Cholelithiasis and cholecystectomy may lower the low density lipoprotein cholesterol in plasma

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Abstract

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

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

Results: One hundred and forty-four cases either with cholelithiasis or already performed 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 was significantly higher (54.8% versus 43.7%, $p<0.01$) in the cholelithiasis group, and the mean body mass indexes were 31.0 versus 28.9 kg/m2 in them, respectively ($p<0.01$). Prevalence 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, significantly. On the other hand, hyperbetalipoproteinemia was significantly lower in the cholelithiasis group (9.7% versus 18.0%, $p<0.05$).

Conclusions: There are significant relationships between cholelithiasis and parameters of the metabolic syndrome including age, female sex, obesity, hypertension, and hypertriglyceridemia, so cholelithiasis may also be found among the terminal consequences of the metabolic syndrome. On the other hand, cholelithiasis may actually be a natural defence mechanism of the body to decrease amount of cholesterol absorbed via decreasing amount of bile acids secreted during entrance of food into the duodenum since cholelithiasis and cholecystectomy may lower the low density lipoprotein cholesterol in the plasma.

Key words: Cholelithiasis, cholecystectomy, metabolic syndrome, low density lipoprotein cholesterol

Introduction

Chronic endothelial damage may be the most common type of vasculitis and the leading cause of aging, morbidity, and mortality in human beings. 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 nature that reduces blood flow and increases 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 other chronic inflammatory processes including rheumatologic disorders, prolonged infections, and cancers for the development of irreversible consequences 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 death. Although early withdrawal of causative factors may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed, completely due to their fibrotic nature. They 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). Even more conflicting results were reported about the associations between cholelithiasis and smoking (12-14). We tried to understand whether or not there is a significant relationship between cholelithiasis and cholecystectomy and plasma lipids.

Material and Methods

The study was performed in the 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 were 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 (15). 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 (16). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already receiving antidiabetic medications were defined as diabetics (16). 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 (16). Patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel's recommendations for defining dyslipidemic subgroups (16). 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 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 normotensives in the office due to the risk of masked hypertension after a 10-minute education session about proper BP measurement techniques (17). 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 minutes 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 (18). Eventually, hypertension is defined as a BP of 135/85 mmHg or greater on HBP measurements (17). Cholelithiasis was diagnosed ultrasonographically. Eventually, all cases either with presenting cholelithiasis or already performed cholecystectomy for cholelithiasis were put into the first group and age and sex-matched control cases were put into the second group. Prevalence of smoking, normal weight, overweight, obesity, hypertension, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia and mean BMI values were detected in both

groups and compared. 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, 119 cases with cholecystectomy for cholelithiasis and 25 cases with already presenting asymptomatic 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, so cholelithiasis is mainly a disorder of females in their fifties. Prevalence of smoking was similar in the cholelithiasis and control groups (18.0% versus 19.4%, p>0.05, respectively). There was not any patient with underweight. Interestingly, 92.3% (133 cases) of the cholelithiasis group had excess weight and only 7.6% (11 cases) had normal weight. 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) and hypertriglyceridemia (25.0% versus 18.0%, p<0.05) were also higher in the cholelithiasis group, significantly. Although the prevalence 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. On the other hand, hyperbetalipoproteinemia was significantly lower in the cholelithiasis group (9.7% versus 18.0%, p<0.05) (Table 1).

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. Bile acids are excreted in bile, which flows from the intrahepatic collecting system into the proximal or common hepatic duct. About 50% of bile secreted in the fasting state passes into the gallbladder via the cystic duct and the rest flows directly into the distal or common bile duct. So gallbladder filling is facilitated during fasting. Up to 90% of water in the gallbladder bile is absorbed as an electrolyte solution, and bile remaining in the gallbladder is a concentrated solution consisting primarily of bile acids. So during fasting, bile acids are concentrated in the gallbladder, and a small amount of bile flows from the liver. Food entering the duodenum stimulates gallbladder contraction, releasing much of body pool (3 to 4 g) of bile acids into the small intestine. Bile flows into the duodenum to mix with food content and to 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 as they enter that organ thus 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 in gastrointestinal function. About 90% of bile acids is absorbed in the terminal ileum into the portal venous circulation by active transport.

