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Obesity May Be an Irreversible Atherosclerotic Endpoint in Human Body

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Abstract

Background: Obesity may be an irreversible atherosclerotic endpoint in human body.
Methods: Sickle cell diseases (SCD) patients were studied.
Results: We studied 222 males and 212 females (30.8 vs 30.3 years of age, 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), stroke (12.1% vs 7.5%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), and digital clubbing (14.8% vs 6.6%, p<0.001) were all higher in males, significantly.
Conclusion: As an accelerated atherosclerotic process, hardened RBC-induced capillary endothelial damage terminates with end-organ insufficiencies in early decades of life in SCD. Although atherosclerotic endpoints are so common, we detected no case of diabetes mellitus (DM) probably due to lower excess fat tissue. As the most common cause of CRD, DM may be a relative insufficiency of pancreas against the excess fat tissue. Increased blood and insulin requirements of excess fat in contrast to decreased blood supply of excess tissue and pancreas both due to excess external pressure and internal narrowing of vasculature may be important for DM. As the most common cause of DM, obesity may be an irreversible atherosclerotic endpoint in human body. Acarbose and metformin are oral, safe, cheap, and effective drugs to prevent obesity.

Keywords: Sickle cell diseases; Excess fat tissue; Obesity; Acarbose; Metformin; Endothelial inflammation; Atherosclerosis

Introduction

Chronic endothelial damage initiated at birth may be the most common cause of aging and death via the atherosclerotic endpoints in human being [1]. Much higher blood pressures (BP) of the arterial system may be the strongest accelerating factor by means of the repeated injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are chiefly involved in the catastrophic process. Therefore, venosclerosis is not a significant health problem in medicine. Due to the chronic endothelial damage, inflammation, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, which terminally reduce blood supply to the end-organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, emotional stress, animal-rich diet, smoking, alcohol, excess fat tissue, chronic inflammation, prolonged infection, and cancers for the development of atherosclerotic endpoints including obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), stroke, abdominal angina,

osteoporosis, dementia, aging, and death [2,3]. Although early withdrawal of the accelerating factors can delay the atherosclerotic endpoints, the endothelial changes cannot be reversed, completely due to fibrotic natures. The accelerating factor and atherosclerotic endpoints have been researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively [4-6]. Similarly, sickle cell diseases (SCD) are highly catastrophic process on vascular endothelium initiating at birth and terminating with an accelerated atherosclerosis-induced end-organ insufficiencies even at childhood [7,8]. Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Loss of elasticity instead of shape may be the main problem because the sickling is rare in peripheric blood samples of cases with associated thalassemia minors (TM), and survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, cancer, surgery, and emotional stress. The hardened RBC-induced chronic endothelial damage, inflammation, and fibrosis terminate with tissue hypoxia in whole body [9]. As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into the body [10,11]. The hardened RBC-induced chronic endothelial damage builds up an accelerated atherosclerosis in earlier decades of life. Vascular narrowing and obstructions-induced tissue ischemia and end-organ insufficiencies are the terminal consequences, so the mean life expectancy is decreased 30 years or more in the SCD because we have patients with the age of 96 years without the SCD but just with the age of 59 years with the SCD [8].

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All cases with the SCD were included. SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgeries, deep venous thrombosis (DVT), epilepsy, and priapism were researched in all patients. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with acute painful crisis or any other inflammatory or infectious process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Checkup 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 magnetic resonance imaging's (MRI) of brain and hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Avascular necrosis of bones is diagnosed via MRI [12]. Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCD with associated TM come with milder clinics than the sickle cell anemia (SCA) (Hb SS) alone [13]. Systolic BP of the pulmonary artery of 40 mmHg or greater are accepted as pulmonary hypertension [14]. Cirrhosis is diagnosed with full physical examination, laboratory parameters, and ultrasonographic evaluation of the liver. 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, dyspnea, and 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a permanently elevated 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 taken in case of an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed in case of a positive exercise electrocardiogram. As a result, CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the heart walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT and/or MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in case of visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

