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Standard and innovative options in the treatment of insulin resistance

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Abstract

Introduction and purpose

Insulin resistance is a state of decreased tissue sensitivity to insulin, despite normal or elevated levels of this hormone in the blood serum. People with insulin resistance for a long time do not show symptoms, which makes it particularly difficult to detect and treat in early stages. It mainly leads to impaired glucose homeostasis and the development of type 2 diabetes, which contributes to the exacerbation of the global problem that diabetes has become. This results in the search for innovative therapies that will help combat insulin resistance better and better. The purpose of this study is to highlight the complexity of the IR and review the current literature for non-pharmacological and pharmacological possibilities of treatment for insulin resistance.

Description of the state of knowledge

Due to the increase in obesity and the metabolic syndrome, the number of people suffering from insulin resistance is constantly increasing. In modern times, there are various diagnostic and therapeutic methods that affect the course of insulin resistance. Early detection and introduction of appropriate therapy become the main goal in preventing complications that may occur in the course of this disease.

Summary

Treatment methods for insulin resistance can be divided into two groups - non-pharmacological and pharmacological. Both of them are often used together in the form of combination therapy aimed at obtaining the best results in the treatment of insulin resistance. For people for whom known therapies do not work, researches for new treatments is becoming a hope.

Key words**:** insulin resistance, treatment, FGF-21, metformin, SGLT-2 inhibitors

Introduction

Insulin resistance (IR) is defined as a disease state in which the body's biological response to insulin is altered primarily in adipose tissue, liver and muscles. As a result, the storage and consumption of glucose and triglycers is disturbed, causing their increase in human blood. In the body's response to hyperglycemia, the beta cells of the pancreas are stimulated to produce more insulin, leading to hyperinsulinemia [1].

The occurrence of insulin resistance is mainly associated with the excess of adipose tissue in the course of obesity and metabolic syndrome, although more and more is mentioned about genetic causes and other pathological conditions such as chronic inflammation, ectopic lipid toxicity and gastrointestinal tract bacteria alterations [1,2].

Epidemiology

Insulin resistance is often associated with obesity and the metabolic syndrome. There is a growing trend in the occurrence of these diseases in the world, which means that more people are also struggling with insulin resistance. It was observed that the lowest percentage occurs in European countries (15.5%), while in countries from other continents it is higher, e.g. Thailand 23.3%, USA 39% (Texas), Lebanon 44.6% or Venezuela 46,5 [3]. Awareness of insulin resistance is increasing in the medical community, which also contributes to the increase in its recognition.

Detection methods of insulin resistance

Early detection of insulin resistance is important in clinical diagnosis due to the increasing metabolic disturbances in its course. The problem is mainly observed in developed countries. The glucose clamp test or the frequently-sampled intravenous glucose tolerance test (FSIVGTT), with glucose and/or insulin infusion are considered to be the gold standard in diagnosing insulin resistance. However, due to their time-consuming and invasive nature, they are not common in medical practice. For this reason, insulin resistance is most commonly diagnosed by measuring blood glucose and insulin levels.

Incorrect results may suggest a metabolic disorder, prompting additional tests and calculation of indirect insulin resistance indices. Indirect indicators of insulin resistance include:

Homeostatic Model Assessment (HOMA), Matsuda Index, Quantitative Insulin Sensitivity Check Index (QUICKI) and Insulin Secretion-Sensitivity Index-2 (ISSI-2) [4].

