) of oleuropein at 50, 30 and 100 $\mu$ g/ml was derived at 17.75%, 21.07% and 22.20%, respectively.

##### Ferrous ion-reducing power

The antioxidants with high ferrous ion-reducing power can exert potent effects in terminating damaging oxidative chain reactions. We observed that the ferrous ion-reducing power of oleuropein increased with increasing its concentration such that the absorbance was derived 0.007 at 25 $\mu$ g/ml, with the highest absorbance (1.958) at 300 $\mu$ g/ml. The EC<sub>50</sub> of oleuropein was derived 95.51 $\mu$ g/ml.

##### Hydroxyl radical scavenging assay

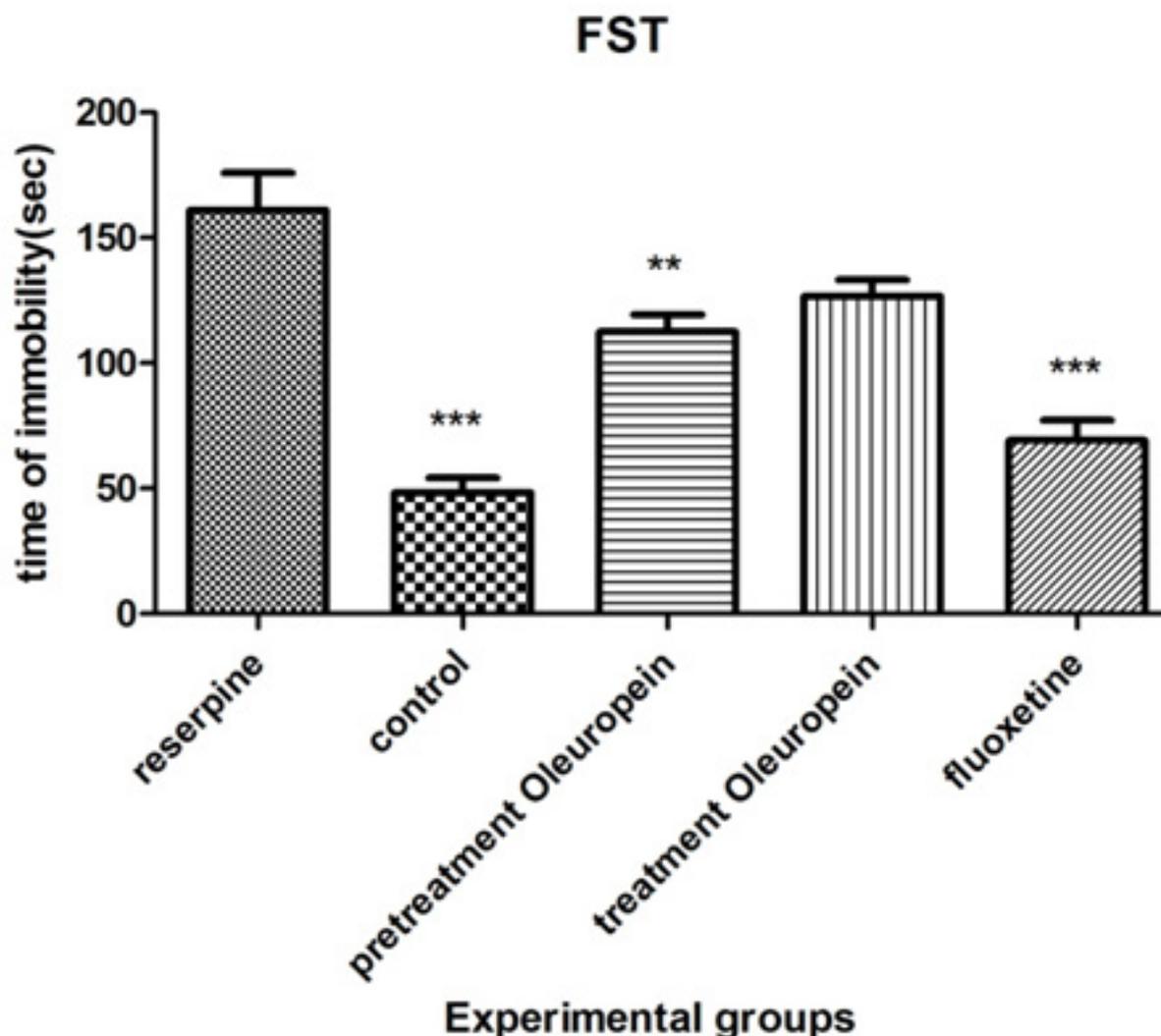
Hydroxyl scavenging activity (%) of oleuropein at 50, 25 and 100 $\mu$ g/ml was derived at 4.98%, 4.88% and 8.8%, respectively.

#### Behavioral Results:

The results of the effect of oleuropein and fluoxetine on the duration of immobility in the FST are illustrated in Figure 1. According to the results, the duration of immobility in the FST was significantly higher in the group receiving reserpine than in the control group ( $P < 0.001$ ).

The oleuropein pretreatment for 3 days in mice receiving reserpine significantly reduced the duration of immobility when compared to reserpine group ( $P < 0.05$ ). The fluoxetine treatment in mice receiving reserpine significantly reduced the duration of immobility when compared to the reserpine group ( $P < 0.01$ ).

