

Acarbose in the Treatment of Cirrhosis

Mehmet Rami Helvacı^{1*}, Hulya Halici², Kevser Erdogan³, Yusuf Aydin¹, Leyla Yilmaz Aydin⁴, Alper Sevinc¹, Celalettin Camci¹, Abdulrazak Abyad⁵ and Lesley Pocock⁶

¹Specialist of Internal Medicine, MD, Turkey

²Manager of Writing and Statistics, Turkey

³Specialist of Public Health, MD, Turkey

⁴Specialist of Pulmonary Medicine, MD, Turkey

⁵Middle-East Academy for Medicine of Aging, MD, Lebanon

⁶Medi-WORLD International, Australia

*Corresponding author

Mehmet Rami Helvacı, Specialist of Internal Medicine, MD, 07400, ALANYA, Turkey .

Received: April 30, 2025; Accepted: May 08, 2025; Published: May 13, 2025

ABSTRACT

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

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

Results: We studied 222 males and 212 females with mean ages of 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 lifespans (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%, $p<0.001$), cirrhosis (8.1% vs 1.8%, $p<0.001$), chronic obstructive pulmonary disease (25.2% vs 7.0%, $p<0.001$), coronary heart disease (CHD) (18.0% vs 13.2%, $p<0.05$), leg ulcers (19.8% vs 7.0%, $p<0.001$), clubbing (14.8% vs 6.6%, $p<0.001$), chronic renal disease (CRD) (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 an accelerated atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan failures in early years of life in the SCD. Excess fat tissue may be much more important than smoking and alcohol for atherosclerosis because excess weight-induced diabetes mellitus is the most common cause of CRD, and CHD and stroke are the main causes of deaths even in cirrhosis. The efficacy of acarbose to lower blood glucose by preventing breakdown of starch into sugar in the small intestine is obvious. Since acarbose is a safe, cheap, oral, and effective drug for excess weight, it should be advised in cirrhosis because there are nearly 33 kg of excess fat even between lower border of normal weight and obesity in adults.

Keywords: Acarbose, Cirrhosis, Sickle Cell Diseases, Excess Fat Tissue, Smoking, Endothelial Inflammation, Atherosclerosis

Introduction

Chronic endothelial damage may be the main cause of aging and death by means of atherosclerotic multiorgan insufficiencies in human being [1]. Much higher blood pressures (BP) of the afferent vasculature may be the chief accelerating factor via recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are chiefly involved in the process. Therefore venosclerosis or phlebosclerosis is not as famous as atherosclerosis in medicine. Due to the chronic

endothelial injury, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are sedentary lifestyle, physical inactivity, animal-rich diet, emotional stresses, smoking, alcohol, excess fat tissue, 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, peripheral artery

Citation: Mehmet Rami Helvacı, Hulya Halici, Kevser Erdogan, Yusuf Aydin, Leyla Yilmaz Aydin, et al. Acarbose in the Treatment of Cirrhosis. J Gastro Endosc. 2025. 3(2): 1-13. DOI: doi.org/10.61440/JGE.2025.v3.28

disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death [2, 3].

Although early withdrawal of the accelerating factors can delay the above terminal consequences, after development of them, the endothelial changes can not be reversed, completely due to their fibrotic natures. The accelerating factors and terminal consequences of the vascular endothelial process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in medicine [4-6]. Similarly, sickle cell diseases (SCD) are chronic inflammatory and destructive processes on vascular endothelium, initiating at birth and terminating with an accelerated atherosclerosis-induced multiorgan failures in much earlier ages [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 main problem since sickling is rare in peripheric blood samples of 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. The hardened RBC-induced chronic endothelial injury, inflammation, edema, 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 major distributor of the hardened RBC into the tissues [10, 11]. The hardened RBC-induced chronic endothelial injury builds up an accelerated atherosclerosis in much earlier ages. Vascular narrowings and occlusions-induced tissue ischemia and multiorgan failures are the terminal 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 done in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All cases with the SCD were studied. The SCD were diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Health histories including smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgical procedures, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A full physical examination was performed by the Same Internist, and cases with disseminated teeth losses (<20 teeth present) were noted. Patients with acute painful crises or other inflammatory events 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 via MRI [12]. Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed by means of HPLC because the 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 (PHT) [14]. Hepatic cirrhosis is diagnosed with full 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 detected clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, 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 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 continuous 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 greater than 1.0, and with the presence of Schamroth's sign [17, 18].

