BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

Stress Hyperglycemia: A Problem that Cannot be Ignored

Daxu Peng[1] Yifan Zhang[1] Xiuyang Cao[2] Jianyi Pu[1*]

1. Department of Intensive Care Unite, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, 063000, China
2. Department of Hepatobiliary Surgery, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, 063000, China

ARTICLE INFO

Article history
Received: 28 May 2021
Accepted: 09 June 2021
Published Online: 12 January 2022

Keywords:
Islet β cells
Hyperglycemia
Insulin resistance
Critical illness
Intensive care

ABSTRACT

Stress hyperglycemia is a strong neuroendocrine reaction in the hypothalamic pituitary adrenal cortex under severe infection, trauma, burns, hemorrhage, surgery and other harmful stimulated, resulting in increased secretion of counter-regulatory hormones. These hormones promoted the production of sugar and cause glucose metabolism disorders with cytokines and insulin resistance. In this condition, the production of sugar exceeds the utilization of sugar by the tissues, which eventually leads to an increase in blood glucose levels in plasma. In the intensive care unit, stress hyperglycemia is very common and can occur in patients with or without diabetes. The incidence is as high as 96%, and it is an independent factor in the death of critically ill patients. Hyperglycemia not only prolongs the hospitalization time, mechanical ventilation time and increased the incidence of serious infections in critically ill patients, but can also lead to the occurrence of type 2 diabetes. Therefore, it is very important to learn the pathological mechanism of stress hyperglycemia, the harm of hyperglycemia and blood sugar management.

1. Introduction

Stress refers to a series of neuroendocrine immune responses and various changes in functions and metabolism that occur after the physical by strongly stimulated [1,2]. A moderate stress response can enhance the physical preparedness, improve physical adaptation to the internal and external environment, and maintain its own homeostasis, while an excessive stress response can lead to disease and even death. Stress Hyperglycemia, also known as Stress Diabetes, since it was first proposed in 1877, many studies have shown that stress hyperglycemia can not only lead to increased catabolism, negative nitrogen balance, poor wound healing, and infection rates [3]. Elevated, it can also

*Corresponding Author:
Jianyi Pu,
Department of Intensive Care Unite, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, 063000, China;
Email: erik_p@163.com

DOI: https://doi.org/10.30564/jer.v4i1.3293

seriously affect the stability of the internal environment of the body, significantly increase the mortality rate of patients, and is an independent risk factor for death. The pathogenesis of stress-induced hyperglycemia is currently not fully understood. It is currently believed that its occurrence is mainly related to neuroendocrine regulatory changes, such as the strong excitement of the hypothalamus-pituitary-adrenal cortex axis (HOA), and the massive release of cytokines, insulin Resistance and other factors are related [4].

2. Pathophysiological Mechanism

2.1 Increased Secretion of Neuroendocrine Hormones

Under the strong stimulation of the stressor, the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic-adrenal system are activated. Increase the secretion of counter-regulatory hormones that promote blood sugar increase, such as adrenal cortisol, growth hormone, epinephrine, norepinephrine, and glucagon. According to research, under severe stress, the secretion of adrenal cortisol is more than 10 times higher than normal [5]. In severe shock patients, the sympathetic-adrenal medulla system is activated, adrenaline secretion is increased by 50 times, and norepinephrine is increased by 10 times [6]. Glucagon, growth hormone, etc. also increased several times more than usual. The increase of these stress hormones is designed to maintain the balance in the body during stress.

The characteristic reactions of increased secretion of neuroendocrine hormones are excessive gluconeogenesis, glycogenolysis and insulin resistance [7]. Cortisol increases blood glucose concentration by activating the key enzyme of liver gluconeogenesis-pyruvate, and inhibits the uptake and utilization of glucose in extrahepatic tissues such as skeletal muscle. Both adrenaline and norepinephrine stimulate liver gluconeogenesis and glycogenolysis. Norepinephrine also has the effect of increasing the supply of glycerol through lipolysis and enhancing the gluconeogenesis of the liver [8]. Glucagon increases blood glucose concentration by inhibiting glycogen synthesis, glycolysis, accelerating fat mobilization, promoting liver glycogen decomposition and gluconeogenesis. Growth hormone can promote the breakdown of fats, inhibit peripheral tissues and the use of glucose, reduce glucose consumption, and increase blood sugar concentration.

