

Cholesterol May be a Negative Whereas Triglycerides Positive Acute Phase Reactants in the Plasma

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ABSTRACT

Background: We tried to understand some undetermined missions of cholesterol and triglycerides (TG) in the plasma in patients with the sickle cell diseases (SCD). **Methods:** All patients with the SCD and age and gender-matched control cases were included into the study. **Results:** We studied 363 patients with the SCD (194 males) and 255 control cases (136 males), totally. Mean ages of the SCD patients were similar in males and females (31.1 vs. 31.0 years, respectively, $P > 0.05$). Although the body weight and body mass index (BMI) were significantly suppressed in the SCD patients (59.9 vs. 71.5 kg and 21.9 vs. 25.6 kg/m², respectively, $P = 0.000$ for both), the body heights were similar in both groups (164.9 vs. 167.0 cm, $P > 0.05$). Parallel to the suppressed mean body weight and BMI, fasting plasma glucose (92.8 vs. 97.6 mg/dL, $P = 0.005$), total cholesterol (121.4 vs. 165.0 mg/dL, $P = 0.000$), low-density lipoproteins (70.4 vs. 102.4 mg/dL, $P = 0.000$), and high-density lipoproteins (26.0 vs. 39.6 mg/dL, $P = 0.000$) values were all suppressed in the SCD patients, significantly. Similarly, both systolic (115.2 vs. 122.6 mmHg, $P = 0.000$) and diastolic blood pressure (73.0 vs. 86.6 mmHg, $P = 0.000$) were also suppressed in them, significantly. Interestingly, only the plasma TG were increased in the SCD patients (129.4 vs. 117.3 mg/dL, $P = 0.000$), significantly. Similarly, mean alanine aminotransferase value was not suppressed in them, too (27.4 vs. 27.3 U/L, $P > 0.05$). **Conclusion:** Cholesterol may be a negative whereas TG positive acute phase reactants in the plasma.

Keywords: Cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides, body mass index, metabolic syndrome, sickle cell diseases

INTRODUCTION

The endothelium is a monolayer of endothelial cells which constitutes the inner cellular lining of arteries, veins, capillaries, and lymphatics. It is the major player in the control of blood fluidity, platelets (PLT) aggregation, and vascular tone. It may be the major actor in immunology, inflammation, and angiogenesis. It may also be important in endocrinology. The endothelial cells control vascular tone and blood flow by synthesizing and releasing nitric oxide, metabolites of arachidonic acid, and reactive oxygen species. In addition, they are also important

for generation of vasoactive hormones such as angiotensin II. An endothelial dysfunction linked to an imbalance in the synthesis and/or release of these endothelial factors may explain the initiation of several cardiovascular pathologies including hypertension (HT) and atherosclerosis. On the other hand, chronic endothelial damage may be the major underlying cause of aging and death by causing disseminated atherosclerosis and end-organ failures in human being.^[1,2] Much higher blood pressure (BP) of the afferent vasculature may be the major underlying factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries is mainly involved in

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the process. Therefore, the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the repeated endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs and increase systolic BP further. Some of the well-known triggering cause or signs of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, hypertriglyceridemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat HT, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, HT, diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), peripheral artery disease (PAD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death.^[3,4] Although early withdrawal of the triggering causes can delay terminal consequences, endothelial changes cannot be reversed completely due to their fibrotic natures after development of the terminal consequences. The issue is researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively.^[5,6] On the other hand, sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium terminating with accelerated atherosclerosis-induced end-organ failures and shortened survivals in both genders.^[7,8] Hemoglobin S (Hb S) causes loss of elastic and biconcave disk-shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the main problem because sickling is rare in peripheral blood samples of thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, and various stresses of the body. The hard RBC-induced repeated vascular endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body.^[9,10] As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium, particularly at the capillary level,^[11] since the capillary system is the main distributor of the hard cells into the tissues. The hard RBC-induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages. Vascular narrowing and occlusions-induced tissue ischemia and infarctions are the terminal endpoints, so the mean life expectancy is decreased by 25–30 years in the SCD patients.^[12] Actually, the SCD and metabolic syndrome may have similar pathophysiologic effects on human body, and SCD can be a chance for us that we can see several consequences of the metabolic syndrome on human body in much earlier ages. We tried to understand some undetermined missions of cholesterol and triglycerides (TG) in the plasma in patients with the SCD.