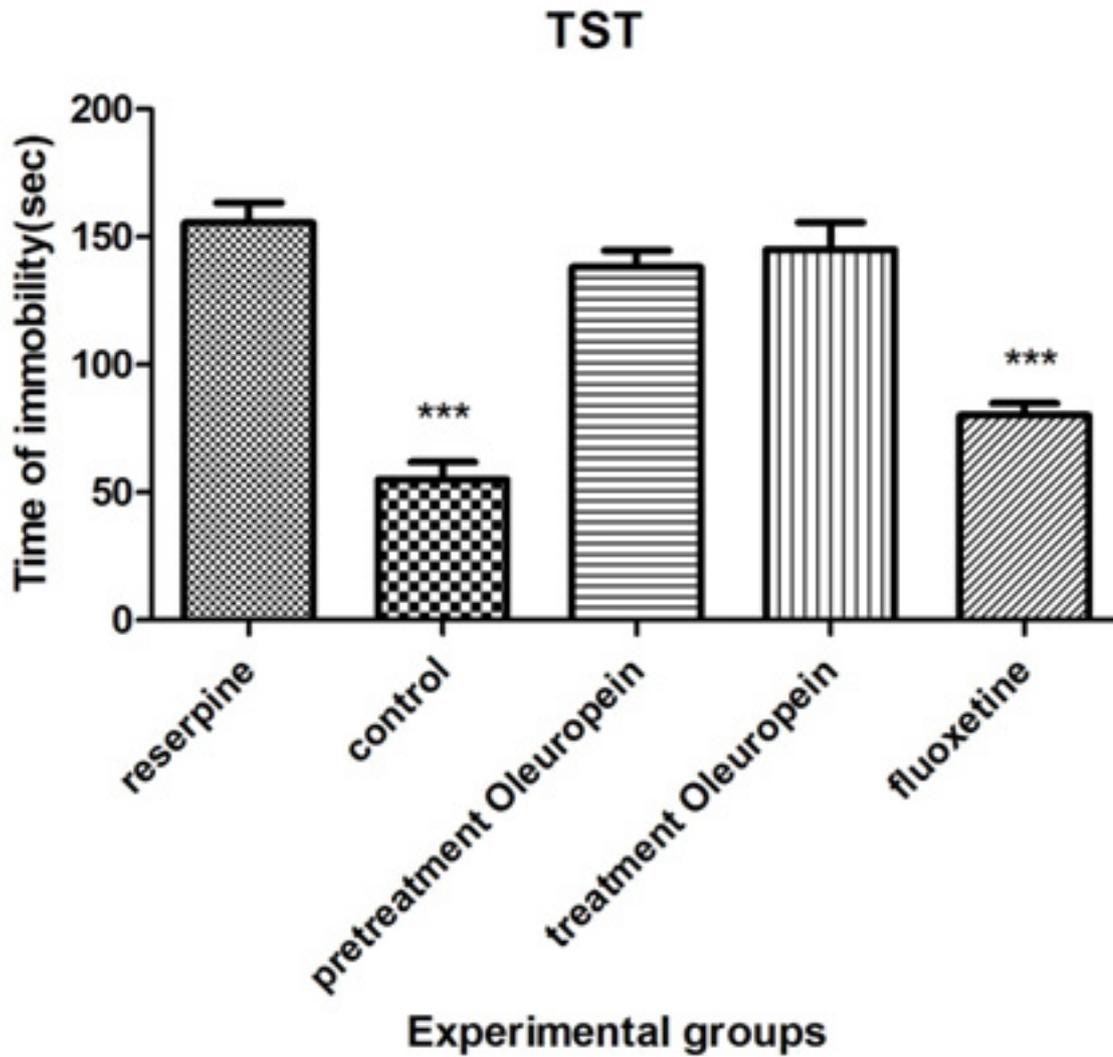
**Figure 1: The effect of oleuropein and fluoxetine on the duration of immobility in the forced swimming test; \*\*\* =  $P < 0.001$ ; \*\* =  $P < 0.01$  # significant difference from reserpine ( $P < 0.01$ ).**



The results of the effect of oleuropein and fluoxetine on the duration of immobility in the TST are illustrated in Figure 2. According to the results, the duration of immobility in this test was significantly higher in the group receiving the reserpine when compared to control group ( $P < 0.001$ ).

