ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

REVIEW ARTICLE

Role of Myokines and prospects for their role in Diabetes Mellitus Therapy

Kharissova Nuriya[1], Mindubayeva Farida[1]*, Rajkamal Sharma[3], Smirnova Liliya[2], Mkhitaryan Xeniya[1], Chergizova Bibigul[1], Salikhova Yelena[1]*, Niyazova Yuliya[1], Ryspayeva Gulnur[1], Evnevich Anna[1], Akimzhanova Neylya[1], Sarsembayeva Sholpan[1]

[1]Karaganda Medical University" NCJSC, Karaganda, Kazakhstan.
[2]Kostroma State University, Kostroma, Russia.
[3]Advisior Cum Administrator Dr. Sarvesh Shukla Group Of Institution, Jaipur, Rajasthan, India.
*Corresponding Author E-mail: **7554422@mail.ru, Salehova_89@mail.ru**

ABSTRACT:

In the last decade, the attention of researchers has been drawn to the ability of skeletal muscles to produce biologically active substances (myokines). To date, several hundred myokines have been identified in the muscle secretome. Myokines have autocrine and paracrine effects. They have their own receptors in various tissues and organs. At certain concentrations, myokines have a systemic effect on tissues and organs, provide metabolic interaction between them and have a huge range of physiological effects. However, the biological activity of many of these myokines and their mechanism of action are either not yet characterized or poorly understood. Modern research is aimed at developing drugs that block myokine signaling pathways and studying the possibilities of their use in the treatment of neuromuscular diseases, obesity, type 2 diabetes mellitus, orthopedic pathology, as well as a decrease in muscle mass and muscle strength. Type 2 diabetes mellitus (T2DM) is a socially significant disease. Currently, there is no effective therapy to completely eradicate/cure diabetes and its associated complications. It is now necessary to consider in more detail the molecular pathways and targets for each pharmacological drug. There is a need to create new anti-diabetic therapy in the future based on myokines, knowing their signaling pathways and their mechanism of action on target cells, but also for the best possible combination therapy and strategies using available drugs and the beneficial effects of physical activity and exercise in the prevention and treatment of T2DM. A few studies in mice and humans have shown that exercise increases the levels of numerous myokines in the blood plasma, leading to the process of active transcription of myokines and accelerating metabolic processes associated with increased load on muscle tissue. It has been suggested that the secretion of myokines depends on the degree of physical training; intensity and duration of the athlete's training; its physiological and anatomical structure; the sport in which the athlete plays. Further scientific research will provide the key to understanding the process of secretion of myokines (proteins) in the body and the mechanism of their effect on various organs/systems and tissues, which will undoubtedly contribute to the success of doctors in the field of practical healthcare in the correction of pathological disorders, including diabetes mellitus.

KEYWORDS: Myokines, Muscles, Physical Exercise, diabetes mellitus type 2, metabolic disease.

INTRODUCTION:

1. Myokines, its function and mechanisms of action on various organs and tissues:

Recently, attention has been paid to the study of the endocrine function of muscle tissue - the secretion of myokines. The formation of myokines consists of two stages: transcription, that is, the rewriting of information from DNA genes to messenger RNA, and translation,

Received on 15.02.2024 Modified on 06.05.2024
Accepted on 27.06.2024
Research J. Pharm. and Tech 2024; 17(10):5119-5131.
DOI: 10.52711/0974-360X.2024.00786

the direct assembly of myokine molecules[1,2]. Myokines are cytokines, peptides, and proteoglycans produced, expressed, and released by muscle fibers (myocytes) in response to muscle contraction that have autocrine, paracrine, or endocrine effects in regulating metabolism in other tissues[3,4]. The influence of myokines occurs through signaling pathways involved in the pathogenesis of many socially significant diseases, usually affect older people: abdominal obesity, type 2 diabetes mellitus (DM), cardiovascular and neurodegenerative pathologies, colon cancer and breast cancer[5,6]. Pedersen et al. put forward the idea of "morbidoma" (originally "diseasome") - a nosological cluster based on the persistence of chronic low-active inflammation, which is a common feature of the pathogenesis of diabetes mellitus, obesity, atherosclerosis, neurodegenerative lesions[7]. The experiment recorded an exponential increase in the concentration of interleukin in proportion to the duration of the contraction and the amount of muscle mass involved in it[8]. The first muscle-derived myokine identified was myostatin[9]. Currently, more than 1000 myokines are known, belonging to various structural and functional groups (cytokines, chemokines, prostaglandin family, etc.)[10].

