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SURGERY AND INSULIN RESISTANCE

Sažetak: Hirurška intervencija je veliki stres za ljudski organizam koji izaziva inflamaciju i insulinsku rezistenciju. Insulinska rezistencija se razvija nekoliko sati od početka operacije i dostiže najveći stepen na kraju operacije. Hiperglikemija i insulinska rezistencija su mogući nezavisni uzroci komplikacija u abdominalnoj hirurgiji. Metabolički odgovor na hirurški stres i druge vrste povreda organizma ubrzavaju metabolizam do stanja hipermetabolizma koji pokreće oksidativne procese i ubrzava katabolizam što dovodi do degradacije glikogena, masti i proteina. Inflamatorni odgovor u perioperativnom periodu je zaštitni mehanizam koji pomaže bržem oporavku ali ako je praćen većim inflamatornim odgovorom u opsežnim oštećenjima tkiva može da doprinose razvoju komplikacija i usporenom zarastanju rane. Faktor tumorske nekroze-alfa (TNF- α), Interleukin-6 (IL-6) i C-reaktivni protein (CRP) su glavni regulatori inflamatornog odgovora u akutnoj povredi tkiva. Inflamatorni odgovor posredovan citokinima može da bude jedan od molekularnih okidača metaboličkog odgovora na hirurški stres. Preoperativna insulinska rezistencija koja se javlja kao odgovor organizma na gladovanje doprinosi smanjenom ulasku ugljenih hidrata u tkiva koja su zavisna od priliva glukoze, kao što je mozak.

Summary

Surgical intervention is an extremely high stress for the human body, leading to the occurrence of inflammation and insulin resistance. Insulin resistance is developing a few hours after the start of the operation, and the most pronounced right after

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its completion. Hyperglycemia and insulin resistance were recognized as a possible independent cause of complications in major abdominal surgery. Metabolic response to surgery or other types of trauma accelerating metabolism to the state of hypermetabolism, which implies an increase in oxidative processes and the acceleration of catabolic reactions, resulting in increased degradation of glycogen, fat and protein. Inflammatory response of the body in perioperative period is a protective mechanism which promotes better recovery, while excessive inflammatory response in severe tissue injury could contribute to development of complications and impaired wound healing. Tumor necrosis factor- α (TNF- α), Interleukin-6 (IL-6) and C- Reactive Protein (CRP) are, among the others, major regulators of the acute phase response to inflammation and tissue injury. Inflammatory response that is mediated by cytokines could be one of the molecular triggers for the metabolic response to surgery. Preoperatively reported insulin resistance, as a response to the starvation, in situations when food intake is reduced, insulin resistance is developed to provide limited supplies of carbohydrates used in tissues which depend of glucose intake, such as brain.

Introduction

Metabolic and inflammatory response is a part of overall stress response on surgical trauma and magnitude of this response depends of severity of the tissue damage (1). Surgical stress develops before, during and after the operation as a result of psychological reaction, tissue injury, anesthetic agents and impaired local circulation (2,3). Surgical intervention is an extremely high stress for the human body, leading to the occurrence of inflammation and insulin resistance. There are several definition of insulin resistance. According to one definition, it is about a condition in which a normal amount of insulin leads to a subnormal biological response (4). Another definition is that insulin resistance is the clinical condition in which normal or elevated insulin levels lead to attenuated biological response (5). According to the definition based on clinical experience, insulin resistance is a condition in which there is a need for the application of 200 or more unit of insulin daily to achieve glycemic control and prevented ketosis. Insulin resistance is developing a few hours after the start of the operation, and the most pronounced right after its completion. Hyperglycemia and insulin resistance were recognized as a possible independent cause of complications in major abdominal surgery (6). The state of acute insulin resistance after elective surgery is associated with the type and magnitude of operation and tissue injury (7,8). Increase in blood glucose after surgery starts simultaneously with the decrease in peripheral glucose uptake (1). Acute, postoperatively developed insulin resistance is temporary phenomenon and last, with large individual variation, for at least 5 days after uncomplicated open cholecystectomy after which insulin sensitivity normalizes with the recovery of the patient (9). Homeostatic model assessment of insulin resistance

(HOMA-IR) is frequently employed in daily practice because of its convenience (10). HOMA-IR has been used as an alternative to the hyperinsulinemic normoglycaemic clamp in studies of surgery induced insulin resistance which is considered as a gold standard (6). Assessment of insulin sensitivity by HOMA IR was proposed as a simple and inexpensive alternative to more sophisticated techniques in the evaluation of in vivo insulin sensitivity in humans (11). A direct positive correlation between the concentrations of C-reactive protein (CRP) and the severity of postoperative inflammation was proposed (12, 13) as well as evidence about link between inflammation and insulin resistance (14).