Complications of insulin resistance

In the course of insulin resistance, there is a disturbed reaction of the body's cells to the action of insulin, which limits its ability to stimulate and use glucose and triglycerides in metabolic processes. The consequences of these processes include: dyslipidemiahypertension, visceral obesity, hyperuricemia, elevated markers of inflammation, prothrombotic status and endothelial dysfunction. Progression of insulin resistance leads to the appearance of type 2 diabetes mellitus, in the course of which there are serious complications that may reduce the life expectancy and quality of the patient. It should be taken into account that they can also occur without fully developed diabetes. Most of the complications take the form of vascular changes in various systems and organs of our body. In the central nervous system, they can lead to the earlier onset of dementia, stroke, mobility problems, and behavioral disorders. In the kidney, microvascular changes occur in the form of nephropathy, leading to chronic renal failure. Retinopathy, which is a complication of the microcirculation of the visual organ, is characterized by damage to the blood vessels and the retina of the eye, which can even lead to blindness. Peripheral neuropaty, in the course of which the sensory disturbance occurs, may lead to the appearance of a diabetic foot and as a result to limb amputation. Insulin resistance is also associated to atherosclerosis, which increases the risk of a heart attack, coronary artery disease and peripheral arterial disease. ll these complications are dangerous for the patient's condition and life [1,5]. To prevent them, various forms of treatment are used, described in the next part of our work.

Treatment

In recent years, there has been development in the field of treatment of insulin resistance. The known non-pharmacological methods used both in the prevention and treatment of insulin resistance are added to new pharmacological methods that positively affect the course of the disease.

1.Diet and physical activity

In obesity, which often coexists with insulin resistance, there is an increase in body fat. One of the factors linking the development of insulin resistance to adipose tissue is free fatty acids (FFA). Their excess causes the impairment of both hepatic and muscle glucose in tissues and negatively affects the action of the insulin receptor - IRS-1 - insulin receptor substrate 1. Other substances secreted from adipose tissue leading to the development of insulin resistance are: adypsin, resistin, tumor necrosis factor, interleukin 6, monocyte chemotactic protein 1 and plasminogen activator inhibitor 1, the action of which causes a chronic inflammatory process in adipose tissue and a reduction in the sensitivity of tissues to insulin. For this reason, the first step in the prevention and treatment of insulin resistance is to reduce the patient's body weight. The best non-pharmacological ways to achieve this goal are a proper low-calorie diet and adapted physical activity. Recommended dietary models include Mediterranean, vegetarian and low-fat diets. Particular emphasis should be placed on the consumption of large amounts of vegetables and fruits, whole grains and sea fish rich in omega 3 polyunsaturated fatty acids. People with insulin resistance should ensure the supply of vegetable fiber in products such as: oats, beans, peas, lentils, grains, seeds, brown rice and noodles. It is recommended to avoid foods high in saturated fat and sugar, sweetened drinks and sweets, and limit alcohol consumption. In turn, the physical activity should be gradually increased and adjusted to the patient's abilities. The most recommended forms of activity are dynamic-static exercises, which is a combination of aerobic effort and strength exercise. Regular exercise has a positive effect not only on body weight, but also on serum lipid levels, blood pressure, glucose tolerance and increases the sensitivity of tissues to insulin. Suliburska J et al. in their study presented evidence that changing lifestyle through proper diet and physical activity, thanks to the loss of 3-4 kg, reduces the risk of developing insulin resistance by as much as 58%. Therefore, in patients already suffering from insulin resistance, it is recommended to reduce body weight by 5-10% in each year of treatment until the body weight is normal (BMI <25- body mass index) [6,7].

2.Metformin

Metformin is a first-line drug in the treatment of type 2 diabetes, but also in pre-diabetes and impaired sensitivity to insulin. The mechanisms of action of metformin are mainly inhibition of hepatic glucose production and increased insulin sensitivity of peripheral tissues. Metformin, due to the mechanism of intracellular oxidation, reduces ATP synthesis and activates AMP kinases. Even a slight ATP deficiency leads to the activation of the AMP kinase. As a result, it follows increase in peripheral muscle glucose consumption, reduction of glucose

production in the liver (glycogenolysis and gluconeogenesis), reduction of lipogenesis and stimulation of the β-oxidation process [8].

Additionally, metformin sensitizes beta cells pancreas to incretin hormones - glucose-dependent insulinotropic peptide glucagon-like peptide (GLP-1). An important effect of metformin is its effect on reducing the demand to insulin, also the exogenously administered one and does not lead to hypoglycemic states [8]. The most common side effects during metformin therapy include gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal pain, gas, vomiting and taste disturbances. Sometimes symptoms are so bothersome that it is necessary to stop treatment [9]. In addition, metformin causes a subclinical rise in lactic acid and can cause lactic acidosis in extreme overdose. Therefore, the use of metformin is not recommended in patients with risk factors for lactic acidosis, for example hepatic impairment, heart failure or chronic kidney disease [10].

