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Research Article

Safer Values of Low Density Lipoproteins in the Plasma

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1. Abstract

1.1. Background: We tried to understand the safer values of low density lipoproteins (LDL) in the plasma.

1.2. Methods: Patients with plasma LDL values lower than 80 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 130 mg/dL into the third, lower than 150 mg/dL into the fourth, and 150 mg/dL and higher into the fifth groups, respectively.

1.3. Results: The study included 815 cases (477 females), totally. The mean age, female ratio, body mass index (BMI), fasting plasma glucose (FPG), triglycerides, LDL, high density lipoproteins (HDL), and white coat hypertension (WCH) increased from the first up to the fifth groups, gradually ($p<0.05$ in most steps). Similarly, smoking, hypertension (HT), and diabetes mellitus (DM) increased up to the fourth group, gradually ($p<0.05$ in most steps). Whereas chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), and chronic renal disease (CRD) were the highest in the first group, significantly ($p<0.05$ for all).

1.4. Conclusions: Although the increased mean age, BMI, FPG, triglycerides, HDL, WCH, smoking, HT, and DM parallel to the increased LDL values, gradually, COPD, CHD, and CRD were the highest in the group with the lowest LDL and HDL values, significantly, which may indicate functions of LDL and HDL as negative acute phase proteins in the plasma.

2. Keywords: Low density lipoproteins; High density lipoproteins; Negative acute phase proteins; Triglycerides; Body mass index; Metabolic syndrome

3. Introduction

Chronic endothelial damage may be the most common vasculitis, and the leading cause of aging and death in the human being [1-4]. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying mechanism by inducing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the destructive process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Because of the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures those reduce blood flow to terminal organs and increase systolic BP further. Some of the well-known underlying causes and indicators of the inflammatory process are physical inactivity, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, White Coat Hypertension (WCH), chronic inflammatory disorders, prolonged infections, and cancers for the development of terminal consequences including obesity, Hyper Tension (HT), Diabetes Mellitus (DM), cirrhosis, Peripheric Artery Disease (PAD), Chronic Obstructive Pulmonary Disease

(COPD), Coronary Heart Disease (CHD), Chronic Renal Disease (CRD), mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, early aging, and premature death [5-10]. Although early withdrawal of the underlying causes can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, and aging, endothelial changes can not be reversed completely due to their fibrotic natures. Up to now, the underlying causes and terminal consequences were researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome, extensively [11-13]. Although its normal limits could not been determined clearly yet, elevated plasma triglycerides values may be one of the most sensitive indicators of the metabolic syndrome [14-17]. Due to the growing evidence about the strong association between higher plasma triglycerides and prevalence of CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II [18, 19]. Although ATP II determined the normal plasma triglycerides values as lower than 200 mg/dL in 1994 [19], World Health Organisation in 1999 [20] and ATP III in 2001 reduced their normal limits as lower than 150 mg/dL [18]. Although these cutpoints, there are still suspicions about the safest values of plasma triglycerides in the plasma [15-17]. Beside that although the higher sensitivity of plasma triglycerides in the metabolic syndrome, roles of high density lipoproteins (HDL) and low density lipoproteins (LDL) are suspicious [21]. We tried to understand the safer values of LDL in the plasma.

4. Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients at and above the age of 15 years were included. Their medical histories including HT, DM, COPD, and already used medications were learned, and a routine check up procedure including fasting plasma glucose (FPG), HDL, LDL, and triglycerides was performed. Current daily smokers with six pack-months and cases with a history of three pack-years were accepted as smokers. Due to the very low prevalence of alcoholism in Turkey [22], we did not include regular alcohol intake into the study. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Additionally, anti-hyperlipidemic drugs, metformin, and/or acarbose users were excluded to avoid their possible effects on blood lipid profiles and/or body weight [23, 24]. Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared [18]. Cases with an overnight FPG value of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics [18]. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG value between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose value of 200 mg/dL or greater is DM [18]. CRD is diagnosed with a persistently elevated serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Additionally, Office Blood Pressure (OBP) was checked after a 5-minute of rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2-hour. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in the normotensives in the office due to the risk of masked HT after a 10-minute education about proper BP measurement techniques [25]. An additional 24-hour ambulatory blood pressure monitoring was not needed due to its similar effectivity with the HBP measurements [3]. Eventually, HT is defined as a mean BP of 135/85 mmHg or greater on HBP measurements, and WCH as an OBP of 140/90 mmHg or greater but a mean HBP measurement of lower than 135/85 mmHg [25]. An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD is diagnosed either angiographically or with the Doppler echocardiographic findings as the already developed movement disorders in the cardiac walls. The spirometric pulmonary function tests were performed in required cases after the physical examination, and the criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% [26]. Eventually, patients with plasma LDL values lower than 80 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 130 mg/dL into the third, lower than 150 mg/dL into the fourth, and 150 mg/dL and higher into the fifth groups, respectively. The mean age, female ratio, smoking, BMI, FPG, triglycerides, LDL, HDL, WCH, HT, DM, COPD, CHD, and CRD 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.

