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Artwork by the late Anthony Syndicas

The UK debate around Assisted dying, Dignity in Dying

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Editorial

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This is the last issue this year and we are proud of the quality of papers and the continuous interest in the journal. We are thankful for our readers that keep growing, for our authors, reviewers, editorial board and above all our editorial office and publishing manager.

Alghamdi, et al., did a cross sectional study to assess diabetes prevalence, diagnostic accuracy, and associated factors in Saudi Arabia. A representative sample will be surveyed on demographics, lifestyle, and medical history, with BMI measurements and blood glucose tests for diagnosis. Statistical analysis will identify key factors linked to diabetes. A total of 964 attendees at primary healthcare centers participated, with a mean age of 47.6 years (± 17.1) and a gender distribution of 50.4% female. Initial screenings found that 32.6% were diagnosed with diabetes, 12.9% were pre-diabetic, and 54.6% had normal glucose levels. A follow-up screening showed 36.8% diagnosed with diabetes, 12.9% pre-diabetic, and 50.3% normal. Among 312 confirmed diabetes cases, 30.1% had Type 2 diabetes and 2.3% had Type 1. Factors linked to a diabetes diagnosis included age (higher odds for those over 50), male gender, obesity (6.5 times higher odds), hypertension (3.1 times), and dyslipidemia (3.8 times). The authors concluded that there is a high prevalence of type 2 diabetes in Saudi Arabia's middle-aged and elderly population, with one-third diagnosed. Risk factors include age, obesity, and hypertension. Undiagnosed cases pose serious complications, burdening the healthcare system and requiring enhanced preventive efforts.

Soliena, et al., reviewed shoulder calcific tendonitis. Shoulder calcific tendonitis is a pathological condition characterized by the deposition of calcium hydroxyapatite crystals within the tendons of the rotator cuff. This condition manifests clinically with acute or chronic shoulder pain, restricted range of motion, and significant functional impairment. Diagnostic evaluation includes a thorough physical examination complemented by imaging modalities such as radiography, ultrasonography, and magnetic resonance imaging (MRI) to identify and assess the extent of calcific deposits. Management strategies encompass conservative treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) and structured physical therapy programs, as well as interventional approaches like corticosteroid injections, ultrasound-guided lavage, extracorporeal shock wave therapy, and surgical intervention in refractory cases. Early and accurate diagnosis, coupled with an individualized treatment plan, is imperative for optimal patient outcomes and the restoration of shoulder function.

Kharel et al., did a cross-sectional study to compare the growth patterns of breast fed and formula fed babies of Duwakot. Several research studies have identified breastfeeding as a significant factor for normal infant growth and development. Childhood obesity is the major ailments seen in formula fed infants which clearly demonstrates the protective role and effect of the exclusive breastfeeding. The objective of this study was to compare the physical health among exclusive breastfed and formula fed infants. The aim of our study was to find Exclusive Breastfeeding and its impact on child's physical growth parameters among formula fed and exclusive breastfed. This was. The growth patterns of 81 exclusive breastfed babies (39 males, 42 females) and 81 formula fed babies (44 males, 37 females) were compared. The

weight for age (WA), Height for age (HA), and weight for Height (WH) Z scores were calculated in 6 to 24 months babies by WHO Anthro Software Version 3.2.2. The prevalence of overweight in exclusively breastfed infant was 6.1% (> +2SD)) and formula fed infant was 17.3%. The prevalence of overweight was significantly higher among formula fed infants. The prevalence of obesity in formula fed infants was 2.5% (> +3SD)) and 1.2% in breastfed infants. The study revealed that overweight was significantly associated with formula fed but no statistically significant difference was observed in the other physical parameters like wasting, stunting and underweight. In Breastfed infants the mean Z score for WA was -0.22, WH was 0.1 and BMI was 0.06 whereas in formula fed infants the mean Z score for WA was 0.3, WH was 0.68 and BMI was 0.71. The authors concluded that the physical growth pattern of exclusive breast fed and formula fed Nepalese babies showed overweight tendency in formula fed babies as compared to breastfed babies.

Helvaci, et al., looked at whether metformin help in prevention of stroke. All patients with sickle cell diseases (SCD) were included. They studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, $p>0.05$, respectively). Smoking (23.8% vs 6.1%, $p<0.001$), alcohol (4.9% vs 0.4%, $p<0.001$), transfused red blood cells (RBC) in their lives (48.1 vs 28.5 units, $p=0.000$), disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), coronary heart disease (CHD) (18.0% vs 13.2%, $p<0.05$), cirrhosis (8.1% vs 1.8%, $p<0.001$), chronic obstructive pulmonary disease (25.2% vs 7.0%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), digital clubbing (14.8% vs 6.6%, $p<0.001$), chronic renal disease (9.9% vs 6.1%, $p<0.05$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher in males, significantly.The authors concluded as a prototype of systemic atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with end-organ failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for the development of atherosclerosis, and stroke and CHD are the two terminal causes of death with any underlying etiology. The efficacy of metformin in loss of appetite is well known for several years. Since metformin is a safe, cheap, orally used, and effective drug for excess weight, it should be prescribed for prevention of stroke after the age of 50 years even in normal weight individuals, since there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight.

Dr. Elghblawi, reviewed the UK debate around Assisted dying, Dignity in Dying? Assisted dying is a conflict-ridden and debatable subject, and a broad range of interests should inform any proposed policy changes to promote autonomy and end and mitigate intense suffering by providing a ‘safe and comfortable’ death to patients who believe they would otherwise have to endure unbearable suffering at the end of life. Some could argue that palliative care can’t do it all, especially with its inconstant availability. The British Medical Association (BMA) and some Royal Colleges have recently changed their attitude on physician-assisted suicide from ‘combated’ to forms of ‘impartial’. For the last few years, the toll took the UK system to vote for assisted dying and wanted to legalize it. Some countries have legalized it for some time, and some British nationals fly to have it conducted. The drugs that are being prescribed and administered, are both for physician-assisted suicide (patient ingestion) and for euthanasia (physician-administered).

Prevalence, Diagnosis, and Associated Factors of Diabetes among Primary Healthcare Center Attendees in Saudi Arabia: A Screening Cross-Sectional Study

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Abstract

Background: Diabetes is a widespread chronic condition, with rising cases due to aging, lifestyle, and dietary shifts. Diagnosis relies on blood glucose tests, and early detection is vital for preventing complications. Key factors include genetics, obesity, poor diet and inactivity. Targeted interventions addressing these can help reduce diabetes rates and improve outcomes.

Aim: The main aim is to determine the prevalence of diabetes, improve diagnostic accuracy, and identify associated key factors.

Methods: This cross-sectional study assessed diabetes prevalence, diagnostic accuracy, and associated factors. A representative sample was surveyed on demographics, lifestyle, and medical history, with BMI measurements and blood glucose tests for diagnosis. Statistical analysis was used to identify key factors linked to diabetes.

Results: A total of 964 attendees at primary healthcare centers participated, with a mean age of 47.6 years (± 17.1) and a gender distribution of 50.4% female. Initial screenings found that 32.6% were diagnosed with diabetes, 12.9% were pre-diabetic, and 54.6% had normal glucose levels. A follow-up screening showed 36.8% were diagnosed with diabetes, 12.9% pre-diabetic, and 50.3% normal. Among 312 confirmed diabetes cases, 30.1% had Type 2 diabetes and 2.3% had Type 1. Factors linked to a diabetes diagnosis included age (higher odds for those over 50), male gender, obesity (6.5 times higher odds), hypertension (3.1 times), and dyslipidemia (3.8 times).

Conclusion: The study reveals a high prevalence of type 2 diabetes in Saudi Arabia's middle-aged and elderly population, with one-third diagnosed. Risk factors include age, obesity, and hypertension. Undiagnosed cases pose serious complications, burdening the healthcare system and requiring enhanced preventive efforts.

Keywords:
Diabetes screening, Prevalence of diabetes, Type of diabetes, Risk factor, Saudi Arabia

Introduction

Globally, the prevalence of diabetes is steadily rising in both high- and low-income nations, making it a serious global health concern [1]. According to the International Diabetes Federation (IDF), 537 million adults between the ages of 20 and 79 had diabetes in 2023; if current trends continue, this number is expected to increase to 783 million by 2045 [2]. While Type 1 diabetes (T1D) and gestational diabetes continue to have a substantial global burden, Type 2 diabetes (T2D) makes up the majority of cases. The Western Pacific, North Africa, and the Middle East have the highest prevalence rates [2, 3]. Aging populations, urbanization, dietary changes, and increased physical inactivity are some of the factors contributing to this rising prevalence [4, 5]. The COVID-19 pandemic has further exacerbated diabetes-related complications, highlighting the urgent need for comprehensive public health strategies to mitigate the impact of diabetes worldwide [6]. The growing burden of diabetes is placing substantial strain on healthcare systems, with costs associated with care and management increasing rapidly [7].

In recent years, there has been a significant increase in the prevalence of diabetes in Saudi Arabia, aligning with global trends of urbanization, lifestyle changes, and rising obesity rates [8-10]. Current estimates indicate that approximately 18.5% of the adult population in Saudi Arabia has diabetes, with Type 2 diabetes (T2D) making up the majority of these cases [9, 10]. Over the past decade, the prevalence of diabetes among Saudi adults has risen by nearly 2% per year, reflecting a substantial rise compared to previous years. Obesity, a major risk factor for Type 2 diabetes, affects nearly 35% of adults in the country and serves as a significant contributor to this alarming trend [11]. Additionally, sedentary lifestyles, unhealthy eating habits, and rapid urbanization are further exacerbating the increasing rates of diabetes. A national survey conducted in 2021 found that nearly 30% of individuals aged 45 to 64 were living with diabetes, with the highest prevalence observed in those over 65 years of age [12, 13].

