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The Influence Of Organ Pathology On The Development Of Diseases Of The Oral Mucosa.

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ABSTRACT

Periodontal disease is one of the most common diseases of the oral cavity. The development of periodontal disease is directly associated with metabolic syndrome, type 2 diabetes and obesity. It is known that cytokines play a key role in the development of periodontal response. In obesity, there is an imbalance in the secretion of adipokines, which contributes to the development of insulin resistance and type 2 diabetes, against the background of which periodontal disease is rapidly developing. Adiponectin and leptin play a key role in the development of metabolic complications, and subsequently and in the onset of periodontal disease. This article will examine the relationship of periodontal disease with the most common metabolic diseases, their relationship with the secretion of adiponectin and leptin.

Keywords: periodontal disease, metabolic syndrome, obesity, type 2 diabetes, adiponectin, leptin.

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INTRODUCTION

The prevalence of systemic oral diseases is growing worldwide at a rapid pace. There is scientific evidence that metabolic syndrome, obesity and type 2 diabetes are directly related to periodontal disease. It has been found that systemic disorders in the body have a direct impact on periodontal tissue. It is known that the main etiological agent in diseases of the oral cavity is bacterial plaque on the teeth. In this case, toxins and enzymes produced by various bacteria cause inflammatory and immunological reactions of the body both at the molecular and cellular levels[53,55]. For example, lipopolysaccharide derived from the bacterium Porphyromonas gingivalis, increases the concentration of TNF-α, which in turn can cause insulin resistance.

The total number of cytokines in particular TNF-α, as well as various hormones such as leptin, adiponectin and resistin modulate the periodontal response, while they play a very important role in the development of periodontal disease. The main functions of leptin include: appetite control, regulation of the immune response and production of inflammatory cytokines. In obesity, there is a decrease in sensitivity to the effects of leptin, which leads to a negative correlation between the level of leptin and gingival fluid.

Such a disease as periodontitis is the most common chronic infection of the adult population, which over time can lead to the loss of the alveolar process and eventually to the loss of a tooth. Type 2 diabetes and periodontal disease are two chronic diseases that are considered biologically interrelated. Hyperglycemia and various end products of progressive glycation (CNG) are among the main causes that lead to classic vascular complications that are involved in the physiopathology of periodontitis and periodontitis. Just glycation end products affect the metabolism of collagen. [11, 29,52]

Objective: to assess the pathophysiological processes in patients with periodontal disease on the background of endocrine pathology.

MATERIALS AND METHODS

The study included data on pathological changes in persons with periodontal disease on the background of metabolic syndrome and type 2 diabetes.

RESULTS AND DISCUSSION

Metabolic syndrome is a complex disorder, a disease characterized by abdominal obesity, insulin resistance, hypertension, dyslipidemia and inflammation. There is evidence that one of the main causes of death among individuals with metabolic syndrome are cardiovascular disease, type 2 diabetes and cirrhosis. Nowadays many different options are offered for the development of the syndrome pathogenesis. According to many authors, the main link in MS is abdominal obesity, with the subsequent occurrence of insulin resistance. [8] In this state, there is a decrease in the activity of lipolysis by reducing the activity germanosilicate lipase, which is able to move into an active state under the action of kateholaminam by adenosine monophosphate.

According to various datasets, the metabolic syndrome during the first 5 years can proceed without obvious violations of carbohydrate metabolism. It takes about 10 years form a complete state, which is called "metabolic syndrome". At this stage of development, of the doctrine of metabolic syndrome comes to the conclusion that there is a single biological substrate for depression and metabolic syndrome. The dominant link is between depression and increased activity of the hypothalamic-pituitary-adrenal system (discussed above). In healthy people, who have no problems with hormonal background, with the processes of eating secrete two groups of peptides that are involved in neuroendocrine regulation of appetite. Orexigenic peptides which referring to: glucocorticoid, acetylcholine, dynorphin, neuropeptide Y, etc. Anorectic peptides: leptin, serotonin, urocortin, insulin, etc.

Due to the presence of leptin resistance in patients with metabolic syndrome, it can be concluded that these peptides have dysfunction, but their neurohormonal activity in people with metabolic syndrome has not yet been studied. [50] It should also be understood that in the development of metabolic syndrome there is important gut microbiota. There is a direct relationship – normal, healthy gut microbiota and complete metabolic health. The gut microbiota contributes to the normal metabolism of the human body through the

saccharolytic fermentation of dietary fibers. Substances such as acetate, propionate and butyrate have a positive effect on satiety, endocrine function, glucose level, adipogenesis, thermoregulation, gluconeogenesis, endothelial function. Also, the microbiota is involved in the conversion of plant polyphenols into biologically active phenolic compounds, which then acting systemically are able to reduce the risk of metabolic disorders. [12,51]

Diabetes is a chronic metabolic disorder with exponential growth in various developing countries. [16] It is type 2 diabetes that accounts for about 95% of all diabetes, which is characterized by chronic hyperglycemia, which results from the presence of defects in insulin-dependent tissue receptors.

Pathogenesis C consists of two main abnormalities: insulin resistance of cells and dysfunction of insulin production, due to which there is a violation in the regulation of blood glucose levels.

Damage to pancreatic β-cells leads to insufficient insulin and adiponectin production, as well as to increased production of anti-inflammatory cytokines. All these causes as a result are the main factors contributing to the development of type 2 diabetes. Due to the fact that insulin resistance has been studied before studying the clinical manifestations of diabetes and that type 2 diabetes is mainly associated with obesity, which is accompanied by an abnormal increased waist-hip ratio, dyslipidemia, hypertension and other disorders. It can be concluded that obesity contributes significantly to insulin resistance in patients with type 2 diabetes. Excessive weight gain, which is a significant cause of obesity, is inextricably linked to chronic, moderately increased inflammation, which occurs due to the "expansion" and infiltration of adipose tissue by activated macrophages. In this case, adipose tissue inflammation is a key factor in the development of insulin resistance and type 2 diabetes in obesity, along with other factors that likely include fat accumulation in other metabolic active tissues. [27] Every year type 2 diabetes with becomes younger . About 2-5% of patients with type 2 diabetes suffer from a monogenic form with an autosomal dominant type of inheritance. This form of diabetes is called diabetes maturity are young people have it (MODY - maturity onset diabetes of the young). Also, this type of diabetes is caused by heterozygous mutations in five different genes that encode transcription factors:

- HNF4-alpha (MODY1),
- HNF1 alpha (MODY3),
- PDX1 (MODY4),
- HNF1beta (MODY5),
- NEUROD1 (MODY6).

Various mutations in the transcription factor genes of this diabetes lead to abnormal gene expression involved in the development and metabolism of pancreatic β-islets. There are some genetically determined insulin disorders that can lead to type 2 diabetes. Different levels of hyperinsulinemia and moderate hyperglycemia to severe diabetes can cause the degree of mutations of the insulin receptor. Diseases such as leprechaunism and Rabson – Mendenhall syndrome in their pathology have genetically determined mutations of the insulin receptor. And of course, such patients have type 2 diabetes. [3] Adipose tissue was originally considered as a simple organ whose main function was the storage of triacylglycerin. Over the past decades, there has been a significant leap in experimental data in the biology and biochemistry of adipose tissue. As a result, adipose tissue is no longer considered inert tissue that simply accumulates fat. Adipose tissue is a metabolic-dynamic organ, which is not only the main place of storage of excess energy, but also serves as an endocrine organ, which is able to synthesize a number of biologically active substances that regulate metabolic homeostasis. Adipose tissue consists not only of adipocytes, but also of other cell types that belong to the vasostromal fraction, including blood cells, endothelial cells, pericytes and adipose tissue precursor cells. Currently, it is generally believed that adipose tissue is the most important organ of the complex network of our body, which is involved in the regulation of many very diverse biological functions. The most important of those are: coagulation, appetite regulation, immune protection, glucose and lipid metabolism, reproduction, angiogenesis, fibrinolysis, homeostasis and vascular tone control. [23, 22, 16] In addition, adipocytes carry a large number of hormone receptors of both the endocrine and Central nervous systems, hence adipose tissue cells are involved in various biological processes such as energy metabolism, neuroendocrine function and immune response. [16]