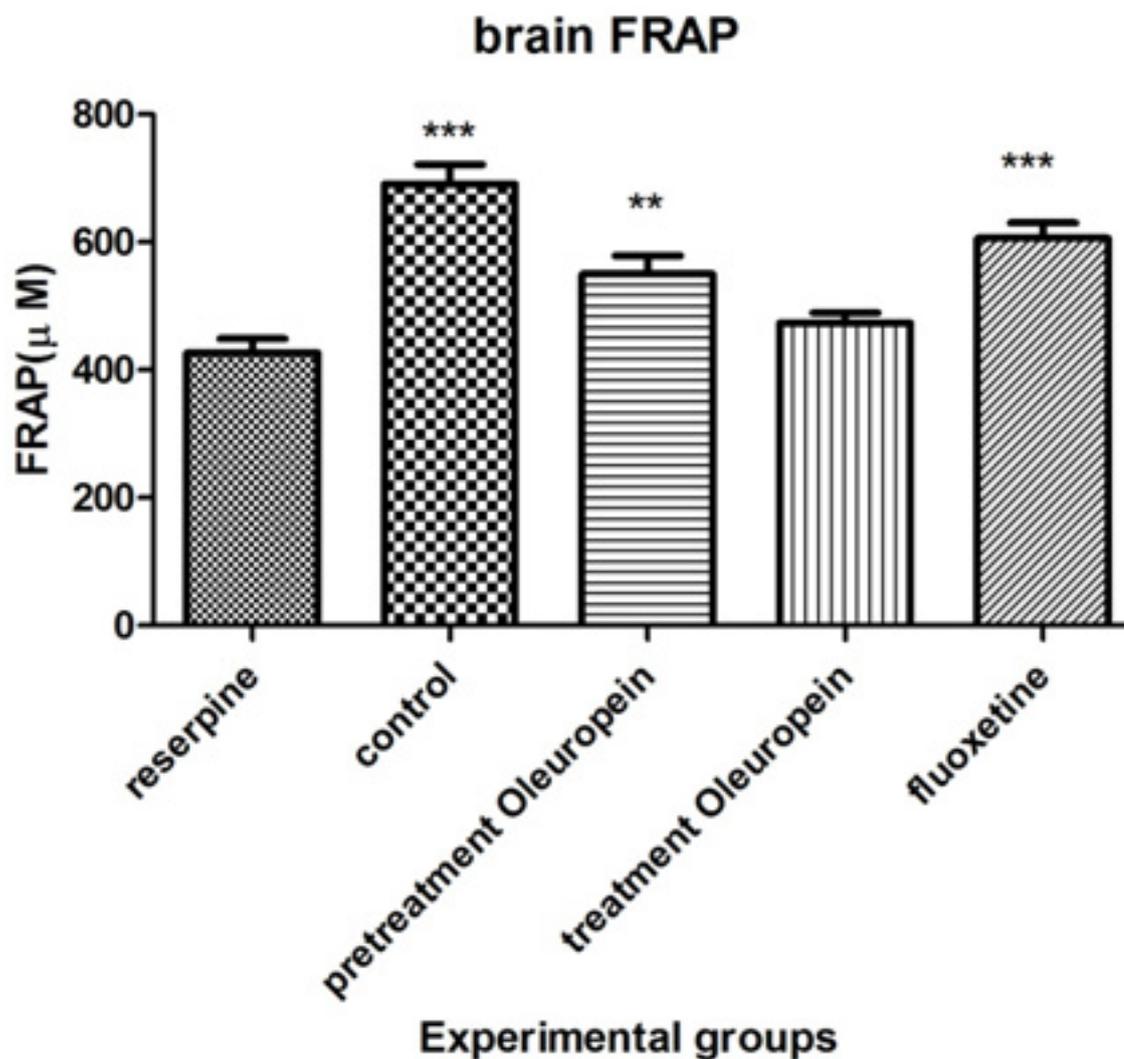
The oleuropein treatment or pretreatment in mice receiving reserpine did not significantly change the duration of immobility compared to the reserpine group. The fluoxetine treatment in mice receiving reserpine significantly reduced the duration of immobility ( $P < 0.001$ ).

**Figure 2: The effect of oleuropein and fluoxetine on the duration of immobility in the tail suspension test; \*\*\* =  $P < 0.001$**



The results of oleuropein and fluoxetine effects on brain antioxidant capacity are illustrated in Figure 3. According to the results, brain antioxidant capacity was significantly lower in the reserpine group than in the control group ( $P < 0.001$ ). The fluoxetine treatment in mice receiving reserpine significantly increased brain antioxidant capacity ( $P < 0.001$ ). The oleuropein pretreatment in rats receiving reserpine for 3 days resulted in a significant increase in brain antioxidant capacity ( $P < 0.01$ ). Single-dose administration of oleuropein 18 hours after reserpine injection did not significantly change brain antioxidant capacity.