Mechanism of development insulin resistance during the operation

Metabolic response to surgery or other types of trauma accelerating metabolism to the state of hypermetabolism, which implies an increase in oxidative processes and the acceleration of catabolic reactions, resulting in increased degradation of glycogen, fat and protein. In the perioperative period, the level of insulin in plasma is often elevated, and the blood glucose level is increased while the insulin / glucose ratio decreases. The result is an increase of gluconeogenesis. The reduction of glucose / insulin ratio is releasing of stress hormones (catecholamines, cortisol and glucagon), as well as the release of cytokines from the side injured tissues (15).

Insulin stimulates the absorption of glucose in insulin sensitive tissues and thereby reduces the release of glucose from the liver. Apart from the liver, insulin is also susceptible to the other two main tissues - skeletal muscle and fat tissue. In response to surgery, insulin resistance occurs in both tissues. Postoperative insulin resistance occurs in extrahepatic tissue, primarily in skeletal muscles. In early postoperative phase, glucose uptake in peripheral tissue dramatically declines. Lower glucose uptake correlates with magnitude of surgical trauma. Insulin resistance during surgical stress occurs as a consequence of elevated fatty acid concentrations, increased liver glucose production and decreased muscle glucose uptake (16). Insulin resistance followed by hyperglycemia after surgical procedure could be one of a possible independent factor for appearance of early and late postoperative complications (6). Serum glucose increment was demonstrated in open as well as in laparoscopic surgical procedures, but elevation was lower in laparoscopic operation (17). Glucose metabolism became normal immediately after patients recovery (18).

Insulin resistance is most often determined using a homeostatic mathematical model, HOMA-IR, and insulin sensitivity by hyperinsulinemic euglycemic clamp. The use of these methods determines the biological effect of insulin on the control of glucose homeostasis in the body. Insulin resistance is not limited only on the metabolism of glucose in the post-operative period. Woolfson and associates showed 30 years ago that postoperative glucose administration has no effect on the correction of nitrogen,

while giving the same amount of glucose to insulin for normalizing glucose levels leads to normalization of urea levels in traumatized patients (19). These data suggest that insulin resistance plays a key role in metabolism in the postoperative course and that overcoming insulin resistance can have beneficial metabolic effects (20). The disorder of glucose homeostasis caused by stress development was first described by Claude Bernard (21), describing the occurrence of hyperglycaemia associated with hemorrhage. In the period after this initial release, it has become apparent that hyperglycaemia was present in many stressful situations, despite the insulin concentration being elevated. These facts have led to the realization that hyperglycaemia is probably the best sign the presence of insulin resistance. Today's knowledge of the development of hyperglycemia associated with haemorrhage supports the release of glucose into circulation from the glycogen reserve in the liver, which represents a purposeful reaction of an organism that increases serum osmolarity and in this way performs redistribution of liquid from the cell into the extracellular space. This process has a decisive role in the outcome of the disease (22). Lately, it is being discussed whether the development is insulin resistance after a surgical procedure is beneficial or harmful to the outcome of the entire intervention and whether it should be removed or treated (23). In response to surgical damage by procedure, within a few minutes there will be activation of neuroendocrine and inflammatory response. The end result is the introduction of the organism into a state of metabolic stress (24). This systemic response stops all anabolic processes, mobilizing all available substrates as fuel to create acute phase proteins or to heal tissue. In this major change in metabolism, the central phenomenon is the development of insulin resistance. In surgical patients, the degree of development of insulin resistance is in direct correlation with the size of surgery (25).

In a study of Witasz and associates, it has been shown that the expression of gene tissue in the fat tissue after elective surgery is characterized by an increase in gene transcription for an inflammatory response and a reduction in the transcription of the insulin gene signal, indicating that fat tissue may be a site for the integration of inflammatory diseases and metabolic pathways, as well as metabolic disorders associated with surgery (26).

In the insulin sensitivity test before and after elective surgical procedures, insulin sensitivity was measured preoperatively and on the first postoperative day. It has been shown that insulin resistance develops even afterwards minor elective surgeries, such as inguinal hernia repair, while the degree of deterioration of insulin resistance was greater after open cholecystectomy. In a study that compared the metabolic response to cholecystectomy, insulin resistance after open cholecystectomy was evaluated in comparison with laparoscopic surgery, where it is insulin sensitivity measured before and after the operation, with the measurement of the concentration of interleukin 6 (IL-6). The authors showed a significant reduction in insulin sensitivity after laparoscopic cholecystectomy in relation to open cholecystectomy, with no difference in IL-6 values. It was concluded that a lower reduction in insulin sensitivity could be a

