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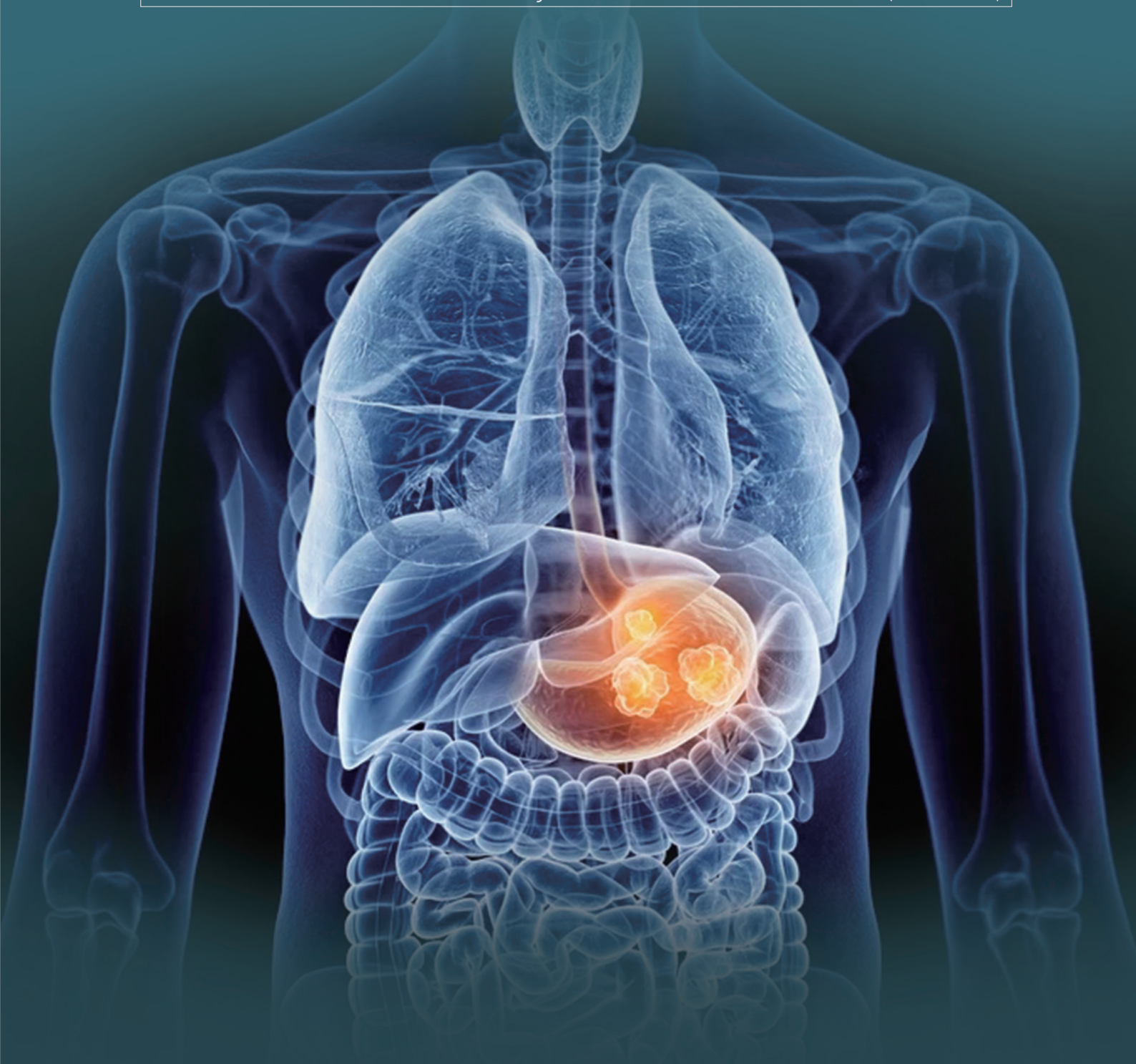
Journal of Endocrinology Research

Volume 4 · Issue 1 · January 2022 · ISSN 2630-5224(Online)



Volume 4 Issue 1 • January 2022 • ISSN 2630-5224 (Online)

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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.

