RESEARCH LETTER

High-sensitivity C-reactive protein as a new predictor of the course of nonalcoholic fatty liver disease in patients after bariatric surgery

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Introduction Excess fat in morbidly obese patients undergoing unique effective treatment such as bariatric surgery is accumulated not only in adipose tissue but also in other tissues and organs. In the liver, this process leads to fatty liver disease, which has a complicated course.[1,2] The disease progresses from simple steatosis, through inflammation to fibrosis, cirrhosis, and liver failure. It should be noted that according to the World Gastroenterological Organization, nonalcoholic fatty liver disease (NAFLD) affects 20% to 40% of the general population and as many as 75% to 95% of people with morbid obesity. Inflammatory form of the disease is present in 10% to 20% of the general population and even in 37% of obese patients.[3]

The only method to diagnose the disease is biopsy, but it is not widely used due to potential complications. Noninvasive imaging modalities (ultrasonography, computed tomography, magnetic resonance imaging) are also available, but have numerous limitations. Some authors indicate also the possibility of using composite biomarkers in the diagnosis of NAFLD with the aim to find the simplest marker possible for use in everyday clinical practice.[4-6] In some studies, high-sensitivity C-reactive protein (hs-CRP) was reported to be an independent risk marker for NAFLD.[7-9]

Since noninvasive methods have limited application in the diagnosis of the disease and assessment of its course, it is virtually impossible to safely monitor the potential evolution of changes in the liver after surgical treatment. The objective of the study was to find a noninvasive predictor of liver disorders in patients after bariatric surgeries as well as to assess the prevalence of NAFLD and the impact of bariatric surgeries on the histopathology of the liver.

Patients and methods In the years 2002 to 2009, 203 patients underwent surgical treatment for morbid obesity at our department. A wedge liver biopsy was obtained in 24 patients during the surgery. Patients with incision hernia underwent another surgery after at least 18 months from the original treatment. A comparative analysis included patients who had wedge liver biopsy obtained during original or repeat surgeries. The body composition analyzer was used to measure body weight and its distribution. Assessed values included baseline excess body weight and weight loss represented by absolute values and the percentage of excess body weight loss (%EWL) and excess body mass index loss (%EBMIL). On the day before the surgery, patients underwent a full medical examination, and a routine sample of fasting venous blood was collected. Bariatric surgery was performed. The obtained liver specimen was placed in a 4% formaldehyde solution immediately after the collection and transported to the histopathology laboratory, where it was stored for 72 hours for fixation. To assess the grade of steatosis or level of inflammation or fibrosis, a histopathologist used a diagnostic algorithm developed by Elizabeth Brunt.[10-12] Simultaneous presence of steatosis, ballooning degeneration, and lobular inflammation is necessary to make a diagnosis of nonalcoholic steatohepatitis (NASH). Reconstruction of liver architecture reflects the stage of the disease and it is correlated with fibrosis advancement. The study protocol was approved by the Bioethical Committee of the Medical University of Warsaw (no. 52/12).

Statistical analysis The Kolmogorov–Smirnov test was used to verify the normal distribution of variables. If the distributions of both

TABLE 1 Anthropometric parameters of the study group at 3 time points: baseline, after 12 months of treatment, and at the end of follow-up

Parameter	Baseline	At 12 months	End of follow-up	*P* value
Weight, kg	137.63 (22.05)	96.19 (17.63)	87.11 (15.26)	<0.001
Body mass index, kg/m^2	49.29 (6.17)	34.48 (5.98)	31.11 (4.28)	<0.001
Fat mass, kg	66.08 (14.90)	35.41 (11.63)	29.30 (9.84)	<0.001
Body fat percentage, %	47.87 (5.58)	36.20 (7.74)	33.06 (8.20)	<0.001
Fat free mass, kg	71.32 (12.72)	60.78 (10.54)	57.81 (10.15)	<0.001
Total body water, kg	52.28 (9.40)	44.49 (7.71)	42.10 (6.88)	<0.001

Data are presented as mean (SD).

variables were normal, the *t* test was used. If the distribution of at least one of the variables deviated significantly from the normal distribution, the Wilcoxon test was used. To compare the difference between related ordinal variables, the Wilcoxon test and signs test were used. To compare the groups in terms of quantitative variables, descriptive statistics were calculated and the Mann–Whitney test was performed to compare 2 groups or the Kruskal–Wallis test to compare 3 or more groups. To assess the significance of changes in the parameters at 3 time points, the Friedman test was used for dependent samples, while the Wilcoxon test for paired samples was used to compare between 2 time points. Relationships between 2 nominal variables or between nominal and ordinal variables were tested using contingency tables and χ^2 independence test. To assess the difference in the probability of increased hs-CRP levels between 2 groups, the odds ratio with 95% CI and the significance test were used. The analysis of the receiver operating characteristic (ROC) curves was used to evaluate the diagnostic power of the test. The results were considered significant at *P* value of less than 0.05. The calculations were performed in SPSS 23.0 (IBM, New York, New York, United States) and MedCalc (MedCalc Softfare, Ostend, Belgium).