5. Results

The study included 815 cases (477 females and 338 males), totally. The mean values of LDL in the plasma were 65.1, 89.8, 114.5, 138.3, and 171.9 mg/dL in the five groups, respectively. The mean age, female ratio, BMI, FPG, triglycerides, HDL, and WCH increased

Table 1: Characteristics features of the study cases according to the low density lipoproteins values.

Variable	Lower than 80 mg/dL	*p*-value	Lower than 100 mg/dL	*p*-value	Lower than 130 mg/dL	*p*-value	Lower than 150 mg/dL	*p*-value	150 mg/dL and higher
Number	81		103		277		168		186
Age (year)	40.1 ± 18.0 (16-82)	Ns*	39.6 ± 17.8 (16-82)	***0.005***	44.6 ± 15.2 (16-88)	***0***	51.5 ± 13.4 (17-82)	Ns	***52.2 ± 11.6 (22-86)***
Female ratio	46.90%	***0.05>***	59.20%	Ns	57.70%	Ns	57.10%	***0.05>***	***65.50%***
Smoking	24.60%	Ns	19.40%	***0.05>***	24.50%	***0.05>***	***31.50%***	Ns	26.80%
BMI† (kg/m²)	26.4 ± 5.6 (17.2-42.6)	Ns	26.7 ± 6.1 (16.7-48.6)	***0.008***	28.2 ± 5.7 (17.6-50.5)	***0.003***	29.7 ± 5.5 (18.1-51.0)	Ns	***30.1 ± 5.8 (20.6-51.1)***
FPG‡ (mg/dL)	102.3 ± 37.2 (59-288)	Ns	99.3 ± 26.6 (63-217)	Ns	102.5 ± 37.3 (63-377)	***0***	114.1 ± 45.9 (70-338)	Ns	***115.8 ± 53.1 (74-400)***
Triglycerides (mg/dL)	145.0 ± 125.4 (30-617)	Ns	122.8 ± 83.9 (27-518)	Ns	135.8 ± 93.7 (39-896)	***0***	153.7 ± 79.1 (37-450)	***0.004***	***174.7 ± 110.7 (47-1.350)***
LDL§ (mg/dL)	***65.1 ± 12.7 (10-78)***	***0***	89.8 ± 5.7 (76-99)	***0***	114.5 ± 8.8 (100-129)	***0***	138.3 ± 5.8 (130-149)	***0***	171.9 ± 22.1 (150-269)
HDL‖ (mg/dL)	***37.5 ± 10.8 (22-77)***	***0.006***	45.2 ± 12.3 (28-80)	Ns	44.7 ± 9.3 (26-72)	Ns	45.8 ± 8.1 (33-72)	***0.006***	50.8 ± 10.4 (32-91)
WCH*	17.20%	***0.05>***	26.20%	Ns	24.90%	Ns	29.10%	***0.01>***	***39.70%***
HT**	16.00%	Ns	11.60%	***0.01>***	16.90%	***0.001>***	***30.30%***	***0.05>***	22.00%
DM**	12.30%	Ns	9.70%	***0.01>***	14.80%	Ns	***17.80%***	Ns	16.10%
COPD***	***13.50%***	***0.05>***	5.80%	***0.001>***	13.30%	Ns	16.00%	Ns	14.50%
CHD****	***16.00%***	***0.01>***	5.80%	***0.001>***	11.50%	Ns	14.20%	Ns	9.60%
CRD*****	***4.90%***	***0.05>***	0.00%	Ns	1.00%	Ns	2.30%	Ns	2.10%

*Nonsignificant (p>0.05) †Body mass index ‡Fasting plasma glucose §Low density lipoproteins ‖High density lipoproteins **White coat hypertension ***Hypertension ****Diabetes mellitus *****Chronic obstructive pulmonary disease ******Coronary heart disease *******Chronic renal disease

from the first up to the fifth groups, gradually ($p<0.05$ in most steps). Similarly, smoking, HT, and DM increased up to the fourth group, gradually, too ($p<0.05$ in most steps). Whereas COPD, CHD, and CRD were the highest in the first group, significantly ($p<0.05$ for all) (Table 1).

