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Research Article

Hypertriglyceridemia may Actually be an Acute Phase Reactant in the Plasma

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Abstract

Background: We tried to understand whether or not there is a significant relationship between cholelithiasis or cholecystectomy and plasma lipids.

Methods: The study was performed in Internal Medicine Polyclinics on routine check up patients. All cases with cholelithiasis or already performed cholecystectomy for cholelithiasis were put into the first and age and sex-matched control cases were put into the second groups.

Results: Onehundred and fourty-four cases either with cholelithiasis or cholecystectomy for cholelithiasis were detected among 3.437 cases, totally (4.1%). Onehundred and sixteen (80.1%) of them were females with a mean age of 53.6 years. Obesity (54.8% versus 43.7%, $p < 0.01$) and hypertension (26.3% versus 13.1%, $p < 0.001$) were significantly higher in the cholelithiasis or cholecystectomy group, and body mass indexes (BMI) were 31.0 versus 28.9 kg/m2 in them, respectively ($p < 0.01$). Although the prevalence of hyperbetalipoproteinemia was significantly lower in the cholelithiasis or cholecystectomy group (9.7% versus 18.0%, $p < 0.05$), hypertriglyceridemia (25.0% versus 18.0%, $p < 0.05$) was significantly higher in them.

Conclusions: There are significant relationships between cholelithiasis and parameters of the metabolic syndrome including age, female sex, BMI, obesity, hypertension, and hypertriglyceridemia, so cholelithiasis may also be found among the terminal consequences of the metabolic syndrome. Although the decreased plasma levels of low density lipoprotein cholesterol probably due to the decreased amount of bile acids secreted during entrance of food into the duodenum and decreased amount of cholesterol absorbed in patients with cholelithiasis or cholecystectomy, the presence of hypertriglyceridemia may actually indicate its primary role as an acute phase reactant in them.

Keywords: *Hypertriglyceridemia; Metabolic Syndrome; Acute Phase Reactant; Cholelithiasis; Cholecystectomy*

Introduction

Chronic endothelial damage may be the most common kind of vasculitis and the leading cause of aging, morbidity, and mortality in human being. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium, and probably whole afferent vasculature including capillaries are involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow to terminal organs and in-

crease systolic BP further. Some of the well-known causes and indicators of the inflammatory process are sedentary life style, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension, and chronic inflammatory processes including rheumatologic disorders, chronic infections, and cancers for the development of terminal complications including obesity, hypertension, diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. Although early withdrawal of causative factors may prevent irreversible complications, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes can not be reversed completely due to the fibrotic natures of them. The accelerator factors and terminal consequences were researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively [1-4]. On the other hand, gallstones are also found among one of the most common health problems in developed countries [5], and they are particularly frequent in women above the age of 40 years [6]. Most of the gallstones are found in the gallbladder with the definition of cholelithiasis. Its pathogenesis is uncertain and appears to be influenced by genetic and environmental factors [7]. Excess weight is a well-known and age-independent risk factor for cholelithiasis [8]. Delayed bladder emptying, decreased small intestinal motility, and sensitivity to cholecystokinin were associated with obesity and cholelithiasis [9]. An increased risk was confirmed in obese diabetics with hypertriglyceridemia [10], and plasma cholesterol levels were also found related with cholelithiasis [11]. We tried to understand whether or not there is a significant relationship between cholelithiasis or cholecystectomy and plasma lipids.

Material and Methods

The study was performed in Internal Medicine Polyclinics of the Dumlupinar and Mustafa Kemal Universities on routine check up patients between August 2005 and November 2007. We took consecutive patients below the age of 70 years to avoid debility induced weight loss in elders. Their medical histories including smoking habit, hypertension, DM, dyslipidemia, and already used medications and performed operations were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and an abdominal ultrasonography was performed. 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. Current daily smokers for the last six months and cases with a history of five pack-years were accepted as smokers. Cigar or pipe smokers were excluded. Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions since there is evidence that heavier individuals systematically underreport their weight [12]. Weight in kilograms is divided by height in meters squared, and underweight is defined as a BMI of lower than 18.5, normal weight as lower than 24.9, overweight as lower than 29.9, and obesity as a BMI of 30.0 kg/m2 or higher [13]. Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already receiving antidiabetic medications were defined as diabetics [13]. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 125 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level 200 mg/dL or greater is DM [13]. Patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel's recommendations for defining dyslipidemic subgroups [13]. Dyslipidemia is diagnosed when LDL-C is 160 or higher and/or triglyceride is 200 or higher and/or HDL-C is lower than 40 mg/dL. Office BP 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 normotensives in the office due to the risk of masked hypertension after a 10-minute education about proper BP measurement techniques [14]. The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5-minute in the seated position before measurement. An additional 24-hour ambulatory BP monitoring was not required due to the equal efficacy of the method with HBP measurement to diagnose hypertension [15]. Eventually, hypertension is defined as a BP of 135/85 mmHg or greater on HBP measurements [14]. Cholelithiasis was diagnosed ultrasonographically. Eventually, all cases either with presenting cholelithiasis or cholecystectomy for

