Early changes in serum visfatin after abdominal surgery: a new pro-inflammatory marker in diagnosis?

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Background. Visfatin is an adipocytokine produced primarily by visceral adipose tissue. In addition to its effect on the insulin receptor, it is a proinflammmatory cytokine with accumulating evidence for its rise in circulation, accompanying systemic inflammation. The aim of this study was to evaluate changes in serum visfatin levels in the early post-abdominal surgery period with serum levels of other proinflammatory cytokines, to determine whether it could be used as a marker of inflammation.

Methods and Results. This was a prospective cross-sectional study of 42 patients undergoing elective laparotomic right hemicolectomy for adenocarcinoma colon. The parameters determined were visfatin, leptin, adiponectin, TNF α, interleukin-6 and C-reactive protein levels. The dynamics of change in these markers were assessed at +12, +24, +48, and +72 h after surgery. Serum levels of visfatin peaked as early as 24 h post-surgery, returning to normal after 72 h. TNF α and IL-6 levels reached their maximum 12 to 24 h later while CRP levels peaked after 72 h.

Conclusions. Significantly increased serum levels of visfatin detected in the early period after abdominal surgery preceded increase in the levels of other proinflammatory markers including TNF α, IL-6, and CRP. Given its dynamics, visfatin could serve as an early predictor of the development of inflammatory changes in patients undergoing surgery, particularly those with obesity (BMI > 30 kg/m^2).

Key words: visfatin, abdominal surgery, proinflammatory cytokines, visceral obesity

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INTRODUCTION

Visfatin is an adipocytokine produced primarily by visceral adipose tissue and recently characterized in more detail[1]. Its metabolic effects include modulation of insulin by binding to the insulin receptor at a site different from the insulin receptor. Originally, visfatin was characterized as a growth factor for B-cell proliferation called the pre-B cell colony-enhancing factor (PBEF) in lymphocytes. Pre-B cell colony-enhancing factor was subsequently identified as a ubiquitous cytokine present in a variety of cells and tissues such as neutrophil leukocytes, hepatic, cardiac, and muscle tissue[2-5].

In a study by Fukuhara et al., PBEF was referred to as a factor with an insulin-mimetic effect[6]. Visfatin levels may also be affected by a change in body weight, i.e., loss of adipose tissue. In addition, visfatin stimulates interleukin IL-6 and IL-8 expression and has been shown to be associated with oxidative stress parameters.

Visfatin is contained in significant amounts in adipose tissue, predominantly in visceral fat and, hence, is closely associated with visceral obesity. A relationship between obesity, serum levels of visfatin and its mRNA expression as well as between visfatin and BMI has been conclusively documented[7]. While an association with visceral obesity has been confirmed, this was not the case for subcutaneous fat. Increased circulating visfatin levels have also been documented in metabolic syndrome patients[8,9].

Obesity is associated with changes in adipocytokines production[10,11].

Recent studies have shown that visfatin is also closely related to immune processes and is a major proinflammatory cytokine in a variety of inflammatory processes (e.g., acute inflammation of the lung and sepsis) (ref.[12-14]). In these conditions, adiponectin has antagonistic properties. Increased levels of visfatin have also been shown to correlate with other proinflammatory cytokines such as IL-1, IL-6, and TNF α.

Visfatin has also been investigated in surgical patients. In patients with cholecystolithiasis and subsequent cholecystectomy, visfatin levels were found to be increased in the long term (1 year after surgery) (ref.[15]). Visfatin levels were likewise found to be decreased in patients with decreased BMI and adipose tissue. Following gastroplasty, visfatin levels depended on body weight changes declining in the early postoperative period at 4 months to subsequently increase at the end of 1-year follow-up, correlating with IL-6 levels and plasma insulin concentration[16]. On the other hand, no changes in visfatin levels were documented in a prospective study of 27 morbidly

obese women (BMI > 40 kg/m^2) followed- up for 1 year after biliopancreatic diversion despite a significant fall in BMI (from 46.1± 13.1 to 35.1± 5.7 kg/m^2) (ref.[17]).