MATERIALS AND METHODS

The study was performed in the Medical Faculty of the Mustafa Kemal University on all patients with the SCD and age and gender-matched control cases between March 2007 and June 2016. The SCD are diagnosed with the hemoglobin electrophoresis performed through high-performance liquid chromatography. Medical histories of the SCD patients were learned. A complete physical examination was performed by the Same Internist. Body mass index (BMI) of each case was calculated by the measurements instead of the verbal expressions. Weight in kilogram is divided by height in meter squared.^[13] Systolic and diastolic BP were checked after a 5-min of rest in seated position using a mercury sphygmomanometer (ERKA, Germany), and no smoking was permitted during the previous 2-h. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A checkup procedure including fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoproteins (HDLs), TG, serum creatinine, alanine aminotransferase (ALT), markers of hepatitis viruses A, B, C, and human immunodeficiency virus, a posterior-anterior chest X-ray film, and an electrocardiogram was performed. Eventually, the mean body weight, height, BMI, FPG, TC, low-density lipoproteins (LDL), HDL, TG, ALT, and systolic and diastolic BP were detected in each group, and compared in between. Mann–Whitney U test, independent-samples *t*-test, and comparison of proportions were used as the methods of statistical analyses.

RESULTS

The study included 363 patients with the SCD (194 males) and 255 control cases (136 males), totally. The mean ages of the SCD patients were similar in males and females (31.1 vs. 31.0 years, respectively, $P > 0.05$). Although the mean weight and BMI were significantly suppressed in the SCD patients (59.9 vs. 71.5 kg and 21.9 vs. 25.6 kg/m², respectively, $P = 0.000$ for both), the mean heights were similar in both groups (164.9 vs. 167.0 cm, $P > 0.05$). Parallel to the suppressed mean weight and BMI, FPG (92.8 vs. 97.6 mg/dL, $P = 0.005$), TC (121.4 vs. 165.0 mg/dL, $P = 0.000$), LDL (70.4 vs. 102.4 mg/dL, $P = 0.000$), and HDL (26.0 vs. 39.6 mg/dL, $P = 0.000$) were all suppressed in the SCD patients, significantly. Similarly, both systolic (115.2 vs. 122.6 mmHg, $P = 0.000$) and diastolic BP (73.0 vs. 86.6 mmHg, $P = 0.000$) were also suppressed in them, significantly. Interestingly, only the plasma TG were increased in the SCD patients (129.4 vs. 117.3 mg/dL, $P = 0.000$), significantly. Similarly, mean ALT value was not suppressed in them, too (27.4 vs. 27.3 U/L, $P > 0.05$) [Table 1].

DISCUSSION

Cholesterol, TG, and phospholipids are the major lipids of the body. Actually, cholesterol is a waxy substance that is

Table 1: Characteristic features of the study cases

Variables	Patients with SCD*	P-value	Control cases
Number	363		255
Age (year)	31.0±9.2 (17–59)	Ns†	31.2±8.6 (16–45)
Male ratio	53.4% (194)	Ns	53.3% (136)
Body weight (kg)	59.9±11.8 (30–122)	0.000	71.5±16.4 (40–128)
Body height (cm)	164.9±9.1 (142–194)	Ns	167.0±8.6 (147–192)
BMI‡ (kg/m ²)	21.9±3.6 (14.3–46.4)	0.000	25.6±5.8 (15.8–53.5)
FPG§ (mg/dL)	92.8±12.5 (57–125)	0.005	97.6±19.7 (66–269)
TC (mg/dL)	121.4±32.2 (65–296)	0.000	165.0±54.3 (72–510)
LDL¶ (mg/dL)	70.4±28.4 (20–270)	0.000	102.4±41.1 (29–313)
HDL** (mg/dL)	26.0±9.4 (4–60)	0.000	39.6±13.2 (7–95)
TG*** (mg/dL)	129.4±90.4 (31–1216)	0.000	117.3±107.4 (24–931)
ALT**** (U/L)	27.4±16.2 (4–118)	Ns	27.3±21.6 (6–117)
Systolic BP***** (mmHg)	115.2±15.7 (80–190)	0.000	122.6±19.4 (80–200)
Diastolic BP (mmHg)	73.0±12.3 (50–120)	0.000	86.6±13.6 (60–120)

*Sickle cell diseases †Nonsignificant ($p>0.05$) ‡BMI §FPG ||TC ¶LDLs **HDLs ***Triglycerides ****ALT *****Blood pressure.

