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☏ +381 11 4092 776, Fax: +381 11 3348 653
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Dušan Micić[1,2,♣], Snežana Polovina[3], Zlatibor Lončar[1,2], Krstina Doklestić[1,2], Pavle Gregorić[1,2], Vladimir Arsenijević[1,2], Miljan Ćeranić[1,2], Dragan Micić[4], Nenad Ivančević[1,2]

Insulin sensitivity and C-reactive protein levels after laparoscopic and open cholecystectomy – seven days follow-up

Инсулинска сензитивност и вредности Ц реактивног протеина после лапароскопске и отворене холецистектомије у току првих седам постоперативних дана

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]University Clinical Center of Serbia, Clinic for Emergency Surgery, Emergency Center, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Clinic for Endocrinology, Diabetes, and Diseases of Metabolism, Belgrade, Serbia;
[4]Serbian Academy of Sciences and Arts, Department of Medical Sciences, Belgrade, Serbia

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♣Correspondence to:
Dušan MICIĆ
University Clinical Center of Serbia, Clinic for Emergency Surgery, Emergency Center, Pasterova 2, 11000 Belgrade, Serbia
E-mail: ducamicic@yahoo.com

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SUMMARY

Introduction/Objective The development of acute insulin resistance after surgery intervention is associated with the type and magnitude of operation and tissue injury.

The aim of our study was to compare insulin sensitivity assessed by homeostatic model assessment of insulin resistance (HOMA-IR) and C-reactive protein (CRP) before and after laparoscopic and open cholecystectomy during seven days follow-up.

Methods In total, 92 patients were divided into two groups: laparoscopic cholecystectomy (Group 1) (n = 61) and open cholecystectomy (Group 2) (n = 31). Glucose, insulin and CRP levels were measured at day 0 and one, three and seven days postoperatively. Glucose, insulin and CRP were determined using commercial assay on Roche Cobas 6000 automated analyzer (Roche Diagnostics, Manheim, Germany).

Results There was no statistical difference between studied groups concerning age (p = 0.626), BMI (p = 0.548), glucose (p = 0.947), insulin (p = 0.212), HOMA-IR (p = 0.390) and CRP (p = 0.546) at day 0. At day one, higher values of CRP were found in group 2 compared with group 1 (p = 0,046). At day three, significantly higher values of glucose and HOMA-IR were found in group 2 compared with group 1 (p = 0.025, p = 0.036, respectively).

Conclusion Increase in CRP precedes deterioration of insulin sensitivity measured by HOMA-IR after cholecystectomy. Impairment of insulin sensitivity was more pronounced at third postoperative day in group with open cholecystectomy. On the basis of our results, laparoscopic cholecystectomy induced less impairment in insulin sensitivity and lower inflammatory response.

Key words: HOMA-IR; CRP; laparoscopic cholecystectomy; open cholecystectomy

САЖЕТАК

Увод/Циљ Развој акутне инсулинске резистенције после хируршке интервенције је повезан са типом и величином операције и оштећења ткива. Циљ наше студије је поредјење инсулинске сензитивности процењене применом хомеостатског модела за процену инсулинске резистенције (ХОМА-ИР) и Ц реактивног протеина (ЦРП) пре и после лапараскопске и отворене холецистектомије током првих седам постоперативних дана.

Методе Испитано је 22 болесника који су подељени у две групе: група са лапараскопском холецистектомијом (Група 1) (н = 61) и група са отвореном холецистектомијом (Група 2) (н = 31). Гликемија, инсулин и ЦРП су мерени у дану 0 и постоперативно у првом, трећем и седмом дану. Гликемија, инсулин и ЦРП су одредјивани коришћењем комерцијалног прибора на *Roche Cobas* 6000 аутоматском анализатору (*Roche Diagnostics*, Манхајм, Немачка).