For early intervention and better health outcomes, screening for diabetes-related complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy is essential [14]. Healthcare professionals can identify high-risk patients and promptly implement treatment plans when screening protocols are effective. This strategy lowers diabetes-related morbidity and mortality [15]. Furthermore, comorbid conditions like obesity, dyslipidemia, and hypertension make managing diabetes more difficult and put a greater strain on medical resources [16]. People with diabetes frequently have comorbid conditions, which makes treatment adherence and clinical outcomes even more difficult [17]. The current study aimed to assess the prevalence, types, and risk factors of diabetes among screened primary healthcare attendants in Saudi Arabia.

Methodology

A screening study was conducted for attendants of primary health care centers where persons coming for regular follow-up, or those for screening, were included after explaining the purpose of the study. Those aged 18 years or more, not previously diagnosed with diabetes were invited to participate in the study. After giving their consent, participants were directly interviewed using a pre-structured questionnaire covering their demographic data, weight, height, medical history, and laboratory findings mainly fasting blood glucose level (FBS) and HbA1c. For the initial screening test, persons were categorized into normal, pre-diabetic, and diabetic persons. Then, FBS and HBA1c tests were repeated if the initial HbA1C was ≥6.5% or FBS ≥126 mg%) to confirm the diagnosis (see the attached pathway plan (Figure 1)). Finally, screened persons were confirmed to be diabetic or not, and diabetics were classified into type I and type II diabetes.

Data analysis

The data were collected, reviewed, and then fed into Statistical Package for Social Sciences version 26 (Released 2019. Armonk, NY: IBM Corp). All statistical methods used were two-tailed with an alpha level of 0.05 considering significance if P value is less than or equal to 0.05. Descriptive analysis for categorical data was done using frequencies and percentages, whereas numerical data were presented as mean with standard deviation. The participants' data were tabulated while the diabetes category and type were graphed. Also, participants' laboratory findings were compared by their diabetes category. Cross tabulation was done showing factors associated with diabetes diagnosis using crude and adjusted odds ratio and its 95% confidence interval based using Pearson Chi-Square test and logistic regression models.

Results

A total of 964 eligible attendants to the primary health care centers were included in the screening. Attendants' ages ranged from 18 to 68 years with a mean age of 47.6 ± 17.1 years old. Exactly 486 (50.4%) participants were females. The vast majority came for follow-up (95.1%; 917) while 47 (4.9%) came for screening. As for initial screening results, 314 (32.6%) were diagnosed as diabetic, 124 (12.9%) were pre-diabetic and 526 (54.6%) were normal. At the repeated screening, 355 (36.8%) were categorized as diabetic, 124 (12.9%) as pre-diabetic, and 485 as normal. The assessed mean FBS among study participants was 121.9 ± 59.5 mg/dl and the average HbA1c was 7.7 ± 1.9% (Table 1).

Figure 1. Prevalence and type of diabetes among screened study attendants of primary health care centers. Exactly 312 (32.4%) were confirmed to have DM, where 290 (30.1%) had type II DM and 22 (2.3%) had type I DM.

Table 2 presents factors associated with a confirmed diagnosis of diabetes among primary healthcare center attendees. As for age, the likelihood of having a confirmed diabetes diagnosis increased with age, with individuals aged 51-60 and over 60 years exhibiting the highest odds of having diabetes (ORA= 1.3, 95% CI 1.01–2.0; p-value = 0.001). Also, males had higher odds of having diabetes compared to females (ORA= 1.6, 95% CI 1.2–2.2; p = 0.017). As for obesity, it was strongly associated with diabetes diagnosis, as individuals with obesity were 6.5 times more likely to be diagnosed with diabetes (ORA= 6.5, 95% CI 4.2–10.3; p = 0.001). Likewise, patients with hypertension had 3.1 times the odds of being diagnosed with diabetes compared to those without hypertension (ORA= 3.1, 95% CI 1.9–6.3; p-value= 0.001). Finally, dyslipidemia was also strongly associated with diabetes, with individuals having dyslipidemia being 3.8 times more likely to have a confirmed diabetes diagnosis (ORA= 3.8, 95% CI 2.3–6.3; p = 0.001).

Table 3 illustrates laboratory findings among study participants by their diabetes category. Regarding Fasting Blood Sugar (FBS), Normal group: The average FBS level in individuals with normal glucose metabolism was 92.9 mg/dL (SD = 15.4), which is within the normal range (typically 70-100 mg/dL). T1DM group: The average FBS in individuals with Type 1 diabetes (T1DM) was 218.2 mg/dL (SD = 103.4), significantly higher than that in the normal group. This is consistent with the typical hyperglycemia observed in uncontrolled Type 1 diabetes. T2DM group: The average FBS in individuals with Type 2 diabetes (T2DM) was 182.6 mg/dL (SD = 67.0), also elevated compared to normal, but generally lower than that observed in the T1DM group. All these differences were statistically significant (P<0.001). As for HbA1c (%), Normal group: The mean HbA1c for individuals with normal glucose metabolism was 6.1% (SD = 0.5), which is within the normal range (typically < 5.7% for healthy individuals). T1DM group: The mean HbA1c for individuals with Type 1 diabetes (T1DM) was significantly higher at 9.2% (SD = 2.6), reflecting poor long-term glucose control, which is common in Type 1 diabetes patients, especially if they have difficulty managing insulin therapy. T2DM group: The mean HbA1c in Type 2 diabetes (T2DM) was 8.3% (SD = 1.9), which was lower than that in T1DM.

Table 1. Personal characteristics of study participants who have undergone diabetes screening, in Saudi Arabia (n=964)

Data	No	%
Age in years		
18-30	188	19.5%
31-40	143	14.8%
41-50	174	18.0%
51-60	211	21.9%
> 60	248	25.7%
Mean ± SD	47.6 ± 17.1	
Gender		
Male	478	49.6%
Female	486	50.4%
Type of Visit		
Follow up	917	95.1%
Screening for diabetes	47	4.9%
HbA1C/FBS Category		
Normal	526	54.6%
Prediabetes	124	12.9%
DM	314	32.6%
Repeated HbA1C/FBS Category		
Normal	485	50.3%
Prediabetes	124	12.9%
DM	355	36.8%

Figure 1. Prevalence and type of diabetes among screened study attendants of primary health care centers (n=964)

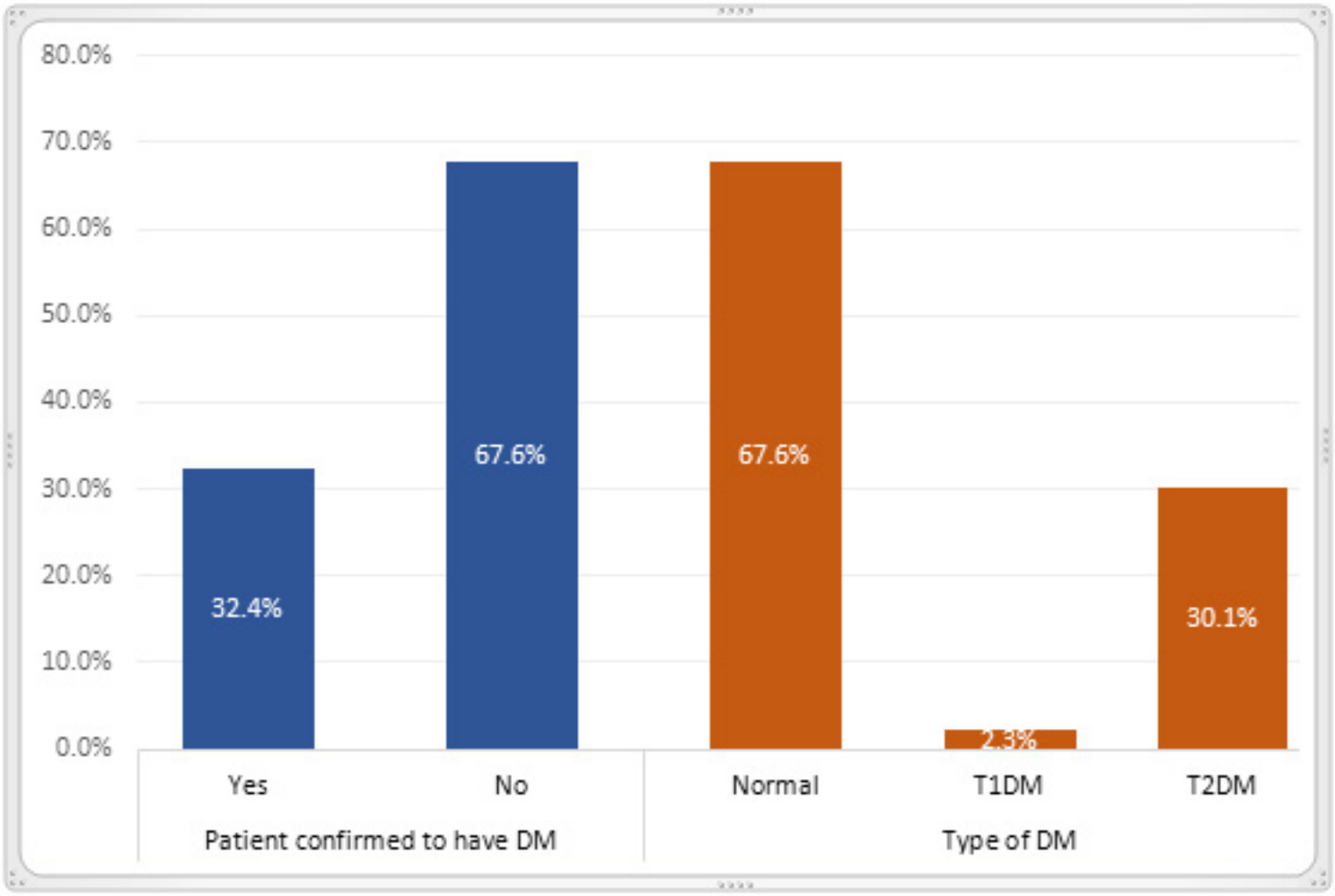

Table 2. Factors associated with a confirmed diagnosis of diabetes among screened study attendants of primary health care centers (n=964)

