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: One hundred and forty-four cases either with cholelithiasis or cholecystectomy for cholelithiasis were detected among 3,437 cases, totally (4.1%). One hundred 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-
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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 gallstones were 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.

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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%). One hundred 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).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases with cholelithiasis or cholecystectomy for cholelithiasis</th>
<th>Control cases</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>144</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>Female ratio</td>
<td>80.5% (116)</td>
<td>80.5% (116)</td>
<td></td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>53.6 ± 9.3 (27 - 70)</td>
<td>53.6 ± 10.2 (28 - 70)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of smoking</td>
<td>18.0% (26)</td>
<td>19.4% (28)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI† (kg/m²)</td>
<td>31.0 ± 6.1 (19 - 51)</td>
<td>28.9 ± 5.7 (19 - 52)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Prevalence of normal weight</td>
<td>7.6% (11)</td>
<td>18.0% (26)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Prevalence of overweight</td>
<td>37.5% (54)</td>
<td>38.1% (55)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of obesity</td>
<td>54.8% (79)</td>
<td>43.7% (63)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Prevalence of hypertension</td>
<td>26.3% (38)</td>
<td>13.1% (19)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prevalence of DM‡</td>
<td>20.8% (30)</td>
<td>19.4% (28)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of hyperbetalipoproteinemia</td>
<td>9.7% (14)</td>
<td>18.0% (26)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Prevalence of hypertriglyceridemia</td>
<td>25.0% (36)</td>
<td>18.0% (26)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Prevalence of dyslipidemia</td>
<td>31.9% (46)</td>
<td>29.8% (43)</td>
<td></td>
</tr>
</tbody>
</table>

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
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 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].

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].

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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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