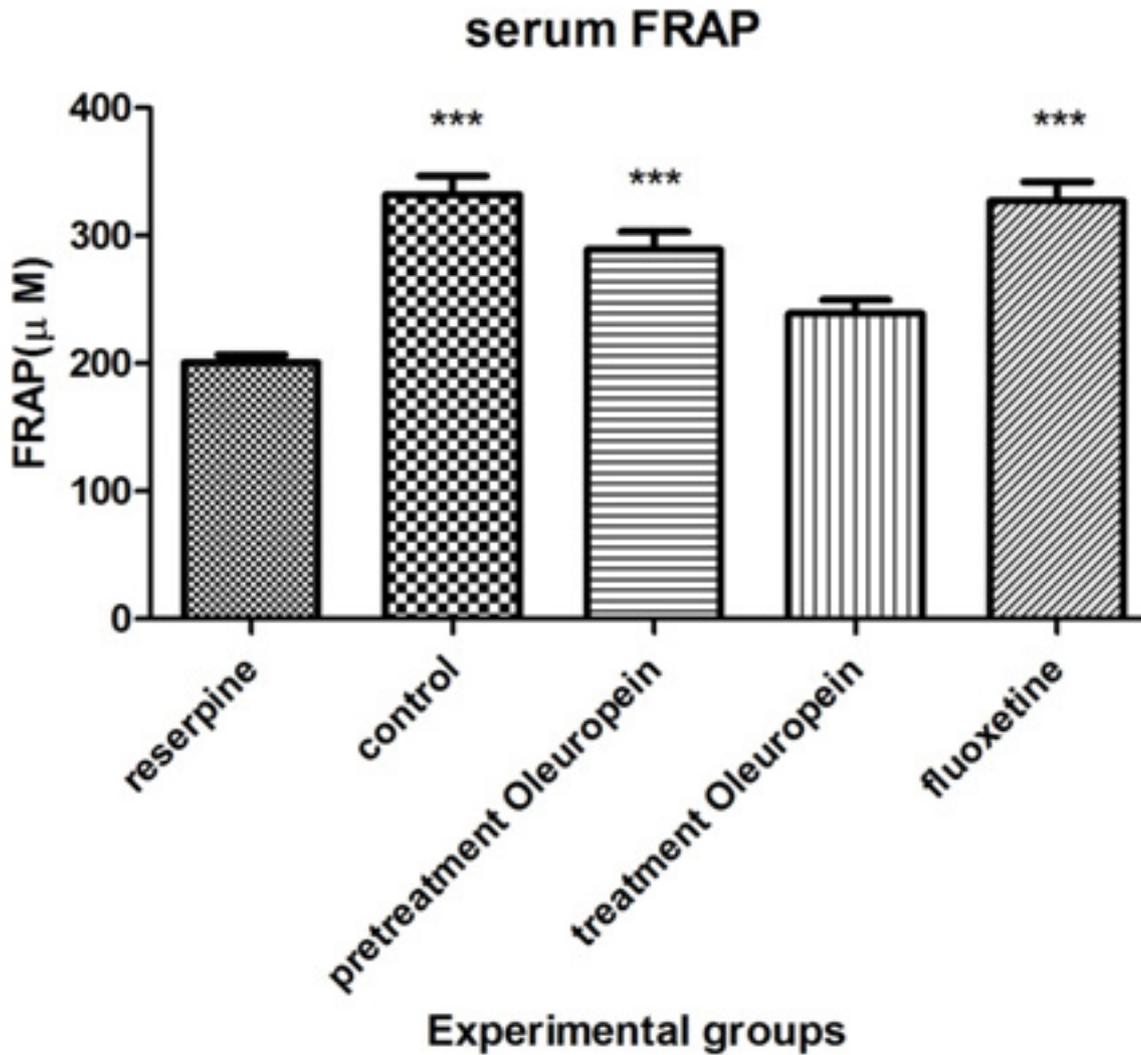
Figure 3: The effect of oleuropein and fluoxetine on the antioxidant capacity of the brain; \*\*\* = $P < 0.001$ ; \*\*= $P < 0.01$



The results of the effect of oleuropein and fluoxetine on serum antioxidant capacity are illustrated in Figure 4. According to the results, serum antioxidant capacity was significantly lower in the reserpine group than in the control group ( $P < 0.001$ ).

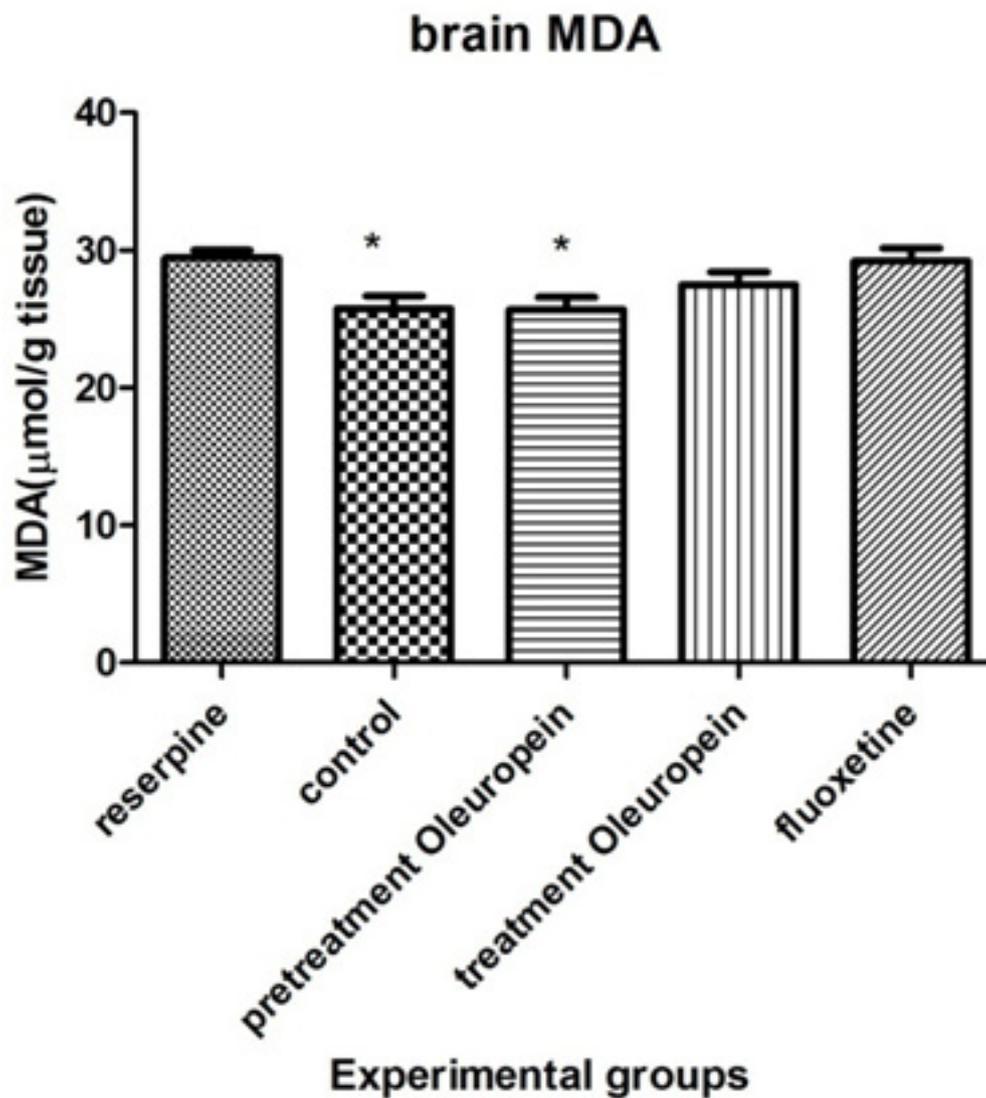
The fluoxetine treatment in rats receiving reserpine significantly increased serum antioxidant capacity ( $P < 0.001$ ). Oleuropein pretreatment for 3 days in rats receiving reserpine significantly increased serum antioxidant capacity ( $P < 0.001$ ). Single-dose administration of oleuropein 18 hours after reserpine injection did not have a significant effect on serum antioxidant capacity.