A study analyzing 200,000 deaths due to sepsis in the USA, showed that visfatin levels significantly rise in sepsis patients and correlate significantly with the risk of death[18]. These conclusions were also confirmed in experimental studies[19] demonstrating that IL-6 was a regulator of the visfatin gene in 3T3-L1 adipocytes[19].

The issue of early diagnosis of inflammatory changes in the perioperative period has also received attention in the Czech literature. Proinflammatory cytokine monitoring may largely affect the prognosis of patients in terms of early diagnosis of postoperative intraabdominal sepsis[20]. Based on the dynamics of changes in cytokines, it is possible to monitor the balance between proinflammatory cytokines and other regulatory mechanisms critical for the development of an inflammatory process, in particular in at-risk patients[21,22]. Given the above facts, mention should be made of an important study of the adipocytokine, leptin which seems to be a very early marker of postoperative stress in the perioperative period[23].

Our previous study was designed to monitor selected proinflammatory adipose tissue cytokines prior to and after scheduled surgery (laparoscopic cholecystectomy) in patients with various stages of reduction in renal function and obesity[24]. Our study noted a significant increase in the levels of proinflammatory adipocytokines and increased infiltration of immunocompetent cells in obese patients (BMI >30 kg/m^2) compared with non-obese individuals. Decreased visfatin levels were also found in non-obese kidney transplant recipients[25].

The aim of the present study was to test the hypothesis whether and how serum visfatin levels vary in the early perioperative period in relation to the probability of developing infection (a proinflammatory marker) using dynamic temporal perioperative monitoring at 0-12-24-48 and 72 h postop, and whether its dynamics differ from those of other proinflammatory cytokines already used in clinical practice. We also sought to determine whether or not visfatin levels vary in relation to the amount of adipose tissue in the preoperative period. All study patients had elective laparotomic intraabdominal surgery (right hemicolectomy for adenocarcinoma colon). Scheduled abdominal laparotomy was chosen as a model of non-infective inflammatory stimulation of the cytokine cascade, that some authors have suggested may play a major role in the activation of visfatin production.

STUDY PATIENTS AND METHODS

The study was conducted in accord with the principles of the Declaration of Helsinki including the current version of current Good Clinical Practice. The selected therapeutic procedures were consistent with institutional rules. Prior to inclusion, all patients received detailed information and gave their informed consent. The study was carried out at the Department of Surgery, 3rd Faculty of Medicine, Charles University in Prague between 1 January 2010 and 31 August 2013; laboratory investigations were undertaken at the Department of Nephrology of the Transplant Center of the Institute for Clinical and Experimental Medicine and the Institute of Rheumatology, 1st Faculty of Medicine, Charles University in Prague and General University Hospital, all based in Prague, Czech Republic.

Our prospective cross-sectional study included 42 patients having elective laparotomic right hemicolectomy for adenocarcinoma colon. Of these, 21 patients were severely obese with a BMI > 30 kg/m^2, (30.3-35.4 kg/m^2), Group I. Group II was made up of another 21 patients with a BMI < 30 kg/m^2, (24.6-29.1 kg/m^2). As regards co morbidities, 6 Group I patients had type-2 diabetes mellitus, which was also true for 4 patients in Group II. Diabetes mellitus was treated using standard oral hypoglycemic agents and lifestyle modifications. Each group included 7 patients with well-controlled systolic-diastolic hypertension. Patients with surgical intraoperative and postoperative complications were not eligible. All patients had a baseline anthropometric examination 1 day before the procedure and their BMI was calculated. Blood samples for biochemistry were obtained as part of the preoperative examination (time 0) and subsequently at 12, 24, 48, and 72 h upon completion of the procedure. Serum was obtained by centrifugation and samples stored first at –20 °C and then at –70 °C for further analysis.