An exercise electrocardiogram is taken in patients with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed for the exercise electrocardiogram positive patients. Eventually, CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement abnormalities in the walls of heart. Rheumatic heart disease is detected with the echocardiographic findings, too. Stroke is diagnosed by the CT and MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in cases 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 ages (30.8 vs 30.3 years, $p>0.05$, respectively), and there was no patient above the age of 59 years neither in males nor in females. Prevalences of associated TM were similar in males and females (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 lifespans (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%, $p<0.001$), 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%, $p<0.001$), CRD (9.9% vs 6.1%, $p<0.05$), 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 size (Table 2). On the other hand, mean ages of the atherosclerotic consequences 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)

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 weight may be the most common cause of vasculitis, and actually the term should be replaced with excess fat tissue in medicine. Probably, obesity is one of the endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide little benefit either to reverse obesity or to prevent its consequences. Excess fat leads to a chronic and low-grade inflammatory process on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat [19]. The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerosis may even decrease the clearance of malignant cells by 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 is considered as a strong factor for controlling of C-reactive protein (CRP) concentration in serum, since excess fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines [23, 24]. On the other hand, individuals with excess fat will also have an increased cardiac output.

The prolonged increase in blood volume may aggravate myocardial hypertrophy and decrease cardiac compliance further. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased parallel to the increased body mass index (BMI) [25]. Similarly, CHD and stroke increased parallel to the increased BMI [26]. Eventually, the risk of death from all causes increased parallel to the severity of excess fat in all age groups, and the cases with underweight may even have lower biological ages and longer survival [27]. Similarly, calorie restriction prolongs survival and retards age-related chronic diseases in human being [28].

Smoking may be the second most common cause of vasculitis. Probably, it causes a systemic inflammation on vascular endothelium terminating with an atherosclerosis-induced multiorgan failures in early years [29]. Its atherosclerotic effect is obvious in 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 seen without smoking. Its characteristics are inflammation, fibrosis, and narrowing and occlusions of arteries and veins, predominantly in hands and feet. Claudication is the most common symptom with a severe pain caused by insufficient blood supply in feet and hands, particularly during exercise.

It typically begins in extremities but it may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also common. Skin ulcerations and gangrene of fingers or toes are the final consequences. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, 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. Multiple narrowings and occlusions in the arms and legs are diagnostic in the angiogram. Skin biopsies are rarely needed 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 constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible.

Due to the obvious role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may be effective in prevention of microvascular infarctions of fingers and toes. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and CRP may be positive acute phase reactants in smokers [31]. Similarly, smoking was associated with the lower BMI values 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 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]. The prevalence of myocardial infarction is increased three-fold in men and six-fold in women with smoking, so smoking may be more dangerous for women probably due to the higher BMI [39]. Several toxic substances found in the cigarette smoke can affect various organ systems. For instance, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis with several mechanisms [40]. First of all, smoking may have some antidepressive effects. Secondly, smoking-induced vascular inflammation may disturb epithelial functions for 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. Eventually, immunosuppression secondary to smoking-induced vascular inflammation may terminate with the GI and GU tract infections causing urolithiasis since 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 bacteria, producing urease. So, urolithiasis was seen in 17.9% of cases with IBS and 11.6% of cases without ($p < 0.01$) [40].

Beside the stroke, CHD is the other terminal cause of death in human being. 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 walls 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 takes its place which may also cause life threatening arrhythmias since the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissue 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, rupture, and sudden cardiac death. Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, emotional stresses, smoking, alcohol, prolonged infections, chronic inflammations, 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 since there are nearly 20 kg of excess fat tissue between the lower and upper borders of normal

weight, 33 kg between the obesity, 66 kg between the morbid obesity (BMI ≥ 40 kg/m²), and 81 kg between the super obesity (BMI ≥ 45 kg/m²) in adults. In fact, there is a huge percentage of adults with a heavier fat mass than their organ plus muscle masses that brings a heavy stress both on the heart and brain.

