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Research Article

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Insulin, More than a Metabolic Hormone; Focuse in Sepsis Beyond Glucose Control

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Abstract

Sepsis is the result of an inadequate and harmful host response caused by an infection. Within this, multiple pathways are activated to resolve the infection, however the inappropriate activation of these comes to compromise different systems that explain the complexity of sepsis. Insulin has been studied extensively in terms of the control of hyperglycemia in sepsis, but the benefits of insulin can not only be attributed to glucose control per se, in this review we present some of the other functions that insulin fulfills in the sepsis beyond the control of glycemia.

***Materials and Methods:** We reviewed Pubmed, Ovid, Embase, Lilacs and published textbook chapters, all articles related to physiopathology and effects of insulin in sepsis. Articles carried out in humans and animals were included, without limit of publication date.*

***Conclusion:** Insulin has different functions in sepsis beyond the control of glucose, in which the control or regulation of the inflammatory response is the fundamental axis, since it is involved in all the mechanisms that relate sepsis to insulin. It can not be determined what percentage or proportion of the insulin benefit is due to the control of glucose or the regulatory mechanism on inflammation, microcirculation, expression of free radicals, etc. The understanding of insulin in the different pathophysiological pathways of sepsis should be further deepened since the decomposition of the functions of this hormone as well as of other alternate routes, is what will allow the optimization of all the therapeutic arsenals that exist to improve the morbidity and mortality of these patients.*

Keywords: Insulin, Sepsis, Glucose, Inflammation

Introduction

Sepsis is defined as deleterious response of host towards a pathogen, in which the number of physiopatological phenomenon implied lead to cell dysfunction, multiorgan failure and death. In this unregulated response, hormones change its functions and metabolism. One example is insulin, a peptide hormone which is not only implied on the glucose's homeostasis and growth pathways but also function as a mediator of inflammatory, hemodynamic and microvascular processes involving sepsis.

Insulin

Insulin is a hormone secreted by the pancreas, which is composed of two polypeptide chains, A and B which contain 21 and 30 amino acid residues respectively. The discovery of this hormone begins in 1889 in Germany with Dr Joseph von Mering and physiologist Oskar Minkowski who for the first time demonstrated that by extracting the pancreas from an animal, it became diabetic [1]. After this important finding in 1921 a group of Canadian scientists demonstrated how extracting the islets of Langerhans from healthy dogs and implanting them in diabetic dogs, the latter improved their metabolic base disorder. This allowed these researchers to hypothesize that there was a protein produced in the pancreas that was responsible for the regulatory effect in the diabetic dogs. This peptide was later called Insulin [2]. A few years later, James B. Collip managed to purify this peptide, which allowed it to be tested in healthy volunteers (Fredrick G. Banting and Charles H. Best) and later in 1922 in a diabetic patient (Leonard Thompson) who showed a significant improvement of its basal state which triggered an important interest in the scientific world, which led to the large-scale production of the hormone. In 1923 researchers Banting and Macleod received the Nobel prize for physiology or medicine.

Insulin and microcirculation, in the context of sepsis and septic shock

In conditions of sepsis and septic shock inflammatory mediators block regulatory signals of GLUT transporters in hyperglycemia,

exposing the cell to glucose uptake in toxic ranges that leads to mitochondrial alterations in liver cells and skeletal muscle. This mitochondrial compromise leads to the nitration of most molecular complexes and voltage-dependent ion channels, for this reason hyperglycemia decreases the response of the microvasculature to vascular tonicity stimuli [3,4]. The final product of anaerobic glycolysis is pyruvate and the activity of the enzyme pyruvate dehydrogenase complex (PDC) leads its metabolism to continue in the Krebs cycle. In sepsis, the increase of PDC kinase enzymes leads to accumulation of pyruvate in plasma that is then converted by lactate dehydrogenase (LDH) into lactate, which is a known marker of severity in sepsis. It has been determined that insulin could play a protective role, being key in the inhibition of PDC kinase enzymes avoiding the decrease of substrates for oxidative phosphorylation and mitochondrial ATP depletion [5-7].

Role on Nitric Oxide

On the other hand, the production of nitric oxide is a key mediator in the response to inflammation, sepsis and shock. Agents that decrease cAMP can decrease the exposure of hepatic nitric oxide through mechanisms that involve akt (protein kinase B) [8]. Experimental data show that insulin inhibits expression of inducible nitric oxide (iNOS) stimulated by cytokine in murine hepatocytes. The suppressive effect of insulin on iNOS was mediated through the regulation of Akt signaling and was not mediated through effects on MAPK p42 / p44 or p3. In addition to controlling glucose levels, insulin can decrease iNOS expression and limit dysfunction or damage to organs and tissues mediated by iNOS during sepsis and shock [9].

Under these circumstances, it is important to understand how the endothelium fails to perform its regulatory functions and its nitric oxide (NO) system is seriously disturbed. There is a heterogeneous expression of inducible nitric oxide synthase (iNOS) in the endothelium of different areas of the organ´s blood vessels in sepsis. There are areas that lack iNOS and have less NO-induced vasodilation and become less permeable, resulting in a pathological derivation of blood flow with hypo perfused areas [10].

In sepsis, the overproduction of nitric oxide (NO) from endothelial cells by positive regulation of iNOS has been associated with altered vascular reactivity, capillary filtration, erythrocytic deformity and refractory hypotension due to loss of vasodilation control [11]. This toxicity by nitric oxide generates inhibition of mitochondrial respiration, reversible or irreversible, depending on the duration of exposure to nitric oxide in the mitochondrial complex [12].

These aspects have been very controversial, given that the concept of nitric oxide inhibition therapy for sepsis is currently debatable and the role of nitric oxide itself is ambiguous with respect to its effect on microcirculation. An improvement in microvascular blood flow has been demonstrated with both nitric oxide donors and iNOS inhibitors, giving variable results [13]. It is important to understand the role of insulin in this concept, where regulating the overexpression of tissue nitric oxide would allow better recovery from septic shock.

Another element to be considered in microcirculation is hypoxia-inducible factor 1 (HIF-1), which is a transcription factor involved in the normal development of mammals and in the pathogenesis of several disease states. It consists of two subunits, HIF-1α, which is degraded during normoxia, and HIF-1β, which is expressed constitutively. In states of infection and sepsis, through lipoprotein saccharides (LPS) induces activation of HIF-1alpha and leads to VEGF secretion that markedly increases vascular permeability, where it is characteristic of the septic phenomenon the increase in vascular permeability with tisue edema and vascular leaks that end in shock. This dangerous clinical condition could be caused by the activation of HIF-1 alpha induced by bacteria and by VEGF. Therefore, it is not surprising that the neutralization of VEGF by regulation of HIF-1alpha results in an intense decrease in vascular permeability and mortality in sepsis. Several genes regulated by HIF-1alpha have been associated with the protection of vascular barrier function during inflammation and hypoxia [14, 15].

The contradictory in this order of ideas is that there is experimental evidence that insulin activates the expression of the HIF-1α protein in a dose-dependent manner with a maximum reached within 6 hours post injection, leading to increased tissue VEGF. The activity of HIF-1α correlates with the level of DNA binding of HIF-1 and the transactivation of a promoter gene dependent on HIF-1. Insulin does not appear to affect the transcription of HIF-1α mRNA, but regulates the expression of HIF-1α protein through a PI3K / TOR dependent pathway, resulting in an increase in VEGF production at least transiently [16].

The control of microcirculation in a state of infection and sepsis, is regulated by complex systems regulated by energy metabolism, cytokines, gene expression and nitric oxide, it is important to define experimental and clinical models in the context of sepsis and shock that allow understanding of the role of insulin plays at this level.

Protein Control

The process of synthesis and degradation of proteins is regulated dynamically through different mechanisms, this is important in the gain or loss of muscle mass, which is evident in different pathologies. There are two mechanisms recognized by which the catabolism of the muscle occurs, among which are the inhibition of synthesis and the stimulation of proteolysis [17, 18]. However, protein degradation is undoubtedly an important contributor to the development and progression of muscle wasting in a variety of conditions in which sepsis is included, whose basis for inhibiting it under such conditions is likely to be multifactorial and includes resistance to growth factor 1 similar to insulin, expression of proinflammatory cytokines, malnutrition, corticosteroids and / or physical inactivity [19]. Sepsis being an inflammatory state and therefore catabolic, there is a great loss of body proteins, due in part to an impairment in protein synthesis. Studies show that the decrease in protein synthesis is associated with the inhibition of the activity of eIF2B GEF, which is one of the best characterized mechanisms and the signaling, repressed through TORC1, which are factors that intervene in the processes of mRNA translation. Associated with this, the inflammatory response provoked by sepsis and the production of inflammatory cytokines suppresses the assembly of the 43S preinitiation ribosomal complex (19)(21). The results of the first studies provide strong support for the hypothesis that the inhibition sepsis-induced protein synthesis is a consequence of the repressed expression of eIF2B [19, 20].

Protein synthesis is a complex process where different factors and biochemical structures are associated, among which are the ribosomal subunits (40S, 60S), messenger RNA, cofactors (GTP and

ATP), protein factors known as eukaryotic initiation factors (eIF), which have as their main objective to carry the translation of RNA, which occurs in three phases initiation, elongation and termination, processes that are affected by the inflammatory cascade, cytokines triggered by sepsis [17-22].

The modification of protein synthesis is associated with inflammation, malnutrition, high levels of myostatin and insulin resistance. Hormones such as insulin and insulin-like growth factor 1 (IGF-1) stimulate protein synthesis through the Akt / mTORC1 signaling pathway and eIF2B activation, while amino acids activate mTORC1 signaling to through the Rag proteins [19]. It has been seen that the altered response to known stress hormones or counter regulatory hormones (glucocorticoids, glucagon, epinephrine) and anabolic hormones (insulin, growth hormone, IGF-1) has been implicated as a major cause of induced metabolic disorders due to sepsis, especially in protein regulation [17]. It is important to bear in mind that the effects of sepsis on protein metabolism are reversible, which suggests that this may be modified as it progresses with the septic process [17]. It has been seen that the process of proteolysis is accelerated in septic patients, which indicates that protein degradation remains elevated during the hypermetabolic phase of sepsis [23, 24]. On the other hand, there is stimulation and therefore an increase in the rate of proteolysis through different routes, one of the most studied has been the lysosomal. Several lysosomal enzymes are part of this pathway, among which we find cathepsin B, H, L, D [25].

Studies have shown that there is an increase in the activity of cathepsin B in septic processes [26, 27]. In addition, as mentioned earlier there are changes in the muscle response to the main anabolic hormones such as insulin, IGF-1, and growth hormone, which play a role in muscle turnover which has been the source of multiple investigations. It has been seen that insulin improves the overall rate of protein synthesis and on the other hand reduces proteolysis under a wide variety of conditions [28]. In sepsis, the major reason for the inability of insulin to stimulate protein synthesis is the failure to maintain plasmatic and intracellular concentrations of amino acids during hyperinsulinemia, which becomes an important therapeutic and investigative target [29, 30].

In a study carried out in animal models, it was evidenced that the insulin infusion stimulated the protein synthesis with maximum effects at 150mcg/ml, however when administering together amino acids an effect was observed at 20 mcg/ml, which shows a proportional relationship between the stimulation of protein synthesis by insulin and the concentration of amino acids, which supports the raised hypothesis [31]. The sensitivity of muscle tissue to insulin has been seen to improve with the infusion of amino acids and thus increase protein synthesis when used as a substrate for protein synthesis [31]. The latter was investigated with different variations in various studies which is why it requires further investigation.

In the states of sepsis and shock, it has been perceived that glucose absorption or uptake is altered, and there is evidence of a lack of response to insulin despite the high levels of insulin that are present in these patients, due to the influence of different inflammation factors such as interleukin 1-2 (IL-1, IL-2) as well as the tumor necrosis factor alpha (TNFa), whose role and function has already been described [32].

Insulin in catabolic states is incapable of exerting its optimal and physiological action, the aforementioned given by peripheral resistance to insulin, especially in muscle tissue and liver tissue, which is explained by an increase in the clearance or metabolism of insulin associated with alterations in the phosphorylation of the insulin receptor and activation of skeletal muscle protein kinase, which has repercussions on the intracellular cascade stimulated by insulin, such as the synthesis of membrane proteins [33-35]. In septic states there is an increase in the expression of glucose transporter protein 1 (GLUT-1), which internalizes glucose that is metabolized into lactate unlike the physiological expression of transporter proteins of glucose-4 (GLUT-4) [32-36]. It is possible that, at least to some extent, the physiological action of insulin can be restored to normal by the continuous infusion of insulin under the glucose -insulin -potassium regimen [32]. Insulin possesses the ability to inhibit the production of proinflammatory molecules (alpha tumor necrosis factor, inhibiting factor of the migration of marcrofagos, free radicals and Interleukins 1 and 6) as well as to improve the production of vasodilators (nitric oxide), production of anti-inflammatory molecules and correction of hyperglycemia generated by sepsis [32].

Not only is there an alteration in the skeletal muscle metabolism, it is evident in the cardiac muscle as well, which manifests itself in cardiac dysfunction in the form of myocardial depression, which is the main manifestation during septic shock [37]. Cardiovascular homeostasis is altered by the different cytokines released in the inflammatory process of sepsis, which leads to cardiac dysfunction in the context of septic shock, where various etiologies have been described by which this process is developed like hypoperfusion not only systemic but also myocardial caused by the endothelial dysfunction that occurs [37]. Associated to this, circulating depressant substances have a place in the development of myocardial depression due to its potential to produce alterations in the cardiac muscle such as prostaglandins, leukotrienes, platelet activating factor, histamine, among others [37]. Many of these act in some way in the development of sepsis and that in turn possess action over insulin and its function on tissues. Many studies show that the Insulin-glucose-potassium regimen improves cardiac function during septic states, by increasing cardiac output, stroke volume, blood pressure and the consumption of O2 by the myocardium [38]. This reflected in studies such as the one performed by Hinshaw et al. where he compares the infusion of intravenous glucose with the infusion of intravenous insulin at a rate of 6 Units / minute, where he shows that when using the latter intervention, the signs of heart failure are reduced with an adequate performance despite the variability of the levels of glucose [39]. Which leave Yogesh.H.Ss an open door to the use of insulin in a patient with signs of cardiac dysfunction and septic shock.

On the other hand, the interstitial fluid pressure is involved in the flow of the fluids through the capillary wall [40]. This interstitial fluid pressure has regulatory mechanisms to prevent the uptake of fluids and the subsequent formation of edema and one of these are connective tissue cells, which exert tension on the extracellular matrix composed of collagen fibers and substances such as hyaluronan and proteoglycans, which does not allow the formation of edema [41]. The above shown in studies that show that interstitial fluid pressure can act with an active force in the formation of edema [42]. It is at this point of tension on the collagenous network that the role of the integrins plays a role in the homeostasis of the fluids, demonstrated in a study where when administering IG anti

integrin B1 a decrease is evident in the interstitial fluid pressure is evidenced, which contributes to the formation of edema in epidermis of rats [43]. And based on these results Oyvind et al, proposes that the damage of integrins B1 secondary to an inflammatory states decreases interstitial fluid pressure which predisposes to a loss in the extracellular matrix tension, extravasation of fluids and interstitial edema [42]. In addition, it has been seen that various substances stimulate or inhibit collagen contraction, influence whether it increases or decreases the interstitial pressure. It is this way that IG anti integrin B1, prostaglandin E1, interleukin 1 (IL-1) inhibit the contraction of the collagen matrix and decrease interstitial fluid pressure promoting edema, whereas prostaglandin F2 alpha stimulates collagen contraction and returns to the decreased interstitial fluid pressure at the control levels [44]. The role of insulin in the control of interstitial fluid pressure has been studied by demonstrating that it restores pressure to physiological values, thereby counteracting the edema induced by the inflammatory process [45]. This was demonstrated in animal studies where, with an initial interstitial pressure of 7 mmHg a dose of bacterial lipopolysaccharides decreases to 2 mmHg, with subsequent administration of insulin with which the interstitial fluid pressure presents an improvement of almost 50% when increasing to 4 mmHg [45]. In addition to this, the effect of stimulating the contraction of the collagen extracellular matrix that possesses insulin [42].

The mechanism by which insulin normalizes interstitial fluid pressure involves the contraction of connective tissue around blood vessels, based on the fact that insulin normalizes interstitial fluid pressure when blood volume was stopped during the measurement time. Which excluded the possibility that endothelial cells and plasma proteins participated in fluid transport and/or caused a change in interstitial fluid pressure. Associated, insulin induces a contraction of collagen tissue mediated by integrin alfav B3 [42]. At the biochemical level, the effect of insulin envelops the PI3K system activating it, which leads to a contraction of the collagen tissue, since its inhibition generates a decrease in the interstitial fluid pressure [45].

Insulin resistance in sepsis

Insulin is a hormone that fulfills various functions, among which are the transport of nutrients within cells, regulation of gene expression, and modification of enzymatic activity [46]. Which is reflected in the ability of insulin to reduce hepatic glycogenesis, adipose tissue suppress the lipolysis rate, stimulate the reception of glucose by the skeletal muscle in addition to the increase in protein synthesis and suppression of proteolysis, this under physiological conditions [47]. Insulin resistance in critically ill patients can develop and its main manifestations can be reflected in hyperglycemia and hyperinsulinemia [48]. This is where the inflammation caused by multiple causes whether it is a viral, parasitic, bacterial or fungal infection, ischemic events that can generate a systemic inflammatory response syndrome has a great influence on the functioning of insulin and its metabolic effects [47]. It is known that patients with sepsis develop a state of hypermetabolic stress, which is associated with a number of alterations in the metabolism of carbohydrates which is reflected in hyperglycemia and insulin resistance [49].

It is necessary to take into account that the immune system and metabolism are closely related, and alterations in either one system can cause dysregulation in the functioning of the other. The detection of an infectious agent by pattern recognition receptors located in cells of innate immunity, results in an inflammatory response leading to the activation and production of multiple inflammatory proteins and cascades [47]. This inflammatory response generates an energy cost for the organism, for which it sacrifices those non-essential tissues to compensate the energy expenditure that is required [50]. The identification of the infectious agent in turn involves the TLR (Toll like receptors) receptors, where the TLR type 4 plays a fundamental role since on the one hand it recognizes the bacterial lipopolysaccharides - important in triggering endotoxemia and inflammatory process - and on the other hand side it has been seen that it can act as a sensor of free fatty acids [47]. Studies in mice have shown that the lack of TLR type 4 offers some degree of protection against insulin resistance induced by lipid infusion [51]. This is explained because the TLR type 4 regulates energy metabolism through the inhibition of insulin signaling [52], and also the lipids or fatty acids fulfill the function of TLR4 ligand able to produce the expression of cytokines proinflammatory in liver, macrophages, and adipocytes [51].

As mentioned above, TLR4 receptors have a role in the metabolism of lipids through the inhibition of signaling mechanisms by insulin in which the AKT pathway is involved, an important insulin signaling pathway [52]. Which is explained later, from the adipose tissue -considered as an endocrine organ-, a series of substances called adipokines are released which are involved in the inflammatory process and of course in insulin resistance and among the main ones are leptin, resistin, visfatin, quemerin, tumor necrosis factor-α (TNF-α), interleukins (IL) -1, IL-6, IL-8, IL-10, tissue plasminogen activator 1 (PAI-1), chemoattractant protein monocytes - 1 (MCP-1) with different mechanisms that generate insulin resistance [53]. In the case of adiponectin, considered as an anti-inflammatory adipokine, also has stepsibling effects to the action of insulin. Thus, several studies have shown that plasma levels correlate inversely with the degree of insulin resistance of patients in this case with diabetes mellitus type 2 and obesity [54]. However low serum levels of adiponectin have been seen in patients critically ill patients [55, 56]. This is seen in a study conducted by Hillebrand et al. in which the profile of serum adipokines of critically ill patients in the intensive care unit is compared, among them patients with sepsis with patients under morbid obesity, whose results show a statistically significant negative relationship ($p = 0.043$) between the low levels of adiponectin and the SAPS II and SOFA scale used for the clinical follow-up of patients [55]. There are several mechanisms by which adiponectin acts. First, it suppresses the function of mature macrophages and inhibits the formation of foam cells (macrophages with intracellular accumulation of lipids), as well as the growth of macrophage precursors [57]. And on the other hand this adipocin attenuates the production of proinflammatory substances such as tumor necrosis factor alpha (TNFa) and IL-6 in macrophages and induces the secretion of IL-10 which has anti-inflammatory effect, added to this it inhibits signaling in the TLR receptor family [58, 59].