TG: Triglyceride, SCD: Sickle cell disease, BMI: Body mass index, TC: Total cholesterol, LDLs: Low-density lipoproteins, HDLs: High-density lipoproteins, BP: Blood pressure, FPG: Fasting plasma glucose, ALT: Alanine aminotransferase

classified as a steroid. It is synthesized by the liver, adrenal glands, reproductive organs, and intestines. It plays a central role in many biochemical processes in human body. It is an essential structural component of animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and Vitamin D. Cholesterol crystallizes in the gall bladder and forms the major constituent of most gallstones. Cholesterol is oxidized by the liver into a variety of bile acids. These, in turn, are conjugated. A mixture of conjugated and nonconjugated bile acids, along with cholesterol itself, is excreted from the liver into the bile. Approximately, 95% of the bile acids are reabsorbed from the intestines. By this way, 50% of the excreted cholesterol is reabsorbed by the small bowel again. The excretion and reabsorption of bile acids form the basis of the enterohepatic circulation, which is essential for digestion and absorption of dietary fats. Cholesterol is kept in balance by homeostatic mechanisms in human body, and cholesterol biosynthesis is directly regulated by the cholesterol levels present. The higher dietary intake leads to reduced synthesis of cholesterol in the body and vice versa. In addition, most of dietary cholesterol is esterified, and esterified cholesterol is poorly absorbed by the bowels. For these reasons, dietary cholesterol has little effect on plasma cholesterol values. On the other hand, when the cell has abundant cholesterol, LDL receptor synthesis is blocked so new cholesterol in the form of LDL molecules cannot be taken up and vice versa again. Cholesterol is found only in foods that come from animals but not in fruit, vegetable, cereal, nut, and other plants. On the other hand, TG are the fat found in our foods. Most of the fat in the human body is stored in the form of TG again. Calories not burned by the body are automatically converted into TG, which explains why eating too much of anything can lead to excess weight. Fatty acids

in stored TG are used to provide energy for muscles. On the other hand, when stored by the body, TG help to protect and insulate internal organs and cushion the blow of a fall. Actually, the number of fat cells in the body does not fluctuate along with changes in weight instead the fat cells themselves get bigger or smaller. In addition, TG are the major lipids transported in the blood. In another word, TG provide energy for muscles, are stored as body fat, and are used to produce LDL in the body. TG are composed of even smaller units of fat called as fatty acids that are attached to a chemical base of glycerol. Fatty acids are known as the building blocks of fat. Fatty acids are described as saturated, polyunsaturated, or monounsaturated depending on how much hydrogen they contain. Saturated fatty acids contain the most hydrogen, and they are considered as the most dangerous ones for the health. Interestingly, along with the cholesterol we get from foods, saturated fats can raise the blood cholesterol levels more than anything else in the foods. Saturated fats may increase blood cholesterol levels by slowing down the removal of LDL. Therefore, blood cholesterol values may increase even if the diet is rich for saturated fats but poor for cholesterol. Foods containing saturated fats mainly come from animals, too. These foods also contain too much cholesterol actually, so they can raise blood cholesterol levels in two ways at the same time. Phospholipids are TG that are covalently bound to a phosphate group. Phospholipids regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol.

Cholesterol, TG, and phospholipids do not circulate freely in the plasma instead they are bound to proteins, and