Due to the significantly increased number of molecules that have been identified as myokines, many authors have addressed the problem of their classification, according to chemical nature and physiological effect.Silja Raschke and Jurgen Eckel[12] proposed to form three groups - myokines, adipomyokines and adipokines[11,12,13,14,15]. The discovery of myokines and the mechanisms of their secretion into the blood is the basis for uncovering the mechanisms of the influence of physical activity on metabolism and anti-inflammatory effects. Physical activity of varying intensity leads to the launch of a large number of biochemical, molecular and genetic mechanisms that underlie the body's adaptive reactions to physiological stress[15,16,17,18]. Myokines perform a variety of functions during physical activity[19,20]. As a consequence, myokines are considered important factors in maintaining homeostasis and muscle adaptation to physical activity[21]. The discovery of myokines has opened a new direction in understanding the effects of exercise on humans[22].

Myokines play a role in the implementation of numerous processes, such as myogenesis, osteogenesis, thermogenesis, lipolysis, increasing the sensitivity of tissues to glucose[23,24,25]. Type 2 diabetes mellitus (T2DM) is a socially significant disease. Insulin resistance (IR) is the first link in the pathogenesis of T2DM and is associated with a decrease in the ability of insulin to enhance the uptake of glucose from the bloodstream by target cells. The molecular mechanisms and markers of IR have not been sufficiently studied, which hinders early diagnosis and the development of preventive drug therapy. Reliable global estimates of diabetes prevalence are needed to monitor public health strategies and develop effective future interventions. Treatment of diabetes is aimed at preventing complications and maintaining a satisfactory quality of life. Many drugs are currently being developed to treat diabetes.[26,27,28,29,30]

Myokines are formed, expressed on the surface of muscle fibers and released into the bloodstream. They are regulators of myogenic differentiation, fiber type switching, and muscle mass maintenance[31,32]. Myokines are involved in the regulation of various physiological processes and have both local and systemic effects[33]. Myokines are involved in bone metabolism, influencing bone resorption and formation by interacting with factors associated with bone cell secretion or influencing bone metabolic pathways[34].

Experiments on mice showed that after physical exercise there was an increase in the concentration of osteocalcin (OCC) and the myokine IL-6, but in the presence of IL-6 deficiency, the level of OCC did not change[35].

It is also worth noting that during physical activity the level of myostatin decreases, thereby stimulating the process of muscle tissue growth[36,37,38]. Myokines play a key role in regulating myocardial and skeletal muscle rejuvenation, weakening muscle metabolic homeostasis, and protecting against ischemic damage and apoptosis[39].

Fibroblast growth factor (FGF-21) improves tissue sensitivity to insulin[24]. Myostatin inhibits the growth and differentiation of muscle tissue and regulates the growth of adipocytes[40]. Myostatin leads to resorption in bone tissue, while increasing osteoclastogenesis and inhibiting osteoblastogenesis[41]. Irisin improves lipid metabolism, facilitates the deposition of glucose in the liver, and prevents the occurrence of hyperglycemia and hyperlipidemia. It has a beneficial effect in the pathogenesis of obesity and type 2 diabetes[24,42]. Interleukin-6 (IL-6) promotes the development of insulin resistance (IR) in adipose tissue and hepatocytes during physical exercise (PE) for more efficient mobilization of glucose and fatty acids as energy sources, as well as in obesity, metabolic syndrome, diabetes mellitus[43,44]. IL-6 in the blood and tissues serves as a signal of energy deficiency, which enhances the action of insulin in muscle cells and inhibits it in tissues supplying energy substances. Its increased level leads to a lipolytic effect[23,24,45]. IL-6 enhances lipolysis and insulin sensitivity in adipose tissue[46], optimizes insulin production in the pancreas[47] and increases glycogenolysis and lipolysis in the liver[48]. A sharp increase in plasma concentrations of IL-6 has an anti-

inflammatory effect and regulates acute inflammatory reactions[49].