6. Discussion

Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines acting as acute phase reactants in the plasma [27, 28]. Excess weight-induced chronic low-grade inflammation on vascular endothelium may play a significant role in the pathogenesis of accelerated atherosclerosis in whole body [1, 2]. Additionally, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of increased oxygen requirement of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors will eventually terminate with increased left ventricular stroke work and risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalences of CHD and stroke increased parallel to the increased BMI values in the other studies [29, 30], and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups [31].

The relationship between excess weight, elevated BP, and plasma triglycerides is described in the metabolic syndrome [14], and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states [12]. For example, prevalences of excess weight ($p<0.01$), DM ($p<0.05$), HT ($p<0.001$), and smoking ($p<0.01$) were all higher in the hypertriglyceridemia (200 mg/dL and higher) group [32]. On the other hand, the prevalences of increased LDL cases were similar both in the hypertriglyceridemia and control groups in the same study [32]. Similarly, although the higher trigycerides ($p<0.001$), plasma LDL and HDL values were lower in the group with plasma HDL levels lower than 40 mg/dL in the other study ($p<0.000$ for both) [33].

Alcohol and smoking may be found among the most common causes of vacuities all over the world. Both of them cause a chronic inflammatory process on the vascular endothelium, probably depending on the concentrations of alcohol and smoke in the blood that terminates with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Thus alcohol and smoking should be included into the major components of the metabolic syndrome. Strong and terminal atherosclerotic effects of smoking are the most obvious in the Buerger's disease. It is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Although the well-known strong atherosclerotic effects of smoking, smoking in the human being and nicotine administration in animals may be associated with decreased BMI values [34]. Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [35]. According to an animal study, nicotine may lengthen inter meal time and decrease amount of meal eaten [36]. Additionally, the mean BMI seems to be the highest in the former, the lowest in the current and medium in never smokers [37]. Smoking may be associated with a post cessation weight gain [38]. Similarly, although CHD was detected with similar prevalence in both genders, prevalences of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females [39]. Similarly, the incidence of a myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day [40]. In another definition, smoking may be more dangerous for women probably due to the associated higher BMI and its consequences in them. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite [41]. Smoking-induced weight loss may be related with the smoking-induced chronic inflammation on vascular endothelium all over the body, since loss of appetite is one of the major symptoms of the disseminated inflammation in the body. Physicians can even understand healing of the patients via their normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a vascular endothelial inflammation until their clearence from the circulation. But due to the repeated smoking habits, the clearence process never terminates. So the patients become ill with loss of appetite, permanently. In another explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy [35-37]. After smoking cessation, normal appetite comes back with a prominent weight gain but the returned weights are the patients' physiological weights, actually.

Although ATP III reduced the normal limits of plasma triglycerides as lower than 150 mg/dL in 2001 [18], much lower limits may provide additional benefit for health [15-17]. In the above study [16], prevalence of smoking was the highest in the group with the highest triglycerides values that may also indicate inflammatory role of smoking in the metabolic syndrome, since triglycerides may actually be some acute phase reactants in the plasma. The mean age, male ratio, smoking, BMI, FPG, WCH, HT, DM, and COPD increased parallel to the increased plasma triglycerides values from the first up to the fifth groups, gradually [16]. We think that significantly increased plasma triglycerides values by aging may be secondary to the aging-induced decreased physical and mental stresses, those eventually terminate with onset of excess weight and many associated health problems. Although the borderline high triglycerides values (150-199 mg/dL) is seen together with physical inactivity and overweight, the high (200-499 mg/dL) and very high triglycerides values (500 mg/dL or greater) may be secondary to smoking, genetic factors, and terminal consequences of the metabolic syndrome such as obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke [18]. But although the underlying causes of the borderline high, high, and very high plasma triglycerides values may be a little bit different, probably risks of the terminal consequences of the metabolic syndrome do not change in them. For example, prevalences of HT, DM, and COPD were the highest in the group with the highest triglycerides values in the above study [16]. Eventually, although some authors reported that lipid assessment can be simplified as the measurements of total cholesterol and HDL values alone [42], the present study and most of the others indicated significant relationships between plasma triglycerides, HDL, and LDL values and terminal consequences of the metabolic syndrome [33, 43].