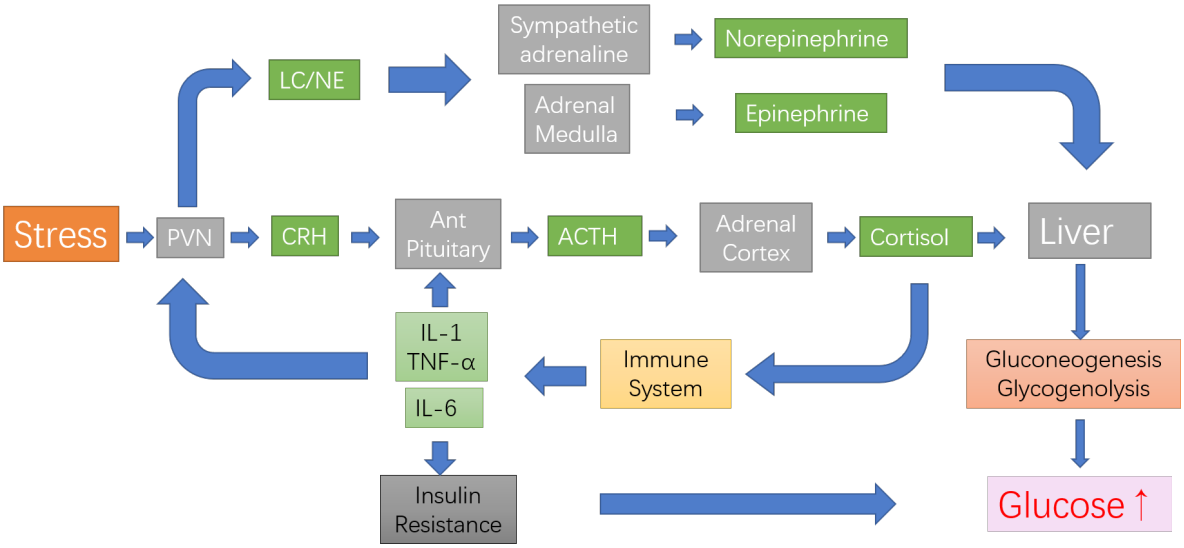

Figure 1. Mechanisms of stress hyperglycemia

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,

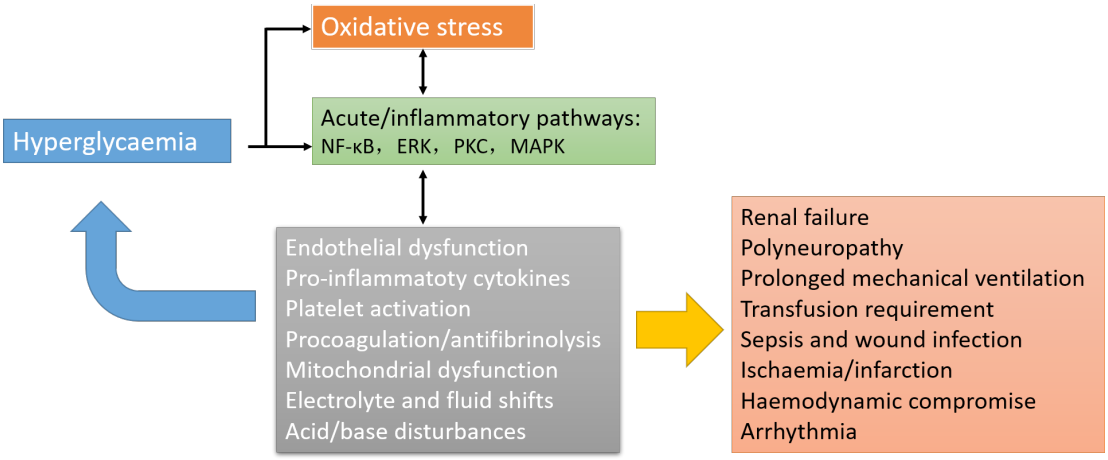

Figure 2. The adverse effects of hyperglycemia

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.

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ARTICLE

Importance and Risk Prediction of ABO Blood Group and Rh Factor in Papillary Thyroid Cancer

Dilek Geneş* **Zafer Pekkolay** **Mehmet Şimşek** **Hüsna Saraçoğlu** **Mehmet Turgut Alpaslan Kemal Tuzcu**

Dicle University Faculty of Medicine, Department of Adult Endocrinology and Metabolism, Diyarbakir, 21090, Turkey

ARTICLE INFO

Article history
Received: 24 November 2021
Accepted: 11 January 2022
Published Online: 20 January 2022

Keywords:
Papillary thyroid cancer
Blood types
ABO
Rh

ABSTRACT

Objective: There are limited data in the literature regarding the potential relationship between thyroid cancer and ABO blood types and Rh factor. The aim of our study was to investigate whether papillary thyroid cancer (PTC) is associated with blood type.

Materials and Methods: The present study included patients who presented to Dicle University Faculty of Medicine between June 2009 and December 2020 and were diagnosed with PTC as a result of postoperative (thyroidectomy) histopathological analysis. The control group consisted of individuals whose blood type was analyzed at a random blood center.

Results: Of the 223 patients diagnosed with PTC, 163 (73.1%) were females and 60 (26.9%) were males. In the comparison of patients based on ABO blood types and Rh factor, A Rh positive blood type was found 31% less frequently in the PTC group compared with the control group, and thus it was associated with a lower risk of PTC (OR:0.69; 95% Confidence Interval: 0.50–0.96, p=0.029).

Conclusions: In our study, we found A Rh positive blood type to be significantly less frequent among patients with PTC. A Rh positive blood type can be considered as a protective factor indicating a reduced risk of PTC.

1. Introduction

Thyroid cancers are the most common endocrine malignancy and account for approximately 3% of the global cancer incidence [1]. Differentiated thyroid cancers (DTCs) arising from thyroid follicular epithelial cells account for the vast majority of thyroid cancers. A total of 3%–9% of DTCs are familial [2], and approximately 85% of these DTCs are papillary thyroid cancers (PTCs) [3]. Increased incidence rates are mainly due to increased PTC diagnosis rates. Detection of small and subclinical PTCs has become easier with the improvements in imaging techniques, biopsy methods (fine needle aspiration biopsy), medical surveillance, and healthcare accessibility [4]. Therefore, the incidence of thyroid cancer is still increasing [5].

*Corresponding Author:
Dilek Geneş,
Dicle University Faculty of Medicine, Department of Adult Endocrinology and Metabolism, Diyarbakir, 21090, Turkey;
Email: dilekgenes21@gmail.com

DOI: https://doi.org/10.30564/jer.v4i1.4133

The well-known risk factor for the development of thyroid cancers, particularly PTC, is exposure to ionizing radiation, particularly during childhood [2,6-9]; however, it is considered that other factors (family history, sex, obesity, smoking, alcohol consumption, hormonal exposure, and some environmental pollutants) may also play a role [1,9,10]. It is believed that exposure to certain chemicals during intrauterine life and early childhood, especially along with possible epigenetic changes, may result in a mutagenic tendency in thyroid cells [6]. An inverse relationship between smoking and alcohol consumption and thyroid cancer has been mentioned in some studies [9,10]. Other factors that are believed to cause thyroid cancer include high dietary iodine content (especially PTC) [8], as well as intakes of selenium, goitrogens, and carcinogens. High thyroid stimulating hormone levels and genetic syndromes (Gardner, Cowden, and Werner syndromes) have been associated with DTC [7]. Because most flame retardants have chemical structures similar to thyroid hormones, they have been reported to alter thyroid hormone homeostasis and have ultimately become one of the suggested causes owing to their potential effects on the risk of thyroid cancer [10].

Blood type analysis is a key procedure in the blood transfusion process along with genetic analyses and associated disease examinations. The first blood type antigen system was the ABO system [11]. ABO blood type antigens are defined by the carbohydrate moieties on the outer surface of the erythrocyte cell membrane [12]. ABO antigens are also secreted from many sites other than erythrocytes, including platelets, vascular endothelial cells, mucous, and epithelial tissues [13]. The Rh system is the second most important blood type system in the preliminary transfusion test [11].