Резултати Није било статистички значајне разлике измедју испитиваних група у погледу старости ($p = 0.626$), индекса телесне масе ($p = 0.548$), гликемије ($p = 0.947$), инсулина ($p = 0.212$), ХОМА-ИР ($p = 0.390$) и ЦРП ($p = 0.546$) у нултом дану. Првог дана, више вредности ЦРП су надјене у групи 2 у поређењу са групом 1 ($p = 0,046$). Трећег дана, сигнификантно више вредности гликемије и ХОМА-ИР су нађене у групи 2 у поређењу са групом 1 ($p = 0.025$, $p = 0.036$, респективно).

Закључак Повишење ЦРП претходи погоршању инсулинске сензитивности измереном помоћу ХОМА-ИР после холецистектомије. Оштећење инсулинске сензитивности је било више наглашено трећег постоперативног дана у групи са отвореном холецистектомијом. На основу наших резултата, лапараскопска холецистектомија изазива мање оштећење инсулинске сензитивности и нижи инфламаторни одговор.

Кључне речи: ХОМА-ИР; ЦРП; лапараскопска холецистектомија; отворена холецистектомија

INTRODUCTION

Development of perioperative hyperglycemia during surgery may result in appearance of

insulin resistance [1]. Insulin resistance development during perioperative period may induce complications in major abdominal surgery [2]. It was shown that cholecystectomy may result in variety of metabolic changes [3].

Definition of postoperative insulin resistance is an effect of insulin below normal for the effect of insulin for glucose, protein, and/or fat metabolism in the period after the operation [4]. Acute insulin resistance development after elective surgery depends on the type and magnitude of operation and tissue injury [5, 6, 7]. It was observed that the increase in blood glucose after operation starts simultaneously with the decrease in peripheral glucose uptake due to development of insulin resistance [8]. Such postoperatively developed insulin resistance is temporary phenomenon and last approximately for at least 5 days after uncomplicated open cholecystectomy. After that period insulin sensitivity normalizes with the recovery of the patient [9]. Homeostatic model assessment of insulin resistance (HOMA-IR) is frequently employed method in everyday practice because of its convenience [10, 7]. HOMA-IR method has been used from practical standpoints as an alternative to the hyperinsulinemic normoglycemic clamp in studies of surgery induced insulin resistance which is established as a gold standard for the measurement of insulin resistance [2, 11]. Determination of insulin sensitivity by HOMA IR was therefore accepted as a simple and inexpensive alternative to more sophisticated techniques in the evaluation of in vivo insulin sensitivity in humans [12, 7]. A direct positive correlation between the concentrations of C-reactive protein (CRP) and the severity of postoperative inflammation was demonstrated [13, 14] as well as evidence about link between inflammation and insulin resistance [15, 16]. Hence, the aim of our study was to measure insulin sensitivity by HOMA-IR and CRP in a group of our patients after laparoscopic and open cholecystectomy in early perioperative period.

METHODS

The non-randomized, prospective study on 92 patients with cholecystectomy was conducted in Clinic for Emergency Surgery in University Clinical Center of Serbia in Belgrade. Exclusion criteria were known diabetes Type I or II, liver, renal (serum creatinine over 150 mol/l) or heart failure, mental diseases, malignancy and severe infection. All the patients were divided in two groups: group with laparoscopic cholecystectomy and group with open cholecystectomy. Laparoscopic cholecystectomy was performed in 61 patients (Group 1) and open cholecystectomy in 31 patients (Group 2).

Fasting glucose, insulin and CRP were determined before operation (baseline, day 0) and 1, 3 and 7 days after the operation. Glucose was measured using commercial assay on Roche Cobas 6000 automated analyzer (Roche Diagnostics, Manheim, Germany). Reference range for glucose was 3.9–6.1 mmol/L. The serum C-reactive protein (CRP) concentration was measured using commercial assays on Roche Cobas 6000 automated analyzer. Reference range for CRP was 0–10 mg/L. The serum insulin measurement was done by an electrochemiluminescence immunoassay on Roche Cobas 6000 automated analyzer. Insulin assay has a measurement range of 0.20–1000 μU/ml with a limit of detection of 0.20 μU/ml. The validation of the Roche Insulin assay in our laboratory revealed intra- and inter-assay coefficients of variation between 1% and 4.5%. Reference values for fasting insulin was < 25 μU/L. Homeostatic model assessment-insulin resistance (HOMA-IR) is based on fasting glucose and insulin levels and the index is calculated as follows: HOMA-IR = Go x Io /22.5, where Go= fasting glucose concentration (mmol/L), Io fasting plasma insulin concentration (μU/mL).