We included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p>0.05$, respectively) into the study, and there was no patient above the age of 59 years. Associated TM were detected with similar prevalences in both genders (72.5% vs 67.9%, $p>0.05$, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were both 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), CRD (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly. 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, the mean ages of the atherosclerotic endpoints 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 endpoints 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 vasculitis and aging, and obesity may be an irreversible atherosclerotic endpoint in human body. Excess fat tissue causes both excess external

pressure and internal narrowing of vasculature in addition to the already increased blood and insulin needs of the excess tissue. DM may be an irreversible atherosclerotic consequence caused by the excess fat tissue in whole body rather than the pancreas alone. Although all kinds of atherosclerotic consequences are so common with the SCD, we have detected no case of DM, probably due to the lower excess fat tissue in them [10]. The body mass indexes (BMI) were 20.7 vs 24.9 kg/m2 in the SCD and control groups, respectively with the mean age of 28.6 years (p= 0.000) [10]. The body heights were similar in both groups (166.1 vs 168.5 cm, respectively, p>0.05) which may indicate that the height is determined, genetically [10]. Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be riskier than aging, smoking, alcohol, or chronic inflammatory or infectious processes for the development of DM. Excess fat tissue leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes increases parallel to its severity [19]. The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerotic process may even decrease clearance of malignant cells by the natural killers [20]. The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity [21,22]. Excess fat tissue is considered as a strong factor for controlling of C-reactive protein (CRP) since the excess tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines [23,24]. On the other hand, excess fat tissue will also aggravate myocardial hypertrophy and decrease cardiac compliance. Fasting plasma glucose (FPG), triglycerides, and low-density lipoproteins (LDL) increased and high-density lipoproteins (HDL) decreased parallel to the severity of BMI [25]. Similarly, CHD and stroke increased parallel to the severity of BMI [26]. Eventually, the risk of death from all causes increased parallel to the severity of excess fat tissue in all age groups, and people with underweight may even have lower biological ages and longer overall survival [27]. Similarly, calorie restriction prolongs survival and retards age-related chronic sicknesses [28]. So, the term of excess weight should be replaced with the amount of excess fat tissue in human body since there are nearly 19 kg of excess fat tissue even between the lower and upper borders of normal weight in adults.

Smoking may be the second most common cause of vasculitis all over the body. It causes a systemic inflammation on vascular endothelium terminating with atherosclerotic endpoints [29]. Its atherosclerotic effects are the most obvious in the Buerger's disease and COPD [30]. Buerger's disease is an obliterative vasculitis in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Its characteristic features are chemical toxicity, inflammation, fibrosis, and narrowing and occlusions of arteries and veins. Claudication is the most significant symptom with a severe pain in feet and hands caused by insufficient blood supply during exercise. It may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also a common symptom in them. Skin ulcerations and gangrene of fingers or toes are the terminal endpoints. 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 the main cause of severity of Buerger's disease in the lower extremities. Several narrowing and occlusions of the arm and legs are diagnostic in the angiogram. Skin biopsies may be risky, because a poorly perfused area will not heal, completely. Although most patients are heavy smokers, the limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituents of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible. Due to the well-known role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may even be life threatening by preventing microvascular infarctions. On the other hand, FPG and HDL may be negative whereas triglycerides, LDL, erythrocyte sedimentation rate, and CRP positive acute phase reactants (APR) in smokers [31]. Similarly, smoking was associated with the lower BMI due to the systemic inflammatory effects [32,33]. An increased heart rate was detected just after smoking even at rest [34]. Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [35]. Nicotine may lengthen intermeal time, and decrease amount of meal eaten [36]. Smoking may be associated with a post cessation 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 white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females [38]. The risk of myocardial infarction is increased three-fold in men and six-fold in women with smoking [39]. Chemical toxicity of smoking can affect all organ systems. For instance, it is usually associated with irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, urolithiasis, and depression with many possible mechanisms [40]. First of all, smoking may also have some anxiolytic properties. Secondly, smoking-induced vascular inflammation may disturb epithelial absorption and excretion in the gastrointestinal (GI) and genitourinary (GU) tracts [41]. Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis [42]. Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the GI and GU

tracts terminating with IBS and urolithiasis. Finally, immunosuppression secondary to smoking may terminate with the GI and GU tract infections and urolithiasis because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced by the urease producing bacteria. As a result, urolithiasis was higher in the IBS patients, significantly (17.9% vs 11.6%, $p<0.01$) [40].