Clinical studies have shown that the ABO blood type plays a role in various diseases and malignancies [14]. The relationship between ABO blood types and cancer was first reported in 1953. Since then, numerous studies have been published with often conflicting results [13]. Although some studies evince a relationship between ABO blood type antigens and various cancer types, there is limited data on its prognostic significance in patients [12]. Further large-scale studies are warranted to determine whether ABO antigens have a function and, if they do, how this function contributes to tumorigenesis [13]. In this study, we aimed to determine whether PTC, a type of DTC, is associated with blood type.

2. Materials and Methods

Patients who presented to Dicle University Faculty of Medicine between June 2009 and December 2020 and were diagnosed with PTC as a result of postoperative (thyroidectomy) histopathological analysis and a control group consisting of individuals whose blood type was analyzed at a random blood center were retrospectively included in the present study.

The control group consists of people who applied to the emergency department of our hospital between these dates for any reason and whose blood groups were studied in the blood center. Individuals were selected by simple randomization to avoid bias from the hospital system. No disease screening was performed in the control group. Adults older than 16 years were included in the control group. It is known that the prevalence of thyroid diseases is higher in female gender. Therefore, gender matching was not done between the groups so that the control group represents the real population.

The blood types of these individuals were recorded. ABO and Rh blood types were determined at the blood center using the gel centrifugation method (column agglutination; Ortho AUTOVUE INNOVA). Individuals aged <16 years, patients with concomitant non-thyroid malignancies, and those with other non-PTC thyroid malignancies were excluded from our study. This study was approved by Dicle University medical ethics committee (No: 145/2021) in accordance with the ethical standards of the Declaration of Helsinki.

The data were analyzed using SPSS Version 22. The control and PTC groups were compared. Chi-square test was used to compare categorical variables and Mann-Whitney U test was used to compare numerical variables between groups. For statistical significance, results with $p<0.05$ at 95% Confidence Interval (CI) were considered significant.

3. Results

Of the 223 patients with PTC in the study, 163 (73.1%) were females and 60 (26.9%) were males. Their median age (minimum–maximum) was 43 (16–86) years. Of the 1040 individuals in the control group, 547 (52.6%) were females and 493 (47.4%) were males. Their median age (minimum–maximum) was also 43 (16–90) years. PTC was observed at a significantly higher rate in females ($p<0.001$). A comparison based on ABO blood types and Rh factor revealed that A Rh positive blood type was observed at a lower rate in the PTC group than in the control group (OR:0.69; 95% CI: 0.50–0.96, $p=0.029$). However, there were no significant differences among other blood types and Rh factors. The occurrence rates of blood types in the PTC and control groups and the demographic characteristics of the individuals are presented in Table 1.

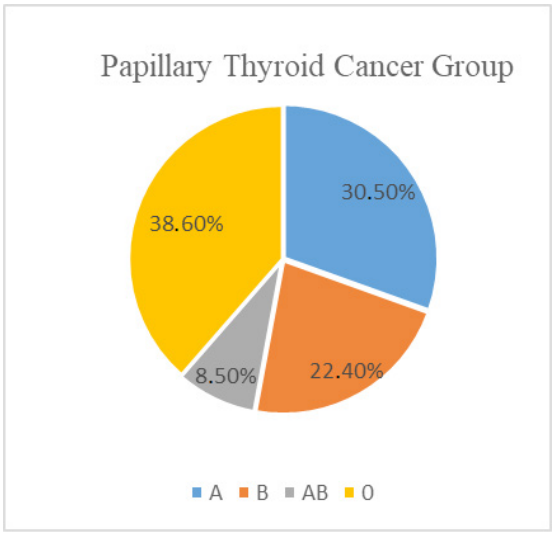
Although A blood type was the most common blood

type in Diyarbakir, Turkey (control group), with an occurrence rate of 37.6%, O blood type was found to be the most common blood type in the PTC group, with an occurrence rate of 38.6%. Percentage distributions of blood types are presented in Figure 1. In Figure 2, the distributions of ABO blood types and Rh factor in the PTC and control groups are presented. A Rh positive blood type was found at an occurrence rate of 33.6% in the control group and 26% in the PTC group, whereas O Rh positive blood type was found at an occurrence rate of 32.1% in the control group and 35% in the PTC group.

Table 1. Distribution of ABO blood types and Rh factor in the control and papillary thyroid cancer groups

	PTC n = 223(%)	Control n = 1040(%)	p value
Age (years)*	43 (16-86)	43 (16-90)	0.261
Sex			
Female	163 (73.1%)	547 (52.6%)	<0.001
Male	60 (26.9%)	493 (47.4%)	<0.001
ABO			
A Positive	58 (26%)	349 (33.6%)	0.029
A Negative	10 (4.5%)	42 (4%)	0.761
B Positive	40 (17.9%)	172 (16.5%)	0.612
B Negative	10 (4.5%)	27 (2.6%)	0.129
AB Positive	16 (7.2%)	74 (7.1%)	0.975
AB Negative	3 (1.3%)	12 (1.2%)	0.811
O Positive	78 (35%)	334 (32.1%)	0.408
O Negative	8 (3.6%)	30 (2.9%)	0.577
Rh factor			
Rh Positive	192 (86.1%)	929 (89.3%)	0.229
Rh Negative	31 (13.9%)	111 (10.7%)	0.575

PTC: Papillary thyroid cancer; $p < 0.05$ was considered statistically significant. * Median (minimum–maximum)



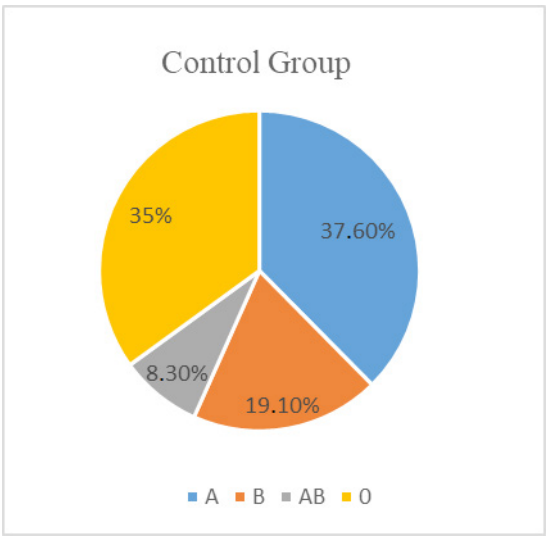


Figure 1. Schematic distribution of ABO blood types

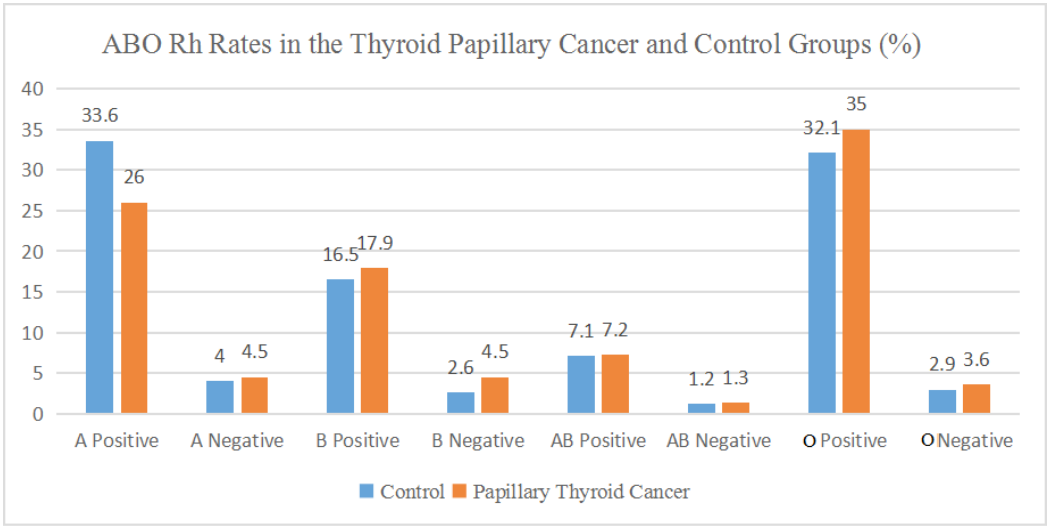


Figure 2. Occurrence rates of ABO blood types and Rh factor in the thyroid papillary cancer and control groups (in percentages)

4. Discussion

Over 90% of thyroid cancers are of the follicular or papillary variants often termed differentiated thyroid cancer [15]. Many factors other than ionizing radiation have been reported to be associated with the etiology of thyroid cancer, but a definite causality has not yet been established. There are limited data in the literature regarding the possible relationship between thyroid cancer and ABO blood types and the Rh factor [14]. Blood types have been investigated in the etiology of many malignancies. Meta-analyses have detected a decreased risk of gastric, pancreatic, breast, ovarian, colorectal, esophageal and nasopharyngeal cancers for patients with O blood type. Although associations between some malignancies and blood types have been demonstrated, the link between the expression of blood type antigens and tumor formation has not been clarified for most tumor types in various studies. It was thought that genome-wide association studies may provide prognostic support for the association between the ABO glycosyltransferase gene and cancer risk [13]. In a study, blood group A was associated with significantly higher risk for malignancy including hepatocellular carcinoma, pancreatic and breast cancers while biliary and esophageal cancer risk was significantly associated with blood type B [16]. In another study both B and AB blood types have been associated with a significantly lower risk of gastrointestinal cancer, colorectal cancer. Blood group B was also associated with a significantly lower risk of stomach cancer and bladder cancer, while blood group AB was observed to significantly increase the risk of liver cancer. It has been found that the risk of gastric cancer, colorectal cancer increases with blood group A [17]. We investigated the relationship between PTC and blood types in the present study.

The distribution of ABO blood types and Rh factor varies between populations and races [18]. In a research conducted in Diyarbakir in Turkey, ABO and Rh blood type ratios were found to be similar to our study. The blood groups of a total of 206.673 people who applied to blood centers were found respectively; 36.55% A Rh(+), 29.70% O Rh(+), 16.65% B Rh(+), 6.26% AB Rh(+), 4.26% A Rh(–), 3.95% O Rh(–), 1.88% B Rh(–), 0.72% AB Rh(–). 89.17% of the applicants were Rh positive and 10.82% were Rh negative. As a result, it was stated that there were few differences with the blood group distributions in other regions of our country, and the blood group distribution determined in the study was similar to our country in general [19]. In the present study, the A blood type was the most common blood type, with a slightly higher occurrence rate than the O blood type, which was found at a similar rate to the control group. In the PTC group, blood type A was observed less frequently, whereas blood type O was observed relatively more frequently. The lower occurrence rate of A blood type was statistically significant; however, the higher occurrence rate of O blood type was not statistically significant.

Recent studies have reported a relationship between polymorphisms in the ABO gene locus and circulating tumor necrosis factor-alpha, intercellular adhesion molecule-1, E-selectin, and P-selectin levels. It is considered that altered ABO glycosyltransferase activity affects cell proliferation, tumor invasion, and metastatic invasion, thereby playing a key role in carcinogenesis. This suggested that ABO blood type may directly influence tumorigenesis and tumor spread and provide a biological basis for its putative effect on cancer survival. The results of studies evaluating the prognostic significance of ABO antigens in various cancers are rather contradictory. Blood type O appears to be protective against cancer development and progression in pancreatic cancer, whereas the expression of A blood type antigen in tumor cells is reportedly a positive prognostic factor in lung cancer [12]. In our study, A Rh positive blood type was found to be a positive protective factor for PTC.

There are limited data in the literature regarding the relationship between blood types and Rh factor in thyroid cancer. Initially, the keratan sulfate epitope was considered as a specific marker of PTC cells and was observed to be produced simultaneously with poly-N-acetyllactosamine, which carries blood type antigens [20]. In another study, the expression of blood type-related antigens was demonstrated in thyroid follicular epithelial cells [21]. In a similar study, it was reported that the neoplastic transformation of thyroid gland was accompanied by progressive re-expression of blood type-related antigens, which are not found in normal tissues. The results of that study suggested that poly-N-acetyllactosamine structures are produced in papillary carcinomas in a linear fashion, and these structures are of promising diagnostic value for distinguishing PTC from other thyroid malignancies [22]. Because of these findings that support the role of blood type in cancer pathogenesis, it is believed that there may be a relationship particularly between PTC and blood type.

In a study investigating the relationship between thyroid cancer, diabetes, and ABO blood type [23], 87 patients with thyroid cancer (68 of them had PTC) were compared with a control group. The most common blood type was O in both groups. It was observed that, compared with the control group, blood type A was significantly less common in patients with thyroid cancer and reduced the risk of thyroid cancer by 43%. Borderline (increased risk

of 60%) thyroid cancer risk was reported in patients with blood type B. It was considered that blood type A could significantly reduce the risk of thyroid cancer, whereas blood type B could increase this risk. However, there was no significant relationship between PTC and ABO blood type. The low number of patients with PTC in that study may explain the inability to reveal any relationship with blood type A. As a matter of fact, we found that the risk of PTC decreased significantly by 31% in patients with A Rh positive blood type in our study (OR:0.69, 95% CI: 0.50–0.96). In addition, in the present study, although blood type B was found to be relatively more common in the PTC group, this increase was not statistically significant.

In another study evaluating Rh factor together with ABO blood types [14], 1299 patients with benign and 744 patients with malignant thyroid disease (700 of them had PTC) were compared based on their histopathological features. Individuals with malignant disease were more frequently Rh positive than individuals with benign disease. However, no significant relationship was noted between ABO blood types and thyroid malignancy. Blood type B was considered to potentially contribute to the development of thyroid cancer and as a risk factor for autoimmune thyroid disease. It was considered that the aforementioned study was not sufficient to evaluate the differences in blood types of patients with thyroid cancers and the normal population because it only compared patients with benign thyroid disease and those with malignant thyroid disease. In our study, no significant difference was found between the PTC group and the control group in terms of blood Rh factor.

The limitation of our study in cancer risk assessment was the inability to evaluate the genetic transition of PTC and the environmental exposure of the patients because it was a single-centered, retrospective study.

In conclusion, genetic transitions and potential exposure to environmental carcinogens and ionizing radiation are considered to be the main factors responsible for the pathogenesis of thyroid cancer. However, A Rh positive blood type can be considered as a protective factor indicating a reduced risk of occurrence of PTC.

Acknowledgment

We would like to thank Fatma Şener who contributed to the collection of data in our study.

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EDITORIAL

Lessons from Immune Escape Mechanisms of Embryo Development in Uterus

Shuang Zhang*

Department of Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China

ARTICLE INFO

Article history
Received: 27 December 2021
Accepted: 17 January 2021
Published Online: 24 January 2022

The development of semi-allogenic embryo in uterus during pregnancy is an immunological paradox, the immune tolerance in the fetomaternal interface is naturally established to prevent the embryo rejection. Solid tumors exist as a "new life" develop years, employ local or distant body nutrients to adapt, grow and metastasize to different organs of host. The development of embryo and tumor shares numerous similarities across the immune landscape and microenvironmental factors. Lessons from embryo development can increase our understanding on tumorigenesis and its components that could potentially transform anticancer therapeutic interventions.

Embryo implantation is occurring in a precisely controlled "window" period. In response to implanting embryo, the surrounding endometrium undergoes cellular transformation, a process known as decidualization, to accommodate embryonic growth and invasion [1]. The uterus decidua as well as the upcoming developed placenta are physical barriers between the mother and the fetus, play key roles in promoting the anti-inflammatory environment necessary for embryo development and pregnancy progression.

Distinct factors, including genetical, biological and immunological, work corporately in guiding fetus prevention during pregnancy [2]. Here we mainly illustrate major mechanisms of allogenic embryo escape the mother's immune systems.

lack of expression of classic HLA-I molecules

Healthy placental trophoblast cells are lack of paternal MHC class II or Ia molecules, which normally present

*Corresponding Author:
Shuang Zhang,
Department of Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China;
Email: Zhangshuang0122@gmail.com

DOI: https://doi.org/10.30564/jer.v4i1.4356

antigens to the cytotoxic T lymphocytes. However, class Ib non-polymorphic molecules, such as HLA-G, HLA-E and HLA-F, are highly expressed on tropoblasts, and play roles in inhibiting the proliferation and cytotoxic of T lymphocytes and NK cells [3]. This point was believed to be one explanation of why embryo escape the immunosurveillance of the mother. However, this view has been questioned recently since the rate of pregnancy was not affected by transgenic expression of parental MHC molecules in several studies, suggesting that the lack of MHC class is dispensable in maintaining the fetomaternal tolerance [4].

Activation of a type Th2 regulatory lymphocyte response

The T helper type 1 (Th1)-Th2 theory defines that Th1 cells-derived cytokines, such as IFN-γ, predominantly promote cell-mediated immunity, whereas cytokines produced by Th2 cells, such as IL-4, induce humoral immunity and the production of immunoglobulin antibodies. Pregnancy was proposed as a Th2 phenomenon, and a shift from Th1 to Th2 is essential for a successful pregnancy. However, this Th1-Th2 paradigm has been challenged since IFN-γ that is detrimental to human pregnancy facilitates uterine vascular modification, decidualization and uNK cells differentiation in mice [5]. With the evidences of more subtypes on differentiation of CD4+ T helper cells, The Th1/Th2/Th17 and regulatory T cells (Tregs) paradigm during pregnancy has been proposed and drawn extensive attention of immunologists [6].

Production of immunosuppressive cytokines

The uterus could produce multiple cytokines, such as IL-4, IL-10, IL-5, PGE2 and M-CSF, to induce Th2 response for successfully pregnancy. On another hand, T cell attracting chemokines in decidua were epigenetically silenced, which lead to the effector T cells fail to infiltrate into the decidua in response to fetal challenge [7]. Besides, DC cells were entrapped by decidua and thus minimizing the activation of naïve T cells that responsible for fetal rejection during early pregnancy at the fetomaternal interface [8]. NK cells in placenta present different CD56+ cells secreting IL-8 and IL-6 to reduce vascular resistance [9]. It has been reported that the number of NKs significantly reduced in pregnancy and their capability to produce IFNγ is also dampened. Placental Tregs modulate active T cells using a series of repressive reactions including expropriation of IL-2 as well as increased release cytokines and other molecules [10].

In general, precise modulations of immune system maintain successful pregnancy till parturition, while uncontrolled immune suppression preserves the tumor for an indefinite period. A comprehensive study of immunoregulatory mechanisms of embryo development during pregnancy could provide fresh ideas on how to overcome tumor immune evasion and inspire more durable approaches to arrest cancer progression.

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REVIEW

The Role of Vitamin D on Thyroid Antibodies in Patients with Chronic Autoimmune Thyroiditis

Nino Turashvili[1*] Lali Javashvili[2] Elene Giorgadze[1,3]

1. Department of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, 0179, Georgia
2. Cortex Clinic Ltd., Tbilisi, 0177, Georgia
3. National Institute of Endocrinology, Tbilisi, 0159, Georgia

ARTICLE INFO

Article history
Received: 24 January 2022
Accepted: 17 February 2022
Published Online: 18 February 2022

Keywords:
Hashimoto's thyroiditis
Chronic autoimmune thyroiditis
Vitamin D

ABSTRACT

Vitamin D deficiency is a global problem, which has taken the form of a pandemic. Existing data indicate that vitamin D is not only a nutrient. It has also a hormone-specific activity. Vitamin D is characterized by anti-inflammatory and immunomodulatory properties. Chronic autoimmune thyroiditis is a disease of autoimmune genesis, in which lymphocytic infiltration gradually destroys thyroid tissue. There are some evidences about vitamin D deficiency and the development of chronic autoimmune thyroiditis. The article has reviewed the current literature about the impact and the benefits of vitamin D on thyroid antibodies levels.

1. Introduction

The active form of vitamin D-1,25 $(OH)_2$ D, also called calcitriol - is a steroid hormone. Its important function is to regulate the level of calcium and phosphorus in blood [1]. Recent data indicate that in addition to participating in the metabolism of the musculoskeletal system, vitamin D is characterized by immunomodulatory effects. It is especially interesting that vitamin D can reduce the risk of developing various chronic diseases, including cancer, autoimmune diseases, infectious and cardiovascular pathologies [2]. According to various studies, vitamin D can prevent or inhibit some autoimmune diseases. Calcitriol is associated with disease activity and anti-citrullinated protein antibodies in rheumatoid arthritis patients [3]. The prevalence of vitamin D deficiency is very common in patients with type 1 diabetes [4,5]. Multiple sclerosis has also been shown to be associated significantly with environmental factors such as the lack of vitamin D [6-8].

Chronic autoimmune thyroiditis, also called Hashimoto's thyroiditis (HT) is one of the most widespread endocrine autoimmune diseases. It is characterized by lymphocytic infiltration of the thyroid parenchyma and increased levels of thyroid antibodies (thyroid peroxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-TG)) in

*Corresponding Author:
Nino Turashvili,
Department of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, 0179, Georgia;
Email: ninoturashvili88@yahoo.com

DOI: https://doi.org/10.30564/jer.v4i1.4408

blood. The basis for the development of chronic autoimmune thyroiditis is the autoimmune destruction of thyroid tissue by T and B lymphocytes [9-11]. Some studies have suggested a possible link between vitamin D level and the development of chronic autoimmune thyroiditis. The article has reviewed the current literature about the role and benefits of vitamin D on thyroid antibodies levels during chronic autoimmune thyroiditis.

2. Vitamin D and Its Immunomodulatory Effects

Vitamin D was first identified in the early 20th century and was considered as a necessary nutrient for the prevention of rickets, although it is currently considered as a prohormone [12].

Vitamin D is produced by the human body - in the skin under the influence of sun ultraviolet rays (UVB), although in small quantities it can be obtained from food. There are two main forms of vitamin D: D2 and D3 [13]. Vitamin D (both ergocalciferol or cholecalciferol) is biologically inactive. To achieve its main effects, vitamin D needs hydroxylation first in the liver, to form the basic circulating form with little biological activity - 25- hydroxyvitamin D (25(OH)D2 or 25(OH)D3). 25(OH)D is then converted into a bioactive form 1,25 dihydroxy-vitamin D ($1,25(OH)_2D$ or calcitriol) in the kidney [14,15]. For further action, calcitriol needs to bind to the vitamin D receptors (VDRs). These receptors are located in all organs and cells. Therefore, vitamin D has a great impact on all organ systems.

Vitamin D has long been considered as an essential vitamin for the musculoskeletal system [16,17], but newer studies indicate its influences on various organ cells and systems [18], including the immune system [19]. The active form of vitamin D has a significant impact on the innate and adaptive immune system. Vitamin D is an important factor for the maturation of macrophages and can promote the differentiation of monocytes into macrophages, as well as enhance phagocytosis and chemotaxis and promote the anti-tumor action of mononuclear macrophages. Vitamin D inhibits the production of inflammatory cytokines (e.g. TNF-a, which plays an important role in the inflammatory process) and inhibits inflammation [20]. The active form of vitamin D promotes the differentiation of monocytes and inhibits the maturation of dendritic cells. Calcitriol can also inhibit cytokines such as IL-1, IL-2, IL-6 [21].

As mentioned, calcitriol promotes the innate immune system response but inhibits the action of the adaptive immune system. Vitamin D reduces the production of inflammatory cytokines by monocytes, such as tumor necrosis factor (TNF) and interleukin 6 (IL-6). Calcitriol promotes apoptosis of B cells and thus inhibits their proliferation and differentiation into plasma cells [22].

T lymphocytes are also a major target for the action of vitamin D [23,24]. Vitamin D receptors are expressed on T cells, therefore vitamin D can have a direct effect on T cells and regulate their response. There are some direct endocrine, intracrine, paracrine and indirect mechanisms by which vitamin D may influence T cell function [25]. In addition, vitamin D can have an effect on the distribution of Th1, Th2 and Th17 cells. Th1 cells produce proinflammatory cytokines (including IFN-y and IL-2). Th17 cells can produce another pro-inflammatory cytokines such as IL-17 and IL-22. Calcitriol inhibits the activity of Th-17 and Th1 cells. The activity of these cells leads to the development of various chronic inflammatory processes due to the secretion of several cytokines [26]. $1,25\ (OH)_2$ D3 promotes the polarization of CD4 + cells in favor of Th2 cells, which promotes increased cytokine secretion, such as IL-4, IL-5, IL-10 [27]. Calcitriol inhibits maturation of dendritic cells, reduces antigen uptake and promotes activation of naïve T lymphocytic cells, which are an important factor in inhibiting autoimmune processes [20,28].

3. Chronic Autoimmune Thyroiditis (Hashimoto's Thyroiditis)

Chronic autoimmune thyroiditis (Hashimoto's thyroiditis (HT)) is a widespread autoimmune endocrine disease. It belongs to the group of chronic autoimmune diseases of the thyroid gland and is characterized by increased levels of thyroid auto- antibodies in the blood (thyroperoxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-TG), and lymphocytic infiltration of the thyroid tissue. All of the above contributes to the gradual decrease of thyroid function and often leads to various degrees of thyroid hypofunction [29,30].

