Low density lipoproteins may actually be some negative acute phase proteins in the plasma

Mehmet Rami Helvaci (1)
Abdulrazak Abyad (2)
Lesley Pocock (3)

(1) Specialist of Internal Medicine, MD
(2) Middle-East Academy for Medicine of Aging, MD
(3) medi+WORLD International

Corresponding author:
Dr Mehmet Rami Helvaci,
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

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ABSTRACT

Background: **We tried to understand whether or not low density lipoproteins (LDL) may actually be some negative acute phase proteins (APP) in the plasma.**

Methods: **Patients with plasma triglycerides values lower than 100 mg/dL were collected into the first, lower than 150 mg/dL into the second, lower than 200 mg/dL into the third, and 200 mg/dL and higher into the fourth groups, respectively.**

Results: **We studied 457 cases (266 females and 191 males), totally. The male ratio, mean age, body mass index (BMI), fasting plasma glucose (FPG) and prevalences of smoking, white coat hypertension (WCH), hypertension (HT), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) increased parallel to the increased plasma triglycerides values from the first towards the fourth groups, continuously ($p<0.05$ nearly in all steps). Whereas the mean LDL values increased just up to the plasma triglycerides value of 200 mg/dL and then decreased, significantly (140.9 versus 128.2 mg/dL, $p= 0.009$).**

Conclusions: **Increased plasma triglycerides values may be one of the most significant parameters of the metabolic syndrome that is characterized with disseminated endothelial damage, inflammation, fibrosis, accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Although the continuously increased male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD, parallel to the increased plasma triglycerides values, the mean LDL values increased just up to the plasma triglycerides values of 200 mg/dL and then decreased, significantly. The significant decrease can be explained by the hypothesis that LDL may actually be some negative APP in the plasma.**

Key words: **Low density lipoproteins, triglycerides, acute phase proteins, metabolic syndrome**

Introduction

Chronic endothelial damage may be the most common sort of vasculitis, and the leading cause of early aging and premature death in human beings (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 predominantly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Because of the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature that reduces blood flow to terminal organs, and increases systolic BP further. Some of the well-known components 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), rheumatologic disorders, chronic infections, and prolonged cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, stroke, early aging, and premature death (5-10). Although early withdrawal of the predisposing factors may delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, or aging, endothelial changes cannot be reversed completely due to their fibrotic nature. Up to now, the predisposing factors and terminal endpoints have been researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medicine, extensively (11-14). Although its normal limits could not been determined clearly yet, increased plasma triglycerides may be one of the most significant indicators of the metabolic syndrome (15-17). 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 value as lower than 200 mg/dL in 1994 (19), World Health Organisation in 1999 (20) and ATP III in 2001 reduced their normal limit as lower than 150 mg/dL (18). Although these cutpoints are usually used to define limits of the metabolic syndrome, there are still suspicions about the safest value of plasma triglycerides in the medicine (16, 17). Although the absolute significance of plasma triglycerides in the metabolic syndrome, role of low density lipoproteins (LDL) is suspicious (21). We tried to understand whether or not LDL may actually be some negative acute phase proteins (APP) in the plasma.

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 learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglycerides, and LDL was performed. Current daily smokers with six pack-months and cases with a history of three pack-years were accepted as smokers. 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 (22, 23). 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). Additionally, office blood pressure (OBP) was checked after a 5 minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. 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 (24). 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 (24). 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% (25). Eventually, patients with plasma triglycerides values lower than 100 mg/dL were collected into the first, lower than 150 mg/dL into the second, lower than 200 mg/dL into the third, and 200 mg/dL and higher into the fourth groups, respectively. The male ratio, mean age, BMI, FPG, triglycerides, and LDL, and prevalences of smoking, WCH, HT, DM, and COPD 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

We studied 457 cases (266 females and 191 males), totally. The male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD increased parallel to the increased plasma triglycerides values from the first towards the fourth groups, continuously ($p<0.05$ nearly in all steps). Whereas the mean LDL values increased just up to the plasma triglycerides value of 200 mg/dL and then decreased, significantly (140.9 versus 128.2 mg/dL, $p= 0.009$) (Table 1).