**Figure 4: The effect of oleuropein and fluoxetine on serum antioxidant capacity; \*\*\* = $P < 0.001$ ;**



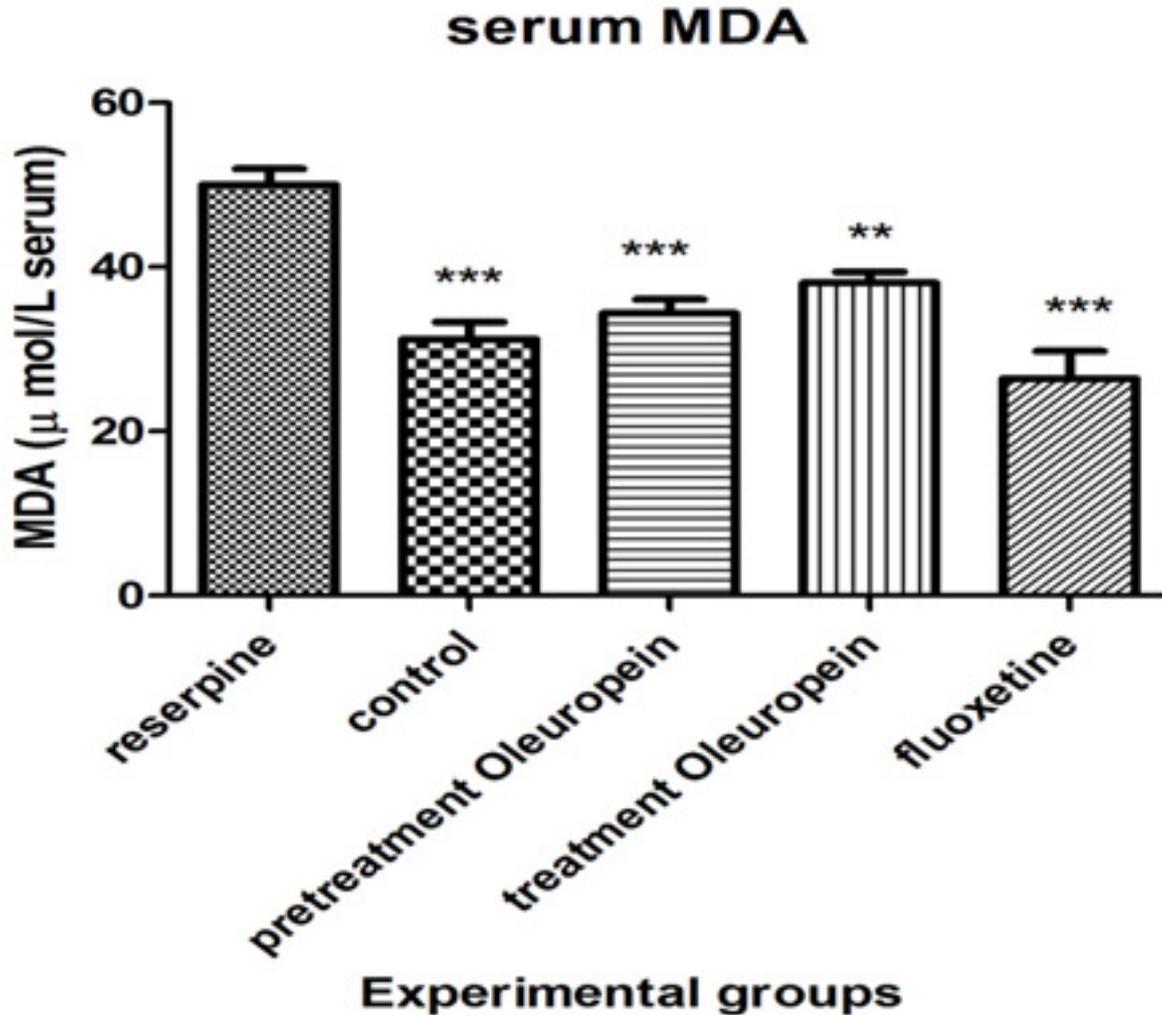
The results of the effect of oleuropein and fluoxetine on brain MDA levels are illustrated in Figure 5. According to the results, brain MDA levels were significantly higher in the group receiving reserpine than in the control group ( $P < 0.001$ ). The oleuropein pretreatment for 3 days in rats receiving reserpine caused a significant decrease of brain MDA level ( $P < 0.05$ ). Single-dose administration of oleuropein 18 hours after reserpine injection did not have a significant effect on the MDA levels in the brain.