Results The study group included 24 patients diagnosed with grade 3 obesity (TABLE 1). The effectiveness of surgical treatment was assessed on the basis of anthropometric analysis performed at the beginning of the therapy, 12 months after the surgery, and 1 day before the abdominal wall plasty. The treatment was considered effective if %EWL was at least 50% and %EBMIL was 60%.

The analysis of anthropometric parameters in the study group revealed significant differences (TABLE 1). At 12 months, a positive therapeutic effect (ie, at least minimal required %EWL and %EBMIL) was observed in 62.5% and 87.5% of patients, respectively. At the end of the study, regardless of the criterion used, the whole group achieved positive therapeutic effect. The results of surgical treatment were also evaluated in terms of the histopathology of the liver. There were only small differences identified in %EWL and %EBMIL between patients with different severity of steatosis. These differences, however, were not significant.

Histopathological examination of liver specimens obtained during bariatric surgeries led to a diagnosis of NAFLD in 75% of patients, 55.56% of whom had steatohepatitis. Normal histopathology of the liver was demonstrated in 8.33% of patients, and isolated fibrosis, in 16.67% of patients. A control biopsy obtained at abdominal wall plasty revealed remission of inflammation in all patients in whom it had been previously observed. Additionally, steatosis regressed in 88.9% of patients.

Comparative analysis of clinical biochemical tests was performed between the following groups: normal vs NAFLD, normal vs expandisolated steatosis (IS), normal vs NASH, and IS vs NASH. The comparison of patients with NAFLD and those with normal histopathology of the liver revealed that the first group had higher levels of hs-CRP (mean [SD], 7.95 [3.63] mg/l vs 4.75 [1.48] mg/l, *P* = 0.045) and glycated hemoglobin A_{1c} (HbA_{1c}) (mean [SD], 6.07% [1.06] vs 5.4% [0.36], *P* = 0.03). There were no significant differences in the results between the group with normal histopathology of the liver and IS. Compared with patients with normal histopathology of the liver, patients with steatohepatitis had higher levels of alanine transaminase (mean [SD], 43 [22.3] U/l vs 23.83 [8.68] U/l, *P* = 0.03), hs--CRP (mean [SD], 9.65 [2.34] vs 4.75 [1.48], *P* = 0.001) and HbA_{1c} (mean [SD], 5.9% [0.29] vs 5.4% [0.36], *P* = 0.02). Within the group of patients with liver disorders, patients with hepatitis had higher levels of aspartate transaminase (mean [SD], 29.50 [10.64] U/l vs 19.88 [6.18] U/l, *P* = 0.04) and hs-CRP (mean [SD], 9.65 [2.34] mg/l vs 5.82 [3.96] mg/l, *P* = 0.03), and lower levels of triglycerides (mean [SD], 113.3 [35.38] mg/dl vs 170.38 [54.01] mg/dl, *P* = 0.03). Evaluation performed after the treatment showed a decrease in all biochemical parameters in all groups.

The analysis of the area under the ROC curve (AUC) revealed a higher risk of notably increased hs-CRP levels in patients with NASH compared with those without NASH (AUC, 0.879; *P* = 0.002). This correlation disappeared when the required excess weight loss was achieved (AUC, 0.486; *P* = 0.91). It was demonstrated that in patients with NASH, hs-CRP levels more often exceed 7.3 mg/l

(χ^2 = 10.971; df = 1; P = 0.001). At the same time, the risk of NASH increased when hs-CRP levels were 7.3 mg/l or higher (odds ratio, 33; 95% CI, 2.91–374.33; P = 0.01).

Discussion The levels of hs-CRP can be used to identify obese patients with an increased risk of NAFLD. The parameter may be also used as a marker of regression of hepatitis in patients with excess weight loss. Bariatric surgery helps achieve sustained weight loss without the risk of worsening liver histopathology. Steatosis and inflammation in the course of NAFLD are reversible.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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