Data are expressed as mean ± standard deviation (SD). Student's t test was used for comparison between groups. Non-normally distributed data are presented as median and interquartile range (25^{th}, 75^{th} percentile) and compared by Mann-Whitney U-test. Pearson's

chi-square test was used comparison between groups for data presented as frequencies and percentages. Pearson correlation was used for testing the correlations between the examined variables. General linear model for repeated measures was used for evaluating the changes in measured variables from 0 to the 1st, 3rd and 7th day and changes are presented by boxplot. Statistical analysis was performed using SPSS statistical software (SPSS for Windows, release 21.0, SPPSS, Chicago, IL, USA). In all test, p value < 0.05 was considered to be statistically significant.

The study protocol was approved by Ethics Committee of Faculty of Medicine, University of Belgrade (No 29/IV-11), and all patients gave informed consent to participate in the study.

RESULTS

Baseline anthropometric and laboratory characteristics of this study population are presented in Table 1. There was no statistical difference between studied groups concerning age (p = 0.626), BMI (p = 0.548), glucose (p = 0.947), insulin (p = 0.212), HOMA-IR (p = 0.390) and CRP (p = 0.546) at day 0.

Changes in glucose, insulin, HOMA-IR and CRP during the study period (from day 0 to day 7) are presented in Table 2.

There was significant difference in glucose over time in group 1 (p = 0.017) and group 2 (p < 0.001). In group 1, glucose levels were significantly higher the first day after operation compared with baseline 0 day (p = 0.024), continue to decrease significantly on day 3 and reach its lowest level at day 7, significantly lower than day 1 (p = 0.042). The glucose levels in group 2 follow the same trend, but with more significant increase of glucose the first day after operation (p < 0.001) and decrease of glucose values at day 7 compared with day 1 (p = 0.001).

There was significant difference in insulin over time in group 1 (p < 0.001) and group 2

($p < 0.001$). In group 1, insulin had its highest level at day 1, decreased significantly at day 3 (compared with day1) ($p=0.001$) and finally reached its lowest level at day 7 compared with values measured at day 3 ($p = 0.012$). In group 2, the same trend was noticed: insulin increased significantly after operation compared with values at day 0 (baseline value) ($p < 0.001$), and significantly decrease at day 7 (compared with day 3) ($p < 0.001$).

Changes of HOMA-IR at day 0 and 1, 3 and 7 after laparoscopic and open cholecystectomy are presented at Figure 2. In group 1, HOMA-IR values increased significantly at day 1 compared with day 0 ($p < 0.001$) and significantly decreased at day 7 compared with 3rd day ($p = 0.012$). In group 2, HOMA-IR was significantly higher at day 1 (after operation) compared with baseline and it significantly decrease at day 7 compared with 3rd day ($p < 0.001$).

There is significantly higher values of glucose and HOMA-IR at day 3 ($p = 0.025$, $p = 0.036$, respectively) in group 2 in comparison with group 1.

Changes of CRP at day 0 and 1, 3 and 7 after laparoscopic and open cholecystectomy are presented at Figure 2. CRP increased significantly at day 1, 3 and 7 in comparison with day 0 ($p < 0.001$) in both groups. At day 1, CRP was significantly higher in group 2 (56.0 ± 39.6 vs. 36.0 ± 77.9; $p = 0.046$) in comparison with group 1 (Figure 2).

DISCUSSION

Stress response to surgery depends on the extent of the injury. Insulin resistance during the surgery may be associated with increased inflammation, organ dysfunction and mortality [17, 18]. It was demonstrated that cholecystectomy may increase insulin resistance and diabetes, although mechanisms of connections between cholecystectomy and insulin release and sensitivity are still not clear [19]. It was suggested that abnormal metabolic consequences may be generated by abnormal transintestinal flow of bile acids that produce metabolic signals

that are performed without gallbladder rhythmic function [20].

