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Gallstones associated with nonalcoholic steatohepatitis (NASH) and metabolic syndrome

Safra kesesi taşlarının non-alkolik steatohepatit ve metabolik sendromla birlikteliği

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Background/aims: *We aimed to evaluate the prevalence of non-alcoholic steatohepatitis and metabolic syndrome in patients with symptomatic gallstones undergoing laparoscopic or open cholecystectomy.* ***Methods:*** *A study of 95 patients was performed. Simultaneous liver biopsies were taken during cholecystectomy between 2006 and 2007. There were no postoperative complications. Patients with significant alcohol intake, hepatitis B or C (virus-positive), autoimmune diseases, and Wilson's disease were excluded. Demographics, liver function tests, lipid profile, and ultrasound findings of patients with and without non-alcoholic steatohepatitis were compared.* ***Results:*** *A total of 95 patients completed the study. The mean age was 52.15 years, and 29 patients were male and 66 female. Fifty-two patients (55%) had biopsies compatible with non-alcoholic steatohepatitis.* ***Conclusions:*** *Fifty-five percent of patients with gallbladder stones had associated non-alcoholic steatohepatitis. Awareness of this association may result in an earlier diagnosis. The high prevalence of non-alcoholic steatohepatitis in patients with galbladder stone may justify routine liver biopsy during cholecystectomy to establish the diagnosis and stage and possibly direct therapy.*

Key words: Gallbladder stone, nonalcoholic steatohepatitis, metabolic syndrome

Amaç: *Bu çalışmada semptomatik safra kesesi taşı nedeniyle açık veya laparoskpopik kolesistektomi yapılan hastalarda NASH ve metabolik sendromun sıklığını değerlendirmek amaçlanmıştır.* ***Yöntem:*** *2006 2007 tarihleri arasında 95 hastadan kolesistektomi esnasında karaciğer biopsisi alınmıştır. Postoperatif komplikasyon oluşmamıştır. Alkol alımı, HBV HCV otoimmün hastalıklar ve Wilson hastalığı çalışma kapsamı dışına alınmıştır. Hasta demografik bulguları karaciğer testleri lipid profili ve ultrason bulguları NASH olan ve olmayan grupta karşılaştırtılmıştır.* ***Bulgular:*** *Toplam 95 hasta çalışmaya alınmıştır. Ortalama yaş 52.15 olup 29 hasta erkek 66 hasta kadındı. 55 hastanın biopsisi NASH ile uyumluydu.* ***Sonuç:*** *Safra taşı olan 55 hastada NASH saptanmıştır. Bu birlikteliğin erken dönemde farkına varılmalıdır. NASH safra taşlarıyla yüksek oranda birlikteliği nedeniyle kolesistektomi esnasında rutin karaciğer biopsisi teşhis tedavi açısından önemlidir.*

Anahtar kelimeler: Safra taşı, steatohepatosis, metabolik sendrom

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is a term applied to accumulation of fat in the liver accompanied by indicators of hepatocellular damage in the absence of significant alcohol consumption (1). NASH is currently considered to be a major cause of cryptogenic cirrhosis. Various studies report up to 22% progression to cirrhosis among patients with NASH. Most, but not all, patients are overweight, and gradual weight reduction is known to be effective in many of these patients, although maintaining sustained weight reduction is a problem. In spite of the importance of this condition, there is currently no well-established medical treatment known to prevent the progress of NASH to cirrhosis or to reverse the biochemical and histologic changes (2).

The pathogenesis of NASH appears to be a two-hit process. In the first hit, accumulation of triglycerides occurs in the liver without hepatocellular damage. In the second hit, hepatocellular damage occurs. It is believed that oxidative stress and lipid peroxidation somehow play a major role in this phase. Many mechanisms have been suggested. Induction of CYP2E1, mitochondrial dysfunction, iron overload, portal endotoxemia, cytokines, hyperinsulinemia and insulin resistance, Kupffer

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cell dysfunction, and altered ATP homeostasis are among the suspects (3,4). Patients with symptomatic gallstones have a high prevalence of NASH, as well as a significant association with metabolic syndrome. NASH, the more progressive form of nonalcoholic fatty liver disease (NAFLD), has been associated with hepatocellular injury and progressive fibrosis. Symptomatic gallstones are often associated with obesity, hypertriglyceridaemia, insulin resistance, and type 2 diabetes mellitus, which may in turn be linked to NASH. Metabolic syndrome is characterized by three of the following criteria: increased waist circumference, hypertriglyceridemia, hypercholesterolemia, hypertension, and hyperglycemia (5).