CHD is the other major cause of death in the human being together with the stroke. The most common triggering cause is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaques are the gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls in decades of life. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheroma's to rupture. After the myocardial infarction, a collagen scar tissue takes its place which may also cause life threatening arrhythmias because the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissues can trigger re-entry or a feedback loop that is believed to be the cause of 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. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm and rupture. Aging, physical inactivity, animal-rich diet, excess fat tissue, smoking, alcohol, emotional stress, prolonged infection, chronic inflammation, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence of CHD [43]. Probably, excess fat tissue may be the most important cause of CHD because there are approximately 33 kg of excess fat tissue between the lower borders of normal weight and obesity, and 66 kg between the lower borders of normal weight and morbid obesity (BMI $\geq$ 40 kg/m2) in adults. In other definition, there is a high percentage of adults with heavier fat tissue masses than their lean body masses that brings a greater stress on the heart, liver, kidneys, lungs, brain, and pancreas.

DM is the most common cause of blindness, non-traumatic amputation, and hemodialysis in adults. As the most common cause of CRD, DM may be an irreversible atherosclerotic consequence affecting the pancreas, too. Increased blood and insulin needs of the excess fat tissue in contrast to the decreased blood supply of the excess tissue and pancreas both due to excess external pressure and internal narrowing of the vasculature may be the underlying mechanisms of DM. For instance, excess fat tissue in the liver and pancreas are called as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAFPD). They are usually accepted as components of the metabolic syndrome. NAFLD progresses to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Blocking triglycerides secretion, subcellular lipid sequestration, lipolysis deficiency, enhanced lipogenesis, gluconeogenesis defects, or inhibition of fatty acid oxidation may be some of the development mechanisms [44]. NAFLD may just be an atherosclerotic process, and strongly associated with an accelerated atherosclerotic process not only in the liver instead in whole body. For example, NAFLD is seen in one-third of cases with hepatitis B virus-related chronic liver disease [45]. Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas [46]. The liver density on contrast abdominopelvic CT of colorectal cancer patients was low that is consistent with the NAFLD [47]. As one of the APR, serum thrombopoietin levels increased in the NAFLD [48]. Although serum levels of oxidizing agents including nitrate and advanced oxidation protein products increased, serum nitrite did not adequately increase as an antioxidant agent in the NAFLD [49]. As a result, NAFLD is associated with an impaired carotid intima-media thickness (IMT) and flow-mediated dilation which are considered as early markers of systemic atherosclerosis [50]. Carotid IMT was correlated with the BMI ($p<0.001$), age ($p= 0.001$), and grade 2-3 NAFLD ($p<0.001$) [51]. Patients with the NAFLD have more complex CHD, and carotid IMT and grade 2-3 NAFLD were associated with the severity of CHD ($p<0.001$ for both) [51-53]. Similarly, there were reductions in hepatic artery flow volume, portal vein flow volume, and total flow volume in contrast to the increased NAFLD [54]. As the most common pathology of pancreas in adults, there may be reductions in flow volume of pancreatic arteries in the NAFPD, too [55]. NAFPD is usually associated with the aging, increased BMI, and insulin resistance [56]. Replacement of more than 25% of pancreas by fat tissue is associated with the risks of systemic atherosclerosis and DM [57]. Insulin is stored in vacuoles in beta cells of islets of Langerhans in whole pancreas and released via exocytosis. Pancreatic fat infiltration may lead to a reduced insulin secretion [58]. NAFPD may lead to exocrine pancreatic insufficiency by fat droplet accumulation in pancreatic acinar cells and consequent lip toxicity, destruction of acinar cells by both inflammation and fatty replacement, and by negative paracrine effect of adipocytes [59]. It is unsurprising that the NAFPD may even cause pancreatic fibrosis and cancers. NAFPD causes a higher risk of DM [57], and newly diagnosed patients with DM have higher pancreatic fat [60]. DM may actually be a relative insufficiency of the pancreas against the excess fat tissue in whole body. Age-related impairment of beta cells may actually be an atherosclerotic endpoint since 20% of elderly have DM, and just 55% of patients