Serum visfatin was determined by enzyme-linked immunosorbent assay (ELISA) according to the protocol of Bio Vision Research Products, Mountain View, CA, USA. Serum leptin and adiponectin were determined using commercially available ELISA kit (Bio Vendor, Brno, Czech Republic, Linco Research, St Charles, MI, USA). Serum IL-6 and TNF α levels were determined using a human serum adipokine LINCOplex kit (Luminex 200 instrument Linco Research) while serum C-reactive protein (CRP) levels were measured using an ultrasensitive CRP ELISA kit (DSL, Oxon, UK). Other standard biochemical parameters were determined using a device manufactured by Olympus Diagnostica GbmH, Hamburg, Germany. Serum insulin was determined by RIA (Cis Bio Int, Lyon, France), and glycated hemoglobin (HbA_{1c}) by liquid chromatography on a Tosohi HLC-723 G7 system (Shiba, Minato-ku, Tokyo, Japan).

STATISTICAL ANALYSIS

Statistical analysis was performed with Sigmastat software (SPSS Inc, Chicago, IL, USA). Paired and two-sample *t*-tests were used to compare the results of both patient groups. The results were considered statistically significant if $P \leq 0.05$.

RESULTS

Basic clinical and laboratory parameters of both patient groups prior to abdominal surgery are shown in Table 1. The groups did not differ in age, sex ratio, serum creatinine, cholesterol or diastolic BP. There were however, significant differences (P<0.05) in systolic BP, fasting glycemia, and insulin. More marked significant differences (P<0.02) were shown in HbA_{1c} and triglyceride levels. These findings may relate to the significant differences in BMI (P<0.02) between the two groups (33.1 ± 3.4 vs 27.5 ± 3.7 kg/m^2).

The serum levels of selected adipocytokines (visfatin, leptin, adiponectin) and other proinflammatory cytokines (TNF α, IL-6, and CRP) in the preoperative period are shown in Table 2. No significant differences in the preoperative levels of the above cytokines were found except for adiponectin (higher values in Group II) and IL-6 (higher levels in Group I) (both P<0.05).

Table 3 gives the mean values and standard deviations of selected adipocytokines and proinflammatory cytokines in the perioperative period (0 h, +12 h, +24 h, + 48 h, and +72 h post-surgery) in either group. The table also shows the dynamics of changes of individual parameters relative to baseline. It is evident from the table that visfatin levels rose dynamically as early as the early perioperative period (from +12 h onward), more markedly in Group I, and there were significant differences between the groups (P<0.02). In both groups, peak values were reached in the +24 h period (P<0.01); however, again there were differences between the groups (P < 0.01). A slow decline began to occur in the +48h period (P < 0.01), with another decrease in the +72 h period. However, the significant differences between the two groups persisted (P < 0.02), with the values higher in Group I.

An analogous trend for perioperative changes in serum leptin levels was noted (maximum rise in +24 h periods), showing significant changes in the 2 groups, with higher values in Group I. On the other hand, a reverse trend was seen in the dynamics of changes in adiponectin levels, with highest values in both groups preoperatively and a dynamically significant decline beginning with the period +24 h (P<0.02). There were significant differences between the groups, with lower values in Group I. Adiponectin levels correlated inversely with those of the proinflammatory cytokines TNF α and IL-6. TNF α levels were highest in the +24 h periods, and IL-6 in the +48 h period. Serum CRP levels rose gradually peaking in the +72 h period. While significant differences between Groups I and II were shown in the TNF α and IL-6 cytokines, no difference was found for CRP whose values did not differ with respect to BMI.

Fig. 1. presents the dynamics of changes in serum visfatin levels in both groups with a maximum in periods +24 h. An analogous trend is documented in (Fig. 2) showing the dynamics of changes with leptin, also reaching a maximum in periods +24 h. (P<0.01 vs P<0.02). The different dynamics of changes in these adipokines and the classic proinflammatory cytokines TNF α and IL-6 is shown in (Fig. 3 and 4). With both cytokines, but

Table 1. Laboratory parameters in Group I and Group II before surgery.