Due to the inflammatory response they increase the plasma concentrations of IL-1, IL-6, IL-8 and tumor necrosis factor alpha, where the macrophages in the adipose tissue are the main source of these cytokines. It should be noted that the IL- 6 and IL-8 are produced directly by adipocytes [60-62]. Very few studies have shown the potential metabolic effects of IL-6 and its ability to generate alterations in insulin sensitivity [62]. However, in a study carried out in mouse hepatocytes by Senn et al, report that the increase in IL-6 impairs the effect of insulin to increase

tyrosine phosphorylation in substrate -1 of the insulin receptor and phosphorylation of the AKT pathway, participant of intracellular signaling of insulin [63]. With regard to IL-1 and tumor necrosis factor alpha (TNFa) and its mechanism of production of insulin resistance, it has been seen that IL-1 promotes the destruction of pancreatic Beta cells and also generates an alteration in signaling and sensitivity of insulin in the tissues, added to this the TNFa which promotes the process of lipolysis and liberation of free fatty acids and at cellular level this is a potent inhibitor of the tyrosine phosphorylation stimulated by insulin of the receptor, specifically from insulin receptor substrate-1 [64, 65]. Macrophages are closely related to the inflammatory process, and a substance produced by adipose tissue such as the Monocyte Chemotherapeutic Protein 1 (MCP-1), which contributes to the infiltration of macrophages into adipose tissue causing an inflammatory circle. Increased acute serum concentrations of MCP-1 in sepsis appear to contribute substantially to systemic insulin resistance, independently of a preexisting adipose tissue inflammation [66, 67]. According to Tateya et al, in a study in mice, observed that the Macrophage infiltration in adipose tissue is an early event that contributes to the development of systemic resistance to insulin.

Since the activation of the inflammatory response requires and generates a high energy consumption, as mentioned above, adipose tissue becomes the main source of metabolic fuel for all the enzymatic processes that occur, and therefore a great influence in insulin resistance [47]. All coming from stored triglycerides where, enzymes such as lipoprotein lipase and hormone-sensitive lipase generate a process of degradation of the free fatty acids and glycerol that will become energy sources either in the liver or adipose tissue [47].

It has been seen that during the inflammatory process, including sepsis, the serum concentrations of free fatty acids and triglycerides increase, given by the increase in catecholamines and proinflammatory cytokines that inhibit lipoprotein lipase and decrease lipolysis at the extracellular level in the endothelial cell [68]. On the other hand, deregranulation in the control of hormone-sensitive lipase favors lipolysis in adipose tissue, releasing fatty acids in large quantities, which exceeds the capacity for clearance, depuration or metabolism, which leads to hypertriglyceridemia [47]. Mitochondrial and peroxisomal explained by the pathophysiology of sepsis leads to these free fatty acids and plasma triglycerides, do not undergo an oxidation process to be used as an energy substrate, but generate long chains of acyl -CoA, ceramides and diacylglycerol that alter the insulin signaling and contribute to insulin resistance [69, 70]. This explained because, these molecules lead to the activation of protein kinase C and the phosphorylation of substrate 1 of the insulin receptor in a serine residue - when under physiological conditions phosphorylation occurs towards a tyrosine residue-, which prevents the translocation of the GLUT 4 membrane channels and consequently the uptake of glucose [47]. So that the latter becomes one of the mechanisms by which insulin resistance occurs in peripheral tissues.

Hyperglycemia, hypertriglyceridemia and protein breakdown or degradation then become consequences of the phenomenon of insulin resistance that can occur during inflammatory states, and although this phenomenon of resistance is considered a response mechanism, no treatment generates increase in morbidity and mortality [47]. Clinically, extreme insulin resistance is defined as the requirement of 3 or more Units / kg / day of insulin to maintain adequate metabolic control, however very few patients develop this condition and, if developed, it is a factor of poor prognosis increasing its morbidity and mortality [71].