Factor	The patient confirmed to have DM				p-value	OR_C (95% CI)	OR_A (95% CI)
	Yes		No				
	No	%	No	%			
Age in years							
18-30	19	10.1%	169	89.9%			
31-40	20	14.0%	123	86.0%			
41-50	46	26.4%	128	73.6%	.001*	1.8 (1.6-2.1)	1.3 (1.01-2.0)
51-60	102	48.3%	109	51.7%			
> 60	125	50.4%	123	49.6%			
Gender							
Male	172	36.0%	306	64.0%	.017*	1.4 (1.1-1.8)	1.6 (1.2-2.2)
Female	140	28.8%	346	71.2%		1	1
Obesity							
Yes	138	71.9%	54	28.1%	.001*	8.7 (6.1-12.6)	6.5 (4.2-10.3)
No	174	22.5%	598	77.5%		1	1
HTN							
Yes	109	63.4%	63	36.6%	.001*	5.0 (3.5-7.1)	3.1 (1.9-6.3)
No	203	25.6%	589	74.4%		1	1
Dyslipidemia							
Yes	132	73.7%	47	26.3%	.001*	9.4 (6.5-13.6)	3.8 (2.3-6.3)
No	180	22.9%	605	77.1%		1	1

P: Pearson X^2 test *ORC: Crude odds ratio* *ORA: Adjusted odds ratio* ** P < 0.05 (significant)*

Table 3. Laboratory findings among screened study attendants of primary health care centers by their diabetes category

Lab tests	Type of DM						p-value
	Normal		T1DM		T2DM		
	Mean	SD	Mean	SD	Mean	SD	
FBS	92.9	15.4	218.2	103.4	182.6	67.0	.001*
HbA1C (%)	6.1	0.5	9.2	2.6	8.3	1.9	.001*

P: One Way ANOVA
* P < 0.05 (significant)

Discussion

The study sample features a diverse age distribution, with the largest group (25.7%) over 60 years old, followed by age 51-60. Notably, 19.5% of participants were aged 18-30, which is high for a diabetes screening study. Research from other regions, such as the U.S. and Europe, shows similar trends, with a greater proportion of diabetes screenings occurring among middle-aged and older individuals. This pattern reflects the increased risk of diabetes associated with age. For instance, a study by Gerstein et al. [18] in the United States reported that the prevalence of Type 2 diabetes rises significantly after the age of 45, which is consistent with the findings of this study. Similarly, a study by Moller et al. [19] in Europe highlighted that diabetes screenings are more frequently targeted at individuals aged 45 and older, due to the elevated risk of both prediabetes and diabetes in these age groups. Overall, both studies emphasize that diabetes screenings are more common in middle-aged and elderly populations because of their higher susceptibility to the disease.

The current study found that about one-third of participants in primary health care centers had diabetes mellitus (DM), with type II diabetes mellitus accounting for the majority of cases and type I diabetes mellitus (T1DM) accounting for a smaller percentage. These results are consistent with a larger regional and global trend in which T2DM is significantly more prevalent than T1DM, primarily as a result of lifestyle factors like dietary habits, physical inactivity, and rising obesity rates, particularly in urban areas. A national survey conducted in Saudi Arabia found that the overall prevalence of diabetes was approximately 28.8%, with T2DM as the predominant form consistent with the current study findings [20]. A more recent nationwide survey, the Saudi Diabetes Survey in 2019, assessed the prevalence of Type 2 diabetes (T2D) among adults in Saudi Arabia to be nearly 25.5% [21]. The survey revealed that approximately 30% of individuals with diabetes are undiagnosed, highlighting the crucial need for regular screening and early detection. This high rate of undiagnosed cases indicates that many people with diabetes may not be receiving adequate care, which increases their risk of complications such as cardiovascular disease, kidney failure, and neuropathy. A study conducted by Al-Daghri et al. [22] highlighted the significant burden of diabetes in Saudi Arabia, revealing that approximately 30% of the adult population suffers from prediabetes. The authors emphasized that prediabetes is a major risk factor for the progression to Type 2 diabetes, making early screening and intervention essential for preventing the full onset of the disease.

Saudi Arabia has one of the highest rates of diabetes worldwide when comparing its prevalence to that of other regions. The International Diabetes Federation (IDF) Global Diabetes Atlas (2021) states that the prevalence of diabetes in adults worldwide is approximately 9.3%, whereas rates are much higher in the Middle East and North Africa (MENA) region, which includes Saudi Arabia [23]. The prevalence is almost twice as high in Saudi Arabia as it is worldwide, which puts a significant burden on the healthcare system. Research conducted in the U.S. and Europe indicates a rising trend of diabetes prevalence with increasing age, particularly among individuals aged 45 and older, as highlighted in studies by Gerstein et al. [24] and Moller et al. [19]. In the USA, it was reported that diabetes prevalence among adults is around 10.5%, with T2DM constituting the majority [25].

The prevalence of Type 1 Diabetes Mellitus (T1DM) among adults in this study is 2.3%, which aligns with international statistics indicating that T1DM typically accounts for 5-10% of all diabetes cases [26]. Unlike Type 2 Diabetes, T1DM is less affected by lifestyle factors; it is primarily caused by the autoimmune destruction of pancreatic beta cells. Regional and global studies show that while the overall prevalence of T1DM is nearly stable, it is increasing among younger age groups in high-income countries. This trend highlights the importance of ongoing monitoring and the implementation of prevention strategies for that type which starts early in life, with more burden on diagnosed patients [27].

Regarding the risk factors, this study highlights several significant factors associated with a confirmed diagnosis of diabetes. Age, gender, obesity, hypertension, and dyslipidemia all emerged as significant predictors of diabetes diagnosis. The likelihood of being diagnosed with diabetes increased with age, particularly among individuals aged 51-60 years and those over 60 years, reflecting findings from previous studies such as those by Gerstein et al. [28], which show that diabetes risk escalates with age. Additionally, males were found to have higher odds of diabetes diagnosis compared to females, a gender difference also reported in other studies like that of Al-Daghri et al. [22], suggesting that men may be at greater risk due to factors like abdominal fat distribution and lifestyle behaviors. Obesity was the strongest predictor, with obese individuals being 6.5 times more likely to be diagnosed with diabetes, which is consistent with many previous studies [29-31]. Hypertension and dyslipidemia were also strongly

associated with diabetes which is consistent with findings from the National Health and Nutrition Examination Survey (NHANES) and many other studies [32-35]. These findings underscore the importance of early screening for individuals with these risk factors, particularly in regions like Saudi Arabia, where the burden of diabetes is rapidly increasing.

Conclusions and Recommendations

This study reveals a high prevalence of diabetes, particularly type 2 diabetes mellitus (T2DM), among middle-aged and elderly populations in Saudi Arabia, with roughly one-third of participants diagnosed. These were in line with global trends, as diabetes screenings are more common in older adults due to increased risk. Many cases remain undiagnosed, risking serious complications like cardiovascular disease and kidney failure. The main risk factors, including age, obesity, and hypertension, further highlight the vulnerability of this population. Given the high diabetes rates in Saudi Arabia compared to global averages, there is a significant burden on the healthcare system, necessitating enhanced preventive efforts. So, regular nationwide diabetes screening programs targeting middle-aged and elderly populations, especially those with identified risk factors, should be prioritized to improve early detection and management. Also, the conducting of periodic public health campaigns focused on educating individuals about diabetes risk factors and promoting lifestyle changes that can prevent or delay the onset of T2DM, such as healthy eating, regular physical activity, and weight management.

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Exclusive Breastfeeding and its Impact on Child's Physical Health in Duwakot, Nepal

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Abstract

Background: Several research studies have identified breastfeeding as a significant factor for normal infant growth and development. Childhood obesity is the major ailment seen in formula fed infants which clearly demonstrates the protective role and effect of the exclusive breastfeeding. The objective of this study was to compare the physical health among exclusive breastfed and formula fed infants. The aim of our study was to find the impact of Exclusive Breastfeeding on child's physical growth parameters among formula fed and exclusive breastfed infants.

Materials and Methods: This was a cross-sectional study done to compare the growth patterns of breast fed and formula fed babies of Duwakot. The growth patterns of 81 exclusive breastfed babies (39 male, 42 female) and 81 formula fed babies (44 male, 37 female) were compared. The weight for age (WA), Height for age (HA), and weight for Height (WH) Z scores were calculated in 6 to 24 months babies by WHO Anthro Software Version 3.2.2.

Results: The prevalence of overweight in exclusively breastfed infants was 6.1% (> +2SD) and in formula fed infants was 17.3%. The prevalence of overweight was significantly higher among formula fed infants. The prevalence of obesity in formula fed infants was 2.5% (> +3SD) and 1.2% in breastfed infants. The study revealed that overweight was significantly associated with formula feeding but no statistically significant difference was observed in the other physical parameters like wasting, stunting and underweight. In Breastfed infants the mean Z score for WA was -0.22, WH was 0.1 and BMI was 0.06 whereas in formula fed infants the mean Z score for WA was 0.3, WH was 0.68 and BMI was 0.71.