Cirrhosis is the 10th leading cause of death for men and the 12th for women in the United States [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 weight, globally. 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 at the moment. NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis [44]. Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of CHD and stroke [45].

Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) [46]. NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD [47]. Probably smoking also takes role in the inflammatory process of the capillary endothelium in the liver because the systemic inflammatory effects of smoking on the endothelial cells is obvious in Buerger's disease and COPD [36]. Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious and inflammatory processes and cancers may also terminate with an accelerated atherosclerotic process [48]. For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection [49]. As a result, cirrhosis may also be another atherosclerotic consequence of the metabolic syndrome and SCD, again.

Acute painful crises are the severest symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stresses are the most common precipitating factors of the crises [50]. The increased basal metabolic rate during such stresses aggravates the sickling, capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving significant sequelae on the capillary endothelial system all over the body. After a period of time, the sequelae may terminate with sudden multiorgan failures and death during a final acute painful crisis that may even be silent, 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. Rapid RBC supports are usually life-saving for such patients, although

preparation of RBC units for transfusion usually takes time.

Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismatch. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD [51, 52]. According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD [53, 54]. First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during the crises [55].

Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that 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.

Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic consequences in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD [56], and it was associated with the risk of stroke [57]. 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 needed [58]. but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic atherosclerotic background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides via 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 in the SCD [59, 60]. By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some

extent. 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 destructive process is probably exaggerated by the patients' own WBC and PLT.

So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body [61]. Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels [62]. 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. The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea 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. In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates. 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 per year [63].

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 per year ($p < 0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p < 0.000$) (51). Parallel to us, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period. Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival [64]. The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have higher incidences of ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them [65]. If started in early years of life, hydroxyurea may protect splenic function, improve growth, and prevent multiorgan insufficiencies. Although RBC transfusions can also reduce the complications, there are the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult. Therefore RBC transfusions should be kept in hands just for emergencies as the most effective weapon at the moment.

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. This property causes aspirin being different from other NSAID, which are reversible inhibitors. 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.

In another definition, 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 once aspirin has inhibited the enzyme. But aspirin does not decrease the blood viscosity. The antithrombotic property of aspirin is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke [66]. Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction [67]. According to the literature, aspirin may also be effective in prevention of colorectal cancers [68].

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 [69]. Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease. Reye syndrome is a rapidly worsening brain disease. The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye. The syndrome mostly affects children, but it can only affect fewer than one in a million children a year.

Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness. Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases. Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage. 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. 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.

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. The treatment is supportive. Mannitol can be used for the brain swelling. 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 [70-73].

Warfarin is an anticoagulant, and it 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. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly flowing 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 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 [74]. Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the elderly. In the protocol of low-dose warfarin, the target international normalized 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 [75]. When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is enough to reverse the effect, and causes INR to drop below 1.5. Its effects can be reversed with phytonadione (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 enzyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticoagulating 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 current self-testing and management devices are effective methods of monitoring oral anticoagulation therapy, providing outcomes possibly better than achieved, clinically. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3%. All types of bleeding may occur, but the severest ones are those involving the central nervous system. The risk is particularly increased once the INR exceeds 4.5 [76,77]. The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin [78]. But 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 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 ($p>0.05$) [79].

Similarly, warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH). Whereas recurrent ICH occurred in 6.7% of patients who used warfarin and 7.7% of patients who did not use warfarin without any significant difference in between ($p>0.05$) [80]. 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 cases with CVT [81]. Additionally, an INR value of 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 [82]. 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 them. 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 ($p=0.0022$).