transported as lipoproteins. There are five major classes of lipoproteins including chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, and HDL in the plasma. They are classified by their density of protein. The lower the protein, the less dense it is, the higher the cholesterol. The cholesterol within all the various lipoproteins is identical. In another word, there is really only one kind of cholesterol in the body. Chylomicrons are the least dense types of cholesterol transport molecules. Chylomicrons are made of TG, cholesterol, and protein in the intestines, and released into the bloodstream after a meal. Chylomicrons mainly carry exogenous TG from the intestine to the liver through the thoracic duct. VLDL also contains TG, cholesterol, and protein. VLDL are produced in the liver and mainly carry endogenous TG from the liver to the peripheral organs. In the capillaries of adipose and muscle tissues, 90% of TG is removed by a specific group of lipases. Hence, VLDL are converted into IDL by removal of TG. Then, IDL are degraded into LDL by removal of more TG. Hence, VLDL are the main sources of LDL in the plasma. LDL are the major carriers of cholesterol in the blood. LDL deliver cholesterol from the liver to other parts of the body. Although the liver removes majority of LDL from the circulation, a small amount is uptake by macrophages those may migrate into the inner intima layer of arterial walls and become the foam cells of atherosclerotic plaques. The foam cells are filled with fat and cholesterol. They make up most of plaques. The plaques contain mainly cholesterol, calcium, fibrin, and cellular debris. This process can be accelerated when LDL become oxidized by free oxygen radicals that are produced as a byproduct while our cells are using oxygen to burn fat. Remnants of chylomicrons and VLDL may be able to deposit cholesterol onto artery walls in the same manner with LDL. When TG are high, there is a larger number of these remnants in the plasma, and a greater risk that arteries are being exposed to their LDL-like effects. Cholesterol that reaches the intima by way of these remnants may be used to produce new foam cells and that results in more artery-clogging plaque. These remnants may also be vulnerable to oxidation, in which case they pose an even greater threat. Over time these hard deposits thicken the wall of the arteries, forcing blood to squeeze through a narrower space. HDL remove fats and cholesterol from cells including within arterial wall atheroma, and carry the cholesterol back to the liver, adrenals, ovaries, and testes for excretion, reutilization, or disposal. All of the carrier lipoproteins are under dynamic control in the plasma and are readily affected by diet, illness, drug, and BMI. Thus, lipid analysis should be performed during a steady state. However, the metabolic syndrome alone is a low grade inflammatory process on vascular endothelium and may be a cause of the abnormal lipoproteins levels in the plasma. Similarly, due to the severe inflammatory nature of the SCD, plasma TC (121.4 vs. 165.0 mg/dL, $P < 0.000$), and LDL values (70.4 vs. 102.4 mg/dL, $P < 0.000$) were suppressed parallel to the suppressed body weight (59.9

vs. 71.5 kg, $P < 0.000$) and BMI (21.9 vs. 25.6 kg/m², $P < 0.000$), here. On the other hand, although HDL are commonly called as “the good cholesterol” due to their roles in removing excess cholesterol from the blood and protecting the arterial wall against atherosclerosis,^[14] recent studies did not show similar results. Instead low HDL values should alert clinicians about searching of additional metabolic or inflammatory pathologies in human body.^[15,16] Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties.^[15] However, HDL may become “dysfunctional” in pathologic conditions, which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered.^[15] For example, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation as well as the transformation of HDL proteomes into pro-inflammatory proteins. In addition, the highly effective agents of increasing HDL levels such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all-cause mortality, CHD mortality, myocardial infarction, or stroke.^[17] While higher HDL levels are correlated with cardiovascular health, medications used to increase HDL did not improve the health.^[17] Hence, HDL may actually be some indicators instead of being the main actors of the human health. Similarly, BMI, FPG, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence DM was only 3.1% between these values against 22.2% outside of these limits.^[18] In another definition, the moderate HDL values may also be the results instead of causes of the better human health status. Similarly, plasma HDL value was suppressed significantly (39.6 vs. 26.0 mg/dL, $P < 0.000$) parallel to the suppressed body weight and BMI in the patients, probably due to the severe inflammatory nature of the SCD in the present study.

BP is the force that blood exerts on the elastic wall of arteries. Higher BP indicates that heart and blood vessels are being overworked. In most people with HT, increased peripheral vascular resistance accounts for HT while cardiac output remains normal.^[19] The increased peripheral vascular resistance is mainly attributable to structural narrowing of small arteries and arterioles, although a reduction of the number of capillaries may also contribute.^[20] HT is more common in patients with sedentary lifestyle, obesity, alcoholism, and associated diseases such as DM, CRD, and COPD.^[21] HT is rarely accompanied by symptoms in short-term. Symptoms attributed to HT in that period may actually be related with associated anxiety rather than HT itself. However, HT may be the major risk factor for CRD, cirrhosis, COPD, stroke, dementia, and PAD-like end-organ insufficiencies in long-term since it damages the inner lining of arteries and sets the stage for atherosclerosis. Plaque deposits are more likely to develop in the areas of damage. If untreated, HT can also