Cholesterol, triglycerides, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of the animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. Triglycerides are the major lipids transported in the blood and the bulk of our body's fat tissue is in the form of triglycerides. Phospholipids are triglycerides that are covalently bound to a phosphate group, and they regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, triglycerides, 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. Chylomicrons carry exogenous triglycerides to the liver via the thorasic duct. VLDL are produced in liver, and carry endogenous triglycerides to the peripheral organs. In the capillaries of adipocytes and muscle tissue, VLDL are converted into IDL by removal of 90% of triglycerides by lipases. Then IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma, and LDL deliver cholesterol from the liver to the peripheral organs. Although the liver removes majority of LDL from the circulation, a small amount is uptaken by scavenger receptors of the macrophages those may migrate into the arterial walls, and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells, including the arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs such as adrenals, ovaries, and testes for excretion, re-utilization, and disposal. All of the carrier lipoproteins are under dynamic control, and are readily affected by diet, illnesses, drugs, and BMI. Thus lipid analysis should be performed during a steady state. But the metabolic syndrome alone is a low grade inflammatory process on vascular endothelium. Thus the metabolic syndrome alone may be a cause of abnormal lipoproteins levels in the plasma. 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 walls against atherosclerosis [44], recent studies did not show similar results, and low plasma HDL values may alert us searching for some inflammatory pathologies in the body [45-47]. Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory features [45]. However, HDL may become 'dysfunctional' in pathological conditions which means that relative composition of lipids and proteins, as well as the enzymatic activities of HDL are altered [45]. For example, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation of HDL, as well as the transformation of HDL proteomes into the proinflammatory proteins. Additionally, three highly effective agents for increasing HDL levels including niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, and stroke in patients treated with statins [48]. While higher HDL levels are correlated with cardiovascular health, no medication used to increase HDL has been proven to improve health [48]. In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL may not increase cardiovascular health [48]. So they may actually be indicators instead of the main actors. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of CHD [49]. For example, although the similar mean age, gender distribution, smoking, and BMI in both groups, DM and CHD were higher in the group with the plasma HDL values lower than 40 mg/dL in the above study [33]. Similarly, although the lower mean age, smoking, BMI, FPG, triglycerides, LDL, and HDL, the highest COPD, CHD, and CRD may also indicate functions of LDL and HDL as the negative acute phase proteins in the present study.

APP are a class of proteins those plasma concentrations increase (positive APP) or decrease (negative APP) as a response to inflammation, infection, and tissue damage [50-52]. In case of inflammation, infection, and tissue damage, local inflammatory cells (neutrophils and macrophages) secrete several kinds of cytokines into the blood, most notable of which are the interleukins. The liver responds by producing many positive APP. At the same time, productions of many proteins are reduced. Therefore these proteins are called as negative APP. Some of the well-known negative APP are albumin, transferrin, retinol-binding protein, antithrombin, and transcortin. The decrease of such proteins is also used as an indicator of inflammation. The physiological role of decreased synthesis of such proteins may be protection of amino acids for producing positive APP, effectively. Due to the decreased production of some proteins in liver during severe inflammatory conditions, production of HDL and LDL may also be suppressed. By this way, although the similar mean age, gender distribution, smoking, and BMI in both groups, the higher triglycerides, DM, and CHD against the lower HDL and LDL values in patients with plasma HDL values lower than 40 mg/dL can be explained in the above study [33]. Beside that although the lower mean age, smoking, BMI, FPG, triglycerides, LDL, and HDL, the highest COPD, CHD, and CRD of the first group can also be explained by the same theory in the present study.

Similarly, although the mean triglycerides, fibrinogen, C-reactive protein, and glucose values were significantly higher in cases with ischemic stroke, the oxidized LDL values did not correlate with age, stroke severity, and outcome in another study [53]. Additionally, significant alterations occurred in lipid metabolism and lipoprotein composition during infections, and triglycerides increased whereas HDL and LDL decreased in the other study [54]. Furthermore, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke in another study [55].

As a conclusion, although the increased mean age, BMI, FPG, triglycerides, HDL, WCH, smoking, HT, and DM parallel to the increased LDL values, gradually, COPD, CHD, and CRD were the highest in the group with the lowest LDL and HDL values, significantly, which may indicate functions of LDL and HDL as negative acute phase proteins in the plasma.

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