Parameter	Group I. (n=21) (x±sd)	Group II. (n=21) (x±sd)	Statistical significance (P) Group I. vs Group II.
Age (years)	63±7	62±5	NS
Gender (M/F)	10/11	10/11	NS
BMI (kg/m^2)	33.1±3.4	27.5±3.7	<0.02
Waist circumfer. (cm)	107±5	94±6	<0.02
BP syst./diast. (mmHg)	149±10/94±7	135±8/85±6	<0.05/NS
Creatinine (μmol/L)	104.2±8.5	98.4±8.7	NS
Glycaemia (mmol/L)	6.5±4.2	5.7±3.5	<0.05
HbA_1C (%)	6.3±1.2	5.1±1.4	<0.02
Insulin (pg/mL)	370±38	296±38	<0.05
Cholesterol (mmol/L)	6.1±1.9	5.6±1.6	NS
Triglycerides (mmol/L)	3.9±1.6	3.0±1.1	<0.02

Table 2. Selected adipocytokines and cytokines before surgery in Group I and Group II.

Parameter	Group I. (n=21) (x±sd)	Group II. (n=21) (x±sd)	Statistical significance (P) Group I. vs Group II.
Visfatin (ng/mL)	1.26±0.88	0.95±0.82	NS
Leptin (ng/L)	53.3±10.2	47.3±10.1	NS
Adiponectin (μg/mL)	13.3±6.8	18.9±5.0	<0.05
TNF-α (pg/mL)	9.2±2.2	8.4±4.1	NS
IL-6 (pg/mL)	15.1±4.0	9.1±2.2	<0.05
CRP (ng/L)	16.0±4.3	14.2±4.1	NS

Table 3. Dynamics of selected parameters in Group I and Group II before and after surgery (0-12-24-48-72 h).

Parameter	Visfatin (ng/mL)	Leptin (ng/L)	Adiponectin (μg/mL)	TNF-α (pg/mL)	IL-6 (pg/mL)	CRP (ng/L)
Group I. $_0$	1.26±0.88	53.3±10.2	13.3±6.8	9.2±2.2	15.1±4.2	16±4
Group II. $_0$	0.95±0.82	47.3±10.1	18.9±5.0	8.4±4.1	9.1±2.2	14±4
Stat. significance	NS	NS	*	NS	*	NS
Group I. $_{12}$	+1.88±0.60	+165.4±47.2	12.2±5.3	++49.6±16.8	+25.0±7.1	+23±6
Group II. $_{12}$	+1.42±0.30	+135.4±39.2	17.9±7.1	++52.0±17.9	+24.4±6.5	++19±8
Stat. significance	**	*	*	NS	NS	NS
Group I. $_{24}$	+++3.20±1.15	+++310.7±64.5	7.8±3.6	+++92.3±37.2	+++130.1±60.2	++48±23
Group II. $_{24}$	++2.12±0.88	++218.0±59.0	13.3±6.0	++80.0±39.2	++104.7±48.4	++38±16
Stat. significance	***	**	*	*	*	NS
Group I. $_{48}$	++1.52±0.88	++152.2±79.1	+6.7±2.4	++69.1±25.4	++170.2±68.4	++73±24
Group II. $_{48}$	++1.10±0.40	+80.2±39.1	+8.3±4.0	++67.9±20.0	++120.4±60.1	++66±17
Stat. significance	**	**	NS	NS	*	NS
Group I. $_{72}$	+1.32±0.54	+78.3±20.2	+7.2±3.1	+37.1±9.1	++160.0±70.2	+++90±27
Group II. $_{72}$	1.01±0.26	62.1±16.9	+9.9±4.7	+27.1±9.0	++80.3±33.7	++71±12
Stat. significance	*	*	NS	*	**	*

