Alarming consequences of the sickle cell diseases

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Abstract

Background: We tried to understand whether or not there are some alarming consequences of sickle cell diseases (SCDs).

Methods: All patients with SCDs were included.

Results: The study included 434 patients (212 females) with similar ages in males and females (30.8 versus 30.3 years, respectively, p>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males (p<0.001 for both). Disseminated teeth losses (5.4% versus 1.4%, p<0.001), transfused units of red blood cell (48.1 versus 28.5, p=0.000), chronic obstructive pulmonary disease (25.2% versus 7.0%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were also higher in males. There were 31 mortality cases (17 males) with similar ages in males and females (30.2 versus 33.3 years, respectively, p>0.05). Mean ages of leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), deep venous thrombosis (DVT) and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and benign prostatic hyperplasia (BPH) (41.5 years) were higher in SCDs.

Conclusion: SCDs are severe inflammatory processes on vascular endothelium at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders. Leg ulcers, digital clubbing, CHD, DVT and/or varices and/or telangiectasias, cirrhosis, CRD, and BPH may be the alarming consequences of SCDs indicating an advanced disease.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis

Introduction

Chronic endothelial damage may be the leading cause of aging-induced morbidity and mortalities by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures those reduce blood flow and increase systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory and infectious processes including sickle cell diseases (SCDs), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were discussed under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes can not be reversed completely after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, or stroke due to their fibrotic natures (3, 4). Similarly, SCDs are severe inflammatory processes on vascular endothelium at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failures in early years of life. We tried to understand whether or not there are some alarming consequences of the SCDs indicating an advanced disease in such patients.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCDs were included into the study. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, epilepsy, deep venous thrombosis (DVT), transfused units of red blood cell (RBC) in their lives, surgical operations, leg ulcers, stroke, and priapism and benign prostatic hyperplasia (BPH) symptoms in males including urgency, weak stream, incomplete emptying, and nocturia were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, 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. Patients with disseminated teeth losses (<20 teeth present) were detected. Cases with 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, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography 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 (5). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (6). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). 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 (8). 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. 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. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (9, 10). 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 the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, prevalences of the consequences of the SCDs were detected in both genders, and compared in between. Beside that, mean ages of the consequences were detected in the SCDs. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCDs (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively, p>0.05). Prevalences of associated thalassemia minors were similar in males and females, too (72.5% versus 67.9%, respectively, p>0.05). Smoking (23.8% versus

Table 1: Characteristic features of the study patients

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Thalassemia minors	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)

Table 2: Associated pathologies of the study patients according to the gender distribution

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Disseminated teeth loss (< 20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
Transfused RBC‡ units	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
COPD§	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***<0.05***	***13.2% (28)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
Pulmonary hypertension	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
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)
Sinus arrhythmia	4.9% (11)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)

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

6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males (p<0.001 for both) (Table 1). Disseminated teeth losses (5.4% versus 1.4%, p<0.001), transfused units of RBC in their lives (48.1 versus 28.5, p=0.000), COPD (25.2% versus 7.0%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), CHD (18.0% versus 13.2%, p<0.05), CRD (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher in males, significantly. There were 11 males (4.9%) with BPH symptoms with a mean age of 41.5 ± 10.6 (27-58) years. All of the patients could be treated with once daily 4 milligrams of doxazosin, orally. Additionally, there were 23 cases (10.3%) with priapism with a mean age of 33.4 ± 7.9 (18-51) years. There were 31 mortality cases (17 males and 14 females) during the ten-year follow up period. The mean ages of mortality were 30.2 ± 8.4 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (p>0.05) (Table 2). When we evaluated mean ages of the consequences of the SCDs, leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and BPH (41.5 years) may be the alarming consequences indicating an advanced disease in such patients due to the significantly shortened survival of the SCDs patients in both genders (Table 3).