MATERIALS AND METHODS

We prospectively evaluated consecutive patients referred for cholecystectomy due to symptomatic gallbladder confirmed by ultrasonography (US) between January 2006 and January 2007. All patients provided their informed consent prior to enrollment. Demographics, family history, risk factors, comorbid conditions, laboratory tests, alcohol ingestion, medication use, and abdominal US findings were registered and analyzed. Intravenous blood samples were collected from every patient after a 12-hour fast, and the following biochemical tests were performed: complete blood count, glucose, creatinine, uric acid, blood urea nitrogen, total cholesterol, high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, and direct bilirubin. Serum markers of hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) were also performed. Patients with a positive serology for HBV or HCV, and those with a history of alcohol ingestion, liver cirrhosis, autoimmune hepatitis, or other liver disease were excluded. All patients underwent biopsy from the apex of the liver performed at the end of a standard laparoscopic or open cholecystectomy. Hemostasis was secured by using monopolar electrocautery only after the specimen was obtained. Those biopsies with NAFLD were classified according to the system proposed by Brunt et al. (6). Descriptive statistics were used according to the type of variable measured. The odds ratio and its confidence interval were estimated at 95%. The statistical significance of the associations was evaluated by the χ 2 test, and in those cases in which the conditions for its performance were not fulfilled, Fisher's exact test was used. The level of statistical significance was 0.05. For continuous variables, Student's t test was performed. A multivariate analysis was also performed using a logistic regression. Statistical analysis was performed with SPSS 13 for Windows.

RESULTS

Ninety-five patients (29 males, 31%; 66 females, 69%) were evaluated. Their mean age was 52.15±16.82 years (range: 21–84 years). Forty-three subjects (45%) had a normal liver biopsy (Group A). In the remaining 52 patients (55%), there were histological findings compatible with NAFLD (Group B). Sociodemographic characteristics and risk factors for NAFLD among groups are shown in Table 1. Group B patients were significantly older and had higher body mass index when compared to Group A.

Preoperative laboratory test values are shown in Table 2. As expected, Group B subjects had significantly higher values of AST, ALT, ALP, and triglycerides. Preoperative US accurately detected NASH in only seven patients (13%). There were no complications or mortality secondary to the liver biopsies.

DISCUSSION

Gallbladder stones and NASH share common risk and pathogenic factors. Obesity is a well-established risk factor for NASH and a major risk factor for developing gallstones (7).The risk for gallbladder stones is especially high if obesity onsets in yo-

Table 1. Sociodemographic characteristics

	Group A n=43	Group B n=52	p value
Male	14 (%33)	15 (%29)	0,69
Female	29 (%67)	37 (%71)	0,69
Age (mean+/- SD)	48.13±14.8	55.6±17.9	0.02
Body mass index (mean +/-SD)	26.5±3.1	28.8±4.9	0.09

Table 2. Routine laboratory values

	Group A n=43	GROUP B N=52	p value
Glucose (mg/dL)	99.16+/-30.48	106,6+/-29,27	0,23
Cholesterol (mg/dL)	203.7+/-38.21	205,3+/-57,6	0,87
Triglycerides (mg/dL)	136.9+/-44.57	194,7+/-106,45	0,007
HDL-C (mg/dL)	72.76+/-47.52	58+/-27,87	0,07
AST (U/L)	23.8+/-8.31	53,3+/-44.75	0.0001
ALT (U/L)	28.6+/-8.34	58,3+/-35.69	0.0001
ALP (U/L)	73.9+/-21.19	99+/-49.66	0.0001

uth. Gallbladder stones are closely related to central obesity, diabetes mellitus and insulin resistance (8, 9). Other shared risk factors include dyslipidemia (hypertriglyceridemia, low HDL-C) and abnormalities in fibrinolysis and coagulation (10). NASH and gallbladder stones appear to be linked through the metabolic syndrome, insulin resistance and probably hyperhomocysteinemia (11, 12). Fatty liver has been documented in up to 15% of healthy nonobese individuals and about 70% to 80% of obese individuals in some series. Fifteen to 20% of morbidly obese subjects have NASH, and up to 20% of patients with NASH will develop liver cirrhosis over a period of 5 to 10 years (13). In this study, we found that more than 50% of patients with gallbladder stones have associated NASH. Subjects with gallbladder stones and NASH had the typical risk factors for both diseases: older age, family history of hypertension, dyslipidemia and/or obesity, as well as higher body mass index and a higher prevalence of diabetes. The fact that patients with NASH were significantly older than those with normal biopsies suggests that, given enough time, some of the latter patients may develop liver steatosis, increasing the prevalence of NASH in patients with gallbladder stones. It is important to remark that, in some liver and biliary diseases, genetic differences play a key role. Epidemiological studies, especially those of ethnic differences, family grouping and twins, have suggested that genetic background is a risk factor for the development of gallstones (14). The vast majority of patients with NASH seek medical attention due to the incidental finding of elevated liver function tests during routine medical evaluations and for assessment of unrelated symptoms or metabolic syndrome. This apparent asymptomatic presentation does not imply a benign course. We found that only 13% of our subjects had a suspected diagnosis of NASH preoperatively. The rest of the patients were not aware of having any liver disease. NASH patients in our study had significantly higher values of AST, ALT and ALP; nevertheless, as other series have confirmed, normal values do not exclude the diagnosis. A retrospective study by Mofrad et al. (15) found that the entire histological spectrum of NASH can be seen in individuals with normal ALT values.