cholelithiasis were put into the first and age and sex-matched control cases were put into the second groups. The mean BMI values and prevalences of smoking, normal weight, overweight, obesity, hypertension, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia were compared between the two groups. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

Although the exclusion criteria, 25 cases with already presenting asymptomatic cholelithiasis and 119 cases with cholecystectomy for cholelithiasis and were detected among 3.437 cases, totally (4.1%). Onehundred and sixteen (80.1%) of them were females with a mean age of 53.6 years, so cholelithiasis is mainly a disorder of females in their fifties. Prevalences of smoking were similar in the cholelithiasis and control groups (18.0% versus 19.4%, $p > 0.05$, respectively). Interestingly, 92.3% (133 cases) of the cholelithiasis group had excess weight and only 7.6% (11 cases) of them had normal weight. There was not any patient with underweight among the study cases. Obesity was significantly higher (54.8% versus 43.7%, $p < 0.01$) and normal weight was significantly lower (7.6% versus 18.0%, $p < 0.01$) in the cholelithiasis group. Mean BMI values were 31.0 and 28.9 kg/m2, ($p < 0.01$) in the two groups. Probably parallel to the higher mean BMI values, prevalence of hypertension (26.3% versus 13.1%, $p < 0.001$) was also higher in the cholelithiasis group, significantly. Although the prevalences of DM (20.8% versus 19.4%, $p > 0.05$) and dyslipidemia (31.9% versus 29.8%, $p > 0.05$) were also higher in the cholelithiasis groups, differences were nonsignificant probably due to the small sample sizes of the groups. Although the prevalence of hyperbetalipoproteinemia was significantly lower in the cholelithiasis or cholecystectomy group (9.7% versus 18.0%, $p < 0.05$), hypertriglyceridemia (25.0% versus 18.0%, $p < 0.05$) was significantly higher in them (Table 1).

Variable	Cases with cholelithiasis or cholecystectomy for cholelithiasis	Control cases	p-value
Number	144	144	
Female ratio	80.5% (116)	80.5% (116)	
Mean age (year)	53.6 ± 9.3 (27 - 70)	53.6 ± 10.2 (28 - 70)	Ns*
Prevalence of smoking	18.0% (26)	19.4% (28)	Ns
Mean BMI† (kg/m^2)	31.0 ± 6.1 (19 - 51)	28.9 ± 5.7 (19 - 52)	< 0.01
Prevalence of normal weight	7.6% (11)	18.0% (26)	< 0.01
Prevalence of overweight	37.5% (54)	38.1% (55)	Ns
Prevalence of obesity	54.8% (79)	43.7% (63)	< 0.01
Prevalence of hypertension	26.3% (38)	13.1% (19)	< 0.001
Prevalence of DM‡	20.8% (30)	19.4% (28)	Ns
Prevalence of hyperbetalipoproteinemia	9.7% (14)	18.0% (26)	< 0.05
Prevalence of hypertriglyceridemia	25.0% (36)	18.0% (26)	< 0.05
Prevalence of dyslipidemia	31.9% (46)	29.8% (43)	Ns

Table 1: *Comparison of cases with and without cholelithiasis.*

**Nonsignificant ($p > 0.05$) †Body mass index ‡Diabetes mellitus*

Discussion

Bile is formed in the liver as an isosmotic solution of bile acids, cholesterol, phospholipids, bilirubin, and electrolytes. Bile flow is generated by the active transport of bile salts and electrolytes and the accompanying obligate passive movement of water. The liver synthesizes water-soluble bile acids from water-insoluble cholesterol. About 50% of bile secreted during the fasting state passes into the