3.GLP-1 analogues

Glucagon-like peptide (GLP-1) is a hormone that regulates postprandial glucose levels and issecreted by the gut in response to meal ingestion. GLP-1 increases insulin secretion through β-cell apoptosis inhibition, β-cell mass enhancement and promotion of differentiation of islet progenitor cells into beta cells. Moreover GLP-1 decreases gastric emptying subsequently reducing appetite, which in turn results in loss of weight. Other positive effects include reduction of oxidative stress and inflammatory condition as well as memory and learning improvement. GLP-1 levels are decreased in patients with diabetes type 2 in comparison to healthy people. Since GLP-1 has negative effects on gastrointestinal system and its clinical use is restricted by its short half-life, biochemical modifications were necessary to achieve therapeutic benefits of GLP-1 therapy. Therefore binding to albumin was used to extend half-life of GLP-1 analogs liraglutide and semaglutide. Several studies have shown that liraglutide and semaglutide have beneficial effect on glycemic control and body weight regulation. Glucagonostatic properties of GLP-1Ras have been disputed, given inconsistent results of some studies, which showed neutral or even increased response. Yet, decrease in fasting and postprandial glucagon was apparent for semaglutide. Liraglutide and semaglutide both proved to enhance β-cell function and insulin production, with positive proinsulin/insulin ratios in comparison to other glucose-lowering agents, including sulfonylureas, which increase insulin secretion without any impact on its biosynthesis. Clinical studies have shown that semaglutide reduces insuline resistance, however retrospective analysis suggested weight loss as primary

cause [11,12]. The beneficial effects of GLP-1 analogues on insulin metabolism may be limited by the side effects of these drugs. The most frequently mentioned are gastrointestinal ailments such as nausea, vomiting, diarrhea and constipation. There have been isolated reports of acute pancreatitis in patients treated with GLP-1 analogues, but this has not been confirmed in large clinical trias [13].

4. Thiazolidinediones

Thiazolidinediones (TZD) reduce insulin resistance by activating PPARγ receptors, which are responsible for the differentiation of mesenchymal stem cells into adipocytes. Moreover, they promote lipogenesis in peripheral adipocytes, reduce the concentration of hepatic and peripheral triglycerides, and also reduce the activity of visceral adipocytes. Through a number of these actions, TZDs reduce insulin resistance, metabolic syndrome and insulin requirements. They improve not only hepatic but also peripheral insulin sensitivity. Their use in pre-diabetic patients reduces the rate of progression to type 2 diabetes, possibly due to the preservation of pancreatic beta-cell function. The use of TZD is limited due to the potential side effects that may be associated with their use. The most frequently mentioned are cardiovascular events, such as heart failure, fluid retention and edema. Other side effects are weight gain (which appears to be dose-related) or increased risk of bone fractures. Pioglitazone is suspected to be associated with bladder cancer. The TIDE study, which was about to explain this relationship, was completed after 162 days because of FDA concerns about patients' cardiovascular safety [14].

5. Inhibitors of sodium-glucose cotransporter (SGLT2)

The sodium-glucose co-transporter SGLT2 is a low affinity carrier for glucose and high capacity, localized it is almost exclusively found in tubular epithelial cells proximal nephron-the basic functional and structural unit of the kidney. Its expression leads to the reabsorption of glucose from urine reaching 90%. The first substance discovered to inhibit the glucose cotransporter SGLT2 was phlorizin. In studies performed on diabetic rats it caused glucosuria and lowering glycemia, which in turn also improved insulin sensitivity. In humans it has not been used due to its poor absorption from the gastrointestinal tract and non-selective inhibition

of both glucose-sodium symporters (SGLT1 and SGLT2) whose localization includes various organs, including: kidneys, heart, brain. For this reason research has begun on synthetic forms of florin, which will be characterized by better absorbability and selectivity towards SGLT2. This is how: Emapgliflozin, Dapagliflozin, Ipragliflozin, Tofogliflozin, Sergliflozin were created [15].