Carbohydrate control

The response to stress is manifested by a series of alterations consisting of hypermetabolism (ex, increased oxygen consumption, hyperglycemia, hyperlactatemia, protein catabolism), a hyperdynamic cardiovascular state and clinical manifestations of fever or hypothermia, tachycardia, tachypnea and leukocytosis [72]. The body tries to cope with stress by modulating the autonomic nervous system, the neuroendocrine axis, and the metabolic and immune systems [73].

The alteration of carbohydrate metabolism in septic patients can be revealed through the knowledge of the effect of cytokines and the neuroendocrine system. The inflammatory cytokines that mediate the pathogenesis of sepsis plays a key role in the activation of the neuroendocrine system, which can directly alter the metabolism of patients. It should be noted that the activation of neuroendocrine responses and the autonomic nervous system is a process that consumes energy, and the strength of a response is determined by energy deposits and the availability of energy (nutrients) for tissues that face stress [74].

The immune response to the invading microorganisms and their products can trigger many of the physiological and metabolic adjustments to the face of infection. Macrophages produce a series of mediators that probably modulate a variety of responses of invading organisms. It has been shown that two of these mediators, interleukin-1 and tumor necrosis factor produce a broad spectrum of changes. It has been indicated that the infusion of recombinant human TNF increases the metabolism of glucose. It also leads to a transient increase in plasma insulin concentration and a more sustained rise in glucose counter regulatory hormones [74]. Similar to TNFα, infusion of recombinant IL-1β can also induce a hypermetabolic state demonstrated in studies that are carried out before performing any tests on humans [75].

Such an uncontrollable inflammatory response would cause many types of metabolic disorders [76]. During the acute phase of critical illness, stress hyperglycemia is mainly triggered by hepatic glucose production as a result of gluconeogenesis and glycogenolysis associated with muscle glycolysis and lipolysis [77]. A transient fall in the insulin levels precedes hyperinsulinemia, which would normally suppress both pathways. However, it increases the release of counterregulatory hormones such as glucagon, cortisol, growth hormone, catecholamines and proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF) and the macrophages migration inhibitory fsctor (MIF) that seems to play a fundamental role in the development of insulin resistance [77]. Once these cascades are initiated, their mediators and products appear to perpetuate the persistent and increased metabolic rate associated with altered glucose metabolism.

Smith et al. have previously suggested that the elevation of cAMP levels induced by catecholamines inhibits glucose transport stimulated by insulin in rat adipocytes. Insulin resistance depends on the defect in the action of the same in the target tissues. In particular, after stressful stimuli such as injuries and systemic

infection, causing glucose intolerance or hyperglycemia to persist despite hyperinsulinemia or increased insulin secretion in beta cells of the pancreas. It has been considered that these phenomena are mainly due to the increased release of counterregulatory hormones such as catecholamines and cortisol, which results in an increase in the production of hepatic glucose and the inhibition of the action of insulin in peripheral tissues [78].

It should be noted that insulin stimulates the uptake of glucose through an increase in the glucose transporters (GLUT-4) in the plasma membrane. The number of GLUT4 in adipocytes of septic rats was increased through the rapid translocation of a large intracellular set to the plasma membrane, under the influence of insulin [79]. Along with the finding of elevated levels of catecholamines in septic rats, cAMP-mediated inhibition of insulin-induced stimulating action on glucose transporters, including translocation, is associated [78].

In the same way, insulin-stimulated glucose transporter in the rat adipose cell seems to be partly dependent on the presence of adenosine since a small but consistent reduction in the maximum velocity stimulated in response to adenosine deaminase is observed [80]. The inhibition observed in the presence of adenosine deaminase is clearly due to the degradation of adenosine since it is almost completely reversible by phenylisopropyladenosine. This enzyme alone inhibits the glucose transport activity by approximately 25% and is accompanied by a corresponding decrease in the insulin-stimulated concentration of the plasma membrane glucose transporters [81].