Table 1: Characteristics features of the study cases according to plasma triglycerides values

Variable	Lower than 100 mg/dL	p-value	Lower than 150 mg/dL	p-value	Lower than 200 mg/dL	p-value	200 mg/dL or greater
Number	159		133		78		87
Mean age	*40.6 ± 17.6 (16-83)*	*0.001*	*46.9 ± 15.9 (16-82)*	*0.014*	*51.7 ± 11.8 (23-73)*	Ns*	50.5 ±12.3 (21-86)
Male ratio	*35.8%*	Ns	*42.1%*	Ns	*43.5%*	Ns	*50.5%*
Prevalence of smoking	*16.3%*	*0.05>*	*23.3%*	Ns	*28.2%*	*0.01>*	*42.5%*
Mean BMI†	*26.7 ± 5.6 (16.7-49.3)*	*0.000*	*29.5 ± 6.0 (18.4-50.5)*	Ns	30.0 ±4.9 (19.2-49.0)	Ns	29.7 ±4.7 (21.0-42.9)
Mean value of FPG‡	102.7 ±40.3 (59-341)	Ns	*102.7 ± 26.6 (71-244)*	*0.009*	*114.6 ± 43.6 (68-320)*	Ns	*117.1 ± 42.1 (80-287)*
Mean value of triglycerides	*70.3 ± 16.4 (27-99)*	*0.000*	*120.8 ± 14.8 (100-149)*	*0.000*	*174.6 ± 14.9 (150-199)*	*0.000*	*304.8 ± 118.7 (200-1.144)*
Mean value of LDL§	*109.7 ± 33.7 (43-269)*	*0.000*	*132.1 ± 31.8 (64-228)*	*0.048*	*140.9 ± 27.7 (75-210)*	*0.009*	*128.2 ± 39.8 (10-239)*
Prevalence of WCH‖	*23.2%*	*0.05>*	*30.8%*	Ns	*32.0%*	Ns	*34.4%*
*Prevalence of HT***	*11.9%*	*0.001 >*	*23.3%*	Ns	*25.6%*	Ns	25.2%
*Prevalence of DM****	*8.1%*	Ns	*12.7%*	Ns	*16.6%*	Ns	*22.9%*
*Prevalence of COPD*****	*9.4%*	Ns	*11.2%*	Ns	*15.3%*	*0.001 >*	*28.7%*

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

Discussion

Excess weight may lead to both structural and functional abnormalities of many organs of the body. Adipose tissues produce leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines acting as acute phase reactants in the plasma (26, 27). Excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathogenesis of accelerated atherosclerosis in the 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 need 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 prevalence of CHD and stroke increased parallel to the increased BMI values in the other studies (28, 29), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (30). The relationship between excess weight, elevated BP, and plasma triglycerides is described in the metabolic syndrome (15), and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (13). Similarly, prevalence of smoking (42.2% versus 28.4%, $p<0.01$), excess weight (83.6% versus 70.6%, $p<0.01$), DM (16.3% versus 10.3%, $p<0.05$), and HT (23.2% versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in the other study (31). On the other hand, the prevalence of elevated LDL cases were similar both in the hypertriglyceridemia (200 mg/dL and higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (31). Similarly, plasma LDL values increased up to the plasma triglycerides values of 200 mg/dL, but then decreased in the present study, too ($p<0.05$ for all). Beside that, the mean BMI increased just up to the plasma triglycerides values of 150 mg/dL ($p=0.000$) but it did not change with the higher plasma triglycerides values, significantly ($p>0.05$).