with DM are obese. Glucose tolerance progressively decreases by aging. It may be due to the progressively decreased physical and mental activity-induced excess fat tissue secreting adipokines. There is no term of malnutrition-related DM. DM can be cured by gastric bypass surgery in 90% of morbid obese cases [61]. The effect is not due to the weight loss instead decreased insulin requirement daily because it usually occurs just after days of the surgery. This surgery reduced death rate from all causes by 40% [61]. NAFPD is an independent risk factor for CHD, too [62]. Similarly, NAFPD is associated with increased aortic IMT and epicardial fat tissue [63]. As a result, NAFLD, cirrhosis, NAFPD, and DM may be some irreversible atherosclerotic endpoints in human body [64].

Acute painful crises are nearly pathognomonic for the SCD. Although some authors reported that pain itself may not be life threatening directly, infection, medical or surgical emergency, or emotional stresses are the most common precipitating factors of the crises [65]. The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema terminating with tissue hypoxia and end-organ insufficiencies in whole body. So, the risk of mortality is much higher during such crises. Actually, each crisis may complicate with the following crises by leaving sequalae's on the capillary endothelial system all over the body. After a period of time, the sequalae's may terminate with end-organ failures and sudden death with a silent painful crisis, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy [66,67]. Rapid RBC supports are usually life-saving, although preparation of RBC units usually takes a period of time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions and interestingly aging-induced blood group mismatch. Actually, transfusion of each unit complicates the following transfusions via the blood subgroup mismatch. Due to the efficacy of hydroxyurea, RBC transfusions should be preserved just for acute stress and emergencies [66-68]. According to our experiences, simple and repeated transfusions are superior to exchange [69,70]. First of all, preparation of one or two units of RBC suspensions in each time provides time to clinicians by preventing sudden death. Secondly, transfusions of one or two units in each time decrease the severity of pain, and relax the patients and their relatives since RBC transfusions probably have the strongest analgesic effects [71]. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units will decrease transfusion-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions in the secondary health centers prevent deaths developed during the transport to the tertiary centers for the exchange. Terminally, cost of the simple transfusions on insurance system is much lower than the exchange which needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, WBC, platelets (PLT), and endothelial cells, yet. Probably, leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic endpoints. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD [72], and it was associated with the risk of stroke [73]. Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Due to the severity of pain, narcotic analgesics are usually required [74], but simple transfusions are effective both to relieve pain and to prevent sudden deaths which may develop due to the end-organ failures on atherosclerotic background of the SCD.

Hydroxyurea is the life-saving drug for the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides via the inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis [75,76]. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of catastrophic process is probably exaggerated by the patients' own WBC and PLT. So, suppression of proliferation of them can limit the endothelial damage-induced edema, ischemia, and infarctions [77]. Similarly, Hb F levels in hydroxyurea users did not differ from their pretreatment levels [78]. The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo [79]. The study particularly researched effects of hydroxyurea on painful crises, ACS, and need of RBC transfusion. The outcomes were so overwhelming in the favor of hydroxyurea group that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations [79]. In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates [79]. But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5,

