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Original research article

TGF-β and inflammatory blood markers in prediction of intraperitoneal adhesions

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ABSTRACT

Purpose: Intraperitoneal adhesions (IA) develop as a consequence of the healing process in peritoneum injured during surgeries. IA might be formed after all types of surgical interventions regardless the surgical approach with a higher incidence in obese individuals. Here we determine the diagnostic power of TGF-β and blood inflammatory parameters in the prediction of IA in obese patients undergoing second surgical intervention.

Materials and methods: Eighty patients were divided into groups according to body mass index (BMI) values and presence of intraperitoneal adhesions (IA). Evaluation of peritoneal adhesion index (PAI), serum TGF-β and blood inflammatory parameters was performed.

Results: Level of TGF-β, C-reactive protein (CRP), leukocytes, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio were significantly higher in obese patients while TGF-β, CRP, and leukocytes were higher in patients with IA. There was a significant correlation between PAI values and TGF-β concentration ($p < 0.001$; $r = 0.869$) in IA group.

Conclusions: The preoperative TGF-β concentration, BMI, CRP and NLR could be strong predictors of intraperitoneal adhesions in patients with the history of surgeries.

1. Introduction

Intraperitoneal adhesions (IA) develop as a consequence of the healing process in peritoneum injured during surgeries. IA might be formed after all types of surgical interventions regardless the surgical approach [1]. The presence of IA might lead to perioperative as well as postoperative complication including accidental abdominal viscera injuries, longer duration of surgery, chronic abdominopelvic pain, intestinal obstruction, and infertility [2,3].

Peritoneum repair involves a various process e.g. inflammation, angiogenesis, cell migration and adhesion [4]. These interactions are controlled by cytokines and growth factors secreted by mesothelial cells and migrated macrophages [5]. Among many cytokines transforming growth factor-β (TGF-β) has been documented to be associated with IA development [6]. Increased secretion of TGF-β due to tissue injury alters the adhesive properties of cells, expression of integrins, cytoskeletal proteins and induces migration of fibroblasts [6,7].

IA development could be altered by excessive mass of adipose tissue. Low-grade inflammation accompanies obesity. Increased level of numerous inflammatory chemicals including, e.g. C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-1), tumor necrosis factor-α (TNF-α), TGF-β, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), might stimulate the formation IA [8–10].

The aim of the research is an evaluation of the inflammatory markers: TGF-β, WBC, CRP, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio between obese and non-obese patients with the history of abdominopelvic surgical intervention who underwent elective surgeries. Additionally, we aim to assess the diagnostic power of the preoperative value of TGF-β and selected inflammatory blood parameters in the prediction of intraperitoneal adhesions.

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2. Materials and methods

The study enrolled eighty patients admitted to the General, Oncological and Minimally Invasive Surgery Department of the 1 st Military Clinical Hospital in Lublin, Poland for scheduled laparoscopic cholecystectomy, laparoscopic sleeve gastrectomy, transabdominal preperitoneal (TAPP) hernia repair or anterior abdominal wall hernia repair (IPOM). The same team of surgeons operated on all the patients. No complications were reported during the surgeries, and no malignancies were reported in the pathological examination of the removed gallbladders and stomach. The patients included in the study had the history of the abdominopelvic surgery: open or laparoscopic cholecystectomy (n = 10 and n = 32, respectively), laparoscopic inguinal hernia repair (n = 9), open or laparoscopic appendectomy (n = 15 and n = 24, respectively). Patients with symptoms of inflammation (clinical or biochemical) at the hospital admission were excluded from the study. Exclusion criteria also included acute cholecystitis due to gallbladder stones, diabetes, connective tissue disorders, varicose veins, and cigarette smoking. The presence of intraperitoneal adhesions was reported during the surgery and classified according to Coccolini et al. [11]. Patients were informed about the aim of the study and signed written consent forms before the study. The Ethical Committee of the Medical University of Lublin in Poland approved the study (decision no KE-0254/240/2008).

Blood samples were obtained before the surgery. The blood serum was collected, and the level of TGF-β was determined using ELISA kit. Demographics and laboratory values of blood tests were extracted from the hospital medical database records. The evaluation of blood parameters was performed within 1 h after venipuncture. The hematological parameters evaluated in the study: CRP, WBC, platelets, neutrophil, and lymphocyte were measured by ABX Pentra XL 80 (Horiba Medical). Normal values for studied blood parameters (according to our laboratory) ranged as follows: CRP: 0.0–5.0 mg/l, platelets: 150–400 $\times 10^9$/l, WBC: 4.0-10.0 $\times 10^9$/l, neutrophil: 2.0–8.0 $\times 10^9$/l, and lymphocyte: 2.0–4.8 $\times 10^9$/l.

