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Nonalcoholic Fatty Liver Disease is Associated With Erectile Dysfunction: A Prospective Pilot Study

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome (MetS). Although the link between MetS and erectile dysfunction (ED) is well known, clinical studies investigating the association between NAFLD and ED are scant.

Aim: To evaluate the relationship between NAFLD and ED.

Methods: Male patients with biopsy-proven NAFLD were prospectively asked to fill the five-item International Index of Erectile Function (IIEF-5) questionnaire. Their clinical and histologic variables were compared with the IEFF scores.

Main Outcome Measures: IIEF scores; proportions of NAFLD patients who demonstrated ED and/or MetS; association between the severity of histological hepatic damage and ED.

Results: Forty male patients having an age range of 33 (24−57) and a mean age of 40.13 ± 10.22 years with biopsy-proven NAFLD had a median IIEF-5 score of 16 (9−25) and MetS was present in 23 (57.5%). ED severity distributions as moderate, mild, and no ED were 11 (27.5%), 16 (40%), and 13 (32.5 %), respectively. Histological NAFLD score was significantly higher in patients having ED compared with patients with no ED (5.63 ± 1.39 vs 4.15 ± 1.46; $P = .006$). MetS diagnosis was significantly more common in patients having ED, compared with those without ED [19 (70.4%) vs 4 (30.8%), respectively, $P = .018$)]. When patients with and without ED were compared, gamma glutamyl transferase was significantly lower in ED, whereas components of MetS did not correlate with ED. After multivariate analysis, NAFLD score has remained the only significant outcome associated with ED [$P = .03$; OR (95% CI): 2.38 (1.079−5.238)].

Conclusion: The current clinical study demonstrates a significant association between nonalcoholic steatohepatitis and ED for the first time. Our findings suggest liver damage may play role in the pathogenesis of ED in patients with NAFLD. Future studies are needed to expand the underlying common mechanisms responsible for this novel hypothesis.

Key Words: Erectile Dysfunction; Nonalcoholic Fatty Liver Disease; Nonalcoholic Steatohepatitis; Fatty Liver; Metabolic Syndrome

INTRODUCTION

Erectile dysfunction (ED) has implications that go far beyond sexual activity and is now recognized as the harbinger of metabolic syndrome (MetS).[1] A recent meta-analysis examining the association between MetS and erectile dysfunction (ED) revealed a 2.6-fold increase in overall risk of ED in patients with MetS.[1] Nonalcoholic fatty liver disease (NAFLD) is accepted as the hepatic manifestation of MetS.[1] However, clinical studies investigating the link between NAFLD and ED are scant.

The term NAFLD covers a spectrum of histological findings ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), with the latter being a histological state of NAFLD exhibiting hepatic steatosis combined with inflammation and fibrosis.[2] The clinical significance of NASH is reflected by its potential to progress to cirrhosis, and it may lead to hepatocellular carcinoma.[3] Insulin resistance (IR) is the common pathophysiological hallmark of metabolic syndrome and NASH.[2,4] It

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triggers endothelial dysfunction, which also contributes to ED.[5] Moreover, IR is blamed for inducing inflammatory changes in fatty liver disease as well as other manifestations such as cardiovascular disease and diabetes.[5] In a study conducted among young ED patients (age <45), IR was detected in 52% and it was the independent predictor of ED.[6] Patients with IR had higher body mass indices (BMIs) but significantly lower testosterone and sex hormone binding globulin (SHBG) levels than patients without IR.[6]

ED prevalence in healthy men above 40 years of age is 69.2% (mild 33.2%, moderate 27.5%, and severe 8.5%) in Turkey.[7] On the other hand, NAFLD is the most frequent liver disease in developed countries, affecting up to 20% to 30% of the general population.[1] Although NAFLD and ED seem to be quite common, the diagnostic frequency of overlap of both conditions is not known.

To our knowledge, there is no clinical study investigating the association between ED and the hepatic damage in NAFLD patients prospectively. Since most NAFLD patients have accompanying MetS we also aim to evaluate if NAFLD patients having MetS also have accompanying ED.

METHODS

NAFLD was defined according to the guidelines of the American Association for the Study of Liver Diseases (AASLD) required the presence of primary hepatic steatosis diagnosed either by imaging or by histology and exclusion of the reason for secondary hepatic fat accumulation (eg, extensive alcohol consumption, steatogenic medication or hereditary disorders).[8] Male patients 18−75 years of age with NAFLD were deemed eligible for this study. Males having unexplained liver transaminase elevation and suspicion for NAFLD were offered liver biopsy and to complete the 5-item International Index of Erectile Function (IIEF-5) questionnaire that was translated into Turkish and validated.[9,10] The data of patients who turned out to have NAFLD after liver biopsy were evaluated in the final results.

Exclusion Criteria

Patients with other causes of liver disease including viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, biliary obstruction, alpha-1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, or malignancies were excluded. Patients with cirrhosis having a Child-Pugh score >5, history of spinal cord or brain injury, Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke, Peyronie's disease, previous pelvic surgery or trauma involving bowel, bladder, prostate, or rectum, pelvic radiotherapy, patients having past medical history or physical examination findings suggestive of secondary hypogonadism, hyperthyroidism, congestive heart failure, or daily alcohol intake exceeding 20 g/day also were deemed ineligible.

Subjects using diuretics, β-blockers, amiodarone, steroids, tamoxifen, antidepressants or herbal remedies, as well as men without regular sexual experiences for 6 months preceding the study entrance were not included.

Clinical and Biochemical Characterization

All subjects underwent physical examination including blood pressure measurement and anthropometric assessments. BMI was calculated from measurements of height and weight.

Metabolic Syndrome

MetS was defined based on the criteria of the U.S. National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III) and having 3 or more of the following 5 components: Waist circumference >102 cm, triglycerides ≥150 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL, blood pressure ≥130/85 mm Hg, and fasting glucose ≥110 mg/dL.[11]

Insulin Resistance

The estimate of IR was calculated using the homeostatic model assessment (HOMA)-IR index, with the following formula: insulin resistance = fasting plasma insulin × fasting plasma glucose/405.[12]

Liver Histology

An experienced pathologist blinded to the clinical data scored the liver biopsies according to the NAFLD scoring system.[13] Steatosis was scored from 0 to 3 with a 4-grade scoring system from S0 to S3: S0, no steatosis or less than 5%; S1,5−33%; S2, 33−66%; S3, >66%. Lobular inflammation was graded according to the number of inflammatory foci per ×200 field ranging from stage 0 to 3. Ballooning degeneration of liver cells was evaluated and scored from grade 0 to 2. The histological NAFLD score was defined as the unweighted sum of the scores for steatosis (0−3), lobular inflammation (0−3), and ballooning (0−2); thus ranging from 0 to 8. Cases with scores of 0−2 were considered as having simple steatosis, whereas, cases with scores of 5 or greater were diagnosed as definitive NASH. Cases with activity scores of 3 and 4 were considered as borderline NASH.[13] Hepatic fibrosis was staged according to the level of damage in liver lobules, with stage 0 having no fibrosis and stage 4 corresponding to cirrhosis.[13]

Erectile Dysfunction Evaluation

The patients' sexual histories were taken. All patients were asked to complete the 5-item version of IIEF (IIEF-5) questionnaire.[9,10] The IIEF-5 scores range between 5 and 25. We classified ED severity into 4 categories according to IIEF-5 scores: severe (5−7), moderate (8−16), mild (17−21), and no ED (22−25).[9] Those patients having ED were subsequently