Insulin resistance develops after surgery as a part of the metabolic response to stress [21]. The degree of insulin resistance is related to the magnitude of operation [10, 22]. Postoperative insulin resistance is mainly developed due to two reasons - perioperative starvation and release of stress hormones and inflammatory cytokines, including CRP among them. Development of insulin resistance among elective surgical patients in modern surgical practice may be harmful since it prolongs recovery and leads to postoperative complications [21, 22]. Earlier published data indicate that the decrease in insulin sensitivity last over 1 week even for after moderate surgical stress [23]. In clinical practice, different methods were used for the measurement of perioperative changes of insulin sensitivity, from simple methods based on fasting plasma glucose and insulin, like HOMA-IR, up to more laborious one like minimal model (iv GTT with frequent sampling of glucose and insulin) up to gold standard for the measurement of insulin sensitivity, like hyperinsulinemic euglycemic clamp [7, 21]. Based on the experience of the investigators and the equipment which they used, different proposals were published - from one that the static simple methods are suitable for clinical studies up to that clamp method is superior to all the others, and that it measures changes in insulin sensitivity, while HOMA-IR measures something other [2, 24]. Previously, it was suggested that HOMA-IR can be used to assess the effects of treatment [25]. It was suggested that HOMA-IR estimates of insulin sensitivity are usually not normally distributed [25]. Our findings confirmed this statement and we used medians with interquartile ranges to present data without normal distribution (Table 1). Our results demonstrated that HOMA-IR, as marker of insulin resistance, significantly increased in a group with open cholecystectomy. Similar results with the increase in insulin resistance in the first day after surgery was demonstrated by others [26]. There was no significant difference in HOMA-IR between day 0 and day 7 ($p > 0.05$). Previous studies have shown that administration of different forms of oral carbohydrate supplementation before the

cholecystectomy resulted in lower values of postoperative HOMA-IR [26, 27]. In a study with a hyperinsulinemic normoglycemic clamp the fall in insulin sensitivity after surgery was lower in patients after laparoscopic cholecystectomy (22 +/- 2%) compared with patients after open cholecystectomy (49 +/- 5%) [28]. Different results were reported concerning postoperative levels of CRP - from lack of significant difference in the CRP levels between open and laparoscopic cholecystectomy [29] to a significantly higher increase in serum CRP levels in patients following open cholecystectomy in comparison to laparoscopic cholecystectomy [13]. Our study indicates that the level of CRP increased significantly during early postoperative period in both groups in comparison with day 0, but significantly higher increase of CRP was established at day 1 in group with open cholecystectomy in comparison with the group with laparoscopic cholecystectomy. This result is consistent with findings of other investigators and support assumption that minimal invasive surgical procedures such as laparoscopic cholecystectomy impairs inflammatory response less [30].

CRP is a protein of acute phase and starts to increase 4-6 hours after tissue trauma and reaches its peak at 48 hours and starts to fall gradually after 72 hours after surgery without complications [16]. In our study CRP increased at first and third days after operation in both groups and gradually falls at day 7. Peak CRP values were achieved in both groups at day 3. CRP peak values were higher in a group with open cholecystectomy. In early postoperative period we observed a decrease in insulin sensitivity, measured through an increase in HOMA-IR index. Values of HOMA-IR were higher in a group with open cholecystectomy than in a group with laparoscopic cholecystectomy, indicating a greater magnitude of surgical trauma. Previously it was shown that insulin resistance during surgical trauma is produced by elevated fatty acid concentration, decreased uptake of glucose in muscled and increased production of glucose in liver. In our study we detected insulin increase in the circulation in both group at day 1 and day 3. Insulin values were higher at respective days (days 1 and 3) in a group where

open cholecystectomy were performed. In our previous investigation we demonstrated a correlation between CRP and HOMA-IR in some surgical operation, indicating a possible interrelation between increase in cytokines impairment in insulin sensitivity [16]. In our study, comparison between open and laparoscopic cholecystectomy demonstrated less postoperative reduction in insulin sensitivity in a group with laparoscopic cholecystectomy. Such findings may indicate that this could be one of factor for faster recovery after laparoscopic cholecystectomy.