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

Variables	Mean ages of the patients
Sinus arrhythmia	27.2 ± 8.3 (18-50)
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 loss (< 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)
Pulmonary hypertension	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)*
Varices and/or telangiectasias	*37.0 ± 8.4 (17-50)*
Cirrhosis	*37.0 ± 11.5 (19-56)*
CRD§	*39.4 ± 9.7 (19-59)*
BPH¶	*41.5 ± 10.6 (27-58)*

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Coronary heart disease §Chronic renal disease ¶Benign prostatic hyperplasia

Discussion

SCDs are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (11, 12). Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of RBCs. Probably loss of elasticity instead of shape is the main pathology since sickling is rare in peripheric blood samples of the SCDs patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, and various stresses of the body. The hard RBCs induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body (13, 14). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage builds up an advanced atherosclerosis in younger ages of the patients. As a result, mean lifespans of the patients were 48 and 42 years in females and males in the literature, respectively (16), whereas they were 33.3 and 30.2 years in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Antakya region of Turkey (17). Actually, RBC supports must be given immediately during all medical or surgical events in which there is an evidence of clinical deterioration in the SCDs (8). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling-induced endothelial damage and inflammation all over the body.

Digital clubbing is characterized by increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (18). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (19). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (10). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and hepatic disorders those are characterized with chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, and liver are closely related organs those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCDs and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, and edema at the capillary level

in the SCDs. Beside the effects of SCDs, the higher prevalences of smoking, COPD, and clubbing in males ($p<0.001$ for all) may also show some additional roles of smoking, COPD, and male sex on digital clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (20), and the ratio was 13.3% in the present study. Its incidence increases with age, male sex, and HbSS genotype (21). Similarly, its ratio was higher in males (19.8% versus 7.0%, $p<0.001$), and mean age of the patients with leg ulcers was significantly higher than the others (35.3 versus 29.8 years, $p<0.000$), here. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (20). As an evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (20). The hard RBCs induced chronic endothelial damage, inflammation, and edema at the capillary level may be the major cause in the SCDs (21). Prolonged exposure to the hard bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hard RBCs induced venous insufficiencies may also accelerate the process by pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Pooling of blood in the lower extremities may also have effects on the delayed wound and fracture healings in the lower extremities. Beside the hard bodies, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are more common in males. Hydroxyurea is the only drug that was approved by Food and Drug Administration for the treatment of SCDs (15). It is an oral, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (17). Its main action may be suppression of hyperproliferative white blood cells (WBCs) and platelets (PLTs) in the SCDs (22). Although presence of a continuous damage of hard RBCs on endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (23). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to increased WBC and PLT counts induced prolonged endothelial damage, inflammation, and edema at the capillary level in the SCDs.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Related factors include pregnancy, obesity, menopause, aging, and heredity. In another word, varices are more common in females and metabolic syndrome. Normally, leg muscles pump veins to return blood against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Although the relatively younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively) and significantly lower body mass index of the SCDs cases in the literature (14), DVT and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (9.0% versus 6.6% in males and females, respectively, $p>0.05$) indicating an additional venous endothelial involvement in the SCDs.

Both frequency and complications of cirrhosis are increasing in the world. For example, it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (4). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by aging of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents at the moment (24, 25). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (24). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as with increased prevalences of cardiovascular diseases (25). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (25, 26). NAFLD and cirrhosis may be considered as the hepatic consequences of the metabolic syndrome (27). Probably smoking also takes role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (28). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Similarly, aging alone may be another cause of systemic atherosclerosis that prevents adequate tissue oxygenation. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (29). For example, chronic HCV infection raised CIMT, and normalisation of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (29). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be one of the several consequences of the metabolic syndrome and SCDs.