Statistical significance Group I vs Group II in all periods
NS non significant, * P<0.05, ** P<0.02, *** P<0.01

Statistical significance of parameters in Group I and Group II in periods 12-24-48-72 h compared to values before surgery (time 0)
+ P<0.05, ++ P<0.02, +++ P<0.01

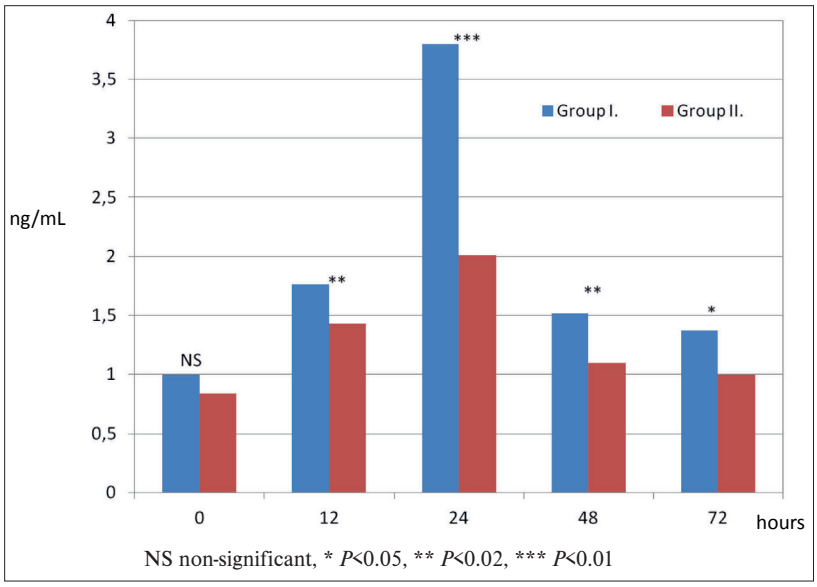

Fig. 1. Serum visfatin before and after surgery in Group I and Group II (mean values).

with IL-6 in particular, the maximum increase is shifted to the later time periods, primarily +48 h with IL-6. These increased levels persisted longer, even in periods +72 h. Different dynamics of change were noted with the typical marker of bacterial infection, CRP. Fig. 5. shows levels increasing with time, simultaneously in both groups, regardless of difference in BMI. The highest values were reached in the last period, +72 h.

The changes in visfatin compared with other proinflammatory cytokines investigated, the highest regression coefficient of leptin was found in the +24 h period (r=0.45; P<0.02), whereas the correlations with the other inflammatory markers (TNF α and IL-6) were (r=0.32 and r=0.20, respectively; P<0.05). The relation to CRP was not significant as was that to adiponectin in our study.

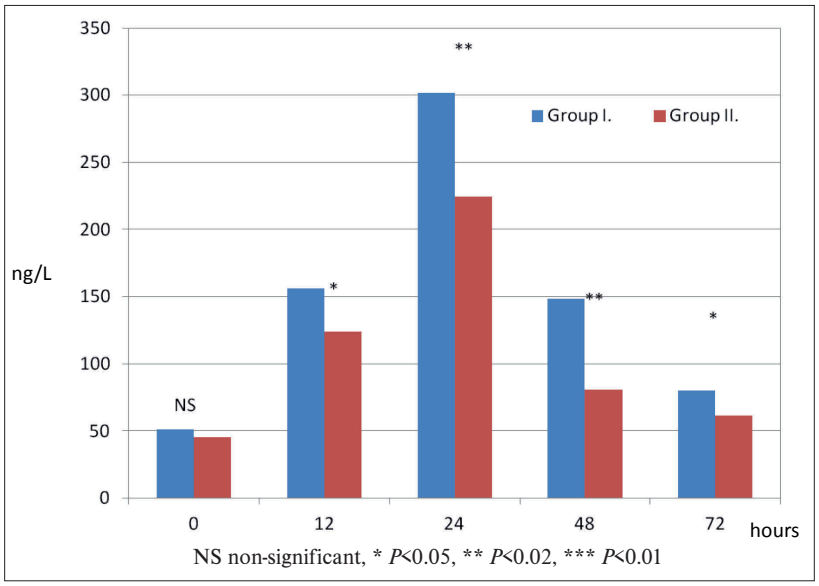

Fig. 2. Serum leptin before and after surgery in Group I and Group II (mean values).