Table 1: Comparison of cases with and without cholelithiasis

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/m2)	***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

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

Bile salts are efficiently extracted by the liver, and secreted back into bile. Bile acids undergo enterohepatic circulation 10 to 12 times per day. During each pass, a small amount of primary bile acids reaches the colon, where anaerobic bacteria containing 7alpha-hydroxylase form secondary bile acids. The most clinical disorders of the extrahepatic biliary tract are related to 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 which greatly increase the cholesterol-carrying capacity of bile. The amount of cholesterol carried in micelles and vesicles varies with the bile salt secretion rate. Supersaturation of cholesterol in bile is a necessary condition of cholesterol gallstone formation. Virtually all gallstones form within the gallbladder but stones may form in the bile duct after cholecystectomy or behind strictures as a result of stasis. In another perspective, cholelithiasis may actually be a natural defence mechanism of the body to decrease amount of cholesterol absorbed via decreasing amount of bile acids secreted during entrance of food into the duodenum. 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 organ systems of the body. Recent studies revealed that adipose tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin which are closely related with the development of complications (19). For example, the cardiovascular field has recently shown a great interest in the role of inflammation in the development of atherosclerosis and numerous studies indicated that inflammation plays a significant role in the pathogenesis of atherosclerosis and thrombosis (20, 21). Adipose tissue is involved in the regulation of cytokines (22). On the other hand, individuals with excess weight will have an increased circulating 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 circulating blood volume can lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of hypertension. In addition to the hypertension, the prevalence of high FPG, high serum total cholesterol, and low HDL-C, and their clustering were all raised with the higher BMI (23). 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 incidence of CHD and stroke have increased with a higher BMI in other studies (23, 24), and risk of death from all causes including cancers increases throughout the range of moderate and severe excess weight for both genders in all age groups (25). As another consequence of excess weight on health, the cholelithiasis cases had a significantly higher mean BMI value in the present study (31.0 versus 28.9 kg/m2, $p<0.01$) similar to the previous reports (8, 9). Probably as a consequence of the significantly higher BMI, the prevalence 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 (26), and clinical manifestations of the syndrome include obesity, dyslipidemia, hypertension, insulin resistance, and proinflammatory as well as prothrombotic states (27). The above confirmed increased risk of cholelithiasis in obese diabetics with hypertriglyceridemia may also be an indicator of its association with the metabolic syndrome (10, 26). Although the presence of some conflicting results in the literature (12-14), we did not find any significant association between cholelithiasis and smoking in the present study ($p>0.05$).

Although the waist circumference, BMI, hypertension, fasting glycemia, insulinemia and insulin resistance index indicated significant differences in the cholelithiasis and cholecystectomy group in patients with the metabolic syndrome, there was no significant differences for the lipid parameters in another study (28). Plasma concentration of total cholesterol, triglycerides, and LDL-C were significantly reduced in patients on day 3 of surgery and 6 months after the cholecystectomy in another study (29). Significantly higher prevalence of cholelithiasis was found among 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 (30). Fifty six percent of patients with cholelithiasis had NAFLD compared with 33% of patients without ($p< 0.0001$) (30). Age above 50 years, triglycerides above 1.7 mmol/l, overweight, obesity, and total cholesterol concentration were the independent predictors of cholelithiasis (30). So NAFLD may represent a pathogenetic link between the metabolic syndrome and cholelithiasis (30). Serum LDL-C values of patients with cholelithiasis above the age of 40 years were significantly elevated ($p<0.05$) in another study (31). Patients with type 2 DM had higher probability of having cholelithiasis, and age, female sex, and higher BMI were independently associated with cholelithiasis (32). Authors have concluded that obesity may lead to fatty infiltration of multiple organs causing organ dysfunction, and BMI was associated with steatocholecystitis in another study (33).

As a conclusion, there are significant relationships between cholelithiasis and parameters of the metabolic syndrome including age, female sex, obesity, hypertension, and hypertriglyceridemia, so cholelithiasis may also be found among the terminal consequences of the metabolic syndrome. On the other hand, cholelithiasis may actually be a natural defence mechanism of the body to decrease the amount of cholesterol absorbed via decreasing amount of bile acids secreted during entrance of food into the duodenum since cholelithiasis and cholecystectomy may lower LDL-C in the plasma.

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