annually [79]. Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7, annually ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) [66]. Similarly, adults using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period [80]. Although the genetic severity remains as the main factor to determine prognosis, hydroxyurea may decrease severity of disease and prolong survival [80]. The complications start to be seen even after birth. For example, infants with lower hemoglobin levels were more likely to have higher incidences of ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of all [81]. If started early, hydroxyurea may protect splenic function, improve growth, and delay atherosclerotic endpoints. But due to the risks of infections, iron overload, and development of all-antibodies causing subsequent transfusions much more difficult, RBC transfusions should be preserved for acute stress and emergencies as the most effective weapon in our hands.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID). Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin inactivates the COX enzyme, irreversibly, which is required for the synthesis of prostaglandins (PG) and thromboxanes (TX). PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TX are responsible for the aggregation of PLT to form blood clots. Low-dose aspirin irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme anymore. But aspirin has no effect on the blood viscosity. The antithrombotic property is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke [82]. Low-dose of aspirin is effective to prevent the second myocardial infarction, too [83]. Aspirin may also be effective in prevention of colorectal cancers [84]. 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 should not be prescribed for febrile patients under the age of 12 years [85], and it was only recommended for Kawasaki disease [86]. Reye syndrome is a rapidly worsening brain disease [86]. The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye [87]. The syndrome mostly affects children, but it can only affect fewer than one in a million children, annually [87]. Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness [86]. Although the liver toxicity and enlargement typically occurs in most cases, jaundice is usually not seen [86]. Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage [86]. It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of children are associated with an aspirin use [87,88]. 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 [86]. When aspirin was withdrawn for children in the US and UK, a decrease of more than 90% in rates of Reye syndrome was seen in the 1980s [87]. Due to the much lower risk of Reye syndrome but much higher risk of death, aspirin must be added into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD [89].

Warfarin is an anticoagulant, and it has no effect on blood viscosity, too. It is the best suited for anticoagulation in areas of slowly flowing blood such as veins and the pooled blood behind artificial and natural valves and dysfunctional cardiac atria. It is commonly used to prevent DVT and pulmonary embolism, and against stroke in atrial fibrillation (AF), valvular heart disease, and artificial heart valves. It is additionally used following ST-segment elevation myocardial infarction and orthopedic surgeries. Initiation regimens are simple, safe, and suitable to be used in the ambulatory settings [90]. It should be initiated with a 5 mg dose, or 2 to 4 mg in the elderlies. In the protocol of low-dose warfarin, the target international normalized ratio (INR) is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR is between 2.5 and 3.5 [91]. Simple discontinuation of the drug for five days is enough to reverse the effect, and causes INR to drop below 1.5 [92]. Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, abilities of clotting factors II, VII, IX, and X are decreased. The abilities of anticlotting protein C and S are also inhibited, but to a lesser degree. A few days are required for full effect which is lasting up to five days. The consensus agrees that current self-testing and management devices are effective providing outcomes possibly better than achieved, clinically. The risk of severe bleeding is just 1-3%, annually, and the severest ones are those involving the central nervous system [92,93]. The risk is particularly increased once the INR exceeds 4.5 [93]. The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin [94]. Thirteen publications from 11 cohorts including more than 48.500

patients with more than 11.600 warfarin users were included in the meta-analysis in which warfarin resulted with a lower risk of ischemic stroke (p= 0.004) and mortality (p<0.00001), but had no effect on major bleeding (p>0.05) in patients with AF and non-end-stage CRD [95]. Warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) [96]. On the other hand, patients with cerebral venous thrombosis (CVT) anticoagulated either with warfarin or dabigatran had lower risk of recurrent venous thrombotic events (VTE), and the risks of bleeding were similar in both regimens [97]. Additionally, an INR value of 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted with no increase in the number of men ever reporting minor bleeding episodes [98]. Non-rheumatic AF increases the risk of stroke, and long-term use of low-dose warfarin is highly effective and safe with a reduction of 86% (p= 0.0022) [99]. The mortality rate was significantly lower in the warfarin group, too (p= 0.005) [99]. The frequencies of bleedings that required hospitalization or transfusions were similar in both groups (p>0.05) [99]. Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer in which the average daily dose was 2.6 mg, and the mean INR value was 1.5 [100]. On the other hand, new oral anticoagulants had a favorable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleedings as for warfarin, but increased GI bleeding [101]. Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all-cause mortality compared with warfarin [102]. The mortality rates were 4.1%, 3.7%, and 3.6% per year in the warfarin, 110 mg of dabigatran, and 150 mg of dabigatran groups with AF, respectively (p>0.05 for both) [103]. Eventually, infection, inflammation, medical or surgical emergency, and emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths [104]. So anti-inflammatory dose of aspirin plus low-dose warfarin may be the other life-saving drug regimen to prevent atherosclerotic endpoints even at childhood in the SCD [105].