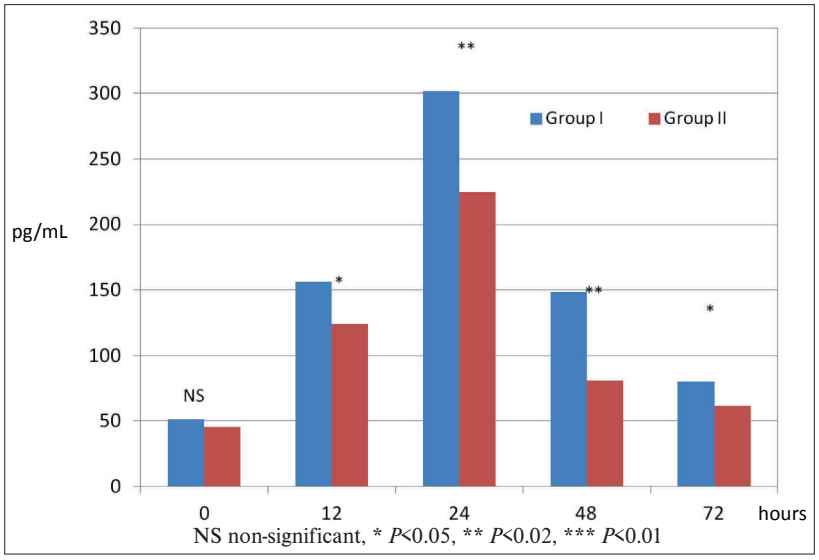

Fig. 3. Serum TNF-α before and after surgery in Group I and Group II (mean values).

DISCUSSION

The response of the body to surgical stress is characterized by a variety of inflammatory, hormonal, and metabolic changes, which altogether produce the picture of an acute phase reaction[5]. The stress-producing stimulus of surgery inducing the release of a number of hormones (ACTH, cortisol, ADH, etc.) and proinflammatory cytokines (e.g., TNF α and IL-6) stimulates the system to produce acute phase proteins in the liver, muscle catabolism, thermogenesis, and numerous other metabolic, psychological, and immunological responses[22].

The initiation, course and prognosis of the systemic inflammatory response to surgery thus depends on the interaction of proinflammatory and anti-inflammatory cytokines and other soluble and membrane mediators. Adipose tissue represents an important endocrine organ producing an array of hormones and cytokines including proinflammatory ones (e.g., TNF α and IL-6 among others). In obese patients, the rate of production of proinflammatory cytokines is generally higher, which may significantly interfere with insulin metabolism (insulin resistance). Experimental and clinical studies have demonstrated that adipose tissue is infiltrated with immunocompetent cells, important producers of proinflammatory cytokines.

Visfatin is a relatively new adipocytokine having, in addition to its effect on energy metabolism, a role in innate immunity and inflammation[24]. Recent studies have documented proinflammatory up to tissue-destroying effects , thus identifying it as an acute phase adipocytokine[14]. Our study was designed to investigate also other