The most important function of adipose tissue is the secretion of biologically active substances-adipocytokines, such as adiponectin, leptin, angiotensin, resistin, visfatin, protein, stimulating acitilation, sex steroids, glucocorticoids, TNF-α, IL-6 and free fatty acids, which affect metabolism. When a person has obesity unbalanced formation of proinflammatory and anti-inflammatory adipokines in adipose tissue occurs, which can contribute to the development of many pathologies including metabolic syndrome. [45] Increased production of TNF-α and decreased secretion of adiponectin lead to the development of type 2 diabetes, hypertension, atherosclerosis and metabolic syndrome. [23, 45, 49] Adipose tissue is a powerful regulator of vascular function. Almost all vessels of our body are surrounded by perivascular adipose tissue, which plays an important role in maintaining vascular homeostasis. It is able to produce "vasocrine" signals, which are called adipokines. Adiponectin and leptin are the most important ones.

Adiponectin is a hormone peptide nature, consisting of 247 amino acids, a molecular mass of 30 kDa and encoded by two genes – ADIPOQ1 and ADIPOQ2. The genes are localized on chromosome 3q26. [10, 23, 48, 47] Gene promoter contains binding sites for PPAR, glucocorticoid receptors and transcription factors. It is produced by adipocytes of white adipose tissue, mainly visceral, and it is named adipose most abundant gene transcript-1. [10, 23] Recent studies suggest its secretion by other tissues: skeletal muscles, hypothalamus, cardiomyocytes, uterus, ovaries and placenta. [20] In plasma, it is represented as a low modecular weight hexamer (LMW), a medium molecular weight hexamer (MMW), and a multi-enzyme high molecular weight complex (HMW). The fourth fraction indentified as globular adiponectin, it's formed by proteolysis. Each such form of adiponectin has its own specific effects. [23, 47, 10, 43, 38, 20, 2] Effector is action of the hormone has in the normal functioning of receptors ADIPOR1-most actively expressed in the muscles and ADIPOR2, which works more actively in the liver. [23, 38, 20, 2] Both adipokine receptors are present on the surface of adipocytes and are expressed like adiponectin in many tissues. It means that adiponectin has a biological effect on adipose tissue by autocrine and paracrine mechanism. [25] ADIPOR1 and ADIPOR2 exert their action through activation of AMRK and PPARy. [20] Adipor1 receptor expression is reduced in obese individuals. This suppresses the passage of the hormonal signal from adiponectin to fat cells in their excessive accumulation. This situation only exacerbates the negative metabolic effect of low concentrations of adiponectin. [25, 2] The result of obesity is often type 2 diabetes, this may be due to adipocyte secretion of adiponectin, mainly due to a decrease in its HMW form. [23, 2] It is known that low concentration of adiponectin leads to the development of insulin resistance, and which in turn contributes to the development of type 2 diabetes. The results of studies suggest that the level of adiponectin in obese people is much lower than in people with normal body weight. Other studies suggest that the risk of developing DM2 is lower when there is a high level of adiponectin, and the concentration of adiponectin is inversely correlated with obesity, insulin levels and fasting plasma glucose. [2] However, the mechanisms of the relationship between adiponectin and type 2 diabetes are not fully understood. [42] There are several theories supported by research that adiponectin plays a key role in the etiology of type 2 diabetes. Genes associated with the concentration of adiponectin in the blood were isolated, moreover, the genetic loci of these genes are associated with the development of insulin resistance, and in chromosome 3q26, in which the adiponectin gene is located, the locus of diabetes was also found. Japanese researchers have revealed that mutations in the gene I164T of adiponectin, are observed in people suffering from type 2 diabetes. Subjects with this mutation showed signs of metabolic syndrome, and the concentration of adiponectin was lower than those without this mutation. [7] Studies of different population groups were Conducted, which involved people with type 2 diabetes and people with a relative risk of developing this disease. As a result, there was an inverse relationship between blood adiponectin levels and type 2 diabetes. The risk of developing DM2 decreased with increasing adiponectin levels, as well as after lifestyle changes. Physical activity led to a decrease in visceral fat and to an increase in HMW forms of adiponectin, which favorably affected the health of the subjects. [31, 43]

Abdominal obesity is the most dangerous, because in which there is hypertrophy and hyperplasia of adipocytes occur with it. It is proved that visceral obesity often leads to the development of insulin resistance. [1] In physiological concentrations, insulin inhibits hormone-sensitive lipase, so at high concentrations of glucose, fatty acid synthesis is reduced. In the event of insulin resistance, insulin is not able to act on hormone-sensitive lipase, which leads to an increase in the content of fatty acids in the blood. As a result, free fatty acids are absorbed by other peripheral tissues, where they are used as an energy source or for the synthesis of other lipids. [25] Secretion of adiponectin in contrast to other adipokines, obesity is significantly reduced – there is a paradox. That is, the more pronounced obesity and the more adipocytes, the less adiponectin is produced. According to one source, this may be due to the fact that altered, hypertrophied adipocytes in obesity secrete various inflammatory mediators that inhibit the transcription of the adiponectin gene in adipocytes 3T3-L1.

[23, 42, 38, 2] For example, TNF-α suppresses the activity of the adiponectin promoter, thereby preventing RNA polymerase from recognizing the starting transcription site. In turn, TNF-α, in contrast to adiponectin, affects the strengthening of the development of insulin resistance in tissues. In studies in obese patients, in addition to low levels of adiponectin, there is an increase in TNF-α and, as a consequence, a decrease in insulin sensitivity. [1, 38] Consequently, the reduction of visceral fat can be a preventive measure for cardiovascular diseases, metabolic syndrome and the development of insulin resistance. [23]

Another equally important hormone is leptin. Leptin is a hormone of polypeptide nature, released mainly by adipocytes of white adipose tissue of skeletal muscles, stomach and the placenta. [46, 5, 23] This adipokine belongs to the family of long-chain spiral cytokines. The information required for the synthesis of this adipokine is encoded by the "obese gene" - ob gene, localized on chromosome 7. The gene was discovered in 1994 by positional cloning. It encodes a peptide consisting of 167 amino acids. Initially, the polypeptide is synthesized immature. The processing, which involves splitting the N-terminal signal sequence of 21 amino acids, produces a functionally mature non-glycosylated protein of 146 amino acids. [15, 35, 13] Leptin levels are highly sex-dependent. It decreases significantly after menopause, but despite this, women have higher levels of the hormone than men.[54,56] This indicates the role of sex steroids, estrogens and androgens, in the regulation of leptin secretion. The fact that subcutaneous fat produces more leptin than visceral fat also contributes to higher levels of leptin in women compared to men. In addition to sex hormones, glucocorticoids, insulin, catecholamines, and inflammatory mediators regulate the expression and subsequent secretion of the hormone. [17] Leptin secretion increases after insulin administration for 15 minutes. Insulin stimulates the secretion of leptin by increasing the synthesis of adipokine, after which the leptin-containing bubbles begin to go towards the endoplasmic network, and then to the Golgi apparatus. Leptin accumulates in the vesicles of the membranes of the endoplasmic reticulum and near the plasma membrane of adiocytes. Ca2 + can trigger exocytosis of synaptic vesicles. However, a single influx of Ca2 + is not enough to complete leptin secretion. Ca2 + is required for ISLS (insulin stimulated leptin secretion), because of its participation in Akt phosphorylation. It follows from the above that insulin stimulates leptin secretion via PI3K (phosphoinositide-3-kinase) / Akt (protein kinase B) [40, 39] Studies show that long-term euglicemic hyperinsulinemia stimulates leptin expression and secretion. There is a gradual decrease in the concentration of glucose in plasma signals to the adipocyte of low secretion of leptin, in response to this, the activity of the hypothalamic-pituitary-adrenal axis and lipolysis of white adipose tissue increases, which is necessary to prevent hypoglycemia during prolonged fasting. [30] leptin circulates freely in the blood or is bound to specific carrier proteins. In thin people, leptin circulates predominantly in a bound form, whereas in obese people it circulates in a free form. [36] Men have less circulating leptin in their blood than women. The more fat mass in the body, the more adipocytes secrete leptin. As you know, obesity increases the level of leptin in the blood, but the "rescue mechanisms" of appetite suppression and weight loss are not always included. This is due to the formation of hypothalamic resistance to leptin. This situation is caused by multiple molecular, genetic, nervous and, behavioral factors. [15, 25, 41, 46, 33] Therefore, when leptin is administered to obese people, a positive effect does not occur. Most overweight patients do not respond to leptin. However, patients with leptin deficiency, chronically low leptin levels (lipodystrophy or anorexia), or insulin deficiency may benefit from leptin treatment. Leptin is highly conservative in function due to the preservation of secondary and tertiary structures. Leptin is involved in the regulation of energy homeostasis, transmitting signals to the brain about the reserves of fat in the body. Leptin can have its effect directly, acting on the target, or through the hypothalamus, where the leptin receptors are located. [15, 25, 41, 21, 4] Leptin acts on the centers of hunger and saturation in the hypothalamus, thereby reducing the secretion and synthesis of neuropeptide-Y, which causes hunger. [32] As a result, leptin controls body weight, has an impact on human eating behavior, acts as an appetite regulator and participates in the regulation of energy balance. [46, 4, 7 41, 5] Leptin is transported across the blood-brain barrier through a regulated transport system. Cross it passively peptide fails because of its considerable size. After passing the barrier, the hormone acts mainly on the arched nucleus of the hypothalamus. [25, 15] Leptin regulates energy homeostasis and human eating behavior, affecting neurons in various parts of the intermediate brain. So, in the arcuate zone there are neurons that are responsible for the synthesis of anorexigenic peptides (appetite-suppressing). [40, 44] these include – proopiomelanocortin, which stimulates the formation of α-melanocyte-stimulating hormone. This hormone promotes weight loss by binding to the melanocortin-3 and melanocortin-4 receptors. [4] When the structure or conformation of MC4R and MC3R changes, leptin resistance and weight gain develop. The synthesis of protein (AgRP) and neuropeptide is stimulated in arcuately area, causing the feeling of hunger. The leptin hormonal signal triggers reactions inhibiting the expression of these peptides. [10, 40] Leptin performs these actions by binding and dimerizing the leptin receptor, which in turn activates many intracellular signaling pathways. [25] Cytoplasmic

tyrosine kinase JAK2 autophosphorylates when meeting leptin. JAK2 phosphorylates three tyrosine sites in LEPRb and activates STAT3, which is transported from the cytoplasm to the nucleus. STAT3 behaves as a transcription factor, acting on various target genes of anorexigenic factors. STAT3 also includes a signal transfer suppressor-SOCS3, which by type of negative feedback inhibits the transmission of signals from leptin after prolonged stimulation. [4, 39] on the balance of Tyr985 - SOCS3 AND SHP2 provide inhibition by the feedback type JAK2. On Tyr1077, STAT5 activation leads to changes in gene expression. On Tyr1138, STAT3 alters gene expression and activates SOCS3, which returns to inhibit JAK2. [25, 40] Phosphorylation of signaling molecules opens the way for the signal to the nuclear neurons(2nd order) of the hypothalamus. There are several ways to transfer information from leptin to the hypothalamus nuclei, which prevent the development of obesity. JAK2/STAT3 path is one of the main. In addition to STAT3 trigger transcription genes, cytoplasmic signal suppressors 3(SOCS3) are included in the nucleus, which inhibit JAK2 kinase. [10, 21] studies have been Conducted on mice that were obese after being fed large amounts of fat, with the level of SOCS3 (a cytokine signaling suppressor) increasing along with leptin. It can be concluded that high levels of leptin provoke the inclusion of SOCS3, which inhibits its signal to the Central nervous system. [14]

In addition to the hypothalamus, leptin acts on receptors of other tissues and organs. These are receptors of adipose tissue, lungs, kidneys, liver, adrenal glands, glandular genitals, skeletal muscles, and hematopoietic stem cells. At the periphery, leptin is involved in the regulation of various processes. It is able to modulate inflammatory and immune responses, is involved in cardiovascular regulation, has a major role in glucose and fatty acid metabolism, and insulin secretion. [36] Adipokine is able to autocrine and paracrine induce apoptosis of white fat cells. Lipogenesis, a process that occurs primarily in adipose tissue as well as in the liver, is inhibited by leptin. [23] A diet rich in carbohydrates activates lipogenesis, while polyunsaturated fatty acids and fasting inhibit this process. In addition to leptin, growth hormone is also an inhibitor of lipogenesis reactions. Endogenous fatty acid synthesis (lipogenesis de novo) translates excess carbohydrates into lipids for storage. DNL provides the formation of these types of lipids, which have excellent biological activity, compared with the activity of lipids obtained from food. Increased DNL in adipose tissue has beneficial effects on painful conditions such as obesity, type 2 diabetes and cardiovascular disease. Leptin has been shown to be able to protect rodent pancreatic β-cells from lipotoxicity. Adenovirus-mediated hyperleptinemia suppresses streptozotocin-induced apoptosis of Langerhans islet cells and preserves β-cell mass, while inhibiting lipogenesis in rats. [19]In addition, leptin causes dilation of the aortic lumen and coronary arteries due to activation of NO-synthase expression in the vessel wall. Adipokine inhibits the increase of Ca2 + by weakening the action of angiotensin II, reduction and proliferation of VSMC (Vascular Smooth Muscle Cells). Violation of the regulation of circulating leptin isoforms and the development of resistance to it, associated with obesity, type 2 diabetes or metabolic syndrome, contributes to the development of cardiovascular disorders. Leptin can inactivate endogenous inhibitors of fat cell apoptosis. This process, unfortunately, is temporary, due to the development of resistance to leptin. In intracerebral leptin administration experiments, it was observed that the hormone had increased the expression of PPAR-g protein in white adipose tissue. Activation of this protein contributed to the development of apoptosis of adipocytes and adipokines. The number of "wrinkled" adipocytes increased, the number of large cells decreased. PPARγ plays an important role not only in the differentiation of adipocytes, but also as a receptor for insulin-sensitizing drugs. It became known that the activation of PPARγ promotes adipogenesis. In turn, this leads to an increase in the number of insulin-sensitive adipocytes. It is also known that the activation of PPARγ increases the production of adiponectin, which increases insulin sensitivity of liver cells and muscles. [9] Leptin has recently been found to be involved in the control of neuronal plasticity. It became known that leptin removes nerve stem cells from the cell cycle. Leptin-dependent output of nerve stem cells from the cell cycle is associated with the induction of apoptosis. Apoptosis was preceded by induction of cyclin D1. Inactivation of Cyclin-D1 specific shRNA prevented a leptin-induced reduction in the number of brain cells. This new biological effect of leptin has a neurotoxicity property that depends on obesity. [34] The hormone also exerts its metabolic effects by stimulating astrogenesis in the hypothalamus. This is due to increased astrocyte proliferation in the postnatal hypothalamus. [32] Leptin plays a significant role in the inflammatory process involving adipose tissue. Inflammatory mediators are also activators of apoptosis in the cell. [37] In the treatment of obese patients, the method of reducing the number of adipocytes by apoptosis can be used. This may complement other treatment options. Unfortunately, knowledge of apoptotic pathways in adipocytes is surprisingly scarce today. [6] Congenital leptin deficiency is a rare autosomal recessive syndrome of monogenic obesity that occurs in homozygous mutations in the leptin gene. Patients with this pathology usually develop metabolic and hormonal changes, for example, hyperinsulinemia, insulin resistance, severe liver steatosis, dyslipidemia. In sick children, immunological changes are observed, manifested by recurrent severe bacterial infections that

can lead to death. [18] In patients with lipodystrophy and congenital leptin deficiency due to mutations in the ob gene, leptin levels are extremely low or not detected at all. For such patients, in contrast to patients with leptin resistance, replacement therapy with leptin, for example, metreleptin has greatly improved their condition. Normalization of endocrine organs, reduction of insulin resistance and improvement of lipid profile were observed. [28] Metreleptin is a pharmaceutical product that is a structural analogue of leptin. It is approved by the FDA for the treatment of severe metabolic disorders, generalized forms of lipodystrophy. [24, 14]

CONCLUSION

New discoveries and findings allow us to link common diseases such as periodontitis, MS, DM2 and obesity, which makes it possible to approach the prevention and treatment of periodontitis from a new perspective. Control of blood sugar levels, various products of progressive glycation, which are directly related to the development of periodontal disease, can prevent the development and progression of this disease. It is important to control the secretion of adiponectin and leptin, which play an important role in the regulation of metabolism. Understanding the mechanisms of their regulation, open the way of prevention and treatment of the most common diseases of the XXI century.

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