Conclusion: The physical growth pattern of exclusive breast fed and formula fed Nepalese babies showed overweight tendency in formula fed babies as compared to breastfed babies.

Keywords: Exclusive breastfeeding; Formula fed; Growth pattern.

Introduction

The role of breast feeding on infant health for growth and development has been the subject of scientific interest for decades (1). The consequences of feeding type on infant physical health and development were first noticed more than seven decades ago when breastfed infants were shown to have better cognitive function over non-breastfed infants with normal physical health (2). The relation between breastfeeding and body composition is of considerable significance to human health. Particular interest highlights the vital role of infant feeding in influencing body composition, overweight, and obesity later in life. Systematic reviews that investigated a relation between early feeding and later-life obesity or BMI have been questionable (3, 4). Breast milk and colostrum are the first natural feeding sources for infants, providing all nutrients including vitamins, necessary growth factors and immunological factors, which are vital for the newborn's optimum physical development and health. Duration of exclusive breast feeding and time of introduction of solid foods is a crucial factor that may alter the Child's physical growth and development (5). More remarkable results have been revealed between formula-fed infants and rapid infant weight gain. Formula-fed infants gained weight more rapidly out of proportion to length than breast-fed infants during the first year of life, which results in a higher BMI and therefore, a higher risk for future obesity. It has been stated that breastfeeding may enhance self-regulatory mechanisms on an infant's energy consumption (6, 7). Beneficial effects of breastfeeding for a child's normal physiological mental health may result from the fact that mothers' milk is a rich source of fatty acids and other vital components essential for the brain development and physical growth of infants (8, 9). The physical touch, affection, mother's and child's positive attitude are significantly enhanced during breastfeeding compared with bottle-feeding which help in enhancing physical growth and mental health. Breastfeeding may also be an indicator of other unmeasured maternal characteristics such as maternal intelligence (10).

The WHO recommends that an infant should be exclusively breast fed for six months and then continued breast feeding for two years with supplementary foods along with breast milk. Globally, less than 40% of infants under six months of age are exclusively breast fed. Increase in this rate can be achieved by improving breast feeding awareness for mothers and families (11). Breastfeeding should be initiated during the hour after the birth of baby and allowed till the baby needs During the first few weeks of life babies may be nursed eight to twelve times per day. The normal duration of a feeding is usually ten to fifteen minutes on each breast. The frequency of feeding diminishes as the child gets older (12).

Evaluating and assessing the true influence of breastfeeding on child development is difficult for several reasons. There are many potential confounding factors. Parental and family status, mothers' educational level, child's birth weight and stimulation of the child during infancy are all associated with child's growth and development (2).

Mothers who breastfeed have been found to report lower levels of perceived stress and negative mood, higher levels of maternal attachment, and perceive their infants with high bondinghan mothers who formula-feed (13).

The aim of this study was to find the variations in physical growth patterns among exclusive breast fed and formula fed infants.

Materials and Methods

A community based cross sectional study was conducted in May 2023 - May 2024 after getting ethical clearance and approval from the Institutional Review Committee (IRC) of Kathmandu Medical College. The study populations were the babies aged between 6 and 24 months. Three study subjects of Duwakot were selected by random sampling. 81 exclusively breastfed babies and the same number (81) formula fed babies of ages 6 to 24 months were enrolled in the study.

Anthropometric assessment of the child was done; their weight and height was measured three consecutive times. Later on, mean was taken as their actual weight and height, which helped in calculating the BMI (body mass index). Anthropometric measurement of the baby was done by LG digital weighing machine (with a difference of only 10 gram), Stadiometer and non-stretchable measuring tape. Internationally recognized and accepted WHO Anthro Software Version 3.2.2 (11) was used for the analysis of the data.

Inclusion criteria: The infants were selected randomly from three wards out of seven in Duwakot. The children aged between 6 and 24 months were enrolled for the study.

Exclusion criteria: The Mothers and children who were not in good health and those who were uncooperative.

During primary selection, all mothers were interviewed thoroughly to learn their medical history (including child), food habits, economic status etc. Before the examination, the purpose of the study was explained to all the mothers and written consent was obtained from them.

Results

A total of 162 infants (81 exclusively breastfed & 81 formula fed) aged between 6-12 months were enrolled in the study. Of these 162 participants 51.07% were males and 49.93% were females (Table 1). Among the exclusively breastfeeding mothers, 59.26% (44) were unemployed and 40.74% (33) were employed whereas in formula feeding mothers, 32.10% (26) were unemployed and 67.90% (55) were employed (Table 2).

Males were more overweight compared to females in both the groups. The prevalence of overweight in males in breastfed males and females was 3.9% and 2.2% respectively whereas it was 11.1% and 6.2% in formula fed males and females respectively. Among the breastfed infants 67% had sound sleep whereas in formula fed infants 58% had sound sleep (Table 3).

The infants who were overweight, including obesity in the formula fed group were 17.3% (14) compared to only 6.1% (05) in the breastfed group. The prevalence of obesity in formula fed infants was 2.5% (> +3SD) and 1.2% in breastfed infants. The right shift of histogram in formula fed babies clearly demonstrates the significant differences (Figures 1 & 2).

Table 1: Prevalence of overweight and obesity in the study population

Participants	Total No	No of overweight Children	Percentage Overweight (> +2SD)	Percentage Obese (> +3SD)	Percentage overweight or obese children	Mean Z Score	SD	P Value
Formula fed	81	14	14.8 %	2.5 %	17.3%	0.68	1.33	0.49
Exclusive Breastfed	81	05	4.9 %	1.2%	6.1%	0.10	1.25	0.92

Table 2: Socio-demographic characteristics of breastfed (81) & formula fed (81) infants (6 to 24 months)

Variables	Numbers	Percentage (%)
Sex of the children		
Breastfed		
Male	39	48.18
Female	42	51.82
Formula fed		
Male	44	54.32
Female	37	45.68
Employment of Mothers		
Breastfed		
Employed		
Unemployed	33	40.74
	48	59.26
Formula fed		
Employed	55	67.90
Unemployed	26	32.10
Annual Household Income		
Breastfed		
Less than 2000$	15	18.51
2000 $ to 5000 $	46	56.79
More than 5000$	20	24.70
Formula fed		
Less than 2000$	08	09.87
2000 $ to 5000 $	47	58.02
More than 5000$	26	32.11

Table 3: Life style factors of the study children

Variables	Numbers	Percentage (%)
Feeding trends		
Breastfed		
Usually takes normal meals	56	69.13
Difficulty in taking normal meals	21	25.92
Overeating trend	04	04.95
Formula fed		
Usually takes normal meals	46	56.79
Difficulty in taking normal meals	23	28.39
Overeating trend	12	14.82
Eating habit		
Breastfed		
Watches TV/Tablets/Mobiles in Duwakot, Nepal	33	40.74
Doesn't watch anything while eating	48	59.26
Formula fed		
Watches TV/Tablets/Mobiles while eating	42	51.85
Doesn't watch anything while eating	39	48.15
Sleeping habit		
Breastfed:		
< 6 hours	13	16.04
6-8 hours	14	17.28
>8 hours	54	66.68
Formula fed		
< 6 hours	15	18.51
6-8 hours	19	23.45
>8 hours	47	58.04