Modern studies demonstrate the active participation of myokines in the regulation of the processes of lipolysis, gluconeogenesis, insulin secretion by pancreatic beta cells, and activation of thermogenesis[50,51,52]. Myokines are capable of modulating the function of cells of the immune system, local blood flow, energy metabolism, processes of proliferation and differentiation of myoblasts[53,54,55,56]. Adipokines and myokines can serve as indicators of obesity phenotypes. Significant differences in the levels of adipokines and myokines and their relationship with indicators of the intestinal microbiome were revealed in patients with different obesity phenotypes[57,58]. Changes in myokine production in diabetes mellitus have been shown[59,60,61,62], obesity[23,63,64] osteoporosis[65,66] as well as for metabolic disorders[67].

It is known that a sedentary lifestyle is associated with the development of obesity, type 2 diabetes, cardiovascular disease, osteoporosis and early mortality, and regular physical activity helps prevent these conditions[68]. By adapting to mechanical, neural and humoral influences, skeletal muscle plays a critical role in physical activity, energy expenditure and glucose utilization[69]. Many research projects led to the discovery of new myokines and an understanding of their role in the physiological regulation of exercise, both in apparently healthy people and in chronically suffering patients[70]. During physical exercise, the following reactions occur in skeletal muscle: an increase in the expression of insulin receptors, the absorption of fatty acids and glucose, glycogen stores, as well as mitochondrial biogenesis. In a study of muscle secretions, hundreds of substances were found to be expressive in response to exercise[71]. Loss of muscle mass in people with chronic heart disease increases risk of death[72]. During exercise, muscle fiber cells express and release more than 3,000 molecules of cytokines and polypeptides known as "myokines"[73]. Myokines have a positive effect on the development of satellite cells and skeletal muscle hypertrophy[74]. Myokines interact with high-affinity receptors (transmembrane glycoproteins) located on the membrane of target cells[75]. After exercise, there is an increase in PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), which stimulates mitochondrial biogenesis, binds to FOXO and inhibits its transcriptional activity, thereby preventing the breakdown of muscle proteins[76]. The primary role of IL-6 is to maintain stable blood glucose levels during exercise. Low pre-exercise levels of intramuscular glycogen have been shown to increase mRNA synthesis IL-6[77]. Oxidative stress, low glucose concentration, low glycogen content and increased Ca^{2+} flux activate IL-6 transcription factors by stimulating mitogen-activated protein kinases[78]. Skeletal muscle secretes myokines, while influencing other organs by binding to target cell receptors in an autocrine, endocrine and paracrine manner[79].

2. The role of myokines in diabetes mellitus:

Myokines promote increased insulin sensitivity, which leads to glucose clearance and regulation of glucose and lipid metabolism[80]. However, long-term hyperinsulinemia leads to dysfunction of pancreatic β-cells and decreased insulin synthesis against the background of persistent IR. Prediabetes occurs, in which carbohydrate metabolism is disrupted. At this stage, it is possible to prevent pathological changes and restore the sensitivity of target cells to insulin. In this regard, early diagnosis of IR is of great practical importance[81,82]. The development of insulin resistance leads to the inability of target cells to respond to insulin, resulting in the development of type 2 diabetes mellitus (T2DM) and metabolic syndrome[83]. Kinases such as NF-κB, IKK, JNK are involved in inflammatory signaling cascades in adipocytes under the influence of cytokines[84]. IRS is used as one of the substrates, which is phosphorylated at several serine residues, rendering it inactive and interrupting signal transmission along the insulin cascade[85,86,87,88,89]. Cytokines and free fatty acids (FFA) have a pro-inflammatory effect. Cytokines and FFAs bind to toll-like receptors TLR4 on adipocytes. An inflammatory cascade is launched involving NF-κB, IKK and JNK. As a result, serine phosphorylation of IRS increases in adipocytes and the insulin cascade is switched off [90,91].

Many antihyperglycemic drugs used to treat diabetes (thiazolidinediones, sulfonylureas, glinides, insulin) activate the key regulator of adipogenic differentiation PPARγ, causing weight gain due to the formation of new fat depots[92]. Studies of cell insulin cascades have shown the possibility of selective effects on cell growth and division in the absence of induction of lipo- and adipogenesis. The transcription factor Prep1 of the TALE family of homeobox proteins not only regulates PPARγ activity, but also enhances the expression of the glucose transporter Glut4 and insulin sensitivity[93,94,95].