The mortality was markedly lower in the warfarin group, too ($p=0.005$). The frequencies of bleedings that required hospitalization or transfusion were the same in both groups ($p>0.05$) [83]. Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer. The average daily dose was 2.6 mg, and the mean INR was 1.5 [84]. 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 bleedings as for warfarin, but increased GI bleeding [85]. Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin [86]. 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 ($p>0.05$ for both) in AF in another study, respectively [87]. On the other hand, infections, medical or surgical emergencies, and emotional stresses-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction and stroke may cause sudden deaths [88]. So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving regimen even at childhood to decrease severity of capillary inflammation and to prevent thromboembolic events in the SCD [89].

COPD is the third leading cause of death in the world [90, 91]. Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major 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 process in whole body. 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 [92].

Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism [93]. 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 [94].

For example, there may be close relationships between COPD, CHD, PAD, and stroke [95]. 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. When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again [96]. In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD [97]. On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD [90].

Leg ulcers are seen in 10% to 20% of the SCD. Its prevalence increases with aging, male gender, and SCA. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year. Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes [98,99]. 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, 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 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 [100]. 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 [11]. Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD [101].

Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by 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 tissue damage and pain [62]. 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.

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 [102]. Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected [103]. 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 [104]. Aging, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory and 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 [105].

Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation [106]. For example, 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 [104]. 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 weight. 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. However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage. 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 much more easily. On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD.

Although some authors reported that alcohol was not related with the CRD, various metabolites of alcohol circulate in blood vessels of kidneys and give harm to the endothelium. Chronic inflammatory and infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature [107-109]. Due to the systemic nature of atherosclerosis, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke [110, 111]. For example, the most common causes of death were the CHD and stroke in the CRD again [112]. The hardened RBC-induced capillary endothelial damage may be the main cause of CRD in the SCD, again [113].

Beside the CHD, stroke is the other terminal cause of death, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess fat tissue may be the major underlying causes. Stroke is also a common complication of the SCD [114]. Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts [115]. Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis [116]. 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 capillary endothelial inflammation and edema [117].

Acarbose, a pseudotetrasaccharide, is a natural microbial product derived from culture broths of *Actinoplanes* strain SE 50. It is an alpha-glucosidase inhibitor. It binds reversibly and competitively, and in a dose-dependent manner to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. As a result, it delays the intestinal hydrolysis of oligo- and disaccharides by alpha-glucosidases mainly in the upper half of the small intestine. By this way, the absorption of monosaccharides after a meal is delayed, and transport through the mucosal surfaces into the circulation is interrupted.

On the other hand, it does not have any direct effect on absorption of glucose. Although the acute effect is seen within a few minutes, its effects may prolong up to 5 hours. Acarbose should be taken with the first bite of the meal. The suppression of alpha-glucosidases is reversible, although pharmacological activity is reliable and persistent with long-term use. Effects with continued use can be maintained over years. Up to now, acarbose failure has not been reported in the literature. Initial therapy with an alpha-glucosidase inhibitor often results with carbohydrates appearing in the colon, where bacterial fermentation occurs, accounting for the frequency and severity of GI adverse effects such as flatulence, loose stool, and abdominal discomfort [118]. If started with a lower dose and titrated slowly, it tends to cause occasional GI side effects that are generally tolerable [119]. Long-term use of acarbose increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in patients with liver cirrhosis and portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use of cases with type 2 DM and cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on epithelial cells of colon that may potentially decrease the risk of carcinogenesis. Acarbose is poorly absorbed and systemic bioavailability is low. 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%. Similarly, it lowers fasting and postprandial insulin levels. The initial improvement in blood glucose with acarbose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years without evidence of decreased effect. The beneficial effects of acarbose on serum lipids were also described with a dose-dependent manner, because dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid

metabolism. Carbohydrate-induced postprandial triglyceride synthesis is reduced for several hours, so acarbose lowers plasma triglyceride levels [120].

The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT) [121]. Significantly elevated levels of ursolic acids in the stool appear to be the additive consequence of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal bacteria. Acarbose may lower serum LDL by means of an increased fecal bifido bacteria, fecal biliary acids, and LDL uptake by the liver. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in cases with type 2 DM when compared with those received insulin alone [122]. Similarly, acarbose may improve release of glucagon-like peptide-1, inhibit platelet activation, increase epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promote weight loss, decrease BP, and eventually prevent endothelial dysfunction [120].