increase the heart's workload terminating with CHD. For example, a reduction of the BP by 5 mmHg can decrease the risk of stroke by 34% and CHD by 21% and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular diseases.^[22] On the other hand, we cannot detect any absolute cause in majority of patients with HT. Physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be found among the possible risk factors of HT. Particularly, excess weight may be the major underlying cause of HT in the world, now. Adipose tissue produces leptin, tumor necrosis factor (TNF)-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, acting as acute phase reactants (APR) in the plasma.^[23] Similarly, excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathogenesis of accelerated atherosclerosis in human body.^[24] In addition, excess weight leads to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors eventually terminates with increased risks of arrhythmias, cardiac failure, and sudden death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI in the other studies,^[25,26] and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups.^[27] The relationship between excess weight, elevated BP, and hypertriglyceridemia is described in the metabolic syndrome.^[28] Similarly, prevalence of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in another study.^[29] Carbon monoxide in cigarette smoke damages the smooth inner surface of arteries. This damage encourages the buildup of plaque on artery walls and makes them hard and narrow. The carbon monoxide molecules hitch a ride on RBC, occupying valuable space that is normally reserved for the oxygen. In addition to narrowing arteries and taking the place of oxygen, cigarette smoke thickens the blood itself by boosting levels of fibrinogen. Furthermore, smoking may also reduce HDL in the plasma probably due to the systemic inflammatory effects on vascular endothelium. On the other hand, the greatest number of deteriorations in the metabolic parameters was observed just above the plasma TG value of 60 mg/dL in another study.^[30] Interestingly, plasma TG were the only lipids those were not suppressed instead increased parallel to the suppressed body weight and BMI in the SCD patients in the present study.

The acute phase response is a facet of the innate immune system that occurs in response to infection, infarction, foreign body, autoimmune disorder, allergy, neoplasm, trauma, and burns. Certain mediators, known as APR, are increased or decreased in the context of acute inflammation.^[31,32] These markers are commonly measured in clinical practice as

indicators of acute illness. The terms of acute phase proteins and APR are usually used synonymously, although some APR are polypeptides rather than proteins. An acute phase reaction classically presents with fever, tachycardia, and leukocytosis. Positive APR are those whose concentrations increase with inflammation. Negative APR are those whose concentrations decrease in an acute phase response. The acute phase response is predominantly mediated by the pro-inflammatory cytokines including TNF, interleukin (IL-1), and IL-6 secreted by macrophages and other immune cells. In case of inflammation, infection, and tissue damages, neutrophils and macrophages release such cytokines into the circulation. The liver and some other organs respond by producing many positive APR to them. Some of the well-known positive APR are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, ferritin, procalcitonin, hepcidin, haptoglobin, ceruloplasmin, complement proteins, and serum amyloid A. CRP is involved in innate immunity, and responsible for activating the complement pathway. Serum CRP rises rapidly, with a maximal concentration reached within 2 days, and it falls quickly once the inflammation has resolved. Measurement of CRP is a useful marker of inflammation in clinic. It correlates with ESR, however, not always directly. This is due to the ESR being largely dependent on elevation of fibrinogen with a half-life of approximately 1 week. Therefore, this protein remains higher for a longer period despite removal of the inflammatory stimulus. In contrast, CRP, with a half-life of 6–8 h, rises rapidly, and returns to normal in case of a successful treatment, quickly. Thus, an elevated ESR is classically used as a marker of chronic inflammation. On the other hand, productions of some other APR are suppressed at the same time, which are called as negative APR. Some of the well-known negative APR is albumin, transferrin, retinol-binding protein, antithrombin, transcortin, and alpha-fetoprotein. The suppression of such proteins is also used as an indicator of inflammation. The physiological role of suppressed synthesis of such proteins may be protection of amino acids for production of positive APR, sufficiently. Due to the same underlying cause, productions of HDL and LDL may also be suppressed in the liver. By this way, although the similar mean age, gender distribution, smoking, and BMI in both groups, TG, DM, and CHD were higher, whereas LDL and HDL were lower in patients with plasma HDL lower than 40 mg/dL, significantly.^[33] Hence, HDL and LDL may be some negative APR of the metabolic syndrome. Similarly, although the lower age, BMI, FPG, LDL, and HDL, the highest CHD of the group with HDL of lower than 40 mg/dL can also be explained by the same theory.^[34] Beside that although the mean TG, fibrinogen, CRP, and glucose values were higher in cases with ischemic stroke, the oxidized LDL values did not correlate with the age, stroke severity, and outcome in another study.^[35] In addition, significant alterations occurred in the lipid metabolism and lipoproteins compositions during infections, and plasma