In pharmacological therapy of T2DM, differentiation of adipose tissue preadipocytes into brown and beige fat cells, which have hypolipidemic and hypoglycemic properties, can be used. Their cells promote the utilization of fats and glucose without obtaining energy. Its key participant is the protein UCP-1, or thermogenin. The expression of thermogenin and the differentiation of fat progenitor cells into "beige" adipocytes is controlled by the local hormone irisin[96-97].

It has been noted that current antidiabetic drugs can cause serious side effects, including heart failure, hepatotoxicity and obesity. Scientists' work aimed at elucidating the mechanism of skeletal muscle sensitivity to insulin, energy metabolism and the role of myokines in endocrine functions will help find new treatment methods in the future[98]. Effect of myokines secreted from healthy and insulin-resistant myotubes is beneficial and harmful in the regulation of insulin secretion, which indicates cross-talk between skeletal muscles and the pancreas[99].As expected, there has been an uptick in research into contraction-regulating myokines that promote β-cell mass and function[100,101]. Beneficial myokines, including irisin, fractalkine, FGF21, myonectin, and IL-15, improve the mass and/or function of β-cells that regulate glucose and lipid metabolism[102,103].

Myostatin can be used to prevent muscle wasting[104]. An example of disparate results is shown in the myokine IL-6, where some investigators report that IL-6 has beneficial effects on β-cell function[105,106,107,108], which casts doubt on the appropriateness of using irisin as a therapeutic agent[108]. Basically, experimental studies have been conducted in rodent models to identify the mechanism of action of myokines on the viability and function of β-cells[109,110].

Persistent IR triggers delayed, long-term adaptation processes in the body; they lead to a restructuring of the entire metabolism during the development of T2DM. Such long-term changes are consolidated at the transcriptional level, where various transcription factors play a key role[111].

In an experiment on mice that were fed a high-fat diet and periodic chronic stress, glucose homeostasis and lipolysis were determined. In the early stages of diet-induced obesity, it was found that glucose intolerance initially occurs, followed by decreased insulin sensitivity and increased sensitivity to epinephrine (EPI). Stress increased myonectin (Myn) levels in serum and skeletal muscle and improved glucose intolerance[112,113].

Decreased insulin receptor sensitivity worsens insulin effects, triggering a vicious cycle of disorders including compensatory insulin hypersecretion, pancreatic β-cell dysfunction, impaired tissue glucose utilization, metabolic and hemodynamic abnormalities, subsequent increases in IR, organ damage, and cardiovascular disease (CVD). Early therapy aimed at improving insulin sensitivity and restoring its effects could become one of the effective methods of primary prevention of type 2 diabetes and CVD[114].

A study conducted on overweight and obese Chinese residents found that low serum irisin levels are usually associated with smoking, type 2 diabetes mellitus, dyslipidemia, and the presence of cardiovascular disease risk factors[115]. The level of irisin concentration depends on the etiology of obesity. For example, with a genetic form of obesity in patients with Prader-Willi syndrome, the content of irisin in the blood serum is significantly lower than with other forms of obesity that are not caused by genetic factors[116]. In patients with type 2 diabetes mellitus, the level of irisin concentration in the blood serum is reduced[117] Vascular complications are the cause of death in patients with type 2 diabetes; it was revealed that irisin prevents endothelial dysfunction by reducing oxidative stress through inhibition of signaling pathways including NF-B/iNOS and PKC-/NADPH oxidases[118]. Thus, irisin and its analogues may be potential drugs for the treatment of complications of diabetes mellitus[119].

There are many models of spontaneous development of type 1 and type 2 diabetes in rodents (rats and mice). Diabetes can be caused by surgery, pharmacological drugs, the prescription of special diets, as well as various combinations of these[120].

The effect of forced running loads on the content of certain cytokines in the skeletal muscles of mice with a model of type II diabetes mellitus was studied. A high-fat diet was used to form a disease model; physical activity in the form of forced running was carried out for 4 weeks. The production of interleukins can be associated with the restructuring of transcriptional mechanisms in muscle fibers associated with calcium-dependent and calcium-independent intracellular signaling pathways[121,123,124].

The study of the role of myokines in the correction of various disorders has significant prospects. A change in the production of myokines has been shown in diabetes mellitus, obesity, osteoporosis, and also in metabolic disorders. This allows us to consider myokines as a possible mechanism through which the therapeutic effects of physical activity are realized in various diseases[125,126].

3. Prospects for myokines in the treatment of diabetes

Adipokines and myokines maintain metabolic homeostasis. When they are imbalanced, metabolic complications develop, such as insulin resistance, low-grade inflammatory remodeling of adipose tissue, extracellular lipid deposition, atherosclerosis, etc[127]. Adiponectin has been shown to have insulin-sensitizing, antiatherogenic and anti-inflammatory effects[128]. But the adipokines leptin and resistin, on the contrary, are

factors of insulin resistance. They have a pleiotropic effect on food intake, neuroendocrine regulation of the hypothalamus, reproductive function and energy metabolism[129]. Data on the adipokine asprosin are extremely fragmentary: there are suggestions that it can influence glucose metabolism and is probably associated with obesity and that its level may be a marker for the early diagnosis of diabetes mellitus[130].

Information about the role of the myokine myostatin in the pathogenesis of obesity and insulin resistance is currently limited. Some authors propose the use of myostatin to identify metabolically unhealthy obesity (MHA)[131]. The insulin-sensitive myokine FGF21 acts as a metabolic regulator involved in the control of glucose homeostasis[132]. Recently, researchers have been interested in the peptide osteocrine, secreted by fibroblasts and osteoblast-like cells. Its pathophysiological role is poorly understood[133]. Single results in patients with obesity and insulin resistance demonstrated a higher level compared to healthy subjects[134].

Exercise has long been a central principle of both the prevention and treatment of type 2 diabetes mellitus (T2DM)[135,136]. The secretion of IL-6 during physical activity depends on the energy state of the cell and on the glycogen content in the cells before exercise. Low glycogen content leads to greater release of IL-6 under conditions of energy crisis in the muscle cell during contraction[137]. In vitro studies demonstrate that IL-6 treatment increases glucose uptake through AMP protein kinase [adenosine monophosphate kinase (AMPK)] and phosphatidylinosotol 3-kinase (PI3K) pathways[138].

Carey et al.[139] reported increased insulin-dependent glucose uptake in vivo in response to IL-6 infusion.In contrast, Harder-Lauridsen et al.[140] found no increase in glucose uptake during euglycemic hyperinsulinemic clamp with IL-6 infusion in individuals with T2DM, although there was a decrease in plasma insulin levels, indicating increased insulin sensitivity[140]. Jiang et al.[141] found a differential effect of IL-6 treatment on primary myotubes compared with normal glucose tolerance and T2DM, suggesting a minor role for IL-6 in T2DM muscle. IL-6 treatment enhanced both insulin-dependent and -independent glucose uptake and glycogen synthesis in healthy myotubes, but this effect was lost in T2DM myotubes. This suggests that from a glucose control perspective, the contraction-inducible myokine IL-6 is effective in preventing T2DM but may not be effective in glucose uptake in patients with existing T2DM.IL-13is released from human primary myotubes in vitro and has been demonstrated to have an "insulin-like" effect on glucose metabolism in human muscle by increasing glucose uptake, glycogen synthesis, and glucose oxidation in primary myotubes in normal and T2DM[141]. This "insulin-like" effect is mediated by activation of the Akt and PI3K pathways. IL-13 expression is increased in response to resistance training in human skeletal muscle[142], but there is no evidence of increased plasma IL-13.

In addition, Gergens et al.[143] demonstrated the expression and release of FSTL-1 from primary human myotubes. Interestingly, contraction of primary ER myotubes did not induce FSTL-1 secretion; however, increases in circulating plasma FSTL-1 have been observed in humans following acute aerobic exercise. In vitro incubation of L6 myotubes (rat cell line) in FSTL-1 has been shown to increase glucose uptake in an AMPK- and calcium-calmodulin kinase-dependent manner[144], resulting in increased expression of GLUT4 mRNA and its translocation to the plasma membrane, mediating improved glucose control.

Optimizing myokine responses for the prevention and treatment of T2DM. Myokines that regulate glucose and fat metabolism can trigger mechanisms during exercise that prevent the onset or progression of T2DM[145]. To date, most of the evidence describing the mechanism by which myokines modulate metabolic function has been characterized using in vitro cell models, which do not necessarily correspond to the in vivo human situation[146]. Tingqing Guo et al. investigated the effect of inhibition of myostatin signaling in skeletal muscle and adipose tissue on body composition, metabolic profile[147]. Mice deficient in myostatin showed normal basal metabolic rate and higher respiratory quotient, indicating an increased rate of carbohydrate oxidation; an increase in the amount of lean mass and a low content of fat mass was also noted over 15 months of observation[148]. Another study showed increased tissue sensitivity to insulin in mice deficient in myostatin due to increased AMPK activity in muscle[149]. Skeletal muscle (SM) is known to generate hypoglycemic and antioxidant responses[150].