So acarbose also prevents COPD and other atherosclerotic consequences in excess weight even in the absence of IGT and DM [123, 124]. According to our experiences, acarbose should be used in patients with COPD even in normal weight because there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight in adults. Although some authors reported as opposite with us [125], acarbose should be considered as the first-line antidiabetic agent. Based on more than 40 years of clinical use, numerous studies did not show any significant toxicity [126]. On the other hand, it does not have any effect on appetite.

As a conclusion, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan failures in early years of life in the SCD. Excess fat tissue may be much more important than smoking and alcohol for atherosclerosis because excess weight-induced DM is the most common cause of CRD, and CHD and stroke are the main causes of deaths even in the cirrhosis. The efficacy of acarbose to lower blood glucose by preventing breakdown of starch into sugar in the small intestine is obvious. Since acarbose is a safe, cheap, oral, and effective drug for excess weight, it should be advised in cirrhosis because there are nearly 33 kg of excess fat tissue even between the lower border of normal weight and obesity in adults.

References

1. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol*. 2003. 42: 1149-1160.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005. 365: 1415-1428.
3. Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. *J Hypertens*. 2006. 24: 2009-2016.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002. 106: 3143-3421.

5. Helvacı MR, Aydın LY, Aydın Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. *HealthMED*. 2012. 6: 3977-3981.
6. Anderson RN, Smith BL. Deaths: leading causes for 2001. *Natl Vital Stat Rep*. 2003. 52: 1-85.
7. Helvacı MR, Gökçe C, Davran R, Akkucuk S, Uğur M, et al. Mortal quintet of sickle cell diseases. *Int J Clin Exp Med*. 2015. 8: 11442-11448.
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994. 330: 1639-1644.
9. Helvacı MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. *World Family Med*. 2018. 16: 12-18.
10. Helvacı MR, Kaya H. Effect of sickle cell diseases on height and weight. *Pak J Med Sci*. 2011. 27: 361-364.
11. Helvacı MR, Aydın Y, Ayyıldız O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. *Health MED*. 2013. 7: 2327-2332.
12. Mankad VN, Williams JP, Harpen MD, Mancini E, Longenecker G, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. *Blood*. 1990. 75: 274-283.
13. Helvacı MR, Aydın Y, Ayyıldız O. Clinical severity of sickle cell anemia alone and sickle cell diseases with thalassemias. *HealthMED*. 2013. 7: 2028-2033.
14. Fisher MR, Forfia PR, Chamara E, Houston-Harris T, Champion HC, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009. 179: 615-621.
15. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013. 187: 347-365.
16. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. *Lancet*. 1984. 1: 36-38.
17. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. *Eur J Intern Med*. 2008. 19: 325-329.
18. Schamroth L. Personal experience. *S Afr Med J*. 1976. 50: 297-300.
19. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999. 341: 1097-1105.
20. Helvacı MR, Aydın Y, Gundogdu M. Smoking induced atherosclerosis in cancers. *HealthMED*. 2012. 6: 3744-3749.
21. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med*. 1999. 340: 115-126.
22. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation*. 2001. 103: 1813-1818.
23. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998. 279: 1477-1482.
24. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA*. 1999. 282: 2131-2135.
25. Zhou B, Wu Y, Yang J, Li Y, Zhang H, et al. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. *Obes Rev*. 2002. 3: 147-156.
26. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases--report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci*. 2002. 15: 245-252.
27. Helvacı MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. *Int Heart J*. 2007. 48: 605-613.
28. Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. *Am J Clin Nutr*. 2003. 78: 361-369.
29. Fodor JG, Tzerovska R, Dorner T, Rieder A. Do we diagnose and treat coronary heart disease differently in men and women? *Wien Med Wochenschr*. 2004. 154: 423-425.
30. Helvacı MR, Aydın LY, Aydın Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. *Pak J Med Sci*. 2012. 28: 376-379.
31. Helvacı MR, Kayabasi Y, Celik O, Sencan H, Abyad A, et al. Smoking causes a moderate or severe inflammatory process in human body. *Am J Biomed Sci & Res*. 2023. 7: 694-702.
32. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, et al. National working conference on smoking and body weight. Task Force 1: Mechanisms relevant to the relations between cigarette smoking and body weight. *Health Psychol*. 1992. 11: 4-9.
33. Helvacı MR, Camci C, Nisa EK, Ersahin T, Atabay A, et al. Severity of sickle cell diseases restricts smoking. *Ann Med Medical Res*. 2024. 7: 1074.
34. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ, et al. The effect of smoking on energy expenditure and plasma catecholamine and nicotine levels during light physical activity. *Nicotine Tob Res*. 1999. 1: 365-370.
35. Hughes JR, Hatsukami DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. *J Subst Abuse*. 1997. 9: 151-159.
36. Miyata G, Meguid MM, Varma M, Fetisov SO, Kim HJ. Nicotine alters the usual reciprocity between meal size and meal number in female rat. *Physiol Behav*. 2001. 74: 169-176.
37. Froom P, Melamed S, Benbassat J. Smoking cessation and weight gain. *J Fam Pract* 1998; 46(6): 460-4.
38. Helvacı MR, Kaya H, Gundogdu M. Gender differences in coronary heart disease in Turkey. *Pak J Med Sci*. 2012. 28: 40-44.
39. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998. 316: 1043-1047.
40. Helvacı MR, Kabay S, Gulcan E. A physiologic events' cascade, irritable bowel syndrome, may even terminate with urolithiasis. *J Health Sci*. 2006. 52: 478-481.
41. Helvacı MR, Dede G, Yildirim Y, Salaz S, Abyad A, et al. Smoking may even cause irritable bowel syndrome. *World Family Med*. 2019. 17: 28-33.
42. Helvacı MR, Algin MC, Kaya H. Irritable bowel syndrome and chronic gastritis, hemorrhoid, urolithiasis. *Eurasian J Med*. 2009. 41: 158-161.