Smoking may be found among the most common causes of vasculitis all over the world. It causes a chronic inflammatory process on the vascular endothelium, probably depending on the concentration of smoke that terminates with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Thus smoking has to be included among the major components of the metabolic syndrome. Strong and terminal atherosclerotic effects of smoking are the most obviously seen in Buerger's disease (thromboangiitis obliterans). It is an obliterative disease 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 medical literature. Although the well-known strong atherosclerotic effects of smoking, smoking in human beinga and nicotine administration in animals may be associated with decreased BMI values (32). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (33), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (34). According to an animal study, nicotine may lengthen intermeal time and decrease amount of meal eaten (35). Additionally, the mean BMI seems to be the highest in the former, the lowest in the current and medium in never smokers (36). Smoking may be associated with a postcessation weight gain (37). 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 (38). This result may show both the strong atherosclerotic and weight decreasing roles of smoking (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. Parallel to the above results, the proportion of smokers is consistently higher in men in the literature (23). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. Smoking-induced weight loss may be related with the smoking-induced chronic vascular endothelial inflammation all over the body, since loss of appetite is one of the main symptoms of the disseminated inflammations 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 habit of the individuals, the clearance 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 (34-36). After smoking cessation, normal appetite comes back with a prominent weight gain but the returned weight is the patients' physiological weights, actually.

Although the several negative effects of excess weight on health, nearly three-quarters of cases above the age of 30 years have excess weight (41). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eight decade of life (41). So 30th and 70th years of age may be the breaking points of life for weight, and aging may be the major determiner factor of excess weight. Probably, partially decreased physical and mental stresses after the age of 30 years and debility and comorbid disorders-induced restrictions after the age of 70 years may be the major causes for the changes of BMI values at these ages. Interestingly, the mean age and BMI increased just up to the plasma triglycerides values of 200 mg/dL in the present study. So smoking remained as the major causative factor for the hypertriglyceridemia after the plasma triglycerides values of 200 mg/dL in the present study.

Although ATP III reduced the normal limit of plasma triglycerides values as lower than 150 mg/dL in 2001 (18), whether or not much lower limits provide additional benefits for health is unknown. In the present study, prevalence of smoking was the highest in the highest triglycerides having group which may also indicate inflammatory roles of smoking in the metabolic syndrome, since triglycerides may actually be some acute phase reactants in the plasma. The FPG, smoking, WCH, HT, DM, and COPD increased parallel to the plasma triglycerides values from the first towards the fourth groups, gradually. As

an opinion of us, significantly increased plasma triglycerides values by aging may be secondary to aging-induced decreased physical and mental stresses, those eventually terminate with onset of excess weight and many associated health problems. Interestingly, although the mean age increased from the lowest triglycerides having group towards the triglycerides values of 200 mg/dL, then it decreased. The similar trend was also seen with the mean LDL and BMI values. These trends may be due to the fact that although the borderline high triglycerides values (150-199 mg/dL) is seen together with physical inactivity and overweight, the high triglycerides (200-499 mg/dL) and very high triglycerides values (500 mg/dL or greater) may be secondary to both genetic factors and terminal consequences of the metabolic syndrome including smoking, obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (18). But although the underlying causes of the high and very high plasma triglycerides values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalences of HT, DM, and COPD were the highest in the highest triglycerides having group in the present study. Eventually, although some authors reported that lipid assessment can be simplified as the measurements of total cholesterol and high density lipoproteins (HDL) values alone (42), the present study and most of the others indicated significant relationships between triglycerides and LDL and terminal consequences of the metabolic syndrome (43).

APP are a class of proteins whose plasma concentrations increase (positive APP) or decrease (negative APP) as a response to inflammation, infection, and tissue damages (44-46). In case of inflammation, infection, and tissue damages, 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 APP. At the same time, production of many proteins is reduced. Thus 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 is generally to save amino acids for producing positive APP more effectively. Due to the decreased production of some proteins in liver during severe inflammatory conditions, production of LDL may also be suppressed. 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 the other study (47). Additionally, significant alterations occur in lipid metabolism and lipoprotein composition during infections, and triglycerides increase whereas HDL and LDL decrease in another study (48). Furthermore, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke in another study (49).

As a conclusion, increased plasma triglycerides values may be one of the most significant parameters of the metabolic syndrome that is characterized with disseminated endothelial damage, inflammation, fibrosis, accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Although the continuously increased male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD parallel to the increased plasma triglycerides values, the mean LDL values increased just up to the plasma triglycerides values of 200 mg/dL and then decreased, significantly. The significant decrease can be explained by the hypothesis that LDL may actually be some negative APP in the plasma.

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