2.2 The Role of Inflammatory Factors

When a stress response occurs, the hypothalamic-pituitary-adrenal axis (HPA) secretes a large amount of adrenocorticotropic hormone releasing hormone (CRH) and Cortisol. CRH and Cortisol stimulate the immune system to produce many inflammatory factors, respectively. Such as TNF-α, IL-1, IL-6, C-reactive protein and so on. Inflammatory factors TNF-α, IL-1, and IL-6 act on the hypothalamus and pituitary gland to increase the secretion of Cortisol, thereby increasing blood sugar. Sympathetic-Adrenaline (AD) and norepinephrine (NE) produced by the adrenal system promote hepatic gluconeogenesis and increase blood sugar. Hyperglycemia can stimulate the body to produce inflammatory factors, which counteracts the sympathetic-adrenal system to increase the secretion of AD and NE and enhance gluconeogenesis. These inflammatory factors can not only stimulate the secretion of counter-regulatory hormones, but TNF-α can also stimulate liver gluconeogenesis. Hyperglycemia, inflammatory factors, and counter-regulatory hormones have potentially established a vicious circle of hyperglycemia.

2.3 Insulin Resistance

The use of glucose transporter (GLUT) to transport across cell membranes is an important mechanism for glucose transport. For non-insulin-mediated glucose uptake (NIMGU), sufficient glucose supply can be obtained through GLUT-1. GLUT-2 can regulate the amount of glucose passing through the liver and intestinal cell membranes, and GLUT-4 is the transporter of insulin-mediated glucose uptake (IMGU). In stress-induced hyperglycemia, the liver characteristic of insulin resistance is the inability to inhibit hepatic glucose production. In extrahepatic tissues, insulin resistance is manifested as a decrease in insulin-mediated glucose uptake. This may be due to defects in post-receptor insulin signaling and down-regulation of glucose transporter (GLUT-4) [9]. Excessive cortisol and epinephrine caused by stress can reduce insulin-mediated glucose uptake, and the inflammatory factor TNF-α and IL-1 can inhibit post-receptor insulin signaling [10]. In skeletal muscle and adipose tissue, the uptake of sugar mainly depends on the GLUT-4 transporter. When insulin resistance occurs, the function of GLUT-4 is down-regulated, and the synthesis of muscle glycogen is reduced, causing disorders of glycolysis products metabolism. Insulin resistance can also inhibit the catabolism of fatty acids. Excessive free fatty acids in the circulation can disrupt the insulin signal transduction and glycogen synthase of IMGU and aggravate insulin resistance [11]. Free fatty acids can also aggravate the inflammatory response and increase the release of inflammatory factors. Ultimately, glycotoxicity, lipotoxicity and inflammation form a vicious circle of elevated blood glucose, a key component of stress-related insulin resistance syndrome.