Nowadays, both frequency and complications of CRD are increasing all over the world, again. For example, 1.9 to 2.3 millions of people have CRD in Canada (30). The

Centers for Disease Control and Prevention in the USA found that CRD affected an estimated 16.8% of adults above the age of 20 years between 1999 and 2004 (31). Similarly, the increased frequency and complications of CRD may be explained by aging of the societies and increased prevalence of excess weight all over the world, since CRD may also be one of the terminal endpoints of the metabolic syndrome, and an eventual advanced atherosclerosis may be the underlying cause of the CRD (32). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory and infectious processes may be the main triggering causes of the endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemical factors by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arteriols. Due to the continuous irritation of the endothelial cells in the above pathologies, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, and tissue hypoxia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance cause various cellular stresses those accelerate tissue inflammation and immune cell activation further (33). 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 CIMT (32). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activation 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 weight (34). Excess weight also causes renal vasodilation and glomerular hyperfiltration those initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (34). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (35). With prolonged weight excess, there are increased urinary protein excretion, lost nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more rapidly (34). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (36). The inflammatory and eventual atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (36), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the vascular endothelium, there. Similarly, aging alone may be another cause of the CRD by means of the systemic atherosclerotic effects. Chronic inflammatory and infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (29). Although CRD is mainly be an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (37). For example, the most common cause of death in the CRD is cardiovascular diseases rather than the renal failure again (38). In another definition, CRD may actually be one of the several consequences of the metabolic syndrome and SCDs, again.

BPH is the most common benign neoplasm in men. Although prostate specific antigen (PSA) may be elevated in these patients because of an increased organ volume and inflammation secondary to urinary tract infections, BPH does not lead to cancer. BPH involves hyperplasia of the stromal and epithelial cells, terminating with the formation of large, commonly discrete nodules in transition zone of the gland. When sufficiently large, the nodules apply pressure on the urethra and increase resistance to urinary flow. This is commonly felt as obstruction, although the urethral lumen is only compressed. Resistance to urinary flow requires the bladder to work stronger during voiding, possibly leading to progressive hypertrophy, instability, and atony of bladder muscle. BPH can be diagnosed by using the UWIN score (urgency, weak stream, incomplete emptying, and nocturia) (39). BPH may be caused by failure of the spermatic venous system resulting with increased hydrostatic pressure and testosterone levels, locally (40). Authors found that the one-way valves in the vertically oriented internal spermatic veins are destroyed in the BPH patients causing an elevated hydrostatic pressure up to 6-fold greater than the normal (40). The elevated pressure propagates to all interconnected vessels leading to a venous flow retrograde from higher pressure of the testicular veins to lower pressure of the prostate. The authors found that free testosterone levels in this blood are elevated up to 130-fold above the serum (40). Consequently, the prostate is exposed to both an increased venous pressure that causes hypertrophy and to an elevated free testosterone levels causing hyperplasia. On the other hand, an age-related impairment of blood supply to the gland may also have a key role in the development of BPH (41). An advanced atherosclerosis in elder men may cause chronic tissue hypoxia, and thus be a contributing factor in the pathogenesis (42). Smooth muscle proliferation may be an important and possibly androgen-dependent step in the development of atherosclerosis and BPH (43). Similarly, there was a larger prostate in men with type 2 DM (p=0.0058), HT (p=0.0317), obesity (p<0.0001), and low high density lipoprotein (HDL)-cholesterol (p=0.0132) and high insulin levels (p<0.0001) (44). The gland volume correlated positively with the systolic BP (p=0.03), obesity (p<0.0001), and fasting insulin (p<0.0001) and negatively with HDL-cholesterol levels (p=0.009) (44). Similarly, frequencies of CHD were 9% and 29% in men with PSA levels below and above 1.0 microgram/L, respectively (p<0.03) (43). These results may suggest that BPH may also be one of the several consequences of the metabolic syndrome and SCDs in the human body.

As a conclusion, SCDs are severe inflammatory processes on vascular endothelium at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders. Although the presence of several consequences, leg

ulcers, digital clubbing, CHD, DVT and/or varices and/or telangiectasias, cirrhosis, CRD, and BPH may be the alarming consequences of the SCDs indicating an advanced disease in such patients.

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