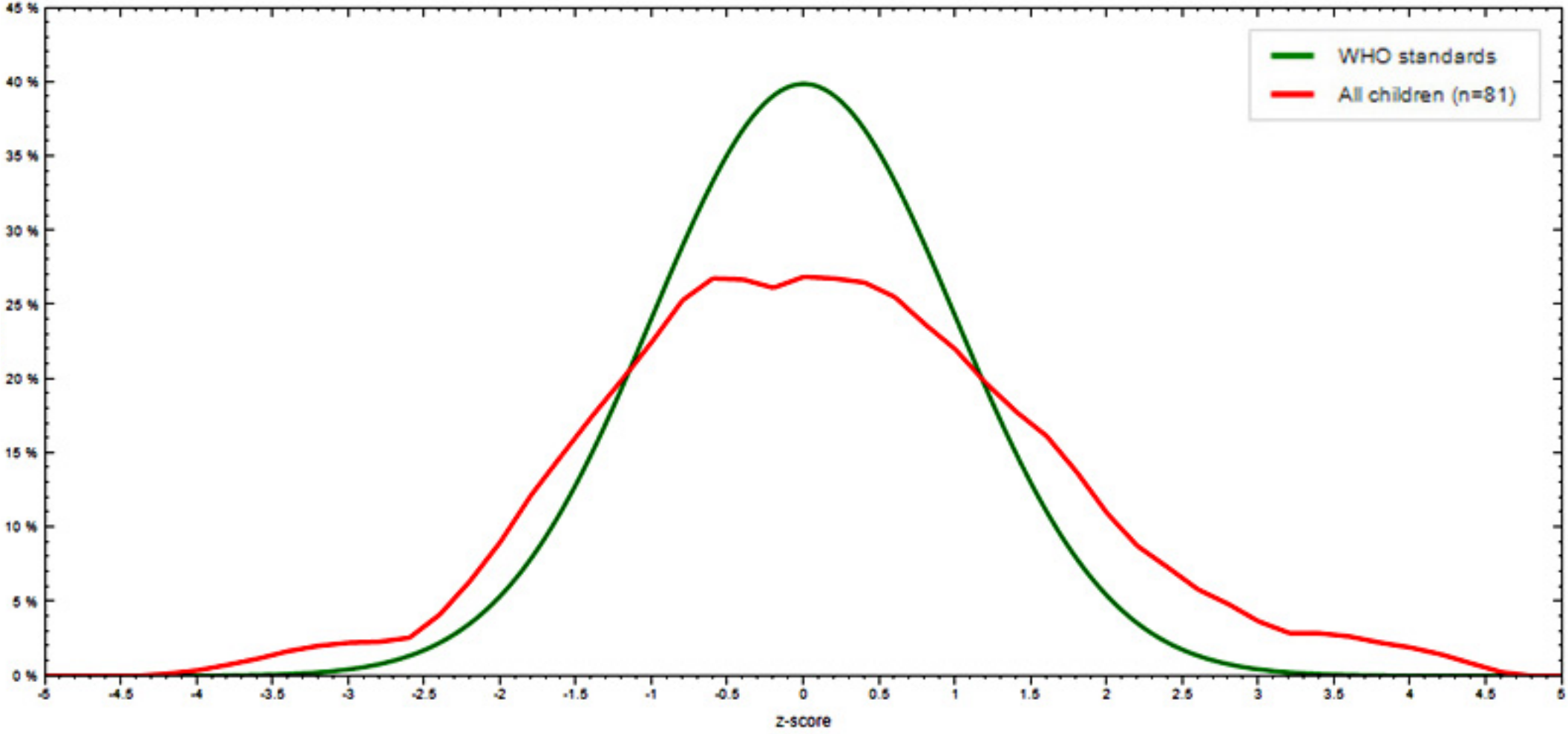

Figure 1: Distribution of breastfed babies with respect to WHO standards (N=81).

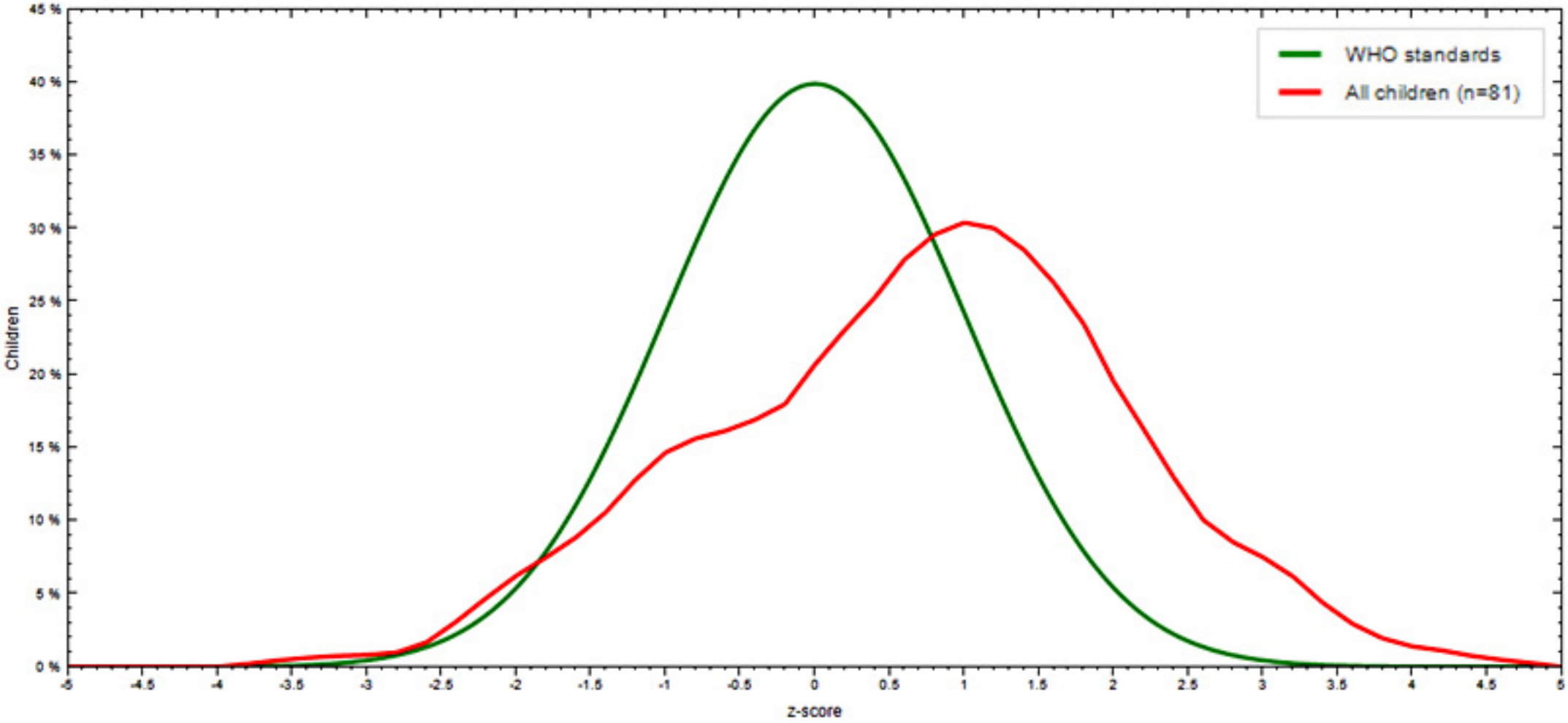

Figure 2: Distribution of formula fed babies with respect to WHO standards (N=81).

Discussion

This cross-sectional study was done to determine the variations in physical health patterns in exclusively breast fed and formula fed infants in urban city of Nepal.

According to our study results in their physical growth, significant difference was found between the breast fed and formula fed babies in terms of overweight and obesity. The higher prevalence of overweight was seen in formula fed infants as compared to breast fed infants. The infants who were overweight, including obesity, in formula fed were 17.3% compared to only 6.1% (05) in breastfed. The prevalence of obesity in formula fed infants was 2.5% (> +3SD)) and 1.2% in breastfed infants. No significant differences were seen in other parameters like wasting, underweight and stunting in the two groups. Our results show similar trends with other studies which also found that children introduced to formula within four months have increased risk of overweight in Western Australia(14), prevalence of childhood obesity in the United States (US) and overweight or obesity trends in the UK based on a very large cohort study (15, 16). Unlike our study results a study done by Ahmed, et al. showed no statistical significant differences between the weight, length, head, and chest circumference of breast-fed and formula fed infants in relation to anthropometric measurements although they studied infants up to 3 months only (17). A very convenient recent study has shown that the development of electrical activity in the brain during infancy differs between those who are breastfed and those fed either with cow's milk or soya milk (18). These studies suggest that the differences in brain electrical activity between breastfed and milk-formula-fed infants could have been influenced by omega-3 polyunsaturated fatty acids that are normally present in breast milk or other bioactive components essential for physical development of a child. There are other possible causes that may explain the relation between breastfeeding and sound maternal attachment status, which has been shown to have a positive influence on the child's psychological and physiological development into later age (19, 20). Moreover, in a similar type of study of 675 mother–infant dyads, longer duration of breastfeeding was associated with mothers' sensitive responsiveness, enhanced attachment security, and diminished attachment disorganization when infants were 14 months of age (21). In another similar study they also found that breast fed infants have better physical growth compared to infants on formula feeding. Moreover, the length was also greater with breast feeding than formula fed infants. The results of our study support the WHO expert recommendations on exclusive breastfeeding for six months (11). Moreover, our study also provides evidence that exclusive breastfeeding of infants brings about beneficial effects in the physical growth of children.

Conclusion

Our study results showed that formula fed infants were overweight compared to exclusively breastfed infants; however no statistically significant difference was observed in the other physical parameters like wasting, stunting and underweight in breast fed and formula fed infants. In our study we found that the overweight tendency in formula fed babies was related to overeating, job compulsion of mothers and socioeconomic factors.

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Conflict of interests: None

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Metformin in prevention of stroke

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Abstract

Background: Atherosclerosis may be the major underlying cause of aging and death.

Methods: All patients with sickle cell diseases (SCD) were included.

Results: We studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBC) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), coronary heart disease (CHD) (18.0% vs 13.2%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), chronic renal disease (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly.

Conclusion: As a prototype of systemic atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with end-organ failure in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for the development of atherosclerosis, and stroke and CHD are the two terminal causes of death with any underlying etiology. The efficacy of metformin in loss of appetite is well known for several years. Since metformin is a safe, cheap, orally used, and effective drug for excess weight, it should be prescribed for prevention of stroke after the age of 50 years even in normal weight individuals, since there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight.

Key words: Sickle cell diseases, stroke, coronary heart disease, excess fat tissue, vascular endothelial inflammation, atherosclerosis, aging

Introduction

Chronic endothelial damage may be the major cause of aging and death by causing end-organ failures in human being (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, emotional stress, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, and dementia-like end-organ insufficiencies and aging, the endothelial changes cannot be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the vascular process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature (4-6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with an advanced atherosclerosis-induced end-organ insufficiencies in much earlier ages of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the cases with associated thalassemia minors (TM), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and additional stresses of the body. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened RBC into the tissues. The hardened RBC-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages. Vascular narrowings and occlusions-induced tissue ischemia and end-organ insufficiencies are the final consequences, so the mean life expectancy is decreased by 25 to 30 years for both genders in the SCD (8).