Patients were divided into groups according to (i) body mass index (BMI) values and (ii) presence of intraperitoneal adhesions (IA). First, BMI classification included two groups: non-obese group (normal weight patients, BMI values less or equal 25 kg/m2) consisted of 40 patients (male:female, M:F = 22:18) and obese group (obese patients, with BMI values, equal or above 30 kg/m2) consisted of 40 patients (M:F = 23:17). Second patients' classification included two groups: group IA consisted of 38 patients in whom IA was reported, and group no-IA enrolled 42 patients without IA.

Statistical analysis was performed using 16.0 SPSS software. Differences between the study groups were accessed using Mann-Whitney *U* test and correlations with Spearman's test. Receiver-operating characteristics (ROC) curve analysis was performed to identify cut-off values of studied parameters. Differences of $p < 0.05$ were considered to be significant.

3. Results

Forty obese and forty non-obese patients were enrolled in the study. The demographics, serum concentration of TGF-β, and laboratory blood parameters of two BMI groups are shown in Table 1. The age and gender distribution did not differ significantly between the studied groups.

The mean value of BMI, TGF-β, CPR, and WBC was significantly higher in obese patients compared to the non-obese group. Nevertheless, NLR and PLR were higher in obese than in the non-obese patients, the difference was not significant.

IA adhesions were reported in 47.5% of the total patients' population and were present statistically more often in the obese than in the non-obese group (72.5% vs. 22,5%, respectively). The mean peritoneal adhesion index (PAI) in IA group was 4.33 ± 2.10 (min.–max. = 1.00–9.00). No statistically significant differences in PAI were observed between obese and non-obese groups.

The number of patients with adhesions in nine regions of the abdominopelvic cavity was presented in Table 2.

Total patients' population was divided according to the presence of IA (Table 3). The mean value of BMI, TGF-β, CPR, and NLP was significantly higher in patients with IA in comparison to non-IA patients group. The mean value of WBC and PLR did not differ significantly between the studied groups.

ROC analysis was performed on parameters which show significant difference when comparing IA and no IA groups. The ideal cut-off value of BMI was 32.13 kg/m^2 (AUC: 0.731, sensitivity: 61.1%, specificity: 84.2%). The cut-off value of CRP and NLR was 4.12 mg/l (AUC: 0.685, sensitivity: 65.9%, specificity: 73.3%) and 2.36 (AUC: 0.597, sensitivity: 54.7%, specificity 75.2%), respectively. The cut-off value of TGF-β was 37637.15 as the (AUC: 0.769, sensitivity: 72.2%, specificity: 68.4%).

Therefore, the patients with IA were divided into low and high groups according to the cut-off values of BMI, TGF-β, CPR, and NLR (Table 4). The mean value of PAI was significantly higher in high compared to the low TGF-β group.

There was a significant correlation between PAI values and TGF-β concentration ($p < 0.001$; $r = 0.869$) in IA group. No significant correlations were observed between PAI value and BMI, WBC, CRP, NLR, and PLR values.

4. Discussion

Numerous surgical procedures using minimally invasive techniques are performed each day. Therefore preoperative knowledge of IA presence would be essential and might limit the ratio of complication or procedure conversions from laparoscopic into open technique [12–14]. Although few studies have attempted to evaluate the occurrence of potential difficulties preoperatively using ultrasonography (US) still there is a need to discover biomarkers for predicting e.g. intraperitoneal adhesions prior the surgical intervention [15,16].

According to our best knowledge, our study is probably the first attempting to evaluate diagnostic power of body mass index and inflammatory blood parameters values as potential biomarkers of intraperitoneal adhesions in patients undergoing surgeries. We evaluated the correlation between body mass index, TGF-β, four routinely measured hematological parameters and the occurrence of IA.

Table 1
Demographics, values of TGF-β, and blood parameters of the study groups according to the BMI value.

	Obese group (n = 40)	Non-obese group (n = 40)	P-value
Age (years)	63.57 ± 7.92	61.24 ± 9.34	0.511
Gender (M:F)	22:18	23:17	0.408
BMI (kg/m^2)	34.54 ± 3,46	22.70 ± 1.84	<0.001
IA (n)	29	9	0.039
TGF-β	46387.39 ± 17571.59	32888.23 ± 15520.15	0.017
CRP (mg/l)	5.88 ± 1.91	3.23 ± 0.74	0.033
WBC (x 10^9/l)	7.22 ± 2.30	5.85 ± 1.56	0.013
NLR	2.28 ± 1.01	2.17 ± 0.82	0.096
PLR	145.75 ± 46.93	139.12 ± 38.46	0.109

Age, BMI, TGF-β and laboratory values of blood parameters are expressed as mean ± SD.
BMI: body mass index, IA: intraperitoneal adhesions; TGF-β: transforming growth factor-β, CRP: C-reactive protein, WBC: white blood cell, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio.