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Response to trauma and metabolic changes: posttraumatic metabolism

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ABSTRACT

Stress response caused by events such as surgical trauma includes endocrine, metabolic and immunological changes. Stress hormones and cytokines play a role in these reactions. More reactions are induced by greater stress, ultimately leading to greater catabolic effects. Cuthbertson reported the characteristic response that occurs in trauma patients: protein and fat consumption and protection of body fluids and electrolytes because of hypermetabolism in the early period. The oxygen and energy requirement increases in proportion to the severity of trauma. The awareness of alterations in amino acid, lipid, and carbohydrate metabolism changes in surgical patients is important in determining metabolic and nutritional support. The main metabolic change in response to injury that leads to a series of reactions is the reduction of the normal anabolic effect of insulin, i.e. the development of insulin resistance. Free fatty acids are primary sources of energy after trauma. Triglycerides meet 50 to 80 % of the consumed energy after trauma and in critical illness. Surgical stress and trauma result in a reduction in protein synthesis and moderate protein degradation. Severe trauma, burns and sepsis result in increased protein degradation. The aim of glucose administration to surgical patients during fasting is to reduce proteolysis and to prevent loss of muscle mass. In major stress such as sepsis and trauma, it is important both to reduce the catabolic response that is the key to faster healing after surgery and to obtain a balanced metabolism in the shortest possible time with minimum loss. For these reasons, the details of metabolic response to trauma should be known in managing these situations and patients should be treated accordingly.

Key Words: Posttraumatic metabolism, stress response, trauma response

INTRODUCTION

Response to trauma includes various endocrine, metabolic and immunological changes. The severity of these changes is related to the amount of exposed stress. In the activation of central nervous system and hormonal responses against injury, the direct effect of mediators like TNF-α and IL 1, which are released from traumatic tissue, on the hypothalamus has been well-known. However, many new studies refer to nuclear factor kappa B (NF-kB) in this regard. In a burn-rat model study, it was stated that melatonin, which is protective against liver damage, played a role in the suppression of NF-kB that is accepted as a mediator of inflammatory response, and melatonin treatment reduced the significantly increased hepatic NF-kB and TNF-α activity (1).

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Protein malnutrition affects defense against infection by disrupting inflammatory response. Glutamine, although considered as a non-essential amino acid, has been shown to be essential in cases such as trauma, surgery, or sepsis where cytokine synthesis is modulated. In a study, it was noted that the effect of glutamine on macrophage activation and TNF-α synthesis is dose-dependent, and it effects the NF-kB signaling pathway in a negative way (2). Cocoa has been shown to suppress inflammation by inhibiting NF-kB (3).

Stress hormones and the release of cytokines play a role in the formation of post-traumatic stress reactions. The greater the stress, the more reactions and catabolic impact it causes. The main issue in these reactions and subsequent metabolic status is reduction of the normal anabolic effects of insulin, i.e., the development of insulin resistance (4). Intensive catabolic reactions usually harm the body. The catabolic state associated with destruction of muscle tissue and reduction of energy storage will prolong recovery time. Faster recovery after surgery is achieved by elimination of the negative metabolic effects with reduction of catabolic response and maintaining metabolic equilibrium as soon as possible. For these reasons, nutritional support within perioperative care is essential for healing.

METABOLIC RESPONSE TO TRAUMA

The relationship between trauma and metabolic response and mortality are well known. The body responds to trauma with tachycardia, an increase in the use of oxygen, an increase in respiratory rate, body temperature and negative nitrogen balance, i.e. catabolism. Cuthbertson showed in trauma patients 50 years ago that the characteristic response that consumes protein and fat as a result of hypermetabolism

and protects body fluid and electrolytes occur primarily during the early phase. These metabolic changes are characteristic in patients with severe infection. However, sometimes a septic cause can not be diagnosed in such a clinical scenario. In order to define this general inflammatory process the Systemic Inflammatory Response Syndrome (SIRS) term has been introduced by the American College of Chest Physicians and the Society of Critical Care Medicine at a consensus meeting. Many authors have proposed a final common pathway that can be applied to all catabolic states. Because the metabolic response is similiar in both infectious and non-infectious conditions, it is not known which one leads to this metabolic response (5-7). Surgical trauma does not significantly influence energy metabolism in adults (6). Cuthbertson et al. (8) reported about 20-25% increase in metabolic rate after trauma, and stated that the size of the metabolic response was associated with the severity of trauma. Changes in the metabolism are associated with changes in body core temperature and heart rate. The increase in energy metabolism in the postoperative period was confirmed by many recent studies. Metabolism has been shown to increase by 15-30%. Cuthbertson et al. (8) determined that the postoperative response may change with alterations in preoperative and postoperative management. The postoperative changes in energy metabolism, thermoregulation and fluid and energy requirements vary between newborns, children and adults (6). The metabolic response to trauma in humans has been defined in 3 phases:

1) Ebb phase or decreased metabolic rate in early shock phase,
2) Flow phase or catabolic phase,
3) Anabolic phase (if the tissue loss can be replaced by re-synthesis once the metabolic response to trauma is stopped) (9, 10).

The Ebb phase develops within the first hours after injury (24-48 hours) (6). It is characterized by reconstruction of body's normal tissue perfusion and efforts to protect homeostasis. In this phase, there is a decrease in total body energy and urinary nitrogen excretion. An early increase is detected in endocrine hormones such as catecholamines and cortisol. Generally, there are hemodynamic disturbances (hypotension) due to the decrease in effective circulating volume.

The flow phase can be defined as an 'all or nothing' reaction. This means that the substrate flow should be high enough for the 'hit-or-run' reaction. Thus, it is tried to prevent situations like bleeding, and infection. Although this response is necessary for survival in the short term, if it persists over a long period of time or if the response is severe it leads to the onset of body damage (2-7. days). As a result of this long lasting response, the adipose tissue, skin and other tissues are destructed. Therefore, the response to stress and how this response can be modified to treat patients should be known as part of the current management of critically ill patients. The flow phase is an early period catabolism that provides compensating response to the initial trauma and volume replacement, except most minor injuries. In this phase, the metabolic response is directly related to the supply of energy and protein substrates in order to protect tissue damage repair and critical organ functions. The increased body oxygen consumption and metabolic rate are among these responses. In the early catabolic stage, mainly catecholamines (adrenaline) are responsible from the increase in energy production and consumption (10).

Surgery affects metabolism and substrate utilization. Postoperatively, the utilization of glucose is reduced due to insulin resistance, with an increase in triglyceride and free fatty acid break down due to an increase in catecholamine secretion (11). The increase in the use of lipid does not affect glucose management (12). However, the relative insulin resistance can be reduced by preoperative glucose loading (13). The degree of hyperglycemia significantly affects postoperative outcome and morbidity (14). The metabolic response to stress is mediated by catabolic hormones such as glucagon, catecholamines and corticosteroids and by insulin resistance. Cytokines, oxygen radicals and other local mediators are also involved in this process. These have both anabolic and catabolic effects. The catabolic effects usually develop in peripheral tissues such as muscle, fat and skin. This is used to create the necessary response to wound healing. Amino acids play a major role in not only the synthesis of acute phase proteins, which are very important, but also in wound healing and successful recovery from a disease. These amino acids include those required for protein synthesis as well as specific but non-essential amino acids such as glutamine, alanine, and even arginine (9). The anabolic phase is the late period of flow phase.

The transition from the catabolic state to the anabolic state during the early phase of the anabolic phase depends on injury severity. This transition occurs approximately 3-8 days after uncomplicated elective surgery. However, it takes weeks after severe trauma and sepsis. This is known as the corticoid withdrawal phase and is characterized by reduction of net nitrogen excretion and appropriate potassium-nitrogen balance (10).

Clinically, this period will coincide with the beginning of diuresis and oral intake request. The early anabolic phase may take a few weeks to a few months depending on adequate nutrition supply and protein storage capacity. The positive nitrogen balance ensures increase in protein synthesis, and a rapid and progressive increase of weight and muscle force. Achieving maximum positive nitrogen balance of 4 g/day results in protein synthesis of approximately 25 g/day and body mass gain of 100 g/day (10).

The late anabolic phase is the final phase of the recovery period, and is characterized by gradual restoration of body protein and fat stores and normalization of positive nitrogen balance after the metabolic response to trauma is stopped. It may take a few weeks to several months after serious injury (10).

METABOLIC CHANGES AFTER TRAUMA

Oxygen and energy requirements are increased in proportion to the severity of the trauma. The sympathetic nervous system and catecholamines are mainly responsible from the increase in energy consumption. A large portion of energy consumption is used to compensate for the deterioration in membrane potential due to endotoxin and cytokines. It is believed that 40% of the total body energy consumption is used for ion pumps and transport process. In the surgical patients, knowledge of changes in amino acid, lipid, and carbohydrate metabolisms is important in determining the appropriate metabolic and nutritional support (10). It is emphasized that the severity of metabolic response and mortality can be predicted by the increased anion gap, particularly in elderly patients (15).

LIPID METABOLIZM: Free fatty acids are primary sources of energy after trauma. Triglycerides provide 50-80% of the energy consumed after trauma and critical illness. The energy necessary for the increased gluconeogenesis is provided from either lactate or amino acids in the liver. Lipolysis is accelerated in the early period because of increased ACTH, cortisol, catecholamine, glucagon, growth hormone, and insulin levels and decreased sympathetic activity (9, 10). The energy released by fat oxidation of fat is the most important energy source for liver cells. Since glucose is only partially oxidized, and 80-90% of the energy required for gluconeogenesis is derived from fat oxidation, the patient's respiratory coefficient is between 0.8 -1.

Body lipid stores are durable and in large amounts. Irrespective of the etiology, increased rate of lipolysis is an expected condition within metabolic responses in critically ill patients, nevertheless, the amount of fatty acids as a result of lipolysis may exceed energy requirements. If the patient is given glucose in a dose more than he can oxidize this will lead to more hepatic steatosis. This phenomenon is more frequent in septic, diabetic, and obese patients. Hepatic ketogenesis is stimulated less in situations where starvation is together with an illness as compared to starvation alone due to high insulin levels. In this way, glucose is used as an energy source in the peripheral injured tissues (9).

The activity of lipoprotein lipase is reduced in fat and muscle by the action of increased proinflammatory cytokines (TNF) in trauma and sepsis. During the ebb phase, plasma fatty acid and glycerol levels increase by lipolysis. Lipolysis continues in the flow phase and the increased free fatty acids inhibit glycolysis. Fatty acid synthesis is inhibited with the effects of increase in glucagon and intracellular fatty acids. However, inhibition is not enough in cases of severe trauma, hemorrhagic shock and sepsis. In contrast to what is detected in prolonged fasting, glycolysis and proteolysis continues. The rate of ketogenesis following trauma is inversely proportional to injury severity. Ketogenesis is reduced in major trauma, shock and sepsis due to an increase in insulin and increased use of free fatty acids. In minor trauma, ketogenesis is increased but this increase will not reach the level of starvation ketozis (10).

PROTEIN AND AMINO ACID METABOLISM

Surgical stress results in alterations in total body protein metabolism (6), characterized by an increase in protein catabolism (16), negative nitrogen balance (17), and increased protein turnover (18, 19). The net changes in protein catabolism and synthesis are related to the duration and the level of injury. In metabolic response to trauma systemic proteolysis begins especially by the action of glucocorticoids, the catabolism is increased and excretion of urinary nitrogen rise upto 30 g/day. This translates to an average of 1.5% daily loss in body mass (6, 7, 10). According to this calculation, a traumatized individual with no oral nutrition is going to lose 15% of his body mass in 10 days. Therefore, amino acids cannot be accepted as long-term fuel reserves, and excess amounts of protein losses are incompatible with life (10).

By gluconeogenesis after posttraumatic protein catabolism, amino acids are provided for the synthesis of acute phase proteins, albumin, fibrinogen, glycoproteins, complement factors and similar molecules (9, 10, 20-22). In studies on radioisotope labeled amino acids, protein analysis revealed that tissues in organs such as the liver and kidneys were being preserved while skeletal muscles were particularly used for this purpose (10).

Elective surgery and minor trauma lead to a decrease in protein synthesis and mild level protein degradation. Severe trauma, burns and sepsis progress with increased protein catabolism (10). Lattermann et al. (23) detected catabolism by a decline in protein synthesis and an increase in amino acid oxidation within the first two hours following surgery, in patients who underwent colectomy. In another study, Carli et al. (24) pointed to decreased protein catabolism intraoperatively and in the first 2 hours postoperatively. Increase in urinary nitrogen levels and negative nitrogen balance can be detected at an early stage after injury peaking at day 7. Protein catabolism may continue upto 3 to 7 weeks (10).

Young men lose more nitrogen, whereas this loss is less in the elderly and women. Previous physical condition of the patient, factors such as age and gender influence the degree of proteolysis. Cortisol increase, insulin resistance, hypoxia and acidosis in muscle cells cause early proteolysis (10). The protein catabolism is significantly increased in sepsis and reaches 260 grams a day. This means the breakdown of muscle mass more than 1 kg per day. In this case, if the patient does not receive nutritional support, he will rapidly lose muscle tissue, cannot be separated from mechanical ventilator and cannot heal (9). Protein catabolism is carried out by degradation of skeletal muscle (6). The amino acids released by muscle cannot be used again for protein synthesis in the critically ill. Therefore, a negative nitrogen balance occurs (9). The increase in protein metabolism is followed by the increase in flow phase. The increase in protein metabolism parallels to changes in oxygen uptake and heart rate. Current isotope studies provide an understanding of the changes in protein metabolism after surgery (6). Muscle catabolism can be reduced by nutritional support during flow phase. Protein synthesis can be stimulated, but complete suppression of muscle catabolism is not possible. Net muscle protein recovery can be obtained during the anabolic period of the disease only with enough exercise and nutritional support. During this period, protein turnover gradually decreases. Protein gain is not due to increased protein synthesis but a consequence of decreased destruction. In the posttraumatic period, the absorption of glutamine and alanine from the intestine and the release from skeletal muscle cells into the bloodstream is increased (9).

CARBOHYDRATE METABOLISM

During starvation, glucose production is carried out by using the protein storage. The proteolysis in this period mainly takes place in skeletal muscle, however, protein degradation is also observed in solid organs. Administration of glucose to surgical patients during fasting aims to reduce proteolysis and to prevent the loss of muscle mass. Daily infusion of 50 g of glucose increases fat oxidation and suppresses ketogenesis. In case of excessive glucose administration excessive carbon dioxide production will occur, resulting in adverse effects in patients with suboptimal pulmonary function. Administration of glucose during fasting reduces protein breakdown for gluconeogenesis, but this reduction is not sufficient to meet the requirements in trauma and sepsis.This situation explains that

there are other hormonal and proinflammatory factors effective in protein degradation under stress conditions, and in this case muscle breakdown is inevitable. Administering insulin in increased stress decreases protein breakdown in muscle tissue. This effect has been found to occur by increasing muscle protein synthesis and by preventing protein degradation in hepatocytes. Circulating galactose, fructose and exogenous mannitol (used for neurological damage) do not stimulate insulin response. Although it is known that intravenously administered fructose protects nitrogen in patients suffering from malnutrition, the effects of fructose after injury remains to be established (10).