43. Kamimura D, Loprinzi PD, Wang W, Suzuki T, Butler KR, et al. Physical activity is associated with reduced left ventricular mass in obese and hypertensive African Americans. *Am J Hypertens*. 2017. 30: 617-623.
44. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? *Eur Heart J*. 2012. 33: 1190-1200.
45. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. *World J Gastroenterol*. 2011. 17: 3082-3091.
46. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. *Nihon Rinsho*. 2011. 69: 153-157.
47. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. *Curr Pharm Des* 2010; 16(17): 1941-51.
48. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. *Gut*. 2010. 59: 1135-1140.
49. Helvacı MR, Ayyıldız O, Gundogdu M, Aydın Y, Abyad A, et al. Hyperlipoproteinemias may actually be acute phase reactants in the plasma. *World Family Med*. 2018. 16: 7-10.
50. Parfrey NA, Moore W, Hutchins GM. Is pain crisis a cause of death in sickle cell disease? *Am J Clin Pathol*. 1985. 84: 209-212.
51. Helvacı MR, Ayyıldız O, Gundogdu M. Hydroxyurea therapy and parameters of health in sickle cell patients. *Health MED*. 2014. 8: 451-456.
52. Helvacı MR, Tonyali O, Yaprak M, Abyad A, Pocock L. Increased sexual performance of sickle cell patients with hydroxyurea. *World Family Med*. 2019. 17: 28-33.
53. Helvacı MR, Atci N, Ayyıldız O, Muftuoğlu OE, Pocock L. Red blood cell supports in severe clinical conditions in sickle cell diseases. *World Family Med*. 2016. 14: 11-18.
54. Helvacı MR, Ayyıldız O, Gundogdu M. Red blood cell transfusions and survival of sickle cell patients. *HealthMED*. 2013. 7: 2907-2912.
55. Helvacı MR, Cayir S, Halici H, Sevinc A, Camci C, et al. Red blood cell transfusions may have the strongest analgesic effect during acute painful crises in sickle cell diseases. *Ann Clin Med Case Rep*. 2024. V13: 1-12.
56. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, et al. Prediction of adverse outcomes in children with sickle cell disease. *N Engl J Med*. 2000. 342: 83-89.
57. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, et al. Stroke in a cohort of patients with homozygous sickle cell disease. *J Pediatr*. 1992. 120: 360-366.
58. Cole TB, Sprinkle RH, Smith SJ, Buchanan GR. Intravenous narcotic therapy for children with severe sickle cell pain crisis. *Am J Dis Child*. 1986. 140: 1255-1259.
59. Miller BA, Platt O, Hope S, Dover G, Nathan DG. Influence of hydroxyurea on fetal hemoglobin production in vitro. *Blood*. 1987. 70: 1824-1829.
60. Platt OS. Is there treatment for sickle cell anemia. *N Engl J Med*. 1988. 319: 1479-1480.
61. Helvacı MR, Aydoğan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. *Pren Med Argent*. 2014. 100: 49-56.
62. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. *Semin Hematol*. 1997. 34: 15-21.
63. Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore). 1996. 75: 300-326.
64. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA*. 2003. 289: 1645-1651.
65. Lebensburger JD, Miller ST, Howard TH, Casella JF, Brown RC, et al. BABY HUG Investigators. Influence of severity of anemia on clinical findings in infants with sickle cell anemia: analyses from the BABY HUG study. *Pediatr Blood Cancer*. 2012. 59: 675-678.
66. Toghi H, Konno S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. *Stroke*. 1992. 23: 1400-1403.
67. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009. 373: 1849-1860.
68. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol*. 2012. 13: 518-527.
69. Macdonald S. Aspirin use to be banned in under 16 year olds. *BMJ*. 2002. 325: 988.
70. Schrör K. Aspirin and Reye syndrome: a review of the evidence. *Paediatr Drugs*. 2007. 9: 195-204.
71. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. *Cell Biochem Funct*. 2008. 26: 741-746.
72. Hurwitz ES. Reye's syndrome. *Epidemiol Rev*. 1989. 11: 249-253.
73. Meremikwu MM, Okomo U. Sickle cell disease. *BMJ Clin Evid*. 2011. 2011: 2402.
74. Mohamed S, Fong CM, Ming YJ, Kori AN, Wahab SA, et al. Evaluation of an initiation regimen of warfarin for international normalized ratio target 2.0 to 3.0. *J Pharm Technol*. 2021. 37: 286-292.
75. Chu MWA, Ruel M, Graeve A, Gerdisch MW, Ralph J, et al. Low-dose vs standard warfarin after mechanical mitral valve replacement: A randomized trial. *Ann Thorac Surg*. 2023. 115: 929-938.
76. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneously vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. *Ann Intern Med*. 2002. 137: 251-254.
77. Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. *J Am Acad Dermatol*. 2015. 72: 524-534.
78. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *CMAJ*. 2007. 177: 347-351.
79. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest*. 2016. 149: 951-959.