The development of chronic autoimmune thyroiditis is facilitated by a combination of different genetic factors and environmental conditions [31,32]. Its prevalence depends on various factors such as age (more common between the ages of 45-55), gender (women are 4-10 times more likely to get this disease than men) and race (more common in whites than blacks, asians and hispanics). Other additional factors such as alcohol consumption, stress, pregnancy and the use of certain medications (e.g. interferon-α, iodine, immunomodulatory agents - pembrolizumab, ipilimumab, nivolumab...) may contribute to the development of chronic autoimmune thyroiditis. Although HLA-DR antigens are not physiologically found on thyrocytes, expression of HLA-DR antigens on the surface of thyrocytes is observed in patients with chronic autoimmune thyroiditis. This factor contributes to the onset of autoimmune

process [33]. It is currently known that the HLA-DR3 allele is associated with chronic autoimmune thyroid disease [34].

Although the exact mechanism of progressive thyroid tissue destruction is not clear, HT is regarded as a disorder of T cell-mediated immunity [30]. Autoimmune thyroid disease is caused by an imbalance between Th1 and Th2 cells. Patients with HT have high levels of Th1 cells secreting the cytokine IFN-y [35]. HT is characterized by low number of CD4+ T cells and increased number of CD8+T cells. CD8+ T cells have cytotoxic properties in HT [36]. Th1 cells activate cytotoxic lymphocytes and macrophages, which directly affect thyroid tissue by destroying thyroid follicular cells. In the tissues of the thyroid in patients with HT, Th1 are the predominant cells. In HT, damaged thyroid follicles with apoptotic thyrocytes (pyknotic nuclei, condensed cytoplasm with enlarged mitochondria and endoplasmic reticulum cisterns) were visible in these tissues. Blood and thyroid Th17 cells, which secrete the cytokine IL-17, are increased in HT. In addition to IL-17, Th17 cells secrete IL-22, a cytokine which targets epithelial cells and which is also secreted by Th22 cells. High levels of Th22 cells have now been reported in the blood and thyroid of HT patients [37]. Whereas vitamin D plays an important role in regulating Th1, Th2, and Th17 cells, as well as the secretion of cytokines, various studies have been conducted to investigate association between vitamin D deficiency and chronic autoimmune thyroiditis.

4. A Possible Link between Vitamin D Deficiency and Anti-thyroid Antibodies Levels

Various studies indicate on a possible association between D hypovitaminosis and HT [38,39] (Table 1). Data indicate that patients with increased thyroid antibodies have lower 25(OH)D3 compared to thyroid antibodies negative subjects: Unal, Asli Dogruk, et al. found a significant correlation between thyroid autoantibodies and vitamin D: Thyroid autoantibodies were higher in patients with lower 25(OH) D status [40]. Kivity, Shaye with coauthors indicate that vitamin D deficiency was more common in patients with thyroid disorder compared to healthy subjects [41]. Sayki Arslan, Muyesser, et al declared that thyroid autoantibody positivity was more frequently in vitamin D deficient patients than in patients with an adequate 25(OH) D level [42]. Bozkurt, Nujen Colak, et al.showed that very low vitamin D (<10 ng/mL) was inversely correlated with serum anti-TPO - anti-TG levels [43]. Muscogiuri, Giovanna, et al. evaluated vitamin D deficiency and its link to chronic autoimmune thyroiditis: There was a statistically negative correlation between vitamin D and anti-TPO titers [44]. In chinese population vitamin D deficiency or/ and insufficiency was more common in anti-TG positive patients and low 25(OH)D was associated with anti-TG titers only in women [45]. The association of vitamin D deficiency with autoimmune thyroid disease (AITD) has been found in premenopausal, but not in postmenopausal women in Korean studies [46,47]. However, there are some studies with different outcomes: Goswami, Ravinder, et al. indicate that vitamin D levels had only weak negative correlation with anti-TPO levels [48]. They think that the narrow range of vitamin D level in their study could have an impact and reduce the protective effect of higher titer of vitamin D on thyroid antibodies. Ma, Jie, et al observed that low vitamin D level is a risk factor for AITD, but any association with the anti-TPO- anti-TG was not found [49]. Authors indicate that patients in their study had very high titer of thyroid antibodies (anti-TPO, anti-TG). Therefore the correlation of thyroid antibodies with vitamin D was inadequately expressed.

Thus, most studies confirm that patients with D vitamin deficiency have higher titer of thyroid antibodies compared to individuals with adequate vitamin D concentration in blood. This may be explained by the immunomodulatory abilities of vitamin D and its impacts on the immune system: D vitamin suppress production of several proinflammatory cytokines and maintains immune tolerance. The statistically significant association of decreased vitamin D levels with higher levels of anti-TPO or / and anti-TG is mostly found in premenopausal women. The reason of this connection may be the fact that chronic autoimmune thyroiditis is mostly noted in women. It should be also noted that there is a possible connection between vitamin D and estrogen in the development of chronic autoimmune thyroiditis: 17-β estradiol could induce greater binding to D vitamin binding protein to T cells and macrophages, after that calcitriol accumulates in immune cells [46]. So, low levels of vitamin D may contribute to the development of chronic autoimmune thyroiditis, predominantly in premenopausal women.

However, the optimal levels of vitamin D to prevent the onset of chronic autoimmune thyroiditis or decrease thyroidal antibodies are still controversial. According to the endocrine society, 25(OH) D less than 20 ng/mL indicates on deficiency, 20-29 ng/mL and 30 ng/mL –on insufficient and sufficient levels of vitamin D respectively [50].