Figure 5: The effect of oleuropein and fluoxetine on malondialdehyde levels in brain;  $*=p<0.05$



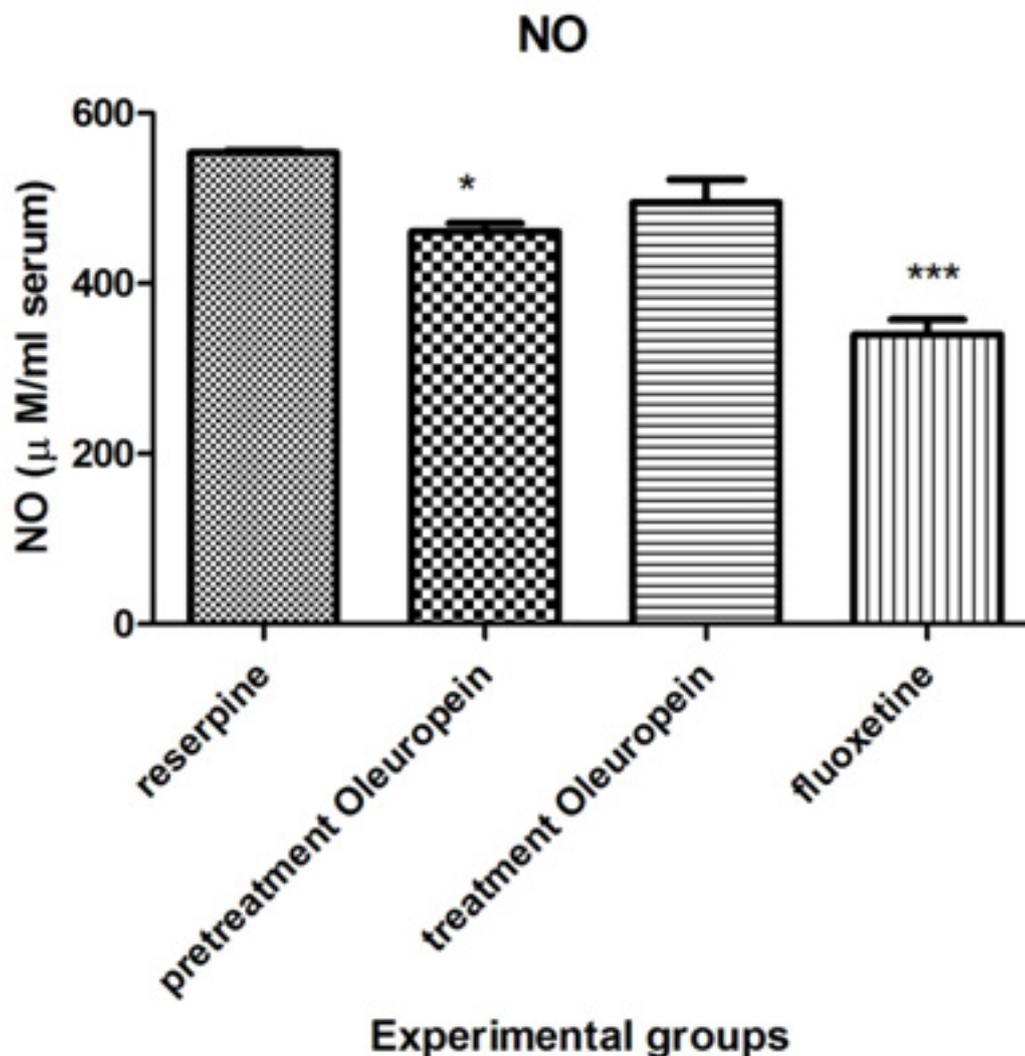
The results of the effect of oleuropein and fluoxetine on serum MDA levels are illustrated in Figure 6. Serum MDA level was significantly higher in the group receiving reserpine than in the control group ( $P < 0.001$ ). Fluoxetine treatment in mice receiving reserpine resulted in a significant decrease of serum MDA level ( $P < 0.001$ ). Oleuropein pretreatment for 3 days in rats receiving reserpine significantly reduced serum MDA levels ( $P < 0.001$ ). Single-dose administration of oleuropein 18 hours after reserpine injection had a significant effect on serum MDA level ( $P < 0.001$ ).

Figure 6: The effect of oleuropein and fluoxetine on serum malondialdehyde levels; \*\*\* = $P < 0.001$ , \*\*= $p < 0.01$



Results of the effect of oleuropein and fluoxetine on serum NO levels are illustrated in Figure 7. Fluoxetine treatment in rats receiving reserpine significantly decreased serum NO level ( $P < 0.001$ ). Oleuropein pretreatment for 3 days in mice receiving reserpine significantly reduced serum NO level ( $P < 0.05$ ). Single-dose administration of oleuropein 18 hours after reserpine injection did not have a significant effect on serum NO level.