In most of our cases determined to have abnormal liver function tests in the preoperative evaluation, this was attributed to gallstone disease (GD) by the referring physician. Moreover, preoperative US was neither sensitive nor specific for the diagnosis of NASH. Our findings also support what other reports have suggested, that imaging methods are of limited value as a screening method for NASH.

Previous studies have reported that almost 10% of patients with NASH have histological findings compatible with NASH or cirrhosis at the time of the diagnosis. In our series, almost 10% of GD with NASH had significant fibrosis. These findings underscore the clinical relevance of NASH and the importance of an early diagnosis in patients at risk. Awareness of the association between NASH and GD may result in an earlier diagnosis. Liver biopsy is currently the only way to confirm a diagnosis of NASH and determine disease severity, yet there are no guidelines as to when to perform a liver biopsy in patients at high risk of the disease (16). Its relevance has been a matter of great controversy and is an unattractive diagnostic option to many. Critics of liver biopsy argue that the quality of liver biopsy specimens is not always optimal and is subject to sampling variability (17). Moreover, there is no agreement on which biopsy technique provides better material for analysis. Wedge biopsy has been criticized as a screening tool for being a subcapsular sample. Fibrous septa spreading from Glisson's capsule to the adjacent parenchyma may mimic cirrhosis, therefore overestimating the stage of liver disease. One recent study found needle biopsies to be as effective as wedge biopsies in assessing the degree of steatosis in morbidly obese patients, but the presence of subcapsular fibrosis in needle biopsies was less than in wedge biopsies (18). Older series report that both wedged and needle biopsy samples are appropriate for assessing the degree of fibrosis or cirrhosis (19). Significant variability has also been observed between right and left lobe liver biopsies (20). Liver steatosis without NASH appears to be a frequent finding, and performing a liver biopsy in all suspected patients may appear overly aggressive, especially when a treatment of proven benefit is lacking. Our study helps to understand the prevalence of asymptomatic liver disease in patients with symptomatic GD and to quantify the effect of certain risk factors. In a population at increased risk of NASH, such as patients with symptomatic GD who undergo cholecystectomy, liver biopsy represents an opportunity to screen for the disease with minimal risk and cost to the patient. Laparoscopic liver biopsy in this group of pa-

tients is a safe and effective method to establish the diagnosis and stage of NASH, and the information obtained could help to better understand the disease and its natural history. Additionally, it would give sufficient grounds to recommend at least the implementation of lifestyle modifications (diet, weight loss, exercise, cessation of alcohol consumption) based on objective information. Severe histological findings may prompt participation of affected individuals in clinical trials of investigational drugs. Although our finding that NASH is highly prevalent in subjects with GD may justify routine liver biopsy in all patients undergoing laparoscopic cholecystectomy, there are some limitations that should be acknowledged. As other reports have shown, there is significant interobserver and intraobserver variability in biopsy specimen interpretation. Our specimens were reviewed by a single experienced pathologist, and we believe that independent corroboration of the diagnosis and grade by another pathologist would strengthen our results. Another limitation in the design of the study is that a diagnosis of diabetes rather than insulin resistance was used; hence, it is likely that some patients could have undiagnosed diabetes. We also acknowledge that the alcohol intake cut-off value of 150 g/week used in our study is higher than that used in other series. Nevertheless, there is no universally accepted threshold level of alcohol intake to distinguish alcoholic fatty liver disease from NASH, and it is generally accepted that fatty liver does not develop with alcohol consumption levels below 20 g/day. Moreover, quantification of alcohol intake is largely subjective and has been known to be notoriously inaccurate in spite of using standardized instruments.

In conclusion, our findings suggest that routine liver biopsy during cholecystectomy for GD may be justified given the high prevalence of NASH in these patients; otherwise, the disease could go unrecognized for several years. Based on our results, obese and/or dyslipidemic patients with abnormal liver chemistry represent a group that would benefit the most from this approach. The information obtained by this practice could help us to better understand the pathogenesis of NASH, lower its impact, and prevent or delay its complications. Even though there were no complications in our series, some complications are eventually inevitable. Therefore, the adoption of a practice of routine liver biopsy during laparoscopic cholecystectomy should not be based on the results of a single study.

Further studies are needed to assess the feasibility, safety, efficacy, and cost-effectiveness of this approach in order to recommend it as a screening tool in this population.

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