factor that contributes to a faster postoperative recovery (8). In a study that monitored the hypoglycemia caused by insulin after elective open-cholecystectomy, a third was found to have fewer hypoglycaemia in the early postoperative period, which led to the conclusion that the surgical trauma induced rapid and noticeable insulin resistance that is not the result of postoperative nutritional restriction and which involves the reduction of post-receptor glucose transport (27). In the evaluation of the effect of preoperative starvation on insulin resistance after laparoscopic cholecystectomy, it has been shown that HOMA-IR index was higher in patients who were starving in their relationship on patients who had the addition of carbohydrate-rich liquids two hours before surgery. It was concluded that the shortening of the period of preoperative starvation and the ingestion of carbohydrate-rich liquids before surgery reduces postoperative insulin resistance and magnitude of the response to the trauma (28).

Previous experiences have shown that insulin sensitivity can be exacerbated by up to 90% and that these changes can last up to 7 days, even after moderate surgical stress. Recent studies have shown that patients, who develop higher levels of insulin resistance and inflammation in the perioperative period, have more severe and more serious complications and require longer recovery. Some mechanisms that control the development of insulin resistance and inflammation after surgery are not sufficiently clarified, and the reasons why some patients become more resistant to insulin compared to others, although both of them are subjected to the same type of surgery. In previous studies of insulin sensitivity during surgical interventions, it has been shown that insulin resistance develops as a reaction to the surgical procedure and that the degree of its change depends on the degree of damage (25).

The development of insulin resistance and the simultaneous occurrence of hyperglycaemia in the circulation of the surgical patients can lead to postoperative complications in the form of development of the infection and cardiac complications (29). It was shown that a drop in insulin sensitivity by 50% after surgery increased the risk of developing major complications by 5 to 6 times, and the risk of developing severe infection by as much as 10 times. These facts emphasize the importance of changes in insulin sensitivity for the postoperative outcome, rather than demonstrated that for uncomplicated open surgery in the upper abdomen insulin enzymes decrease by 50%, increasing both the risk of development of major complications and the development of infection (30). A study in which glucose was used showed that 85-90% of the developed insulin resistance during surgical procedures involved the development of deterioration of glucose uptake by peripheral organs (muscle and fat tissue), and that the remaining 10-15% refers to gluconeogenesis. Significant effect of metabolic controls during surgical interventions was demonstrated in studies aimed at reducing postoperative insulin resistance using epidural anesthesia (31), preoperative carbohydrate loading (33) or using minimally invasive surgical procedures (8). The relevance of this research is related to the fact that by clarifying the mechanism of temporary deterioration insulin sensitivity, or the development of insulin resistance du-

ring operative interventions, may find possible solution for the prevention of the same. One example of the possible prevention is the administration of fluids enriched with carbohydrates in the preoperative period. Adequate prevention of this disorder would allow, on the one hand, the appropriate preparation of the patient before the surgery, and on the other hand, the improvement of the outcome of the surgical intervention itself through the reduction of complications and the acceleration of postoperative recovery in the form of shortening the length of hospitalization after surgery. Based on this experience it follows that metabolic stress in surgery is an unwanted phenomenon and that everything should be done to avoid it or to minimize its effects. In order to further improve modern surgical practice, one of the key research fields is to examine the development of insulin resistance during surgical interventions.

Surgical stress

An acute response to surgical stress induces changes in insulin sensitivity, but mediation and modulation of this response have not been fully explained (34). Although the organism is able to induce metabolic changes caused by stress, classical stress hormones are probably not the only intermediaries. In several observational studies, before and after elective surgery, a hormonal response was unsatisfactory and there was no relationship between the onset of insulin resistance and changes in concentration stress hormones (7). Lately, several cytokines have been identified as sensitive, early markers of an acute response to various types of stress, including elective surgical procedures (35). The correlation between cytokine and the metabolic response to the trauma, especially the development of insulin resistance, has not been sufficiently investigated. Hormones of stress, such as catecholamines, cortisol, glucagon and growth hormone, cause insulin resistance when given through infusion to healthy volunteers. Epidural blockade of release of catecholamine decreases degree postoperative insulin resistance. Minor changes in post-operative stress concentrations were observed hormone in plasma, regardless of the size of the surgical procedure and tissue traumatization, indicating that these hormones are not the only cause of metabolic changes after surgery interventions, and that their concentration was not changed sufficient to maintain insulin resistance during the first one 24 hours after surgery (35).