One of the most important body responses to traumatic stimulation during critical illness is providing sufficient substrate to organs and cells where mitochondrial respiration is not possible. Leukocytes, macrophages, and endangered organs cannot perform mitochondrial respiration. Therefore, endogenous glucose production should increase in trauma patients (150% increase as compared to the control value). In this regard, glucose is an essential substrate since in a certain period of glycolysis oxygen is not required and energy supply continues during that period.

Glucose can be used in hypoxic tissue and inflammatory cells with this feature. Glucose is also important in recovering wounds (where mitochondria has not yet developed). The "fat" cannot reach here because capillaries have not yet developed, and they cannot be used as an energy source. Therefore, immune cells, fibroblasts, granulation tissue and brain tissue mainly use glucose. Moreover, metabolites of glucose may encompass pyruvate-NH2 groups and be transferred to the liver as alanine (9).

The severity of injury and tissue damage after trauma parallels hyperglycemia. In the early period of Ebb phase, glycogen stores, primarily hepatic, are used only for a period of 12-24 hours. A net increase in splanchnic glucose production has been identified at a rate of 50-60% in septic patients, and 50-100% in burn patients (10). It is consumed in a shorter time in critically ill patients. In the late phase of trauma, the flow phase, amino acids, lactate, pyruvate and glycerol is used for renal and hepatic gluconeogenesis. Increased endogenous glucose synthesis occurs in critical illness. This situation cannot be completely inhibited by exogenous glucose and insulin administration. Gluconeogenesis metabolic events taking place in contrast to starvation is not inhibited (9, 10). Gluconeogenesis is an essential process that is driven by stress hormones and cytokines. The first metabolic change after trauma is gluconeogenesis. The increased synthesis of glucose is essential for the continuation of human life in critical conditions and is important.

Hepatic gluconeogenesis provides energy to cells that can utilize glucose without insulin supply such as neurons, erythrocytes and cells that are present in the wound. Posttraumatic insulin resistance is most evident in skeletal muscle. The resultant hyperglycemia also helps to protect the effective circulating volume by osmotic action (10).

Quantitatively, lactate is the most important precursor for gluconeogenesis. Lactate is the result of anaerobic glucose metabolism and circulates glucose carbons between peripheral tissues and the liver (Cori cycle). The lactate metabolism capacity is normally 150 grams, and increases to large amounts under stress. In this cycle, the total energy loss is four molecules of ATP. Glucose is synthesized from alanine in a similar manner. Alanine mainly consists of lactate and amino groups in muscle. In this way, the nitrogen that is formed during amino acid metabolism is introduced to blood stream, and glucose production in the liver is ensured. Glucose may be synthesized from glycerol that results from adipose tissue destruction (lipolysis) (9).

PHYSIOLOGICAL EFFECTS OF INSULIN AND INSULIN RESISTANCE IN STRESS

The decrease in the normal anabolic effect of insulin, i.e. the development of insulin resistance, is the main source of a series of reactions in response to injury and the consequent metabolic state (4). Hinton et al. (25) and Woolfson et al. (26) showed the positive effects of insulin in stress metabolism 30 years ago. Insulin is the most important anabolic hormone in the body. Insulin regulates glucose metabolism to keep glucose levels on very tight limits in healthy people. Insulin provides normalization of glucose level after food intake by activating quick glucose uptake and storing it as glycogen in the liver, muscle and adipose tissue. This uptake is carried through GLUT4, which is a specific glucose transporter activated by insulin. The carriers provide active and rapid glucose uptake in these organs and in many other organs and cells, and can cause a temporary increase in glucose uptake after carbohydrate ingestion. This uptake also uses other carriers that affect glucose levels.

Insulin controls protein metabolism by primarily reducing muscle protein degradation, and supporting protein synthesis in the presence of amino acids. Insulin also controls fat metabolism by stimulating the formation of triglycerides and inhibiting their breakdown. Insulin acts at the cellular level via specific receptors, in insulin sensitive cells such as muscle and fat cells. The specific signalling pathways in insulin sensitive cells are activated to provide anabolic reactions such as glycogen storage, protein synthesis in muscle, or as to block lipolysis in fat cells.