80. Chai-Adisaksopha C, Lorio A, Hillis C, Siegal D, Witt DM, et al. Warfarin resumption following anticoagulant-associated intracranial hemorrhage: A systematic review and meta-analysis. *Thromb Res*. 2017. 160: 97-104.
81. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. *JAMA Neurol*. 2019. 76: 1457-1465.
82. Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. *Am J Cardiol*. 1990. 65: 7C-11C.
83. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990; 323: 1505-1511.
84. Levine M, Hirsh J, Gent M, Arnold A, Warr D, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet*. 1994. 343: 886-889.
85. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014. 383: 955-962.
86. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018. 362: k2505.
87. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009. 361: 1139-1151.
88. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, et al. Terminal endpoints of systemic atherosclerotic processes in sickle cell diseases. *World Family Med*. 2024. 22: 13-23.
89. Helvaci MR, Daglioglu MC, Halici H, Sevinc A, Camci C, et al. Low-dose aspirin plus low-dose warfarin may be the standard treatment regimen in Buerger's disease. *World Family Med*. 2024. 22: 22-35.
90. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. *HealthMED*. 2013. 7: 484-488.
91. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. *Lancet*. 2015. 385: 1778-1788.
92. Schoepf D, Heun R. Alcohol dependence and physical comorbidity: Increased prevalence but reduced relevance of individual comorbidities for hospital-based mortality during a 12.5-year observation period in general hospital admissions in urban North-West England. *Eur Psychiatry*. 2015. 30: 459-468.
93. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. *Chest*. 2016. 149: 905-915.
94. Mannino DM, Watt G, Hole D, Gillis C, Hart C, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J*. 2006. 27: 627-643.
95. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, et al. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. *Arch Intern Med*. 2000. 160: 2653-2658.
96. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med*. 2002. 166: 333-339.
97. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. TORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax*. 2007. 62: 411-415.
98. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. *Adv Skin Wound Care*. 2004. 17: 410-416.
99. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. *Am J Hematol*. 2010. 85: 831-833.
100. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014. 312: 1033-1048.
101. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. *HealthMED*. 2014. 8: 477-482.
102. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing. *JAMA*. 2001. 286: 341-347.
103. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. *Med Hypotheses*. 2010. 75: 511-513.
104. Nassiri AA, Hakemi MS, Asadzadeh R, Faizei AM, Alatab S, et al. Differences in cardiovascular disease risk factors associated with maximum and mean carotid intima-media thickness among hemodialysis patients. *Iran J Kidney Dis*. 2012. 6: 203-208.
105. Helvaci MR, Gokce C, Sahan M, Hakimoglu S, Coskun M, et al. Venous involvement in sickle cell diseases. *Int J Clin Exp Med*. 2016. 9: 11950-11957.
106. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. *Circulation*. 2011. 124: 2933-2943.
107. Hall JE, Henegar JR, Dwyer TM, Liu J, da Silva AA, et al. Is obesity a major cause of chronic kidney disease. *Adv Ren Replace Ther*. 2004. 11: 41-54.
108. Nerpin E, Ingelsson E, Risérus U, Helmersson-Karlqvist J, Sundström J, et al. Association between glomerular filtration rate and endothelial function in an elderly community cohort. *Atherosclerosis*. 2012. 224: 242-246.
109. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology*. 2003. 14: 479-487.
110. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. *Nat Rev Gastroenterol Hepatol*. 2012. 9: 372-381.
111. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, et al. Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries. *World Family Med*. 2024. 22: 6-16.
112. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*. 2006. 17: 2034-2047.