Inflammation in surgical stress

Inflammatory response of the body in perioperative period is a protective mechanism which promotes better recovery, while excessive inflammatory response in severe tissue injury could contribute to development of complications and impaired

wound healing (36). Experimental and clinical trials have shown that a factor involved in the development of insulin resistance is tumor necrosis factor alpha (TNF-alpha). In addition, the degree of postoperative insulin resistance after elective surgical procedures is in direct correlation with the value IL-6. The time period for the release of these mediators and their maximum effect on metabolism differs, indicating that the other factors mentioned above have an impact on the development of post-operative insulin resistance (20). Tumor necrosis factor- α (TNF- α), Interleukin-6 (IL-6) and C- Reactive Protein (CRP) are, among the others, major regulators of the acute phase response to inflammation and tissue injury (37). Inflammatory response that is mediated by cytokines could be one of the molecular triggers for the metabolic response to surgery (38). TNF- α expression is considered as connection between fat mass, inflammation and decrease in insulin sensitivity (39). TNF- α plays one of a key roles in the acute phase response and induces lipolysis and muscle metabolism and it is also responsible for postoperative cachexia (40). Macrophages, neutrophils and some other types of cell are able to product TNF- α which as a cell signaling protein, contributes to weight loss, reduction of appetite, insulin resistance, impaired protein, glucose and lipid metabolism (41). IL-6 is inducer of inflammatory proteins such as CRP. CRP as protein of acute phase starts to increase 4-6 hours after tissue trauma with peak at 48 hours and decreasing gradually after 72 hours after uncomplicated surgical procedure. Concentrations of IL-6 and CRP in serum depends of magnitude of surgical intervention (42). A correlation between alterations in IL-6 levels and the development of insulin resistance have been established in many studies. Also, it was demonstrated that postoperative insulin resistance as a part of metabolic response to surgery correlates with elevated levels of proinflammatory cytokines (43).

Although cytokines are recognized as immunomodulators, for a long time there was a great interest in their role as a mediator in responding to stress. In relation to surgical trauma, most of the studies focused on increasing plasma IL-6 values proportional to the size of the surgical trauma. Increased plasma concentrations of IL-6 have reached their maximum in the period from 3 to 24 hours after surgery and decreased from 24-48h after surgery, which indicates that their role as a stress modulator is most prominent in the early postoperative period. In some cases, increased IL-6 levels last several days. Significant increase levels of IL-6 show that it is a sensitive marker for tissue trauma. The modulation of inflammatory response is influenced by an increase in the level of C-reactive protein (CRP) and other acute phase reactants.

It has been proven that the stress response and degree of postoperative insulin resistance are related to the extent of surgery, and that normalization of insulin sensitivity occurs 2-4 weeks after simple abdominal surgery, which corresponds to the average recovery time of the patient.

Fasting in surgical stress

In modulation of catabolism after surgical trauma, other factors, such as immobilization and malnutrition, may be of importance (35). Preoperatively reported insulin resistance, as a response to the organism starvation in situations when food intake is reduced, is developed to provide limited supplies of carbohydrates used in tissues which depend on glucose such as the brain. As a result, insulin-sensitive tissues use fat instead of glucose as a source of energy. Patients preparing for some of the abdominal surgeries often have restrictions of food intake, caused by abdominal pain, tumor or some kind of inflammation, which increases the energy needs of the body, and the period of preparation for the operation requires a reduction of food intake. Most surgical clinics still apply the preparation of the bowel before colorectal surgery, which leads to dehydration and preoperative catabolism. Despite the evidence from many studies, a large number of patients have postoperatively restrictions of food and fluid. When they are allowed to eat, food intake is insufficient due to lack of appetite, nausea or abdominal pain (15). It has been shown that administration of insulin in the postoperative / traumatic period leads to the normalization of metabolic processes, including the metabolism of fat and protein. Using insulin in patients with burns has led to faster healing of the wounds and reduction of protein catabolism. The clinical effects of insulin use after surgery are associated with glucose control, prevention of toxic effects of glucose on the immune system, and an increase in oxidative stress due to increased glucose intake in the cells. Glucose control, enhanced by intensive insulin treatment in critical illnesses, is associated with a reduction in both inflammatory response and normal mitochondrial structure, as opposed to mitochondrial damage in patients with hyperglycaemia. In a large randomized study, it was found that patients in the intensive care unit who had reduced glucose levels less than 6.1 mmol / l by infusion of insulin had a significantly reduced mortality rate and a number of complications compared to patients who were allowed an increase in the glucose concentration over 12 mmol / l (15).

Conclusion

Elective surgical procedures lead to a temporary worsening of insulin sensitivity. The minimal invasive surgery reduces the postoperative surgery stress and affects less the postoperative insulin sensitivity. The degree of postoperative insulin resistance, or decrease in insulin sensitivity, directly affects the length of stay in the hospital and the occurrence of complications in the postoperative period, regardless of the type of surgical operation.

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