A high-sensitivity C-reactive protein as a new predictor of the course of non-alcoholic fatty liver disease in patients after bariatric surgery

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A High-Sensitivity C-Reactive Protein As A New Predictor Of The Course Of Non-Alcoholic Fatty Liver Disease In Patients After Bariatric Surgery

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Short title: C-reactive protein and non-alcoholic fatty liver disease

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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 non-alcoholic fatty liver disease (NAFLD) affected 20-40% of general population and as much as 75-95% of people with pathological obesity. Inflammatory form of the disease was present in 10-20% of the general population and in even 37% of obese patients[3].

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

Since non-invasive 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 liver after surgical treatment. The objective of the study was to find a non-invasive predictor of liver disorders in patients after bariatric surgeries and to assess the prevalence of NAFLD and the impact of bariatric surgeries on the histopathology of the liver.

In the years 2002-2009, 203 patients underwent surgical treatment for pathological obesity at our department. A wedge liver biopsy was obtained in 24 patients during the surgery. Patients with incision hernia were re-operated on, after at least 18 month from the
original treatment. The comparative analysis included patients who had wedge liver biopsy obtained during original or secondary surgeries. The body composition analyser was used in order 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 (% EBML). 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 incidence of steatosis, ballooning degeneration and lobular inflammation is necessary to make a diagnosis of non-alcoholic steatohepatitis (NASH). Reconstruction of liver architecture reflects the stage of the disease and it is correlated with fibrosis advancement.

Kolmogorov-Smirnov test was used to verify the normal distribution of variables. If the distributions of both 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. In order to compare the difference between related ordinal variables, the Wilcoxon test and signs test were used. In order to compare groups in terms of quantitative variables, descriptive statistics were calculated and Mann-Whitney tests were performed to compare two groups or Kruskal-Wallis tests to compare 3 or more groups. To assess the significance of changes in the parameters at three time points, Friedman's tests were used for dependent samples, while Wilcoxon tests for paired samples was used to compare between two time points. Relationships between two nominal variables or between nominal and ordinal variables were tested using contingency tables and chi-square independence tests. To
assess the difference in the probability of the occurrence of phenomenon (increased hsCRP) between two groups, the odds ratio with 95% confidence interval and the significance test was used. The analysis of ROC curves was used to evaluate the diagnostic power of the test. Significance level below which results were considered significant was P<0.05. The calculations were performed in IBM SPSS 23.0 and MedCalc. The study protocol was accepted by Medical University of Warsaw.

The study group included 24 patients, all were 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 “0”, 12 months after the surgery “12” and one day before the abdominal wall plasty “E”. The treatment was considered effective if EWL was at least 50% and EBMIL was 60%.

Analysis of anthropometric parameters in the study group revealed statistically significant differences (Table 1). One year after surgery, a positive therapeutic effect, that is at least minimal required percentage of EWL and percentage of 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 statistically significant.

Histopathological examination of liver specimens obtained during bariatric surgeries led to a diagnosis of NAFLD in 75% of studied individuals, of whom in 55.56% steatohepatitis was diagnosed. Normal histopathology of the liver was demonstrated in 8.33% of patients and isolated fibrosis in 16.67% of patients. In a control biopsy obtained at abdominal wall plasty, remission of inflammation was found in all cases in which it had previously occurred. Additionally, steatosis regressed in 88.9% of patients.
Comparative analysis of clinical biochemistry tests was performed between following groups: normal vs. NAFLD, normal vs. IS, normal vs. NASH and IS vs. NASH. The comparison of patients with NAFLD and patients with normal histopathology of the liver revealed that the first group had significantly higher levels of hsCRP: 7.95(3.63) vs. 4.75(1.48); P = 0.045 and HbA1C: 6.07(1.06) vs. 5.40(0.36), P = 0.027. There were no statistically significant differences in the biochemistry test results between the groups: normal and IS. Comparison of the biochemistry test results between the group of patients with steatohepatitis and the group of patients with normal histopathology of the liver showed significantly higher levels of ALT: 43.00(22.30) vs. 23.83(8.68), P = 0.028, hsCRP: 9.65(2.34) vs. 4.75(1.48), P = 0.001 and HbA1C: 5.90(0.29) vs. 5.40(0.36), P = 0.019. Within the group of patients with liver disorders, patients with hepatitis had significantly higher levels of AST: 29.50(10.64) vs. 19.88(6.18), P = 0.044 and hsCRP 9.65(2.34) vs. 5.82(3.96), P = 0.026, and significantly lower levels of triglycerides 113.30(35.38) vs. 170.38(54.01), P = 0.025. Re-evaluation performed after the treatment showed a decrease in all biochemical parameters in all groups.

The analysis of area under ROC curve revealed significantly higher risk of remarkably increased hsCRP levels in patients with the diagnosis of NASH compared to patients without NASH (AUC = 0.879, P = 0.002). This correlation disappears when the required excess weight loss is achieved (AUC = 0.486, P = 0.91) (Figure 1). It was demonstrated that in the group of patients with NASH, hsCRP levels significantly more often exceed 7.3 mg/L (chi-square = 10.971; df = 1, P = 0.001). At the same time, the risk of NASH significantly increases when hsCRP level is 7.3 mg/L or higher (OR = 33; 95%CI = 2.91 – 374.33; P = 0.005).

hsCRP levels can be used to identify obese patients with increased risk of NAFLD. hsCRP may be also used as a marker of regression of hepatitis in patients during excess
weight loss. Bariatric surgery help to achieve sustained weight loss without the risk of worsening liver histopathology. Steatosis and inflammation in the course of NAFLD are reversible.

All authors declared no conflict of interests

% EBMIL - % excess body mass index loss

%EWL - % excess body weight loss

NAFLD - non-alcoholic fatty liver disease

NASH - non-alcoholic steatohepatitis

Contribution statement: Study Design A, Data Collection B, Statistical Analysis C, Data Interpretation D, Manuscript Preparation E, Literature Search F,

Paweł Ziemianski: A, B, C, D, E, F

Justyna Domienik-Karłowicz: A, B, E, F

Radosław Cylke: B, D, F

Piotr Pruszczyk: A, B

Maciej Kosieradzki: A, B, C, D, E, F

Wojciech Lisik: A, B, C, D, E, F

Uncategorized References

Table 1. Anthropometric parameters of the study group at three points: 0, 12 and “E”; mean(SD).

<table>
<thead>
<tr>
<th></th>
<th>Start of the treatment („0”)</th>
<th>12 months („12”)</th>
<th>End of follow-up („E”)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>137.63(22.05)</td>
<td>96.19(17.63)</td>
<td>87.11(15.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>49.29(6.17)</td>
<td>34.48(5.98)</td>
<td>31.11(4.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>66.08(14.90)</td>
<td>35.41(11.63)</td>
<td>29.30(9.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat percentage, %</td>
<td>47.87(5.58)</td>
<td>36.20(7.74)</td>
<td>33.06(8.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat free mass, kg</td>
<td>71.32(12.72)</td>
<td>60.78(10.54)</td>
<td>57.81(10.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total body water, kg</td>
<td>52.28(9.40)</td>
<td>44.49(7.71)</td>
<td>42.10(6.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>