**Figure 7: The effect of oleuropein and fluoxetine on serum nitric oxide levels; \*\*\* = $P < 0.001$ ; \*= $P < 0.05$ .**



## Discussion

The aim of this study was to investigate the effect of oleuropein on reserpine-induced depression in mice. Treatment of reserpine at 5 mg/kg 18 hours before behavioral testing significantly increased the duration of immobility in the FST and TST. Reserpine treatment also significantly reduced serum and brain antioxidant capacity and significantly increased serum MDA and NO levels. Reserpine is a drug that is mainly used to treat hypertension. Reserpine is also used as an antipsychotic for management and treatment of delirium (such as delusions and hallucinations), especially in diseases such as schizophrenia. Over the last few decades, it has been acknowledged that reserpine depletes the reserves of the catecholamines and serotonin of the tissues and the central nervous system (CNS), and thus leads to depressive-like behaviors by affecting the postnodular sympathetic nerve endings [17].

In the present study, reserpine injection, as expected, significantly increased the duration of immobility in the FST and TST.

In previous studies, it has been observed that reserpine has depression-inducing effects and increases the duration of immobility in the FST and TST [18, 19]. Reserpine interferes with the release, storage, and reuptake of monoamine neurotransmitters by inhibiting the vesicular monoamine transporter. Reducing the levels of serotonin, norepinephrine, and dopamine in the brain is one of the main causes of reserpine-induced depression. Reserpine also increases the autoxidation of dopamine and catalytic activity of monoamine oxidase. The monoamine oxidase binds to the mitochondrial membrane and causes the oxidation of neurotransmitters norepinephrine, dopamine, and serotonin, and while exerting its activity, produces free radicals and reactive oxygen species. Dopamine autoxidation produces dopamine-quinone, which in turn

degrades glutathione and produces free radicals. When the production of free radicals exceeds the antioxidant defense system, oxidative stress begins [20].

In the present study, a significant decrease of brain and serum antioxidant capacity and a significant increase in serum and brain MDA levels as well as in serum NO levels were observed in mice receiving reserpine, indicating reserpine-induced oxidative stress.

In agreement with these results, Bilska et al. (2007) reported that single-dose injection of reserpine was associated with significant reduction in the levels of non-enzymatic antioxidant enzymes glutathione, glutathione disulfide, and s-nitroxytol, a significant decrease in the levels of antioxidant enzymes such as glutathione peroxidase, glutathione-s-transferase, and L- $\gamma$ -glutamyltranspeptidase, as well as in NO levels in striatum and prefrontal cortex in rat [21].

The study by Angélica et al. in 2009 also showed a significant increase in serum MDA level, which is the index of lipid peroxidation, in the brain of mice receiving reserpine [22].

In the present study, treatment with fluoxetine at 20 mg/kg 15 minutes before behavioral testing in mice receiving reserpine, significantly reduced the duration of immobility in the FST and TST. Fluoxetine also significantly increased the antioxidant capacity of the brain and serum, and significantly reduced the MDA levels in the brain and serum. In addition, fluoxetine treatment in mice receiving reserpine significantly reduced serum NO levels. In a study by Ahmed et al. in 2014, treatment with fluoxetine at 20 mg/kg in mice receiving reserpine significantly reduced the duration of immobility in the FST and TST [20], which is in agreement with our results.

Fluoxetine is an antidepressant drug that is widely used to treat a variety of depressive disorders. Fluoxetine is an SSRI; however, it, at high doses, can inhibit reuptake of dopamine and norepinephrine. It is also the agonist of  $\sigma$ 1 (sigma 1) and inhibitor of the calcium-dependent chloride channel. In the study of Ahmed et al. in 2014, fluoxetine treatment in mice receiving reserpine significantly increased the levels of neurotransmitters serotonin, dopamine, and norepinephrine in the brain of mice receiving reserpine. Fluoxetine also significantly increased glutathione levels and antioxidant capacity in the brain and significantly decreased lipid peroxidation [20]. In the study of Galecki et al. in 2009, fluoxetine treatment in patients with depressive disorders was associated with a significant increase in serum antioxidant capacity [23], which is consistent with the current study.

Fluoxetine may lead to certain side effects such as unusual dreams, abnormal ejaculation and other sexual complications, anxiety, dry mouth, cold-like symptoms, insomnia, tremor, nausea, anger, sweating, sleepiness, and skin complications in people with depression that can lead to discontinuation of drugs by some patients. Besides that, a number of patients do not respond appropriately

to treatment. Therefore, the search for compounds with adequate efficacy and few side effects, especially nature-based ones, has begun [23]. In the present study, oleuropein (20 mg/kg) pretreatment for 3 days in rats receiving reserpine for 3 days caused a significant decrease in the duration of immobility in the FST, a significant reduction in brain and serum MDA levels and also serum NO levels, as well as a significant increase in brain and serum antioxidant capacity.

Oxidative stress is associated with disorders of the CNS including neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, and certain mental-psychological disorders such as schizophrenia, depression, and anxiety [24].