It is not still clear how vitamin D supplementation will reduce anti-TPO and anti-TG concentrations. Various studies have been conducted in autoimmune thyroiditis patients to evaluate the effectiveness of vitamin D supplements (Table 2). Krysiak, R., K. Kowalcze, and B. Okopien. indicate that vitamin D supplementation reduces thyroid antibodies (anti-TPO more than anti-TG). The effect of vitamin D supplementation on anti-TPO

Table 1. Studies on vitamin D and anti-thyroid antibodies levels

Authors	Number of enrolled patients	Country	Definition of vitamin D deficiency	Main findings
Unal, Asli Dogruk, et al. [40]	405	Turkey	< 20 ng/mL	25(OH)D was negatively correlated with anti-TG (P=0.025) and anti-TPO (P = 0.003) levels.
Kivity, Shaye, et al. [41].	190	Hungary	<10 ng/mL	25(OH) D deficiency was higher in patients with AITDs compared with control group (P <0.001); Vitamin D deficiency correlated to anti-thyroid antibodies titer (P=0,01)
Sayki Arslan, Muyesser, et al. [42]	155	Turkey	< 20 ng/mL	A negative correlation was found between anti-TPO, anti-TG and the 25(OH)D3 level (P = 0.017 ; P= 0.05,)
Bozkurt, Nujen Colak, et al. [43]	540	Turkey	<20 ng/mL	Vitamin D negatively correlated to anti-TPO (P< 0.001) and anti-TG levels (P< 0.001). Vitamin D deficiency severity (<10 ng/mL) correlated with thyroid antibody levels.
Muscogiuri, Giovanna, et al. [44]	168	Italy	<20 ng/mL	A correlation between 25(OH) D and anti-TPO (P = 0.03) was found. Any correlation between vitamin D status and anti-TG was not detected (p = 0.25).
Wang, Xinling, et al. [45]	1714	China	<20 ng/mL	A negative correlation (P = 0.014) was found between vitamin D and anti-TG titers only in women.
Kim,Choon-Young, et al. [46]	4356	S.Korea	<10 ng/mL	Vitamin D insufficiency /deficiency were associated with anti-TPO(+) in premenopausal female (P<0.001)
Choi, Yun Mi, et al. [47]	6685	S.Korea	<10 ng/mL	Decreased 25(OH) D3 status was significantly associated with autoimmune thyroid disease, especially in premenopausal female (In TPO-Ab(+) group- P= 0.003. In anti-TPO(+)/US(+) groups- P < 0.001).

and 25(OH)D levels was greater in vitamin D deficiency patients compared to vitamin D insufficiency or normal vitamin D status group [51]. Simsek, Yasin, et al. also indicated that supplementation of the vitamin D reduced anti-TPO, anti-TG titers in vitamin D deficient subjects [52]. Mazokopakis, Elias E., et al. suggested that vitamin D deficiency may have some link to pathogenesis of HT and supplementation with cholecalciferol (CF) may reduce anti-TPO levels and promote of the treatment of chronic autoimmune thyroiditis [53]. Chaudhary, Sandeep, with coworkers showed that vitamin D supplementation with high doses (CF 60000 IU/weekly) in patients with HT was associated with a significant decreasing of anti-TPO levels [54]. Chahardoli, Reza, et al. administered also a high dose of vitamin D3 [55], because supplementation with low doses (vitamin D3 1000 IU/d or 400 IU/d) during 16 weeks did not reveal significant benefits on the thyroid autoimmunity [56]. Most studies indicate that vitamin D could reduce thyroid antibodies parameters, but this effect may be dose-dependent. Data suggested that vitamin D supplementation with doses of ≤1000 IU and durations of ≤2 months did not reach to effects [57]. In contrast to the above studies, Anaraki, Parichehr Vahabi, et al reported that 50000 IU cholecalciferol weekly, for 12 weeks in vitamin D deficient patients with HT could not have significant benefits on the function and autoimmunity of thyroid gland [58]. However, one of the important limitations of their study was small number of participants.

Table 2. The effects of vitamin D supplements on thyroid antibody levels

Authors	Number of enrolled patients	Country	Vitamin D deficiency criterion	Dose and duration of supplementation	Main findings
Chahardoli, Reza, et al. [55]	42 women	Iran	< 20 ng/mL	50 000 IU vitamin D, once a week (for 3 months)	Vitamin D administration decreased anti-TG (P= 0.009) level.
Krysiak, R., K. Kowalcze, and B. Okopien [51]	53 women	Poland	< 20 ng/mL	4000 IU/daily (in vitamin D deficiency group), 2000 IU/ daily (in vitamin D insufficiency group)-for 3 months	Vitamin D reduced levels of anti-TPO. This association was more found in women with vitamin D deficiency (P = 0.065)
Mazokopakis, Elias E., et al. [53]	218 (180 women, 38 men)	Greece	< 30 ng/mL	Cholecalciferol, 1200-4000 IU, daily, for 4 months, (to maintain 25(OH)D ≥ 40 ng/mL)	Supplementation of CF in vitamin D deficient HT patients reduces anti-TPO
Simsek, Yasin, et al. [52]	82	Turkey	<20 ng/mL	Vitamin D 1000 IU/day (for 1 month)	Vitamin D supplementation decreased TPOAb and TG-Ab levels (P = 0.02 and P = 0.03)
Chaudhary, Sandeep, et al. [54]	102	India	<50 nmol/L	CF 60,000 IU /weekly and - for 8 weeks;	A significant reduction of anti-TPO was detected (P = 0.028)
Knutsen, Kirsten V., et al. [56]	251	Norway	Mean serum 25(OH)D3 26 nmol/L	Vitamin D3 supplementation 1000 IU or 400 IU/daily, for 16 weeks	No effects on anti-TPO level.
Anaraki, Parichehr Vahabi, et al. [58]	56	Iran	<20 ng/mL	Vitamin D 50000 IU weekly (for 12 weeks)	TPOAb did not significantly changed (P = 0.14)

Thus, part of the studies indicate that vitamin D supplements (at least 1000 IU daily) in vitamin D deficient patients help reduction of thyroid antibodies levels. However, according to some studies, this effect has not been revealed.

5. Conclusions

Most studies support the negative association between vitamin D and thyroid antibodies levels: Vitamin D deficiency is associated with higher levels of thyroid antibodies compared to individuals with normal vitamin D status. This association is mostly found in premenopausal women. So, vitamin D deficiency may promote to the development of chronic autoimmune thyroiditis, especially in premenopausal women. Some data also indicate the benefit of vitamin D supplements to reduce thyroid antibodies levels. However, additional studies are needed to confirm the effect and usefulness of vitamin D preparations on thyroid antibodies.

Conflict of Interest

The authors declare no conflict of interest.

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