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, acute painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, since the SCD with associated TM show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of higher than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the

cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively), and there was no patient above the age of 59 years in both genders. Prevalences of associated TM were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample sizes (Table 2). On the other hand, mean ages of the other atherosclerotic consequences in the SCD were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
CHD§	***18.0% (40)***	***<0.05***	***13.2% (28)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
COPD¶	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Coronary heart disease
¶Chronic obstructive pulmonary disease **Chronic renal disease ***Pulmonary hypertension
****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

Excess fat tissue may be the most common cause of disseminated vasculitis all over the world at the moment, and it may be one of the terminal endpoints of the metabolic syndrome, since after development of excess weight, nonpharmaceutical approaches provide limited benefit either to improve excess weight or to prevent its complications. Excess fat tissue may lead to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat tissue in all age groups (19). The low-grade chronic inflammation may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (20). Excess fat tissue is associated with many coagulation and fibrinolytic abnormalities suggesting that it causes a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22). For example, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (23). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since excess fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (24). On the other hand, individuals with excess fat tissue will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excess fat tissue. In addition to the common comorbidity of atherosclerosis and HT, the prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased with increased body mass index (BMI) (25). Similarly, the prevalences of CHD and stroke increased parallel with the increased BMI values (26). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess fat tissue for both genders in all age groups (27). The excess fat tissue may be the most common cause of accelerated atherosclerotic process all over the body at the moment, the individuals with underweight may even have lower biological ages (27). Similarly, calorie restriction extends lifespan and retards age-related chronic diseases in human being (28).

Smoking may be the second most common cause of disseminated vasculitis all over the world. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in whole body (29). Its atherosclerotic effect is the most obvious in the COPD and Buerger's disease (30). Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been documented in the absence of smoking. Its characteristic findings are acute inflammation and stenoses and occlusions of arteries and veins of the hands and feet. It is usually seen in young males between the ages of 20 and 40 years. Claudication may be the most common initial symptom. It is an intense pain caused by insufficient blood flow during exercise in feet and hands but it may even develop at rest in severe cases. It typically begins in extremities but it may also radiate to more central areas in advanced cases. Numbness and tingling of the limbs are also common. Raynaud's phenomenon may also be common in which fingers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of fingers and toes are the final consequences. Gangrene of fingertips may even need amputation. Unlike many other forms of vasculitis, Buerger's disease does not keep other organs with unknown reasons, yet. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be important in the development of Buerger's disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic for Buerger's disease. In angiogram, stenoses and occlusions in multiple areas of arms and legs are seen. In order to rule out some other forms of vasculitis by excluding involvement of vascular regions atypical for Buerger's disease, it is sometimes necessary to perform angiograms of other body regions. Skin biopsies are rarely required, since a biopsy site near a poorly perfused area will not heal, completely. Association of Buerger's disease with tobacco use is clear. Most of the patients are heavy smokers, and the disease can also be seen in users of smokeless tobacco. The limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed stenoses and occlusions are irreversible. Due to the clear evidence of inflammation of the disorder, anti-inflammatory dose of aspirin plus low-dose warfarin may probably be effective to prevent microvascular infarctions in fingers and toes at the moment. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and C-reactive protein may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (31). Similarly, it is not an unexpected result that smoking was associated with the lower values of BMI due to the systemic inflammatory effects on vascular endothelium (32). In another definition, smoking causes a chronic inflammation in human body (33). Additionally, some evidences revealed an increased heart rate just after smoking even at rest (34). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (35). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (36). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with

the following years (37). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher prevalences of white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (38). Beside that the prevalence of myocardial infarction is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (39). In another word, smoking may be more dangerous for women about the atherosclerotic endpoints probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (40). There may be several underlying mechanisms to explain these associations (41). First of all, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis, loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (42). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) (40).

Stroke is one of the two terminal causes of death with any underlying etiology, and develops as an acute thromboembolic event on the chronic atherosclerotic background. Although the aging, male gender, smoking, and alcohol may be found among the major underlying causes, excess fat tissue may actually be the most common cause all over the world at the moment. There are around 20 kg of excess fat tissue between the lower and upper borders of normal weight, 35 kg between the lower borders of normal weight and obesity, 66 kg between the lower borders of normal weight and morbid obesity (BMI ≥ 40 kg/m2), and 81 kg between the lower borders of normal weight and super obesity (BMI ≥ 45 kg/m2) in adults. In fact, there is a significant percentage of adults with a heavier fat mass than their organ plus muscle masses in their bodies. This excess fat tissue brings a heavy stress on liver, lungs, kidneys, heart, and of course on brain. Beside the above underlying etiologies, stroke is also a common complication of the SCD (43). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (44). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (45). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation, edema, and fibrosis (46).

CHD is the other terminal cause of death with any underlying etiology. The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaque is a gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial wall in decades. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheromas to rupture. After the myocardial infarction, a collagen scar tissue forms in its place. This scar tissue may also cause potentially life threatening arrhythmias since the injured heart tissue conducts electrical impulses more slowly than the normal heart tissue. The difference in conduction velocity between the injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be cause of many lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Another life threatening arrhythmia is ventricular tachycardia that may also cause sudden cardiac death. Ventricular tachycardia usually results in rapid heart rates which prevent effective pumping. Cardiac output and blood pressure may fall to dangerous levels which can lead to further coronary ischemia and extension of infarct. This scar tissue may even cause ventricular aneurysm, rupture, and sudden death. Physical inactivity, sedentary lifestyle, emotional stress, animal-rich diet, excess fat tissue, smoking, alcohol, chronic infection and inflammations, and cancers are important in atherosclerotic plaque formation in time. Physical inactivity is important since moderate physical exercise is associated with a 50% reduced incidence of CHD (47). Probably, excess fat tissue may be the most frequent cause of CHD, too.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess fat tissue all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (48). NAFLD is a marker of pathological fat deposition combined with a low-

of colorectal cancers (72). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 12 years (73). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (74). Reye syndrome is a rapidly worsening brain disease (74). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (75). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (75). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (74). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (74). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (74). The cause of Reye syndrome is unknown (75). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (75, 76). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (74). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (75). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (75). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (77).

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (78). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (79). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (80). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (81). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (80). The risk is particularly increased once the INR exceeds 4.5 (81). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (82). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (83). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) (83). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (84). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (84). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (84). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between ($p>0.05$) (84). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTE), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran

are safe and effective for preventing recurrent VTE in patients with CVT (85). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (86). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (87). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022) (87). The mortality was markedly lower in the warfarin group, too (p= 0.005) (87). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) (87). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (88). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (88). The average daily dose was 2.6 mg, and the mean INR was 1.5 (88). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (89). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (90). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study (91). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCD (92). So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCD (93).

COPD is the third leading cause of death with various underlying etiologies in whole world (94, 95). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the most significant cause of COPD all over the world due to the excess fat tissue-induced systemic atherosclerotic process in whole body. After smoking and excess fat tissue, regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (96). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (97). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (23, 98). For example, there may be close relationships between COPD, CHD, PAD, and stroke (99). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (100). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (100). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (101). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (94).

Leg ulcers are seen in 10% to 20% of the SCD (102), and the ratio was 13.5% in the present study. Its prevalence increases with aging, male gender, and SCA (103). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (102). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (102). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (103). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities, again. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (104). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (105). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive

process is probably exaggerated by the patients' own immune systems in the SCD. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (66). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial inflammation and edema instead of the terminal fibrosis alone.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (106). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (107). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional role of male gender in the systemic atherosclerotic process.

CRD is also increasing all over the world that can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (108). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (109). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (110). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (108). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess fat tissue (111). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (111). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (112). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess fat tissue, CRD progresses much more easily (111). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (113). Although some authors reported that alcohol was not related with the CRD (113), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (112). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (114, 115). For example, the most common cause of death was the cardiovascular diseases in the CRD again (116). The hardened RBC-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (117).

As a conclusion, hardened RBC-induced capillary endothelial damage initiating at birth terminates with end-organ failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for the development of atherosclerosis, and stroke and CHD are the two terminal causes of death with any underlying etiology. The efficacy of metformin in loss of appetite is well known for several years. Since metformin is a safe, cheap, orally used, and effective drug for excess weight, it should be prescribed for prevention of stroke after the age of 50 years even in normal weight individuals, since there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight.

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Shoulder calcific tendonitis (Symptoms, Diagnosis and treatment options)

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Abstract

Shoulder calcific tendonitis is a pathological condition characterized by the deposition of calcium hydroxyapatite crystals within the tendons of the rotator cuff. This condition manifests clinically with acute or chronic shoulder pain, restricted range of motion, and significant functional impairment. Diagnostic evaluation includes a thorough physical examination complemented by imaging modalities such as radiography, ultrasonography, and magnetic resonance imaging (MRI) to identify and assess the extent of calcific deposits. Management strategies encompass conservative treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) and structured physical therapy programs, as well as interventional approaches like corticosteroid injections, ultrasound-guided lavage, extracorporeal shock wave therapy, and surgical intervention in refractory cases. Early and accurate diagnosis, coupled with an individualized treatment plan, is imperative for optimal patient outcomes and the restoration of shoulder function.

Keywords: shoulder pain, calcific tendinitis

Introduction

Calcific tendinopathy is a shoulder condition characterized by the accumulation of calcium crystals in one or more of the rotator cuff tendons, resulting in pain and impaired function. It is the most common cause of shoulder pain [1,2]. Many cases are self-limiting or resolve with conservative management. Surgery is required in patients with persistent symptoms.

The cause of calcific tendinopathy is still unknown. It may be associated with endocrine disorders such as diabetes, thyroid disorders, nephrolithiasis, estrogen metabolism and it is rarely a part of a systemic disease [3, 4].

This paper will review the pathophysiology, diagnosis, and management of calcific tendinopathy of the shoulder.