gallbladder via the cystic duct. So gallbladder filling is facilitated during fasting. Up to 90% of water in the gallbladder bile is absorbed as an electrolyte solution, so during fasting, bile acids are concentrated in the gallbladder, and little amount of bile flows from the liver. Food entering the duodenum stimulates gallbladder contraction, releasing much of body pool of bile acids to mix with food content and perform its several functions including solubilization of dietary cholesterol, fats, and fat-soluble vitamins to facilitate their absorption in the form of mixed micelles, causing water secretion by the colon promoting catharsis, excretion of bilirubin as degradation products of heme compounds from worn-out red blood cells, excretion of drugs, ions, and endogenously produced compounds from the body, and secretion of various proteins important for the gastrointestinal functions. About 90% of bile acids is absorbed in the terminal ileum into the portal system by active transport. Bile salts are efficiently extracted by the liver, and secreted back into bile, so bile acids undergo enterohepatic circulation 10 to 12 times per day. The most clinical disorders of the extrahepatic biliary tract are related with the gallstones. In the USA, 20% of people above the age of 65 years have gallstones, and each year more than 500.000 patients undergo cholecystectomy. Factors that increase the probability of gallstones include age, female sex, and obesity. Highly water-insoluble cholesterol is the major component of most gallstones. Biliary cholesterol is solubilized in the bile salt-phospholipid micelles and phospholipid vesicles. The amount of cholesterol carried in micelles and vesicles varies with the bile salt secretion rate. In another perspective, cholelithiasis may actually be a natural defence mechanism of the body to decrease amount of bile acids secreted during entrance of food into the duodenum and decrease amount of cholesterol absorbed. Similarly, bile acid sequestrants including cholestyramine and cholestipol effectively lower serum LDL-C by binding bile acids in intestine and interrupting enterohepatic circulation of them.

Excess weight leads to both structural and functional abnormalities of many systems of the body. Recent studies revealed that adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, adiponectin, and other cytokines which act as acute phase reactants in the body [16,17]. For example, the cardiovascular field has shown a great interest in the role of inflammation and numerous studies indicated that inflammation plays a significant role in the pathogenesis of atherosclerosis and thrombosis [18,19]. On the other hand, individuals with excess weight have an increased blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excessive fat tissue. The prolonged increase in blood volume can lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of hypertension. In addition to them, the prevalences of high FPG, high serum total cholesterol, and low HDL-C increased with the higher BMI values [20]. Combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke work with higher risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalences of CAD and stroke increased with higher BMI values in the other studies [20,21], and risk of death from all causes including cancers increased throughout the range of moderate and severe weight excess in all age groups [22]. As another consequence of excess weight on health, the cholelithiasis cases had a significantly higher BMI value in the present study (31.0 versus 28.9 kg/m2, $p < 0.01$) similar to some other reports [8,9]. Probably as a consequence of the higher BMI values, the prevalences of hypertension (26.3% versus 13.1%, $p < 0.001$) and hypertriglyceridemia (25.0% versus 18.0%, $p < 0.05$) were also higher in the cholelithiasis group. The relationship between excess weight and elevated BP and hypertriglyceridemia has already been described in the metabolic syndrome or aging syndrome or accelerated endothelial damage syndrome [23], and clinical manifestations of the syndrome include obesity, dyslipidemia, hypertension, insulin resistance, and proinflammatory and prothrombotic states [24]. The increased risk of cholelithiasis in obese diabetics with hypertriglyceridemia may also be an indicator of its association with the metabolic syndrome [10,23]. Similarly, prevalences 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 hypertension (23.2% versus 11.2%, $p < 0.001$) were all higher in the hypertriglyceridemia cases in another study [25]. Smoking causes a chronic inflammatory process in the respiratory tract, lungs, and vascular endothelium all over the body terminating with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death thus it must be included among the parameters of the metabolic syndrome. On the other hand, smoking-induced weight loss is probably related with the smoking-induced endothelial inflammation all over the body since loss of appetite is one of the major symptoms of inflammations in the body. In another explanation, smoking-induced loss of appetite is an indicator of being ill instead of being healthy during smoking [26-28]. Buerger's disease (thromboangiitis obliterans) alone is a clear evidence to show the strong atherosclerotic effects of smoking since this disease has not been shown

in the absence of smoking. On the other hand, the prevalences of hyperbetalipoproteinemia were similar in the hypertriglyceridemia and control groups (18.9% versus 16.3%, p>0.05, respectively) in the same study [25].