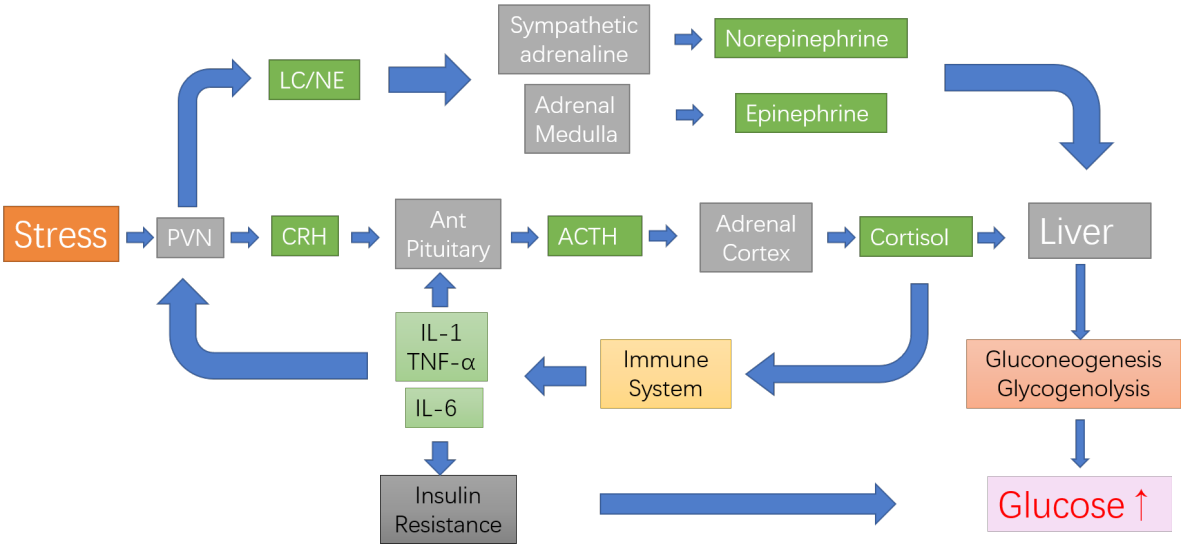

Figure 1. Mechanisms of stress hyperglycemia

3. Other Mechanisms of Stress Hyperglycemia

3.1 Endoplasmic Reticulum Stress

During stress hyperglycemia, islet β-cells may experience severe endoplasmic reticulum stress, leading to cell dysfunction and cell apoptosis. Yi's research shows that excessive endoplasmic reticulum stress can cause islet β-cell dysfunction and trigger type 2 diabetes. Cnop [12] found that severe endoplasmic reticulum stress and eIF2α phosphorylation disorders lead to β-cell failure. The endoplasmic reticulum (ER) is an important organelle involved in normal life activities and complete cell functions. It is involved in the regulation of intracellular calcium, protein translation, lipid synthesis, and cell signal transmission [13]. As the largest organelle of cells, ER is a highly active multifunctional entity, which plays a vital role in cell homeostasis, function and survival. Among them, protein translation occurs on the cytoplasmic surface of the rough endoplasmic reticulum through ribosomes. After translation, the proteins are transferred to the lumen of the ER, where they undergo post-translational modification and folding to complete their functional structure [14]. These functions are mainly performed by ER folding enzymes and molecular chaperones. For example, immunoglobulin (BiP) is also known as glucose regulatory protein 78 (GRP78), which is specifically used to fold proteins into proper forms and prevent their aggregation [15]. Under physiological conditions, GRP78 often reacts with unfolded protein (UPR) transmembrane pressure sensor activated transcription factor 6 (ATF6), protein kinase RNA endoplasmic reticulum kinase (PERK) and serine/threonine in an inactive form. The protein kinase/endoribonuclease inositol requires enzyme 1 (IRE1) to bind together. When the endoplasmic reticulum stress (ERS), the accumulation of unfolded protein in the ER increases, GRP78 is released to bind to the unfolded protein and activate downstream pathways to reduce protein translation and enhance correct folding [16,17]. However, when UPR fails to alleviate stress and re-establish normal ER function, cellular inflammation and apoptosis signals are triggered [18]. The C/EBP homologous protein (CHOP) transcription factor plays an important role in apoptosis induced by endoplasmic reticulum stress. CHOP contains two functional regions, the N-terminal transcription activation domain and a C-terminal basic leucine zipper (bZIP) domain [19]. When Matsumot studied the role of CHOP in cell growth, it was revealed that the bZIP domain is required when CHOP induces apoptosis in a p53-independent manner [20]. Nam [21] experiments in CHOP-deficient mice showed that CHOP is a key signal of MGO-induced cardiomyocyte apoptosis and cardiac dysfunction. Under physiological conditions, the expression level of CHOP is very low. When severe endoplasmic reticulum stress occurs, the expression of CHOP rises sharply and induces cell apoptosis [22]. The activation of CHOP is regulated by PERK, IRE1 and ATF6, and is the convergence point of the three paths. When a strong stress response occurs in the endoplasmic reticulum and the UPR response fails to clear the misfolded protein, the proteins accumulated in the endoplasmic reticulum will activate the three pathways of PERK, IRE1 and ATF6, which will increase the expression of CHOP and activate the downstream apoptosis pathway [23].