In all major stress conditions such as major surgery, the effect of insulin increases due to secretion of stress hormones like glucagon, catecholamines, cortisol and growth hormone and the inflammatory reaction generated by cytokines. Amino acids, free fatty acids and glucose is released into the bloodstream from various tissues in stress response. The substrate metabolism also changes and fat is consumed in the body rather than glucose. These reactions can be corrected with exogenous insulin therapy after operations like colorectal surgery. It has been reported that by infusing sufficient amount of insulin to keep glucose within normal range, the remaining metabolism is normalized (27). In these studies, nutrition was provided by total parenteral nutrition. When nutrition is provided and the effect of insulin on the metabolism re-establishes, protein degradation, free fatty acid levels and substrate oxidation are normalized. From a clinical point of view, insulin infusion sufficient enough to normalize glucose levels can be used as the final aim to achieve these reactions. From a clinical point of view, insulin infusion can be used to achieve glucose control. Tight glycemic control will improve the outcomes of

critically ill patients (6). Postoperative insulin resistance can be prevented in elective surgery by specific perioperative practices (31) such as preoperative carbohydrate administration (28), epidural block (29) and minimally invasive surgery (30). There are significant differences between short or long-term starvation and critically ill patients with trauma or sepsis in terms of metabolic changes and requirements (9).

Stress-hyperglycemia and insulin resistance are extremely common, especially in critically ill patients with sepsis. Multiple pathogenic mechanisms are responsible for the metabolic response. Thus, the release of proinflammatory mediators and counter-regulatory hormones that may play a role increases. Current data indicate that while insulin shows the opposite effect, hyperglycemia may enhance proinflammatory response (32). Cohort studies showed the relationship between intraoperative hyperglycemia during elective surgery and postoperative morbidity, and this can be used as an early stage marker of complications (31).

The incidence of sepsis has increased dramatically in the last decade. The reasons for this are use of immunosuppressive therapy, an increasing number of invasive procedures, and the increasing age in the population (33). Each year, approximately 750 thousand cases of sepsis are admitted in the United States and approximately 225 thousand of them are fatal (34). With the use of antimicrobial agents and advanced intensive care conditions, the mortality rate has remained at 30-40% during the past three decades (34). Recent data suggest that tight glycemic control with insulin can establish a balance between proinflammatory and anti-inflammatory mediators and can improve the condition of critically ill patients (32).

Critical illness related stress is characterized by the activation of hormonal response in the hypothalamic-pituitary-adrenal axis, cortisol is released from the adrenal gland (35). The release of cortisol by the activation of this axis is a major component of general adaptation to disease and stress, and contributes to maintaining cell and organ homeostasis.

In addition to the cortisol increase in stress response, epinephrine, norepinephrine, glucagon, and growth hormone also increase (36). Insulin levels are usually normal or decreased together with increased peripheral insulin resistance (37). As a result of increased activation of pancreatic alpha receptors, insulin secretion is suppressed (37). In addition to insulin resistance, IL1 and TNF also suppress insulin secretion. Low or normal levels of insulin, and increase in other counter-regulatory hormones result in stress hyperglycemia. When the increase in counter-regulatory hormones such as glucagon, growth hormone, catecholamines and glucocorticoids, and cytokines such as IL1, IL6 and TNF is combined with the increase in catecholamines, dextrose and nutritional support, they play an important role in relative insulin resistance (38).

Sepsis is characterized by insulin resistance (37, 39). The insulin resistance in sepsis is directly proportional to the intensity of the stress response (37). Alpha-2 adrenergic blockage is characterized by decreased insulin resistance in septic mice (40). Glucocorticoids correct insulin-mediated glucose uptake in skeletal muscle.