COPD is the third leading cause of death at the moment [106]. Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammation, prolonged infection, and cancers may be the 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 second common cause of COPD due to the excess fat tissue-induced atherosclerotic endpoints in whole body since an estimated 25-45% of patients with the COPD have never smoked [107]. Regular alcohol consumption may be the third leading cause of the systemic exaggerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence [108]. Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism [109]. Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelial cells is exaggerated by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may just be the pulmonary endpoint of the systemic atherosclerotic process since there are several reports about coexistence of associated endothelial inflammation in whole body in the COPD [110]. For example, there may be close relationships between COPD, CHD, PAD, and stroke [111]. 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 multicenter study of 5.887 smokers [112]. When hospitalizations were researched, the most common causes were the cardiovascular diseases, again [112]. In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD [113]. Finally, COPD may also be an irreversible atherosclerotic endpoint in the SCD [106].

Leg ulcers are seen in 10% to 20% of patients with the SCD, and its prevalence increases with aging, male gender, and SCA [114, 115]. The leg ulcers have an intractable nature, and around 97% of them relapse in one year (114). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow [114]. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the main causes [115]. 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. Smoking and alcohol probably have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBC on vascular endothelial cells, severity of the destructive process is probably exaggerated by the immune system. The main action way of hydroxyurea may be the suppression of hyperproliferative WBC and PLT in the SCD [77,116]. Similarly, lower WBC counts were associated with lower crisis rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain [78]. 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 cell edema. Digital clubbing is characterized by the increased normal angle of 165° between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger [117]. The chronic tissue hypoxia is highly suspected in its etiology [118]. 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 smoking and pulmonary, cardiac, renal, and hepatic diseases which are characterized with chronic tissue hypoxia [5]. As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those can affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, too and its prevalence is 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, edema, and fibrosis, particularly at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males (14.8% vs 6.6%, $p<0.001$) may also indicate some additional role of male gender for the atherosclerotic endpoints.

CRD is increasing which can be explained by prolonged survival and increased prevalence of excess fat tissue, too [119]. Aging, animal-rich diet, excess fat tissue, smoking, alcohol, chronic inflammatory or infectious process, and cancers may be the major causes of the renal endothelial inflammation, too. 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 [120]. Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation [121]. Age ($p= 0.04$), high-sensitivity CRP ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT [119]. 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 [122]. 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 [122]. However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage [123]. 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, CRD progresses more easily [122]. The systemic inflammatory effects of smoking on endothelial cells is also important in the CRD [124]. Although the presence of some opposite reports [124], alcohol probably gives harm to the renal vascular endothelium, too. Chronic inflammatory or infectious processes may also terminate with atherosclerotic endpoints in kidneys [123]. There are close relationships between CRD and other atherosclerotic endpoints [125,126]. The most common causes of death were CHD and stroke in CRD, again [127]. The hardened RBC-induced capillary endothelial damage may be the major cause of CRD in the SCD, again [128].