3.2 Oxidative Stress

In addition to causing cell apoptosis, endoplasmic reticulum stress also interacts with oxidative stress. In the cells, the folding of oxidized proteins requires the catalysis of endoplasmic reticulum oxidoreductases, such as disulfide isomerase (PDI), ERp72 and ERp57, and sulfhydryl-disulfide bond pairs in the endoplasmic reticulum lumen, reduction/oxidation Pyridine nucleotides [24]. PDI is a multifunctional oxidoreductase and molecular chaperone that can catalyze the formation of disulfide bonds in the ER. In the process of disulfide bond formation, the cysteine residue in the active site of PDI accepts two electrons from the cysteine residue in the polypeptide substrate, resulting in PDI reduction and substrate oxidation. There is evidence that oxidized protein folding is an important source of ROS production in cells. After PDI accepts electrons, endoplasmic reticulum oxidoreductase 1 (ERO1) transfers the electrons to oxygen molecules and produces hydrogen peroxide (H_2O_2). H_2O_2 is the main ROS produced in the ER [25]. Glutathione (GSH) is a thiol substance in the endoplasmic reticulum, which reduces the wrong disulfide bonds to maintain the balance between GSH and glutathione disulfide (GSSG), thereby maintaining the oxidation in the cell the steady state of reduction [26]. In addition to activating the downstream apoptotic system, CHOP activated during endoplasmic reticulum stress can increase the expression of endoplasmic reticulum oxidoreductase 1 (ERO1) gene, catalyze the oxidation of disulfide isomerase (PDI) and lead to the production of H_2O_2 [27]. The high concentration of ROS in the endoplasmic reticulum lumen will activate calcium ion channels. Calcium ions enter the cytoplasm to activate calcium-sensitive kinase (CaMKII) and the subunit NOX2 of NADPH oxidase on the cell membrane to further promote ROS [28]. Due to the close distance between the endoplasmic reticulum and mitochondria, they interact in physiological functions. During the process of ATP generated by mitochondrial oxidative phosphorylation, about 3% of the electrons will leak. The leaked electrons combine with oxygen molecules to generate ROS, which is the main way to generate ROS in the mitochondria. The known ROS production sites in mitochondria are: pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, 3-phosphate glycerol dehydrogenase, flavin in complex I, ubiquitin in complex I and complex III Quinone binding site and electron transfer flavoprotein: oxidoreductase Q [29]. The unfolded protein response (UPR) caused by the endoplasmic reticulum stress requires a large amount of ATP, and the Ca^{2+} released by the endoplasmic reticulum can enter the mitochondria through special structures (MAMs) on the mitochondrial membrane to stimulate the production of ATP [30]. As the endoplasmic reticulum stress intensifies, the misfolded proteins in the cavity continue to increase, and the demand for ATP rises sharply. A large amount of Ca^{2+} leaks to the mitochondria through MAMs. The production of ATP further enhances the production of ROS in the mitochondrial respiratory chain [31]. Ca^{2+} overload can also cause the permeability transition pore (mPTP) to open, which not only reduces the mitochondrial membrane potential, but also releases cytochrome c (Cyt-c). The loss of Cyt-c inhibits the function of mitochondrial complex III and increases the production of ROS by increasing the intermediates of ubiquinone free radicals. In addition, the increase of Ca^{2+} in the mitochondria will stimulate the dehydrogenase in the Krebs cycle, thereby increasing the consumption of oxygen and the production of ROS. Mitochondrial Ca^{2+} also activates nitric oxide synthase, the product of which disrupts the function of the mitochondrial respiratory chain and enhances ROS production [32]. Low concentration of ROS helps maintain the redox state of cells, and high concentration can cause oxidative stress. Oxidative stress can cause damage to the insulin secretion pathway [33], β-cell apoptosis [34] and local islet inflammation [35].