Increasing oxidative and nitrate stress parameters following induction of depression in animal models has been reported to be due to reserpine treatment [22], exposure to chronic stress [25], and corticosterone.

The increased production of reactive oxygen and nitrogen species, followed by oxidative and nitrate stress, causes peroxidation of membrane lipid and damage to DNA, proteins, and mitochondria of the nerve cells. The oxidative and nitrate stress following depression in different models has been found to lead to the destruction of key antioxidants such as coenzyme Q10, zinc, vitamin E, glutathione, and glutathione peroxidase. These events accelerate neurodegeneration and apoptosis and reduce neurogenesis and brain plasticity [26].

Antioxidant compounds can prevent depressive behaviors by reducing oxidative and nitrate stress parameters; for example, N-acetylcysteine and curcumin have shown significant antidepressant activity in various animal models of depression as well as in double-blind clinical trials. The mechanism of their action occurs via reducing the oxidative and nitrate stress parameters and inhibiting monoamine oxidases [27].

In the present study, oleuropein was observed to exhibit antidepressant effect in the FST, which was associated with reduction in lipid peroxidation in the brain and serum, decrease of serum NO levels, and increase in antioxidant capacity in the brain and serum. The anti-oxidative stress effects of oleuropein have been shown in a number of previous studies. The study of Al-Azzawie et al. in 2006 showed that in the rabbits with alloxan-induced diabetes orally given oleuropein at 20 mg/kg for 12 months, lipid peroxidation significantly decreased lipid peroxidation, and enzymatic and non-enzymatic antioxidants significantly increased [7]. In the study of Sarbishegi et al. in 2014, oral treatment of older mice with oleuropein at 50 mg/kg for 6 months reduced lipid peroxidation and increased the activity of antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase in the brain and serum [28].

In the study of Pourkhodadad et al. in 2016, oleuropein (10, 15, and 20 mg/kg) administration for 10 days in mice receiving significantly reduced the oxidative stress

parameters and significantly increased the activity of antioxidant enzymes in the brain [29].

In the study of Karabag-Coban et al. in 2016, intraperitoneal injection of oleuropein at 20 mg/kg, showed a protective effect against melatonin-induced oxidative stress. Administration of oleuropein reduced MDA, NO, and 8-hydroxy-2'-deoxyguanosine and prevented the oxidative DNA damage. In addition, the total antioxidant capacity and activity of superoxide dismutase and catalase increased in the blood, liver, and kidneys of the mice given oleuropein [30].

One of the most important problems that causes depression is impaired immune system. Studies have shown that depression, on the one hand, suppresses appropriate responses to infectious agents by inducing responses of type II T helper cells (responses involved in causing allergies and certain antibody-dependent autoimmune diseases), and, on the other hand, causes chronic and malignant inflammation by the immune system such that the inflammation per se leads to exacerbation of depression [31].

Chronic inflammation is one of the physical problems caused by depression. On the other hand, researchers argue that chronic inflammation can be one of the causes of depression [32]. Studies have shown that various molecules are involved in inflammation in patients with depression, the most important of which are inflammatory cytokines [33].

In the study of Liu et al. in 2015, the injection of cytokines IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and lipopolysaccharides induced depression and anxiety-related behaviors in mice [32]. In patients with depression, high levels of IL-6, IL-1 $\beta$ , and TNF- $\alpha$  have been observed [31].

In a study conducted by Arora et al. in 2015, induction of depression in rats by reserpine significantly increased levels of inflammatory factors such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$  [33].

Antidepressant drugs, such as fluoxetine and paroxetine, have also been reported to reduce levels of inflammatory cytokines in the brain and serum of mice with depression [34]. With regards to the evidence of anti-inflammatory effects of oleuropein in previous studies [34, 35], the antidepressant effects of oleuropein could be attributed to inhibition of inflammatory mediators. In an experimental study, oleuropein- and hydroxytyrosol-rich olive extracts were found to significantly decrease the pain and carrageenan-induced foot edema in rat [8].

In another study, oleuropein has been shown to have anti-inflammatory effects in mouse model of spinal cord injury. In rats with spinal cord injury, oleuropein significantly decreased levels of TNF- $\alpha$ , IL-1 $\beta$ , nitrotyrosine, nitric oxide synthase, cyclooxygenase-2, and PARP [8].

In the present study, oleuropein was found to exhibit significant antidepressant effects against depression induced by reserpine injection. Regarding the results

of this study, it seems that the antidepressant effects observed for oleuropein are related to its antioxidant and anti-inflammatory effects. However, other mechanisms, such as the synaptic regulation of neurotransmitters such as serotonin, dopamine, and noradrenaline, and the regulation of the function of the hypothalamus-pituitary-adrenal axis, have also been reported to be related to the antidepressant effects of natural compounds and, particularly medicinal plants, culminating in extensive studies to identify the precise mechanism of the antidepressant action of oleuropein. Additionally, it is recommended that the antidepressant effects of oleuropein in other animal models of depression, such as depression induced by repeated corticosterone injections, depression induced by chronic unexpected stress, and depression due to mother-child separation, be studied.

## Conclusion

It can be argued that reducing the parameters of oxidative and nitrate stress reduces the symptoms of depression in depressed mice receiving reserpine; however, further studies are needed to investigate the antidepressant effects of oleuropein in other models of depression, as well as to precisely identify its mechanism of action.

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