Stroke is the other terminal cause of death, together with the CHD, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammatory or infectious process, cancer, and emotional stress may be the major causes. Stroke is also a common atherosclerotic endpoint of the SCD [129]. Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts [130]. Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial damage, edema, and fibrosis [131]. Stroke may not have a macrovascular origin, and an acute onset diffuse capillary endothelial edema may be much more important in the SCD. Therefore, permanent neurological deficits are rare with stroke in the SCD. Infection, inflammation, medical or surgical emergency, and emotional stress may cause stroke by increasing basal metabolic rate and sickling. Low risk of stroke with hydroxyurea can also suggest that a significant proportion of stroke is developed due to the increased WBC and PLT counts-induced an acute capillary endothelial edema [132]. Acarbose is a pseudotetrasaccharide produced as a natural microbial product of Actinophages strain SE 50. It binds to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa with a dose-dependent manner, reversibly and competitively. It inhibits glucoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltose but does not have any effect on beta-glucosidases such as lactase. By this way, it delays the intestinal hydrolysis of oligo- and disaccharides mainly in the upper half of the small intestine. As a result, the absorption of monosaccharides is delayed, and transport into the circulation is interrupted. Its effects may prolong up to 5 hours. The suppression of alpha-glucosidases is persistent with long-term use. Its usage results with carbohydrates appearing in the colon where bacterial fermentation occurs, and causes flatulence, loose stool, and abdominal discomfort [133]. If started with a lower dosage and titrated slowly, side effects are tolerable [134]. Long-term use increases colonic bacterial mass

that of lacto bacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in portosystemic encephalopathy. So acarbose has a favorable therapeutic profile for the long-term use even in cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on the epithelial cells of colon that may potentially decrease carcinogenesis. After oral administration, less than 2% of the unchanged drug enters into the circulation. Therefore, there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% [135]. The initial improvement in blood glucose tends to be modest, but efficacy steadily improves with the long-term use. Its beneficial effects on serum lipids were also seen with a dose-dependent manner [135], because dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglycerides synthesis is reduced for several hours, so acarbose lowers plasma triglycerides levels [135]. The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyper insulinemic and overweight patients with impaired glucose tolerance (IGT) [136]. Significantly elevated Urso cholic acids in the stool appear to be the additive endpoint of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal flora. Acarbose may lower LDL via increased fecal bifido bacteria and biliary acids. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in DM [137]. Probably, acarbose improves release of glucagon-like peptide-1, inhibits PLT activation, increases epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promotes weight loss, decreases BP, and eventually prevents endothelial dysfunction [135]. So, it prevents atherosclerotic endpoints of excess fat tissue even in the absence of IGT or DM [138,139]. Although some authors reported as opposite [140], it should be used as the first-line antidiabetic agent. Based on more than 40 years of use, numerous studies did not show any significant side effect or toxicity [141]. Although 25.9% of patients stopped metformin due to excessive anorexia [142], only 10.6% stopped acarbose due to an excessive flatulence or loose stool [143].

Metformin is a biguanide, and it is not metabolized, and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, inhibition of fatty acid oxidation, and reduction of intestinal glucose absorption [144, 145]. Precise mechanism of intracellular action of metformin remains as unknown. Interestingly, 25.9% of patients stopped metformin due to the excessively lost appetite [142]. Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen [142]. According to our opinion, the major effect of metformin is an inhibition of appetite. Similar results indicating the beneficial effects on the BMI, BP, FPG, and lipids were also reported [146,147]. Probably the major component of the metabolic syndrome may be the excess fat tissue. So, treatment of excess fat tissue with acarbose plus metformin will probably prevent not only IGT or DM but also the other atherosclerotic endpoints. As a conclusion, hardened RBC-induced capillary endothelial damage terminates with end-organ insufficiencies in early decades of life in SCD. Although atherosclerotic endpoints are so common, we detected no case of DM probably due to lower excess fat tissue. As the most common cause of CRD, DM may be a relative insufficiency of pancreas against the excess fat tissue. Increased blood and insulin requirements of excess fat in contrast to decreased blood supply of excess tissue and pancreas both due to excess external pressure and internal narrowing of vasculature may be important for DM. As the most common cause of DM, obesity may be an irreversible atherosclerotic endpoint in human body. Acarbose and metformin are oral, safe, cheap, and effective drugs to prevent obesity.

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