Clinical Presentation

Shoulder pain is a frequent presenting complaint in adults, with lifetime prevalence estimates reaching up to 67 percent [6]. The majority of these patients experience sub acromial pain, which is also characteristic of calcific tendinopathy. The prevalence of calcific tendinopathy in the general population has been reported to range from 3 to 10 percent [2,7], and it affects 7 to 17 percent of individuals with shoulder pain.

Symptoms are different according to the stage of disease [5].

• **Pre-calcific stage:** part of the tendon transforms into fibrocartilaginous tissue; this stage is asymptomatic.

• **Calcific or formative stage:** calcific formations within the tendon. Symptoms are variable from none to pain on movement.

• **Resorptive stage**

It is the most symptomatic phase; the pain is due to leakage of the calcific deposit into the sub acromial bursa causing calcific bursitis. Pain typically lasts two weeks.

• **Post calcific stage** the deposits are absorbed. In this stage the severity and duration of pain varies from one patient to another, some patients experience painful periods that alternate with pain free periods, while others develop severe pain.

Diagnosis

The diagnosis of calcific tendinopathy can be made reliably based on history, clinical examination, and diagnostic imaging (X-ray and US). No abnormal laboratory findings can be detected in patients of calcific tendonitis.

Diagnostic Imaging:

The first step in diagnostic imaging is shoulder X-ray, Anteroposterior (AP), internal and external rotation views. These views enable the clinician to determine the calcific deposits as homogeneous radiopaque density with variable morphology, but typically globular/amorphous with smooth or ill-defined margins [16]. (Figure 1)

Also Ultrasound [8] has an important role in the diagnosis by identifying and localizing calcifications within the rotator cuff tendons. On US deposits appear as an oval shape or curvilinear calcification with shadowing and capsular soft tissue swelling. (Figure 2)

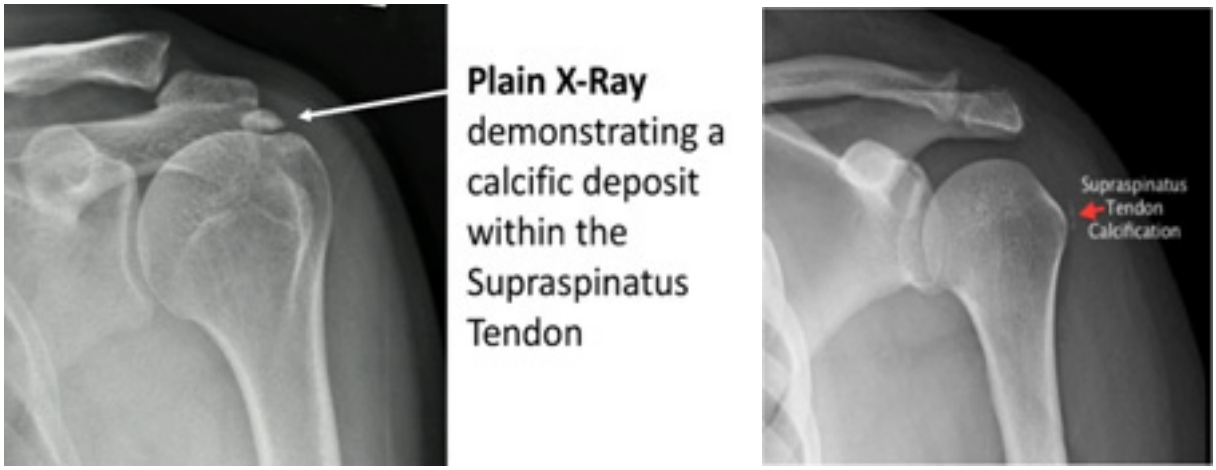

Figure 1

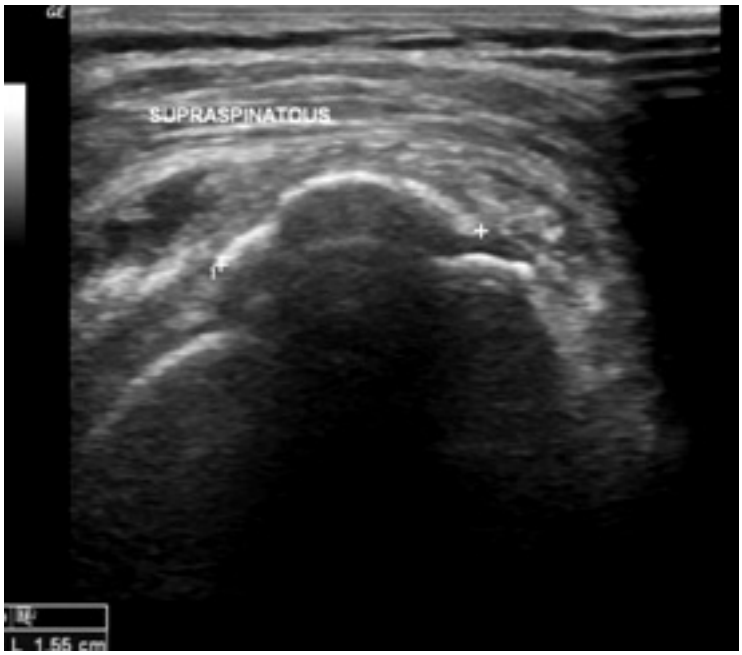

Figure 2

MRI is not routine examination for calcific tendinopathy. MRI may be useful if other shoulder pathologies, such as labral or rotator cuff tears, are suspected. MRI provides excellent soft tissue contrast and enables multiplanar imaging with high spatial resolution. However, calcific deposits appear hypointense across all MRI sequences, making it difficult to reliably distinguish them from artifacts caused by tissue interfaces or hemorrhage [9].

Differential diagnosis

Shoulder calcific tendinopathy can be distinguished from other causes of shoulder pain by demonstrating the calcific deposits on shoulder X-ray or ultrasound (US). Other causes of shoulder pain include [15]:

Rotator cuff tear
Cervical disc prolapse
Osteoarthritis (acromioclavicular and glenohumeral joints)
Frozen shoulder

Management

Calcific tendinopathy of the shoulder is often self-limiting with a relatively benign clinical course. Therefore, the treatment is controversial, and its efficacy is difficult to assess.

First-line therapy is conservative such as analgesic and non-steroid anti-inflammatory medications [11]:

Other treatment options include:
• Subacromial glucocorticoid injection in acute inflammation.
• Physical therapy.
• Barbotage procedure: is a US-guided procedure that involves breaking up and then aspirating pieces of the calcific deposits.
• ESWT Extracorporeal shock wave therapy uses acoustic waves to fragment calcific deposits in the rotator cuff. Improvement can be expected in approximately 70 percent of patients [12].
• Arthroscopy: about 10% of patients don't respond to conservative treatment, ESWT, or barbotage, and may be candidates for arthroscopy [13].

Complications and prognosis

The complications include migration of calcium deposits from tendons into the subacromial-subdeltoid bursa or into the humeral greater tuberosity. This complication may occur spontaneously or following arthroscopic removal of the deposit.

The prognosis of shoulder calcific tendinitis is generally good, as the deposits are resolved spontaneously and therapeutic measures leading to improved symptoms in most cases [14].

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The UK debate around Assisted dying, Dignity in Dying

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Abstract

Assisted dying is a conflict-ridden and debatable subject, and a broad range of interests should inform any proposed policy changes to promote autonomy and end and mitigate intense suffering by providing a 'safe and comfortable' death to patients who believe they would otherwise have to endure unbearable suffering at the end of life. Some could argue that palliative care can't do it all, especially with its inconstant availability.

The British Medical Association (BMA) and some Royal Colleges have recently changed their attitude on physician-assisted suicide from 'combated' to forms of 'impartial'.

For the last few years, the toll took the UK system to vote for assisted dying and wanted to legalize it. Some countries have legalized it for some time, and some British nationals fly overseas to have it conducted. The drugs that are being prescribed and administered, are both for physician-assisted suicide (patient ingestion) and for euthanasia (physician-administered).

Keywords: assisted dying; assisted suicide; physician-assisted suicide; euthanasia; medical ethics; non-maleficence; law.

Introduction

'Assisted dying' is a legal practice in some countries. Physician-assisted suicide, which licenses clinicians to prescribe lethal drugs for patients to self-ingest, is currently legal in all such legislatures. In addition, euthanasia, in which clinicians inject lethal drugs intravenously to end a patient's life, is practiced in Belgium, Luxembourg, Canada, New Zealand, Spain, the Netherlands, some Australian states, and Colombia (4).

'Total pain' depicts the complex assemblage of psychological, social, and spiritual distress that comprises some individuals' suffering. Also, it recognizes the loss of independence as an intolerable indignity.

Assisted dying is defined by The Parliamentary Office of Science and Technology in the United Kingdom as:
'The involvement of healthcare professionals in the provision of lethal drugs intended to end a patient's life at their voluntary request, subject to eligibility criteria and safeguards. It includes healthcare professionals prescribing lethal drugs for the patient to self-administer ('physician-assisted suicide') and healthcare professionals administering lethal drugs ('euthanasia') (3).

In all three models, a doctor prescribes the lethal prescription after confirming the person has mental capacity, is aware of alternatives such as palliative-hospice care (PHC), the request is enduring, was not made under duress, and that the medical eligibility criteria are met(3).

The three most frequently reported end-of-life concerns behind the request for PAS have been a decreasing ability to participate in enjoyable activities (90%), loss of autonomy (90%), and loss of dignity (72%) (3).
Autonomy is where 'no decision about me, without me' is the norm.

Usually, those who are seeking assisted dying will be terminally ill, suffering incurable, inoperable, unbearable pain, and seeking a dignified end. Also, they wish to stop being a burden to their families, loved ones, and medical care professionals (10).