The mechanism of SGLT2 inhibitors is mainly to inhibit the reabsorption of glucose from the kidneys, causing hyperglycuria, thereby reducing glucose levels, providing an antihyperglycaemic effect [16]. This has a positive effect on the improvement of the parameters of carbohydrate metabolism. Additionally, as a result of glucose loss with urine, there is a negative energy balance, which causes the weight and fat loss, which positively affects the treatment of insulin resistance [15]. Their beneficial effects have been noticed in cardiology. They affect the cardiovascular system through improving the load conditions of the ventricles, which leads to a drop in blood pressure, cardiac metabolism and bioenergetics, partial restoration of the balance between pro-inflammatory and anti-inflammatory adipokines [17]. In the course of treatment with SGLT2 inhibitors, the most common side effect is infections of the genitourinary system as a result of glucosuria. Others include diarrhea, pollakiuria, nausea and constipation [15].

6. Dipeptidyl peptidase-4 inhibitors

The enzyme dipeptidyl peptidase-IV (DPP-4) is responsible for the degradation of incretin hormones such as glucagon-like peptide 1 (GLP-1), which have anti-diabetic effects. For this reason, a new group of drugs has been created - DPP-4 inhibitors that can counteract this process [1].

The mechanism of their action is mainly based on the improvement of the sensitivity of pancreatic alpha and beta cells to glucose concentration- during hyperglycemia, the insulin secretion by beta cells increases and the alpha cells reduce the production of glucagon. As a result of their action, there is a significant increase in endogenous GLP-1 and an extension of its half-life, which increases its biological effects. Unlike GLP-1 analogues, they do not affect the speed gastric emptying and weight loss of the body, but due to their different mechanisms of action, they positively influence the treatment of insulin resistance [18].

Few side effects have been recorded in the course of the use of DPP-4 inhibitors. The most common are: increased the incidence of nasopharyngitis and allergic reactions [18].

7. Probiotics

In the last few years, research has begun on the effects of probiotics on insulin resistance. Probiotics are live microorganisms that have a beneficial effect on health. The probiotics consist mainly of lactic acid-producing bacteria of the genera Lactobacillus and Bifidobacterium [19]. In the presented work Alireza Soleimani et.al has shown a beneficial effect of simultaneous supplementation of probiotics from both the Lactobacillus (L. acidophilus, L.casei) and Bifidobacterium (B.bifidum) families. During the 12-week therapy conducted in diabetic patients, the levels of glucose, insulin, HOMA-IR and glycosylated hemoglobin decreased [20]. The use of probiotics is safe and well tolerated for the human orgamism. Unfortunately, like almost all medicines used in medicine, they can cause side effects. The most common are abdominal cramps, nausea, loose stools, and gas. Probiotics should be used with caution in people with reduced immunity due to the possibility of bacteremia and fungemia [21].

8.Vitamin D

Vitamin D (VD) is known to have many beneficial effects on health including enhancing insulin sensitivity, increasing insulin secretion, controlling cell differentiation and proliferation process, and having anti-inflammatory and anti-atherosclerosis properties. Studies have shown that VD deficiency and hyperhomocysteinemia are factors linked to diabetes type 2 (T2DM). As recent research has found, in patients with T2DM level of serum 25(OH)D was considerably lower compared to healthy people and had a negative correlation with HOMA-IR, TNF-α, IL-1β, IL-6 and IL-8. VD can stimulate secretion of anti-inflammatory cytokines, inhibit secretion of inflammatory cytokines and consequently reduce inflammation. Animal experiments have confirmed that VD deficiency increased insulin resistance in rats with T2DM by stimulating inflammation through enhanced p-p65/RelB proportion. These proteins are important part of the NF-kB signaling pathway. NF-kB pathway takes part in controlling numerous crucial physiological processes and can regulate many genes, including TNF-α, IL-1β and IL-6. Many studies have proved that NF-kB signaling pathway is a significant factor in insulin resistance regulation. It is known to cause β cell volume decrease, insulin secretion disorder and insulin sensitivity decline. Enhanced NF-kB activity can lead to leukocytosis of islets and direct β cell damage. In conclusion, animal experiments proved that VD deficiency increases insulin

resistance in rats with T2DM through NF-kB pathway activation which results in inflammatory response [22].

9.Resvestrol

Resveratrol belongs to the group of polyphenols which are plant secondary metabolites. They are found in large amounts mainly in vegetables, fruits, cereals, dry legumes, cocoa and coffee, tea and wine. The beneficial effect on the biological functions noticed in research related to resveratrol has made scientists from various fields of science more and more interested in them. In a publication presented by Abbasi Oshaghi et al., using both animal and human studies, a positive effect of resvestrol on the course of insulin resistance was show such as reactive oxygen species and lipid peroxidation, normalization of blood glucose levels, inhibition of insulin secretion, which protects pancreatic beta cells from destruction as a result of chronic activation in states of insulin resistance, improving cell sensitivity to insulin, normalizing lipid and lipoprotein levels, inhibiting LDL oxidation, activating lipolysis stimulating fatty acid oxidation, reducing adipogenesis, alleviating de novo lipogenesis. The positive aspects of taking resveratrol and limiting the side effects of its use to rare vomiting and diarrhea suggest the possibility of a new approach to the therapy of insulin resistance treatment [23].

10. FGF21 gene therapy

Currently accessible pharmacologic treatment possibilities have proved successful in many cases, however these are not applicable to all patients with obesity/diabetes type 2 (T2DM) and carry undesirable side effects, therefore the demand for innovative therapies. One of promising agents for obesity/T2DM is fibroblast growth factor 21 (FGF21). A study on rodents was conducted with use of adeno-associated viral (AAV) vectors to achieve prolonged production of FGF21 with the purpose of treating obesity and IR. Using AAVs, liver, adipose tissue and skeletal muscle were genetically modified in order to produce FGF21, resulting in considerate weight loss, decrease in adipose tissue hypertrophy, inflammatory condition, hepatic steatosis and IR. In spite of continuously increased FGF21 levels, no side effects were observed. Moreover, elevated FGF21 in healthy individuals on standard diet prevented weight gain and IR related to aging. A single application of AAV vectors encoding FGF21 resulted in long-term elevation of FGF21 levels in the bloodstream, leading to counteraction of obesity and IR. What’s crucial, after body weight normalization in obese animals, the weight was stable for the

whole follow-up period.However, studies must be conducted to examine long-term safetyand efficiency in large animals before FGF21 gene therapy can be administered to humans [24].

Summary

Insulin resistance is becoming a global problem that significantly affects human health. The side effects of untreated insulin resistance can lead to severe chronic diseases in which decompensation can have disastrous consequences. Therefore, more and more attention is paid to its treatment. First of all, you should persuade the patient to introduce an appropriate diet and increase physical activity. When lifestyle changes alone are not sufficient, both non-pharmacological and pharmacological treatments should be implemented.

The drug used in the first place is still metformin, although GLP-1 analogues, which significantly reduce the patient's body weight, are becoming more and more popular. Additionally, as part of their intolerance, we can still reach for DPP-4 inhibitors, thialysodones and SGLT-2 inhibitors. In the distance, we can also see new methods of treatment, such as FGF-21 gene therapy or Resvestrol, which may be hope for people for whom known pharmacological therapies are insufficient.

Contribution of authors:
J.Metelski- study concept and design; critical revision of the manuscript for important intellectual content; study supervision;
K.Krauze-Kuc - acquisition of data; analysis and interpretation of data; technical support;
A.Metelska - acquisition of data; analysis and interpretation of data; technical support;
D.Sereda- acquisition of data; analysis and interpretation of data; technical support;
H.Nieścior- acquisition of data; analysis and interpretation of data; technical support

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