METABOLISM IN SURGICAL PATIENTS

Adequate nutrition of patients who lost weight and will undergo surgical procedures is critical. Nutritional support is not only required for survival but also to reduce postoperative complications, and shorten recovery time. These patients generally die not due to their present diseases, but because of secondary complications due to malnutrition.

In starvation, glucagon and epinephrine stimulate glycogenolysis through the cAMP pathway, while cortisol and glucagon stimulate gluconeogenesis. Following the first 24 hours of fasting, liver and kidney glycogen stores will be depleted, and the glucose demand of tissues is provided by protein degradation and gluconeogenesis. For the first 5 days of fasting, there is upto 75 g/day of protein degradation. After the fifth day, the stress hormone response decreases and protein degradation levels decrease down to 15-20 g/day (10).

FACTORS AFFECTING SURGICAL RESPONSE

Age: Surgically induced metabolic and endocrine responses are usually different in children than in adults (41). Differences even between term and preterm neonates have been identified. As age increases, the hormonal response in the postoperative period lasts longer (42).

Nutrition and diet: Perioperative nutritional status and especially the degree of diet affect the metabolic response to surgery. Postoperative metabolic response is increased by preoperative nutritional support. Patients who received nutritional support for prolonged periods have more postoperative insulin resistance (13). The type of fluid given intraoperatively also affects the metabolic response directly or indirectly.

Anesthesia: The type of anesthesia also affects surgical stress response. Both general and local/regional anesthesia has been used to reduce the inflammatory response to surgery. Some authors suggested that mortality was reduced in newborn infants with major cardiac surgery by reduction of metabolic response with administration of deep anesthesia and postoperative analgesia (43). It was reported in a randomized controlled trial that endocrine response to surgery and postoperative complications were reduced in preterm with the addition of fentanyl to general anesthesia (44). Epidural block with local anesthetic agents particularly alters the metabolic response to surgical stress (45). Epidural block significantly decreases protein degradation without affecting whole body protein synthesis in adults, within the first 24 hours after surgery. Epidural block with bupivacain has no effect on protein, carbohydrate, or lipid metabolism when a surgical procedure is not performed (46). Epidural block alters postoperative response rather than directly affecting the metabolism (6).

Surgical method: Insufflation of the abdominal cavity with CO_2 or other gases affect response to metabolism. It is important to define metabolic changes associated with CO_2 pneumoperitoneum. CO_2 insufflation can cause both local and systemic responses affecting metabolic response to surgery. As shown in the example of cholecystectomy, metabolic response is less common in minimally invasive surgery (30). Carli et al. (48) identified similar findings in laparoscopic segmental colectomy. Laparoscopic hysterectomy resulted in less and shorter IL6 and CRP elevation as compared to open surgery.

Therefore, it caused less tissue trauma and less inflammatory response. Cytokine synthesis from mesothelial cells were less after laparoscopy as compared to open surgery (49).

Operative stress: Surgical trauma/stress level is one of the factors that affect the magnitude of inflammatory and metabolic response to surgery. The metabolic response to trauma defined by Cuthbertson have been confirmed in infants and children with new findings (47).

Intraoperative and postoperative thermoregulation in response to surgery: Intraoperative thermoregulation is one of the main determinants of metabolic response. Changes in thermoregulation also play an important role in determining the postoperative metabolic response. Thermoregulation varies intraoperatively depending on effects of anesthetic drugs, opened body cavities and loss of most of the normal regulatory control mechanisms (8).

Anatomical and physiological differences in thermoregulation of the newborn, child and adult are partly responsible for the different patterns of postoperative metabolic response (6).

Knowledge on the body's response to trauma and surgical intervention in cases of major stress such as trauma and sepsis, the recognition of changing metabolic requirements, understanding the priority of metabolic changes for survival during critical illness, and aiming at reducing catabolic response, which is the key for rapid recovery after surgery, are recommended to provide return to a balanced metabolism in the shortest possible time, with a minimum loss. Physicians should gain information regarding treatments that may be effective in post-traumatic metabolic response.

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