4. Diagnostic Criteria for Stress Hyperglycemia

The diagnostic criteria for stress hyperglycemia have not yet been unified. Some scholars and institutions will be diagnosed as stress hyperglycemia in non-diabetic patients with fasting blood glucose> 6.9 mmol and random blood glucose> 11.1 mmol [36]. The latest American ADA [37] released the diagnostic criteria for stress hyperglycemia as follows: 1) Diabetes was diagnosed before admission, and the blood glucose after admission to the hospital rose higher than the stress threshold after admission 2) Fasting blood glucose after admission>6.9 mmol or random blood glucose> 11.1 mmol, diagnosed as diabetes during hospitalization or after discharge 3) Admission fasting blood glucose> 6.9 mmol or random blood glucose> 11.1 mmol, non-diabetic patients whose blood glucose returned to normal range after discharge or during hospitalization.

5. The Harm of Stress Hyperglycemia

Stress-induced hyperglycemia is a common concomitant of serious diseases and was initially considered part of the adaptive response, which is beneficial to survival. However, in the past two decades, more and more evidence has shown that hyperglycemia is associated with increased mortality and morbidity. Hyperglycemia can cause oxidative stress, and oxidative stress activates var-

ious signaling pathways in cells, such as NF-κB, ERK, PKC, and MARK. Subsequently, it causes the secretion of inflammatory factors, endothelial cell dysfunction, platelet activation, procoagulant and anti-fibrinolysis, mitochondrial dysfunction, water and electrolyte disorders, and acid-base balance disorders. Eventually, the patient will develop critical conditions such as renal failure, polyneuropathy, sepsis and wound infection, prolonged mechanical ventilation, thrombosis and cerebral infarction, hemodynamic instability, arrhythmia, and blood transfusion therapy.

The study of Yang [38] showed that stress hyperglycemia can enhance the oxidative stress of mice and aggravate myocardial infarction by activating nicotinamide adenine dinucleotide phosphate oxidase. When stress hyperglycemia occurs after hip fracture, the risk of acute myocardial infarction increases, and the frequency of AMI reaches 9.31% [39]. In terms of the nervous system, the activation of microglia in patients with hyperglycemia increased by 3.7 to 7 times, the number of astrocytes decreased, and the apoptosis of neurons and glial cells increased by more than 9 times [40]. In the rabbit model of critical illness induced by burns, the activity of the mitochondrial respiratory chain in the stress-induced hyperglycemia group was severely reduced, and mitochondrial dysfunction caused acute kidney injury [41]. Gornik's follow-up study showed that after 5 years of follow-up of 193 patients with stress hyperglycemia in ICU during a certain period, 33 (17.1%) of them had type 2 diabetes. In another study by Ali Abdelhamid, 698 patients with stress hyperglycemia developed diabetes in the follow-up. It can be found that stress hyperglycemia not only affects the survival rate of patients in the acute phase, but can also lead to the occurrence of diabetes.

6. Management of stress hyperglycemia

In 2001, the Van den Berghe research team published an article called Leuven Intensive Insulin Therapy Trial. The article mentioned that the use of intensive insulin therapy for strict blood glucose control (target blood glucose is 3.9 mmol/L~6.1 mmol/L) significantly improves the outcome of surgical patients. Subsequently, intensive insulin therapy set off a wave of research in the ICU. A large-sample prospective randomized controlled clinical trial in 2010 showed that severe blood glucose control did not reduce mortality, infection rates, or renal replacement therapy [42]. In 2012 [43], the management of hyperglycemia in hospitalized patients in the Clinical Practice Guidelines of the Endocrinology Society pointed out that observational and randomized controlled studies have shown that the improvement of blood glucose control can reduce the incidence of hospital complications. In the same year, the clinical practice guidelines issued by the American Academy of Critical Care Medicine [44] recommended that intervention measures should be triggered when blood glucose is greater than 8.3 mmol/L to maintain blood glucose below this level and absolutely <10 mmol/L. Various research teams, associations and organizations have issued different guidelines for controlling hyperglycemia in critically ill patients, reflecting that the treatment of hyperglycemia has not yet been unified. Currently, in critically ill patients, there is no universally accepted insulin therapy for blood sugar control, and limiting blood sugar fluctuations is very important. In a large retrospective cohort study of patients with sepsis and septic shock, glucose variability was independently associated with increased mortality [45]. Similar studies have shown that higher blood glucose fluctuations are associated with negative results,

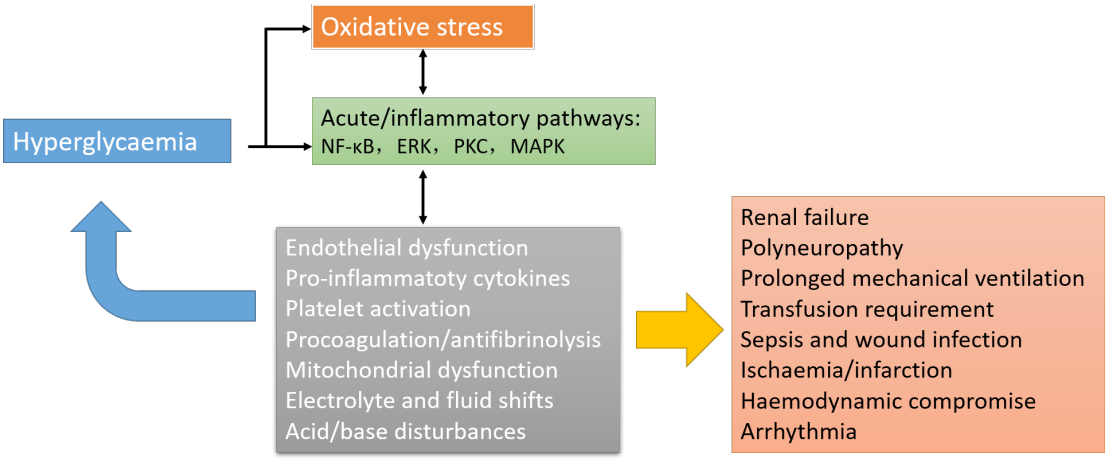

Figure 2. The adverse effects of hyperglycemia

indicating that reducing blood glucose variability is an important treatment goal. The latest guidelines recommend a target blood glucose level of 7.7 mmol/L~10.0 mmol/L, rather than a more stringent target (4.4 mmol/L~6.1 mmol/L) or a larger range (10.0 mmol/L~11.1 mmol/L). In this way, severe hyperglycemia is avoided, and the risk of iatrogenic hypoglycemia and its consequences is minimized.

7. Conclusions

Current research believes that the occurrence of stress hyperglycemia is the result of increased secretion of counter-regulatory hormones, inflammatory factors, and insulin resistance. Stress hyperglycemia can cause serious complications in clinical practice, and it has become an independent factor in the death of critically ill patients. Therefore, clinically, when facing stress hyperglycemia, they usually choose to actively use insulin to reduce hyperglycemia in order to reduce the occurrence of complications. However, is there any dysfunction in islet β-cells during stressful hyperglycemia? Does islet β-cell dysfunction induced insufficient insulin secretion and participate in the development of stress-induced hyperglycemia? What is the mechanism of its dysfunction? None of these issues are known. Further research on the functional status of islet β cells during stress hyperglycemia can supplement the pathogenesis of stress hyperglycemia and provide experimental basis for further research in the future.

References

[1] Mechanick, J.I., 2006. Metabolic mechanisms of stress hyperglycemia. Journal of parenteral and Enteral Nutrition. 30(2), 157-163.

[2] Chu, Z., Takagi, H., 2010. Hyperpolarization-activated currents in gonadotropin-releasing hormone (GnRH) neurons contribute to intrinsic excitability and are regulated by gonadal steroid feedback. The Journal of neuroscience : the official journal of the Society for Neuroscience. 30, 13373-13383.

[3] Marfella, R., Siniscalchi, M., Esposito, K., et al., 2003. Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. Diabetes care. 26(11), 3129-3135.

[4] Harp, J.B., Yancopoulos, G.D., 2016. Glucagon orchestrates stress-induced hyperglycaemia. Diabetes, obesity & metabolism. 18, 648-653.

[5] Sprung, C.L., Annane, D., Singer, M., et al., 2009. Steroids in patients with septic shock. Chest. 136(1), 323-324.

[6] Chernow, B., Rainey, T.G., Lake, C.R., 1982. Endogenous and exogenous catecholamines in critical care medicine. Critical Care Medicine. 10(6), 409-416.

[7] Tziomalos, K., Dimitriou, P., Bouziana, S.D., et al., 2017. Stress hyperglycemia and acute ischemic stroke in-hospital outcome. Metabolism. 67(9), 99-105.

[8] Barth, E., Albuszies, G., Baumgart, K., et al., 2007. Glucose metabolism and catecholamines. Critical care medicine. 35(9), S508-S518.

[9] Fan, J., Li, Y.H., Wojnar, M.M., et al., 1996. Endotoxin-induced alterations in insulin-stimulated phosphorylation of insulin receptor, IRS-1, and MAP kinase in skeletal muscle. Shock (Augusta, Ga.). 6(3), 164-170.

[10] Lang, C.H., Dobrescu, C., MEszAros, K., 1990. Insulin-mediated glucose uptake by individual tissues during sepsis. Metabolism. 39(10), 1096-1107.

[11] Dresner, A., Laurent, D., Marcucci, M., et al., 1999. Effects of free fatty acids on glucose transport and IRS-1–associated phosphatidylinositol 3-kinase activity. The Journal of clinical investigation. 103(2), 253-259.

[12] Voeltz, G.K., Rolls, M.M., Rapoport, T.A., 2002. Structural organization of the endoplasmic reticulum[J]. EMBO reports. 3(10), 944-950.

[13] Braakman, I., Bulleid, N.J., 2011. Protein folding and modification in the mammalian endoplasmic reticulum. Annual review of biochemistry. 80(2), 71-99.

[14] Ibrahim, I.M., Abdelmalek, D.H., Elfiky, A.A., 2019. GRP78: a cell's response to stress. Life sciences. 226(23), 156-163.

[15] Pfaffenbach, K.T., Lee, A.S., 2011. The critical role of GRP78 in physiologic and pathologic stress. Current opinion in cell biology. 23(2), 150-156.

[16] Hendershot, L.M., 2004. The ER function BiP is a master regulator of ER function. The Mount Sinai journal of medicine, New York. 71(5), 289-297.

[17] Ghemrawi, R., Battaglia, S.F., Arnold, C., 2018. Endoplasmic reticulum stress in metabolic disorders. Cells. 7(6), 63-70.

[18] Pandey, V.K., Mathur, A., Kakkar, P., 2019. Emerging role of Unfolded Protein Response (UPR) mediated proteotoxic apoptosis in diabetes. Life sciences. 216(6), 246-258.

[19] Ubeda, M., Wang, X.Z., Zinszner, H., et al., 1996. Stress-induced binding of the transcriptional factor CHOP to a novel DNA control element. Molecular and cellular biology. 16(4), 1479-1489.

[20] Matsumoto, M., Minami, M., Takeda, K., et al., 1996. Ectopic expression of CHOP (GADD153) induces apoptosis in M1 myeloblastic leukemia cells. FEBS

letters. 395(2), 143-147.

[21] Nam, D.H., Han, J.H., Lee, T.J., et al., 2015. CHOP deficiency prevents methylglyoxal-induced myocyte apoptosis and cardiac dysfunction. Journal of molecular and cellular cardiology. 85(1), 168-177.

[22] Yao, Y., Lu, Q., Hu, Z., et al., 2017. A non-canonical pathway regulates ER stress signaling and blocks ER stress-induced apoptosis and heart failure. Nature communications. 8(1), 1-15.

[23] Oyadomari, S., Mori, M., 2004. Roles of CHOP/GADD153 in endoplasmic reticulum stress. Cell Death & Differentiation. 11(4), 381-389.

[24] Tu, B.P., 2004. Weissman J S. Oxidative protein folding in eukaryotes mechanisms and consequences. Journal of Cell Biology. 164(3), 341-346.

[25] Santos, C.X.C., Tanaka, L.Y., Wosniak, Jr.J., et al., 2009. Mechanisms and implications of reactive oxygen species generation during the unfolded protein response: roles of endoplasmic reticulum oxidoreductases, mitochondrial electron transport, and NADPH oxidase. Antioxidants & redox signaling. 11(10), 2409-2427.

[26] Hwang, C., Sinskey, A.J., Lodish, H.F., 1992. Oxidized redox state of glutathione in the endoplasmic reticulum. Science. 257(5076), 1496-1502.

[27] Rao, J., Zhang, C., Wang, P., et al., 2015. C/EBP homologous protein (CHOP) contributes to hepatocyte death via the promotion of ERO1α signalling in acute liver failure. Biochemical Journal. 466(2), 369-378.

[28] Li, G., Scull, C., Ozcan, L., et al., 2010. NADPH oxidase links endoplasmic reticulum stress, oxidative stress, and PKR activation to induce apoptosis. Journal of Cell Biology. 191(6), 1113-1125.

[29] Brand, M.D., 2010. The sites and topology of mitochondrial superoxide production. Experimental gerontology. 45(7), 466-472.

[30] Carreras-Sureda, A., PihAn, P., Hetz, C., 2018. Calcium signaling at the endoplasmic reticulum: fine-tuning stress responses. Cell Calcium. 70(12), 24-31.

[31] GOrlach, A., Klappa, P., Kietzmann, D.T., 2006. The endoplasmic reticulum: folding, calcium homeostasis, signaling, and redox control. Antioxidants & redox signaling. 8(9), 1391-1418.

[32] St-Pierre, J., Buckingham, J.A., Roebuck, S.J., et al., 2002. Topology of superoxide production from different sites in the mitochondrial electron transport chain. Journal of Biological Chemistry. 277(47), 44784-44790.

[33] Men, X., Wang, H., Li, M., et al., 2009. Dynamin-related protein 1 mediates high glucose induced pancreatic beta cell apoptosis. The international journal of biochemistry & cell biology. 41(4), 879-890.

[34] Wang, M., Liu, Y., Liang, Y., et al., 2021. Systematic understanding of pathophysiological mechanisms of oxidative stress-related conditions—diabetes mellitus, cardiovascular diseases, and ischemia–reperfusion injury. Frontiers in Cardiovascular Medicine. 4(8), 649785.

[35] Burgos-Morón, E., Abad-Jiménez, Z., Martinez de Maranon, A., et al., 2019. Relationship between oxidative stress, ER stress, and inflammation in type 2 diabetes: the battle continues. Journal of clinical medicine. 8(9), 1385.

[36] Kerby, J.D., Griffin, R.L., MacLennan, P., et al., 2012. Stress-induced hyperglycemia, not diabetic hyperglycemia, is associated with higher mortality in trauma. Annals of surgery. 256(3), 446-452.

[37] Clement, S., Braithwaite, S.S., Magee, M.F., et al., 2004. Management of diabetes and hyperglycemia in hospitals. Diabetes care. 27(2), 553-591.

[38] Yang, Z., Laubach, V.E., French, B.A., et al., 2009. Acute hyperglycemia enhances oxidative stress and exacerbates myocardial infarction by activating nicotinamide adenine dinucleotide phosphate oxidase during reperfusion. The Journal of thoracic and cardiovascular surgery. 137(3), 723-729.

[39] Chen, Y., Yang, X., Meng, K., et al., 2013. Stress-induced hyperglycemia after hip fracture and the increased risk of acute myocardial infarction in nondiabetic patients. Diabetes care. 36(10), 3328-3332.

[40] Sonneville, R., den Hertog, H.M., GUiza, F., et al., 2012. Impact of hyperglycemia on neuropathological alterations during critical illness. The Journal of Clinical Endocrinology & Metabolism. 97(6), 2113-2123.

[41] Vanhorebeek, I., Gunst, J., Ellger, B., et al., 2009. Hyperglycemic kidney damage in an animal model of prolonged critical illness. Kidney international. 76(5), 512-520.

[42] Kavanagh, B.P., McCowen, K.C., 2010. Glycemic control in the ICU. New England Journal of Medicine. 363(26), 2540-2546.

[43] Umpierrez, G.E., Hellman, R., Korytkowski, M.T., et al., 2012. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 97(1), 16-38.

[44] Jacobi, J., Bircher, N., Krinsley, J., et al., 2012. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Critical care medicine. 40(12), 3251-3276.

[45] Ali, N.A., O'Brien, Jr.J.M., Dungan, K., et al., 2008. Glucose variability and mortality in patients with sepsis. Critical care medicine. 36(8), 2316.