Myokines and exercise. Exercise is a well-established treatment for muscle metabolic defects that occur in T2DM.

Physical activity promotes the process of active transcription of myokines, which accelerate metabolic processes associated with increased stress on muscle tissue. Thus, by explaining the process of formation of these proteins in the body, doctors will be able to correct various disorders that are associated with the body's complex adaptation to physical activity after severe injuries[151,152]. It is also worth noting that during physical activity the level of myostatin decreases, thereby stimulating the process of muscle tissue growth. Its concentration in mouse myocytes decreases after

running exercise, promoting the growth and differentiation of satellite cells[153]. Similar results have been obtained in humans[154,155].

A 2020 meta-analysis including seven studies involving 125 normal-weight, overweight, and obese adults (21–64 years) found that bouts of physical activity (PE) increased serum FGF-21 levels regardless of body weight. In this case, the increased level of FGF-21 persists for 1 hour and decreases to a level close to the initial values after 3 hours[156]. However, there was no increase in FGF-21 levels in patients with type 2 diabetes[157].

Studies in mice have shown that irisin improves glucose tolerance and reduces insulin resistance (IR)[158]. Irisin also stimulates lipolysis using hormone sensitive lipase (HSL, hormone sensitive lipase) and inhibits lipogenesis in mouse adipocytes[159].

In the work of Miyamoto-Mikami E. et al. In healthy adults, after 8 weeks of endurance training, increases in circulating irisin levels were positively correlated with decreases in fat mass[160]. Irisin has antioxidant and anti-inflammatory effects on hepatocytes, which could be useful in reducing the activity of steatohepatitis[161].

Some of the best studied exercise-induced myokines influence bone formation and bone resorption[162].

Dynamic and static exercises differentially affect the content of myokines in the blood plasma of athletes and untrained individuals [24,156,160,163].

A study of the effect of forced running in mice with a model of type II diabetes mellitus showed that in healthy animals there was a decrease in the concentrations of IL-6 and IL-15 and an increase in the concentration of leukemia inhibitory factor (LIF) in muscle tissue after 4 weeks of regular forced running. At the same time, in diabetic mice, the concentrations of IL-6 and IL-15 after exercise increased, and LIF, on the contrary, decreased[164].

The production of interleukins can be associated with the restructuring of transcriptional mechanisms in muscle fibers associated with calcium-dependent and calcium-independent intracellular signaling pathways[165,166,167,168].

An increase in IL66 mRNA transcription was shown in the nuclei of muscle cells isolated from human muscle biopsies after a single exercise[169,170].

This is also of interest given that lack of physical activity is strongly associated with the occurrence of T2DM. There is a need to determine the secretion of myokines in patients with T2DM to identify potential therapeutic targets for the treatment of this disease[171]. The synthesis of IL-6 during physical exercise is due to glycogen-independent mechanisms and changes in the level of calcium in the cytosol of myocytes. It consists primarily of regulating glucose homeostasis, which is necessary for intensely contracting muscles. With an increase in the intensity of muscle contractions and a decrease in glycogen concentration in the muscles, mechanisms associated with the activation of mitogen-activated protein kinase are activated[172].

4.Challenges and limitations associated with the use of myokines for therapeutic purposes:

The occurrence of diabetes mellitus is associated with myokines, but the mechanism of damage to target organs is still unclear and requires further study. Cytokines such as interleukin-4 and interleukin-10 are capable of suppressing type 1 diabetes in animal models when delivered as part of a plasmid or viral vector[173].

When creating a new drug, it takes a long time from the idea to its entry into the market and widespread use in practice. The algorithm for entering the market of a new pharmaceutical has the following stages: 1) idea, 2) development of production technology, 3) preclinical testing of the pharmaceutical (previously only on animals, now also on cell cultures in in vitro models), 4) after clinical trials (CT), 5) entering the market, 6) additional clinical trials (CT) are being conducted at a new level[174].