CONCLUSIONS

Change in insulin resistance during the early postoperative period after cholecystectomy is one of the most fundamental reactions to injury and stress. Increase in CRP precedes deterioration of insulin sensitivity, indicating the role of inflammation in the development of insulin resistance after surgical procedures. On the basis of our results, laparoscopic cholecystectomy causes less impairment in insulin sensitivity and inflammatory response then open procedure. The use of HOMA-IR may be useful for fast and easy determination of insulin sensitivity changes in perioperative period in abdominal surgery patients. Keeping metabolism under optimal control should be one of the priorities for the benefit of the surgical patients, allowing early implementation of preventive measures against further deterioration of insulin sensitivity.

Conflict of interest: None declared.

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Table 1. Baseline characteristics of studied population

Variable	Group 1 (n = 61)	Group 2 (n = 31)	p
Age*, years	51.2 ± 15	57.5 ± 13.5	0.626
Male sex, n (%)	29 (48%)	16 (52%)	0.712
Body mass index*, kg/m^2	24.6 ± 1.2	24.7 ± 1.7	0.548
Glucose*, mmol/L	4.6 ± 0.91	4.63 ± 0.83	0.947
Insulin**, μU/mL	5.7 (7.7)	6.6 (5.3)	0.212
Homeostatic model assessment of insulin resistance **	1.3 (1.8)	1.2 (1.3)	0.390
High sensitivity C-reactive protein**	8 (9.8)	8 (1)	0.546

*Data are presented as mean ± standard deviation
**Data are presented as median with interquartile range

Table 2. Changes in glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and high sensitivity C-reactive protein (hs-CRP) during follow-up

Variable	Baseline	Day 1	Day 3	Day 7
Glucose*, mmol/L				
Group 1	4.60 ± 0.91	5.10 ± 1.09	4.70 ± 0.99	4.63 ± 0.72
Group 2	4.63 ± 0.83	5.80 ± 1.58	5.23 ± 1.19	4.71 ± 0.56
Insulin, μU/mL**				
Group 1	5.7 (7.7)	10.1 (10.7)	9.8 (4.8)	5.7 (6.2)
Group 2	6.6 (5.3)	12.1 (9)	10.6 (7.7)	6.9 (4.9)
HOMA-IR**				
Group 1	1.3 (1.8)	2.3 (3)	2.0 (1.3)	1.2 (1.4)
Group 2	1.2 (1.3)	2.9 (2.9)	2.2 (1.8)	1.3 (1)
CRP, mg/L**				
Group 1	8 (9.8)	36.0 (77.9)	43.5 (64.4)	23.0 (51.6)
Group 2	8 (1)	56.0 (39.6)	72.1 (55.2)	27.0 (45.0)