However, in certain situations, the doctor made an erroneous diagnosis of a terminal condition, and the patients have made an unexpected or even "miraculous" recovery. Therefore, the fault of assisting death is not revocable; but the error of keeping alive is revocable (8-9). Also, the peril of agonising, deadly suffering has become exaggerated and is infrequent due to advancements in medicine, pain alleviation, medications, improved palliative care, and hospice. Thus, palliative care should constantly be tried first before any other deadly measures (8).

Some countries such as Switzerland were the first to start it in 1942. However, in the US, ten states have conducted it as a way of physician-assisted dying with Oregon being the first state to commence in 1997. In 2002, in the Netherlands, a doctor was immune from punishment for the magnitude of suffering of some patients from incurable unbearable sufferings including minors under 12 who needed parental approval. In Belgium, it was legalized for terminally ill patients in 2002 and psychiatric conditions. In Canada, it was introduced in 2016 for those whose death is anticipated. In Australia, voluntarily assisted dying for terminally ill or those with intolerable suffering was introduced in 2019 in Victoria. In Spain, a law started in 2021 to allow euthanasia to be legal in debilitating conditions. Austria, Luxembourg, Portugal, and Colombia also joined the cause.

It has been transpiring that annually, over 120,000 patients have no access to specialist palliative care, yet only 10 travels to Switzerland annually to access assisted suicide, which requires traveling and a payment of nearly £15,000 (2).

The term assisted dying can be confusing and misleading for some, as 43% only understand the implied term. A recent poll showed that three-quarters of Britons are in favour of doctor-assisted suicide for terminally ill conditions.

Suicide is higher among anaesthetists as they are experts in handling drugs with lethal potential. Additionally, there is no evidence to legalize physician-assisted suicide where the suicide rate increases, undermining prevention efforts, plus the 'assisted dying' applicants are at risk of distressing deaths (2).

Also, if doctors are expected to administer death, actively ending life would incur profound adverse effects like shock, sense of powerlessness and isolation. Other moral injuries consequently would be conflict and disagreement with families, fear of coercion accusation, feeling guilt, and thus leaving their professions as doctors are meant to save a life, not to end it.

Given the widespread disquiet felt by doctors, a law with minimal medical involvement would be the most reasonable (3).

Medications used for physician-assisted suicide, enteral route

The following are employed

Sedatives: Chloral hydrate, 20 gm Amitriptyline not reported Barbiturates Pentobarbitone 9-15 gm Phenobarbitone 20 gm Secobarbital 9-15 gm Brallobarbital not reported Sodium thiopental not reported **Cardiotoxic:** Digoxin 50 mg Propranolol 2gm **Entiemetics**	**Benzodiazepines:** Diazepam 1gm Lorazepam 0.25-2 gm IV Midazolam 10 mg IV **Analgesics:** Morphine 15 mg-3gm Detroproproxyphene not reported Metoclopramide 10-20 mg Ondansetron 8 mg Haloperidol 5 mg **Neuromuscular block:** Backup as required IV. Not reported

Medications used for physician-assisted suicide, central route

The following are employed:

Sedatives/ hypnotics: Propofol, 1-2 gm Vesparax not reported Chloral hydrate 35-40 mg Thiopentone 1-2 gm, 20 mg/kg Pentobarbitone 1-15 gm Phenobarbitone 3gm Secobarbital 9 gm **Benzodiazepines:** Diazepam 10-120 mg Lorazepam 1.5-5 mg Midazolam 2-120 mg Morphine 16-480 mg Fentanyl 25-1500 microgram	**Cardiotoxic:** Potassium chloride not reported Bupivacaine 400 mg **Neuromuscular block:** Rocuronium 50-300 mg Pancuronium 18-20 mg Cisatrancurium 30-40 mg Vecuronium 10-60 mg

The most common lethal drugs used by clinicians to assist suicide were high doses of barbiturates, frequently either pentobarbital or secobarbital. Very high-dose barbiturates have long been a popular method for assisted suicide.

Drug combinations have been used called ‘DDMA’ (diazepam, digoxin, morphine sulfate, and amitriptyline) and ‘DDMP’ (diazepam, digoxin, morphine sulfate, and propranolol).

In countries where euthanasia is practiced, drug combinations also vary widely and include benzodiazepines, sedatives, neuromuscular blocking agents, opioids, and cardiotoxic agents (1,4).

In the process of euthanasia, practitioners usually administer a general anaesthetic first, often a barbiturate or another sedative like propofol, to prompt coma. Some similarly administer an anxiolytic (benzodiazepine) before the coma-inducing sedative and, where used, to alleviate propofol-induced pain.

After the anaesthetic, a neuromuscular blocking agent tracks in to paralyze all striated muscles, and to eliminate any movements, equally to impede respiratory effort and to abolish muscular spasms (4).

The Hippocratic oath of medicine implies and emphasizes that doctors should commit to not cause harm, to preserve life, and thus, killing in itself is something doctors don't want to do and have the blame and the guilt. Ending life is a harm in itself and has no place in healthcare per se. It's fundamental for patients' safety and the foundation to trust doctors. Thus, the concept is a fallacy, and treatment is lawful if it will help, work, and benefit. Therefore, nature is allowed to work its way if pathology is incurable. However, in palliative care, a deep sedative can be continued to mitigate the pain felt on the patient's request to stay unconscious in their final days, which can be defended, not to speed up death. However, physician-assisted suicide is a kind of independent act and is different (6). Thus, medical ethics forbid and prohibit physicians from committing killing as the arguments have consequences for the profession, patients' well-being, and patient-doctor relationships and undermine the public trust as a whole, to safeguard all and meet the four pillars of medical ethics (6).

Additionally, suppose this conduct is legalised and allowed. In that case, it will raise risks of abuse by the unscrupulous to persuade or coerce individuals to opt for assisted dying, jeopardise the vulnerable, complicate patient care, and increase clinician workload, potentially causing stress on patient care (8).

Beneficence and non-maleficence

Doctors seek to act in the best interests of their patients and not cause harm whatsoever. In case of doubt, doctors should weigh the benefits with risks, as they don't want to be known as "Doctor Death".

The two parties argue between proponents who see relieving suffering by ending a life that allows patients to define their needs in terms of benefits and harm to avoid loss of control and dependence, while opponents see it from a compassion prospect through a combination of pharmacological, physical, social, psychological, and spiritual interventions, to change patients' perceptions and understand what is happening to them to help mitigate pain and distress. It's not an easy thing, though.

However, it seems it might be legalized in the future as activists are campaigning for a law change in England, Scotland, and Wales (3).

There are three existing models of physician-assisted suicide: Switzerland, Oregon (USA), and Victoria (Australia) (3).

Up-to-date debates about the issue cover a series of medical, legal, moral, ethical, and religious aspects. Hitherto, public views stay underexplored and thus won't count for the formation of public policy (7).

The UK and the bill

Politicians are contending to allow terminally ill patients to end their own lives if they wish to do so by some criteria: being 18 years old and over, registered with a medical practice, and declaring their wishes clearly and explicitly without coercion for 12 months. However, if only diagnosed with a mental disorder or a disability, it won't apply, as defined by the bill. Additionally, medical practitioners are not obliged to raise the matter with a patient. The law proposes that a medical professional can discuss the concept and exercise their professional judgment if needed. Also, if a medical professional doesn't want to discuss it, they can refer to another who is willing to engage with the matter (11). This preliminary discussion will involve the patient's diagnosis, prognosis, treatment available, palliative care, hospice, and any other care options. If there is any doubt about the patient's terminal illness, an assessment by a specialist can be conducted in regard to the capacity to decide by a registered psychiatrist. Should the patient confirm their wishes to go ahead, a coordinating doctor must witness the first declaration signed by the patient, followed by the first assessment to ensure the proposed bill of terminal illness is a clear statement of intention without being pressured. Then, a second assessment is to be carried out by an independent doctor who checks the eligibility and the assessment about coercion. This would take a seven day period of reflection, and if there is any disagreement after the second assessment, to refer to a different medical professional. Both doctors should have the necessary training concerning the qualifications needed and the experience and are not materially gaining after their death. The bill explains how this will take place, the nature of the substance used, how it will bring death, if complications arise, further steps, and if to withdraw at any time (11).

The high court will decide if the bill's requirements are fulfilled, and if the judge refuses to certify the declaration, then it goes to the court of appeal. Once all are approved, a second 14-day period of reflection will follow unless death is imminent within a month, to reduce to a 48-hour reflection period. Then, the coordinating doctor and another person should witness a second declaration. Also, if there is a disability and the patient is unable to sign, the patient should know a person for 2 years with good standing in the community to act as a substitution. Once all is done and the period of reflection comes to an end, the proceeding with the assistance to end life can go ahead. If the patient decides to change their mind, they can inform the coordinating doctor or the GP, and they can decide not to self-administer the approved substance to end the process (11).

The coordinating doctor would prepare the lethal substance for the patient to self-administer or a medical device to allow the patient to end their life. The doctor won't administer the deadly substance. However, they must remain with the patient until death happens, but they won't need to be in the same room. If the coordinating doctor isn't able, or is unwilling to continue, an auxiliary can be appointed.

Religion

There are divisions between religious and non-religious as the belief that assisted dying is wrong and unlawful and the belief that life is holy (11).

Conclusion

The subject carries a lot of debate and is divided between morality and public trust in medical professionals, and how it could benefit or harm patients who wish to end their lives. It is not easy though as doctors are meant to treat, alleviate and travel through their patient's illness journey and not to end it.

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