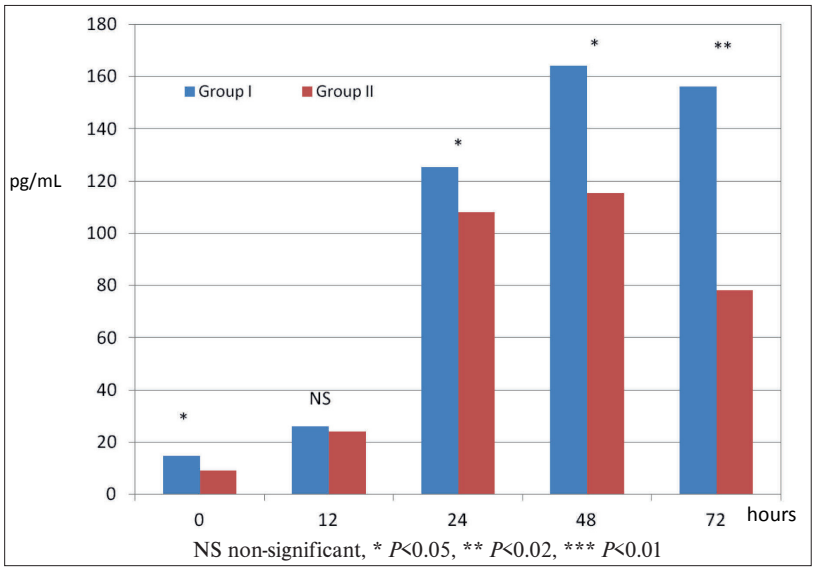

Fig. 4. Serum IL-6 before and after surgery in Group I and Group II (mean values).

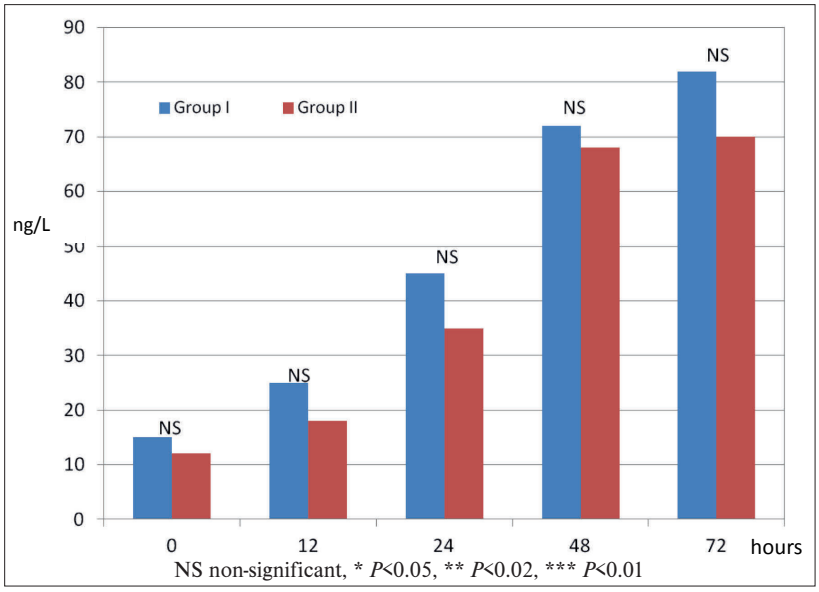

Fig. 5. Serum CRP before and after surgery in Group I and Group II (mean values).

adipocytokines (leptin, resistin, adiponectin) and classic proinflammatory cytokines (TNF α, IL-6, and CRP). The follow-up period (0 h, +12 h, +24 h, +48 h, and +72 h) is consistent with the dynamics of cytokine expression in the early postoperative period. Investigations of clinical and laboratory inflammatory demonstrated only marginal differences in both of our groups – higher values of fasting glucose, levels of insulin, triglycerides, and BP in Group I with BMI 33.1±3.4 kg/m^2; P<0.05. There is little doubt this finding is related to the presence of higher amounts of visceral fat and insulin resistance. The higher proportion of adipose tissue also seems to be related with the not high, yet significantly higher levels of IL-6 and the decrease in adiponectin levels in the preoperative period in Group I.