Group 1 – laparoscopic cholecystectomy; Group 2 – open cholecystectomy

*Data are presented as mean ± standard deviation

**Data are presented as median with interquartile range

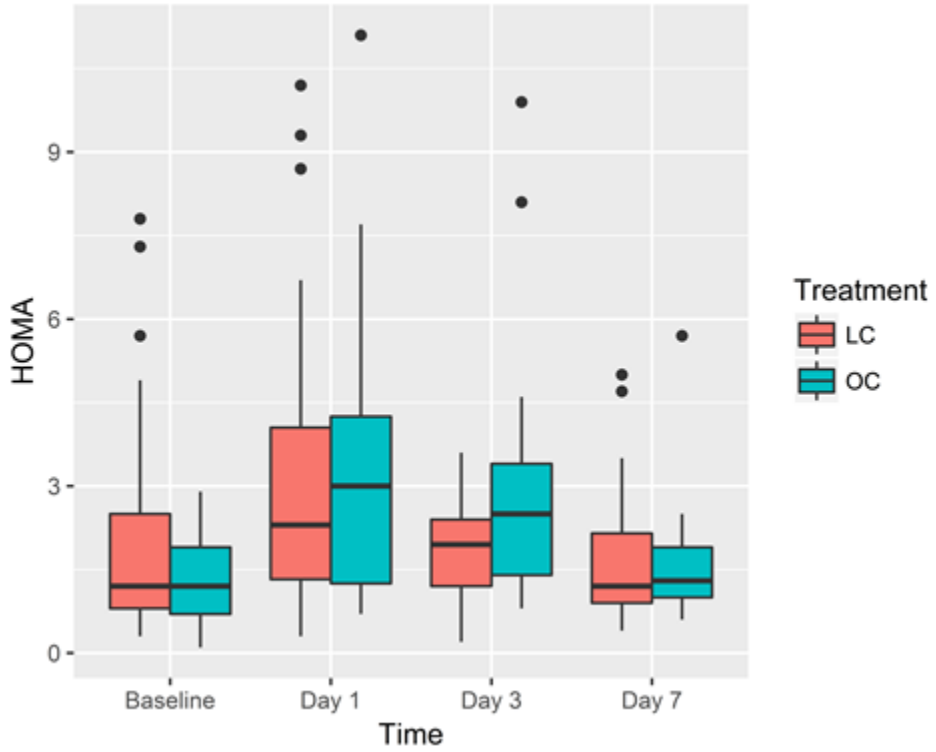

Figure 1. Homeostatic model assessment of insulin resistance (HOMA-IR) at day day zero and one, three, and seven after laparoscopic cholecystectomy (LC) and open cholecystectomy (OC)

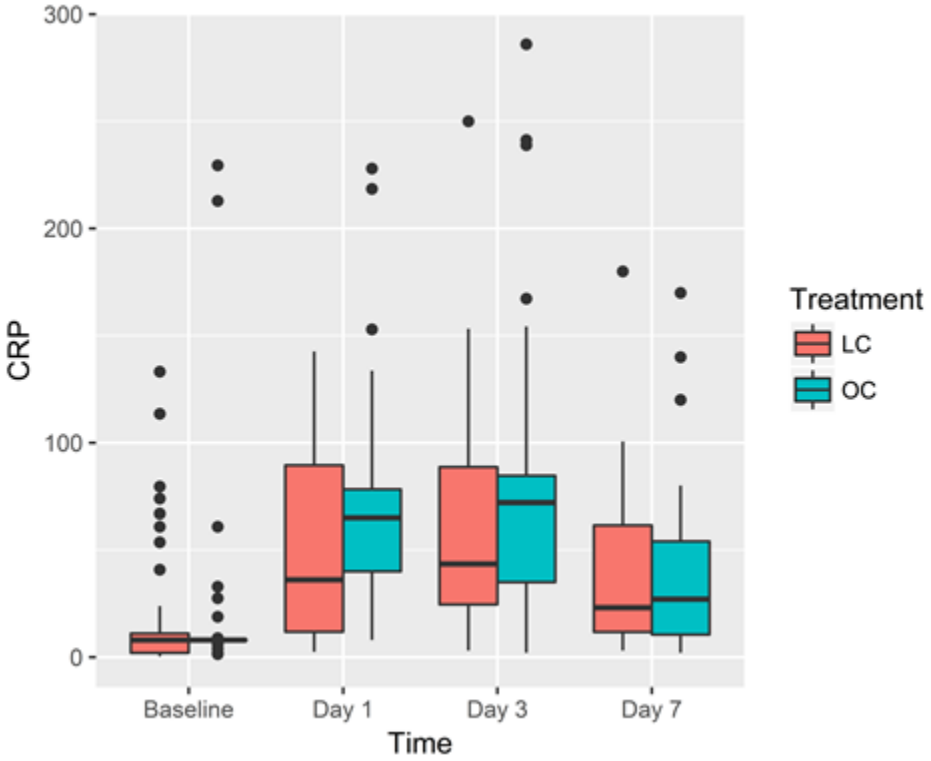

Figure 2. Changes in high sensitivity C-reactive protein (hs-CRP) at day zero and one, three, and seven after laparoscopic cholecystectomy (LC) and open cholecystectomy (OC)