Experts from Tomsk State University (TSU) are developing a new method of treating diabetes[175].

Although an increase in the number of clinical trials indicates renewed interest in cytokines, antibodies targeting cytokines or corresponding receptors are being used more often[176].

Exercise-induced increases in IL-6 production may be involved in protecting pancreatic β-cell mass and function. It is well known that exercise can improve insulin sensitivity, whereas it is less clear whether exercise can improve insulin secretion and whether there is a link between insulin-resistant skeletal muscle and pancreatic β-cells[172,177,178].

In diabetes mellitus, glucose metabolism is impaired, which leads to increased blood glucose levels (hyperglycemia) and the production of free radicals. Drugs, used to treat metabolic disorders are not flawless. Basic knowledge of diabetic patients regarding insulin therapy is insufficient. Urgent steps are needed to improve the knowledge of diabetic patients and create

appropriate awareness about insulin therapy. Complications of diabetes can be avoided by regularly monitoring and maintaining blood glucose levels within normal limits.The current approach to treating both type 1 and type 2 diabetes is to achieve the best possible glucose control[179,180,181,182,183]. In diabetes, self-monitoring and patient compliance with prescribed medications, as well as lifestyle changes, are very important, and the pharmacist can play an important role in counseling[184].

A promising direction is the introduction of artificial intelligence in the management of diabetes. Artificial intelligence is able to correctly interpret external data, learn from such data and use the acquired knowledge to achieve specific goals and objectives through flexible adaptation[185]. The artificial intelligence of the SNAQ app automatically identifies foods and calculates the protein, fat and carbohydrate content. Throughout the day, the app receives self-monitoring data and marks meal times on a graph, helping to illustrate how certain foods affected your blood glucose levels. Using the SNAQ app as part of nutrition counseling may be a promising technology as it provides real-time information on food intake and allows for personalized recommendations[186,187].

Currently, there is no effective therapy to completely eradicate/cure diabetes and its associated complications. There is a need to create better, new anti-diabetic therapy in the future based on myokines, knowing their signaling pathways and their mechanism of action on target cells, but also for the best possible combination therapy and strategies using available drugs[188].

Neuromuscular electrical stimulation (NMES) is emerging as an effective exercise substitute for myokine induction. NMES is safe and effective and has been shown to improve muscle strength, functionality and quality of life. This alternative method of exercise induces hypertrophy and neuromuscular adaptations in skeletal muscles. NMES stimulates the secretion of circulating myokines, promoting a cascade of endocrine, paracrine and autocrine effects. NMES is an effective exercise replacement for stimulating myokine production and its potential applications in health and disease[189].

5. Key findings and insights regarding the role of myokines in diabetes mellitus:

Diabetes mellitus (DM) has become a global threat to human health around the world. Currently, there is no effective therapy to completely eradicate/cure diabetes and its associated complications. Current antidiabetic drugs (thiazolidinediones, sulfonylureas, glinides, insulin) can cause serious side effects, including heart failure, hepatotoxicity, and obesity.

The work of scientists aimed at elucidating the mechanism of skeletal muscle sensitivity to insulin, energy metabolism and the role of myokines in endocrine functions will help in the future to find new treatment methods based on knowledge of signaling pathways and the mechanisms of their action on target cells.

They found that myokines promote insulin sensitivity, which leads to glucose clearance and regulation of glucose and lipid metabolism. Several myokines (irisin, fractalkine, FGF21, myonectin, and IL-15) improve the mass and/or function of β-cells, which regulate glucose and lipid metabolism.

Myokines as therapeutic targets for the treatment of T2DM are a promising area. Harnessing the beneficial effects of myokines on insulin secretion, insulin sensitivity, and energy metabolism may lead to the development of important new treatments for T2DM.

A few studies in mice and humans have shown that exercise increases the levels of numerous myokines in the blood plasma, which leads to the process of active transcription of myokines and acceleration of metabolic processes associated with increased load on muscle tissue.

It has been suggested that the secretion of myokines depends on the degree of physical fitness; intensity and duration of the athlete's training; its physiological and anatomical structure; the sport in which the athlete plays. Neuromuscular electrical stimulation (NMES) is emerging as an effective replacement for myokine induction by exercise.

A promising direction is the introduction of artificial intelligence in diabetes management.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

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