The early postoperative period is associated with a rapid rise in visfatin levels reaching three-fold values within 24 h (P<0.01). This increase can be detected already at 12 h (P<0.02) whereas a gradual decrease does not occur until 48 h (P<0.02) to be followed by a return to a non-significant increase at 72 h. Throughout our study, there were significant differences between the two groups, with Group II with BMI 27.5±3.7 kg/m^2 showing visfatin levels at all time periods, as documented in (Fig. 1). An analogous dynamics of changes was observed when monitoring leptin levels, also peaking as early as 24 h postoperatively (sixfold and fourfold increases in Group I and Group II, respectively) (Fig. 2). In the case of visfatin, no relevant experimental and clinical data relating directly to the surgical procedure are available. With leptin, it has been shown that, in the early postoperative period, surgical stress results in a transient elevation in leptin whose levels subsequently correlates with those of the proinflammatory cytokines IL-6 and TNF α, albeit with an earlier onset of changes[23]. As our study documented

analogous temporal dynamics of changes in visfatin and leptin, with a documented significant positive correlation (r=0.43; $P<0.02$), one may be speculate about analogous expression (both in time and quantity) of both adipose tissue adipocytokines in the early perioperative period. At the same time, we confirmed a perioperative increase in the proinflammatory cytokines TNF α and IL-6 with a maximum of changes in the later period. C-reactive protein showed a markedly delayed dynamics, with relatively high values persisting even after study completion. The levels of the "protective" adiponectin were highest prior to the onset of surgical stress to subsequently decline with inter-group differences of borderline significance.

The reported findings of dynamics of the two investigated cytokines (early increase) are most important as, when compared with the dynamics of changes of the "classic" proinflammatory cytokines, the changes were observed later and differences in the inflammatory response were not related to the amount of adipose tissue. As a result, serum visfatin monitoring could serve as an early marker of inflammatory changes in the perioperative period also indicating an increased risk of expression of inflammatory cytokines in connection with the present visceral adipose tissue (unlike leptin, visfatin is expressed by visceral adipose tissue). In the setting of inflammatory complications, CRP-based diagnosis could be delayed by as long as 48 h compared with early diagnosis using selected adipocytokines, and visfatin in particular. However, its predictive value in terms of a longer-term inflammatory response is yet to be established.

The present study may have several limitations, most importantly due to its selected groups of patients. As one of more accurate anthropometric examination to predict the amount of visceral fat was additionally performed measurement of body waist circumference (BMI could be inaccurate measure in this respect). Other potential limitations may include pre- and post-operative management of diabetes or hyperglycemia,as insulin and visfatin share one receptor, with the implication insulin may directly affect visfatin levels, but however, maximum short-term insulin dose used in one case was of 20 U/day and fasting glycaemia and glycated Hb were tightly controlled.

CONCLUSION

Our study documented significantly increased levels of the adiponectin visfatin, which correlated with leptin levels and were higher in the group of patients with higher BMI (visceral obesity) in the early postoperative period after abdominal surgery. The levels began to gradually decrease gradually after 72 h. The postoperative rise in classic proinflammatory cytokines (TNF α and IL-6) was delayed by 24-48 h. The dynamics of increasing CRP levels was gradual with an increase persisting at the last examination at 72 h, without a significant difference between the two groups.

Given its dynamics, visfatin may serve as an important predictor of early inflammatory changes in patients after abdominal surgery, particular in those with visceral obesity.

ABBREVIATIONS

ACTH, Adrenocorticotropic hormone; ADH, Antidiuretic hormone; BMI, Body mass index; CRP, C-reactive protein; DM, Diabetes mellitus; IL-1, Interleukin 1; IL-6, Interleukin 6; IL-8, Interleukin 8; IL-10, Interleukin 10; NAG, Nicotinamide adenin dinucleotide; TNF α, Tumor necrotis factor alpha.

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Author contributions: VT: literature search; VT, RG: manuscript writing; RG, VT: study design; VT, MS: data collection; VT, LS, HH, MS, RG: data analysis; VT, RG, LS, HH: data interpretation; VT, RG: statistical analysis, figures; VT, RG: final approval.

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