TG increased whereas HDL and LDL decreased in another study.^[36] Furthermore, a 10 mg/dL increase of plasma LDL value was associated with a 3% lower risk of hemorrhagic stroke in another study.^[37] Similarly, the highest prevalence of HT and DM parallel to the increased values of LDL and HDL, and the highest prevalence of COPD, CHD, and CRD in contrast to the lowest values of LDL and HDL may show initially positive but eventually negative APR functions of LDL and HDL in the plasma.^[38] Hence, the most desired values were between 80 and 100 mg/dL for LDL, between 40 and 46 mg/dL for HDL, and lower than 60 mg/dL for TG in the plasma.^[30,34]

SCD are hereditary hemolytic anemia characterized by the presence of Hb S. Hb S causes RBC to change their normal biconcave disk shape to a sickle shape under the effects of various stresses. The RBC can take their normal shapes after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, hemolysis occurs. Hence, lifespan of the RBC decreases from the normal 120 days to 15–25 days. The chronic hemolytic anemia is mainly responsible for the anemia that is the hallmark of the SCD. Painful crises are the most disabling symptoms of the SCD. Although painful crises may not be life threatening directly,^[39] infections are the most common triggering factors of them. Hence, the risk of mortality is significantly higher during the crises. On the other hand, the severe pain may be the result of complex interactions between RBC, white blood cells (WBC), PLT, and endothelial cells. Probably, leukocytosis contributes to the pathogenesis by releasing several cytotoxic enzymes. The adverse actions of WBC and PLT on the endothelial cells are of particular interest with regard to the stroke and cerebrovascular diseases in the SCD.^[40] For example, leukocytosis in the absence of any infection was an independent predictor of the severity of the SCD,^[41] and it was associated with an increased risk of stroke.^[42] Occlusions of vasculature of the bone marrow, bone infarctions, inflammatory mediators, and activation of afferent nerves may take role in the pathophysiology of the severe pain. Due to the severity of pain, narcotic analgesics are generally used. Due to the repeated infarctions and subsequent fibrosis, a functional and anatomic asplenism develops due to the decreased antibody production, prevented opsonization, and reticuloendothelial dysfunction in adults. Terminal consequence of the asplenism is an increased risk of infections with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*-like encapsulated bacteria. Particularly, pneumococcal infections are so common in early childhood with higher mortality rates. The causes of death were infections in 56% of infants in a previous study.^[41] In another study, the peak incidence of death among children occurred between 1 and 3 years of age, and the deaths under the age of 20 years were predominantly caused by pneumococcal sepsis.^[43] Adult patients, even those who appear relatively fit, are susceptible to sepsis, multiorgan

failures, and sudden death during acute painful crises due to the severe and prolonged inflammatory process initiated at birth in the SCD.^[44,45] SCD can affect all vascular organ systems of the body.^[46,47] Aplastic crises, sequestration crises, hemolytic crises, acute chest syndrome, avascular necrosis of the femoral and humeral heads, priapism and infarction of the penis, osteomyelitis, acute papillary necrosis of the kidneys, CRD, occlusions of retinal arteries and blindness, pulmonary HT, bone marrow necrosis induced dactylitis in children, chronic punched-out ulcers around ankles, hemiplegia, and cranial nerve palsies are only some of the several presentation types. Eventually, the median ages of death were 42 years in males and 48 years in females in the literature.^[12] Delayed initiation of hydroxyurea therapy and inadequate RBC supports during medical or surgical problems may decrease the expected survival further.^[48] Actually, RBC supports must be given immediately during all medical or surgical emergencies, in which there is an evidence of clinical deterioration.^[49] RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBC. Hence, it decreases sickling-induced endothelial damage and inflammation in whole body. Due to the great variety of clinical presentation types, it is not surprising to see that the mean weight and BMI were significantly suppressed in patients with the SCD ($P < 0.000$ for both) in the present study. Probably parallel to the significantly suppressed body weight and BMI, the FPG, TC, LDL, HDL, systolic BP, and diastolic BP were also suppressed in the SCD, which can be explained by definition of the metabolic syndrome.^[33,50] On the other hand, the non-suppressed ALT value may indicate the hepatic involvement in the SCD.^[51]

CONCLUSION

As a conclusion, cholesterol may be a negative whereas TG positive APR in the plasma.

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