Therefore, this state of hyperglycemia can produce a series of adverse effects, one of these occurs in the innate immune system since it affects the ability of the host to fight the infection, which reduces the activity of neutrophils, such as chemotaxis, formation of reactive oxygen species and phagocytosis of bacteria despite accelerated diapedesis of leukocytes in peripheral tissue. As well as specific alterations in cytokine patterns, with increased concentrations of early proinflammatory cytokines, tumor necrosis factor α and interleukin (IL) -6, and a reduction in endothelial nitric oxide formation [76].

Insulin and the control of lipids in the context of the septic patient

It is known that the metabolism of lipoproteins is affected by inflammatory situations, in infectious and septic processes. These changes occur in lipids, apolipoproteins and enzymes involved in lipoprotein metabolism. These alterations are part of the acute phase response of the organism that has even been called septic lipemia. In animal and human models of sepsis, an increase in serum levels of triglycerides, total cholesterol, LDL cholesterol and VLDL has been found. On the other hand, there is a decrease in HDL cholesterol and cholesterol transported in LDL and HDL, due to the reduction of cholesteryl ester content of lipoproteins. In addition, a significant correlation has been established between the decrease in HDL cholesterol levels and an increase in the severity of sepsis, with an increased risk of death [82].

The use of substrates is fundamental to guarantee the vital functions in living beings, that is why when the contribution is deficient the organism goes to alternative sources to generate energy. Under normal conditions lipid homeostasis depends on the balance between the anabolic effects given by insulin and, catabolic given by catecholamines and glucagon [83, 84]. In the context of a septic patient, there is a predominance of catabolic activity, the activity of insulin is suppressed with an increase in tissue resistance to insulin, on the other hand, there is an increase of anti-regulatory hormones that increases lipolysis and the consequent liberation of free acid acids and ketone bodies [85]. In this same way there is an alteration in the transport of long chain free fatty acids to the mitochondria, this generates inhibition of the dehydrogenated pyruvate complex (PDC), which produces intracellular acidosis and compromise in the production of phosphates and their derivatives that ultimately affect intracellular energy sources from lipids. In this sense, insulin as a regulator, inhibits hormone-sensitive lipase, which is key in the mobilization of free fatty acids to the systemic circulation [85, 86].

It has been determined that insulin induces the release of HDL cholesterol that has anti-atherogenic and anti-inflammatory effects. Likewise, it has been observed that it has action in the innate immunity since it is able to sequester the lipopolysaccharides (LPS) of bacterial origin and eliminate it by the hepatobiliary route, this way limiting the inflammatory cascade that participates in sepsis and shock. In a population study, the role of HDL cholesterol as a prognostic marker in sepsis is being studied [87].

On the other hand, it is interesting the role of fenofibrates used as triglyceride reducing agents in clinical practice, exhibiting antioxidant and anti-inflammatory activities through activation of the peroxisome proliferator-activated alpha receptor. In experimental studies conducted on sepsis, it was observed that treatment with fenofibrate corrected endothelium-based vasodilator hyperactivity [88].

The intervention in the management of carbohydrate and lipid metabolism in sepsis / shock have been increasingly recognized in the literature. However, more controlled clinical trials are needed to be able to draw definitive conclusions regarding the role of insulin in metabolic control and sepsis.

Conclusion

Insulin mediates multiple processes in sepsis, it is not known what proportion of the protective effect of insulin is due to the control of hyperglycemia or to the regulation of the different processes of the inflammatory cascade. The use of insulin has changed over the years, where initially the management of patients was performed with high doses to achieve strict controls; currently a more conservative strategy is used given the presence of negative results with the use of strict control. Similarly, it has even been questioned whether it is beneficial to control hyperglycemia, since it is also known to be a protective mechanism. Despite these contradictions, gaps in knowledge are common and expected when talking about sepsis, an example are immunomodulatory therapies in which, despite great knowledge, they have not shown an absolute benefit in the mortality of these patients, which does not It means that they do not work, on the contrary, like insulin, it forces us to know more about each of its mechanisms, adverse effects, doses, interactions and find a way to find the reasons why many strategies in sepsis work in animal models while in people no. This review shows a small part of the importance of insulin in sepsis.

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