Although the mean age, female sex, BMI, obesity, hypertension, and hypertriglyceridemia indicated significant differences in the cholelithiasis or cholecystectomy group in the present study, there was no significant difference for the lipid parameters in another study [29]. Whereas total cholesterol, triglycerides, and LDL-C were significantly reduced in patients on day 3 of surgery and 6 months after the cholecystectomy in another one [30]. Significantly higher prevalence of cholelithiasis was found in patients with nonalcoholic fatty liver disease (NAFLD) (47% versus 26%, $p < 0.0001$), and type 2 DM, overweight, obesity, and cholelithiasis were identified as independent predictors of NAFLD [31]. Fifty six percent of patients with cholelithiasis had NAFLD compared with 33% of patients without ($p < 0.0001$) [31]. Age above 50 years, triglycerides above 1.7 mmol/l, overweight, obesity, and total cholesterol concentration were the independent predictors of cholelithiasis [31]. So NAFLD may represent a pathogenetic link between the metabolic syndrome and cholelithiasis [31]. As an opposite finding to ours, serum LDL-C values of patients with cholelithiasis above the age of 40 years were significantly elevated ($p < 0.05$) in another study [32]. Patients with type 2 DM had higher probability of having cholelithiasis, and age, female sex, and higher BMI were independently associated with cholelithiasis [33]. Obesity may lead to fatty infiltration causing organ dysfunctions, and the higher BMI values were associated with steatocholecystitis in another study [34].

Although ATP II determined the normal triglyceride value as lower than 200 mg/dL [35], WHO in 1999 [36] and ATP III in 2001 [13] reduced this normal limit as lower than 150 mg/dL. Although these cutpoints are usually used to define limits of the metabolic syndrome, whether or not more lower limits provide additional benefits for human being is unclear. In a previous study, patients with a triglyceride value lower than 60 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and equal to or greater than 200 mg/dL were collected into the fifth groups, respectively [23]. The mean ages of the groups increased up to the triglyceride value of 200 mg/dL, significantly ($p < 0.05$ in all steps). Prevalence of smoking was the highest in the fifth group which may also indicate inflammatory role of smoking in the metabolic syndrome. The mean body weight increased continuously, parallel to the increasing value of triglyceride, whereas BMI increased up to the triglyceride value of 200 mg/dL. Similarly, the mean LDL-C reached its highest value in the fourth, and decreased significantly in the fifth groups (142.0 versus 128.5 mg/dL, $p= 0.008$). Prevalence of white coat hypertension (WCH) was the highest in the fourth, and decreased significantly in the fifth groups, too (48.2% versus 32.5%, $p < 0.01$). As the most surprising result, prevalences of hypertension, type 2 DM, and CAD, as the terminal end points of the metabolic syndrome, showed their most significant increases after the triglyceride value of 100 mg/dL [23]. On the other hand, although there were progressive increases in parameters of the metabolic syndrome, the most significant increases were seen after the triglyceride value of 100 mg/dL. As one of our opinion, significantly increased mean age by the increased values of triglyceride may be secondary to aging induced decreased physical and mental stresses, which eventually terminates with onset of parameters and terminal end points of the metabolic syndrome. Interestingly, although the mean age increased from the lowest triglyceride having group towards the triglyceride value of 200 mg/dL, then decreased. The similar trend was also seen in the mean LDL-C and BMI values, and prevalence of WCH. These trends may be due to the fact that although the borderline high triglyceride values (150 - 199 mg/dL) is seen together with overweight, obesity, physical inactivity, smoking, and alcohol like acquired causes, the high triglyceride (200 - 499 mg/dL) and very high triglyceride values (500 mg/dL and higher) are usually secondary to both acquired and secondary causes such as type 2 DM, chronic renal failure, and genetic patterns [13]. But although the underlying causes of the high and very high triglyceride values may be a little bit different, probably risks of the terminal end points of the metabolic syndrome do not change in these groups. For example, prevalences of hypertension and type 2 DM were the highest in the highest triglyceride value having group in the above study [23]. Although some authors reported that lipid assessment in vascular disease can be simplified by measurement of either total and HDL-C levels without the need of triglyceride [37], some others indicated a causal association between triglyceride-mediated pathways and CAD [38]. Similarly, another study indicated moderate and highly significant associations between triglyceride values and CAD in Western populations [39]. Surprisingly, we detected in the above study that even a triglyceride value of smaller than 60 mg/dL is better according to the parameters of the metabolic syndrome [23].

As a conclusion, there are significant relationships between cholelithiasis and parameters of the metabolic syndrome including age, female sex, BMI, obesity, hypertension, and hypertriglyceridemia, so cholelithiasis may also be found among the terminal consequences of the metabolic syndrome. Although the decreased plasma levels of LDL-C probably due to the decreased amount of bile acids secreted during entrance of food into the duodenum and decreased amount of cholesterol absorbed in patients with cholelithiasis or cholecystectomy, the presence of hypertriglyceridemia may actually indicate its primary role as an acute phase reactant in them.

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