113. Helvaci MR, Aydin Y, Aydin LY. Atherosclerotic background of chronic kidney disease in sickle cell patients. *HealthMED*. 2013. 7: 2532-2537.
114. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014. 371: 699-710.
115. Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, et al. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. *Br J Haematol*. 2014. 165: 707-713.
116. Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. *Arch Pediatr*. 2014. 21: 404-414.
117. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med*. 1995. 332: 1317-1322.
118. Rosak C, Mertes G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. *Diabetes Metab Syndr Obes*. 2012. 5: 357-367.
119. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin Pharmacokinet*. 1996. 30: 94-106.
120. DiNicolantonio JJ, Bhutani J, O'Keefe JH. Acarbose: safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes. *Open Heart*. 2015. 2.
121. Leonhardt W, Hanefeld M, Fischer S, Schulze J. Efficacy of alpha-glucosidase inhibitors on lipids in NIDDM subjects with moderate hyperlipidaemia. *Eur J Clin Invest*. 1994. 24: 45-49.
122. Li FF, Fu LY, Xu XH, Su XF, Wu JD, et al. Analysis of the add-on effect of alpha-glucosidase inhibitor, acarbose in insulin therapy: A pilot study. *Biomed Rep*. 2016. 5: 461-466.
123. Heine RJ, Balkau B, Ceriello A, Del Prato S, Horton ES, et al. What does postprandial hyperglycaemia mean. *Diabet Med*. 2004. 21: 208-213.
124. Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care. *Diabetes Care*. 2011. 34: 120-127.
125. Wettergreen SA, Sheth S, Malveaux J. Effects of the addition of acarbose to insulin and non-insulin regimens in veterans with type 2 diabetes mellitus. *Pharm Pract (Granada)*. 2016. 14: 832.
126. Van De Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, et al. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes Care*. 2005. 28: 154-163.