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Effects of common Myokines on Diabetes Mellitus

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Abstract

Skeletal muscle secretes protein factors (myokines) that can exert multiple actions. To study the control of myokine regulation of β-cell function, SkM biopsies were taken from non-diabetic and Type 2 diabetic (T2D) subjects and satellite cells cultured to myotubes (MT). Cell viability, total insulin content, glucose-stimulated insulin secretion (GSIS) and maximal IS was monitored. Diabetes mellitus, a type of chronic metabolic disease, is occurring more frequently and causes severe threats to human health. In vivo, exercise can stimulate skeletal muscle cells to secrete and release myokines into blood circulation, which will participate in metabolism and act on multiple organs or systems. Recently, the relationship between myokines and diabetes mellitus was a hot research topic, and myokines may be potential targets for the diagnosis, monitoring, prevention and treatment of diabetes mellitus. In this review, we elucidated the multiple effects of common myokines in the pathogenesis and therapy of diabetes mellitus, which will provide a theoretical foundation of the mechanism in the positive effects of exercises on humans.

Keywords: Diabetes; Myokines; Islet cells; Insulin resistance

Introduction

Diabetes mellitus is a metabolic disease caused by absolute or relative insufficiency of insulin secretion and is mainly manifested as hyperglycemia. Statistics from the Worth Health Organization demonstrate that about 0.46 billion people were attacked by diabetes mellitus worldwide in 2021. Diabetes mellitus is mainly divided into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) as well as gestational diabetes mellitus (GDM), monogenic diabetic syndrome, and drug- or chemical-induced diabetes mellitus. T2DM is most common in clinic, accounting for about 90% of all diabetes mellitus and mostly occurs in middle-aged and old people. T2DM, the fifth cause of death worldwide, often occurred in the background of insulin resistance [1]. When the function of β cells in the pancreatic islet fails to compensate for insulin resistance, hyperglycemia and impaired glucose tolerance eventually lead to T2DM. With the application of exercise therapy in diabetes mellitus and other metabolic diseases, the indispensable roles of skeletal muscles have attracted wide attention. Skeletal muscles are important organs in physical exercises, posture maintenance and energy metabolism regulation. They are important endocrine organs, secreting various myokines through autocrine or paracrine function. Skeletal muscles participate in energy metabolism, insulin resistance, glucolipide metabolism and other processes. Interleukin (IL)-6, the first named myokine, is positively correlated with the incidence of diabetes mellitus. Other myokines including IL-10, IL-15, growth differentiation factor (GDF)-8, fibroblast growth factor (FGF), meteorin-like and irisin were discovered subsequently. The levels of myokines in surm will change during insulin resistance and exercise therapy for diabetes mellitus, which can be used as a target for diabetes therapy and prognosis. In this work, the development of common myokines and effects on the occurrence and development of diabetes mellitus as well as the roles of myokines in diabetes mellitus are reviewed. This work emphasizes the role of myokines, and provides evidence for the prevention, early diagnosis and treatment of diabetes mellitus [2].

IL-6

IL-6, the first discovered myokine, has a molecular weight of 21 - 30 KD and is composed of 184 amino acids. Initially, IL-6 was thought as an inflammatory factor. When the body is under the inflammatory status, monocytes and macrophages rapidly secrete IL-6 and thereby induce C-reactive protein and procalcitonin to participate in the inflammation process. Previous evidence has shown that in addition to mediating inflammation, IL-6 also regulates glucose homeostasis and lipid metabolism.

A meta-analysis demonstrates that IL-6 disturbs insulin signals and damages the functions of islet β cells, thereby participating in the occurrence of T2DM, and IL-6 level are positively correlated with the incidence of T2DM. In addition, IL-6 plays a dual role in maintaining blood glucose stability. IL-6 is a beneficial glucose metabolism regulatory factor in the healthy body, but may increase the severity of insulin resistance in obese or inflammatory patients. Kurauti et al. found that IL-6 may enhance insulin resistance by increasing the ratio of cyclic adenosine phosphate and AMP/ATP in rat skeletal muscle to activate 5'-adenosine monophosphate activated protein kinase (AMPK) to enhance the expression and activity of insulin degrading enzymes in liver and skeletal muscle, avoiding the sudden drop of blood glucose level during exercising. Other studies have found that IL-6 not only improves glucose uptake by stimulating AMPK and phosphatidylinositol 3 kinase activity, but also impacts insulin in a dependent manner by C-Jun amino-terminal kinase [3]. Additionally, the IL-6 level is also associated with the subclinical inflammation and obesity of T2DM, indicating weight control may be a measure to prevent inflammation in T2DM patients.

The coronary artery disease (CAD) is a major cause for the morbidity and mortality of T2DM patients. There is increasing evidence that chronic vascular inflammation is driven by inflammatory factors and can mediate vascular complications of T2DM. Thus, it is significant to study the increase of inflammatory cytokine IL-6 in

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T2DM patients. Recent studies have suggested that, IL-6 is related to left ventricle dysfunctions and can be one of the methods to detect left ventricle dysfunctions in T2DM patients. Elevated IL-6 levels can interfere with glucose metabolism and lead to insulin resistance, which together with tumor necrosis factor (TNF)-α and IL-1β can induce chronic inflammation and promote the occurrence of CAD in diabetic patients. Adela et al. found that IL-6 was elevated in both CAD and T2DM-CAD groups, especially in THE T2DM-CAD group, by studying the serum protein characteristics of CAD in Indian T2DM patients. Moreover, high blood glucose level can lead to inflammation of vascular endothelial cell (EC) and migration and proliferation of smooth muscle cells (SMC) through activating the JAK-STAT signal to stimulate IL-6 release [4]. As a result, high IL-6 level is associated with the vascular EC inflammation and uncontrollable SMC migration/proliferation in T2DM patients.

IL-10

IL-10, also known as cytokine synthesis inhibitor, is a multifunctional inflammatory suppressor that plays an immunological role in many cell types. IL-10 is mainly produced by Th2 cells and mononuclear macrophages and can inhibit the production of cytokines by activated T cells, which inhibit cell immunity response. In addition to the important regulating effects in immune responses in vivo, there is growing evidence that IL-10 is involved in type 2 diabetes.

At locus 1082 of transcription initiation loci, the existence of G allelic gene is related to the high expression of IL-10. IL-10 inhibits the production of inflammatory factors by inhibiting T cells, monocytes and macrophages, and the IL10-1082G/G genotype can down-regulate the immune response. The clinical significance of IL-10 level in insulin resistance has also been confirmed, and IL-10 level is positively correlated with insulin sensitivity. Meanwhile, Zeng Jing et al. showed that IL-10 was negatively correlated with the severity of diabetic peripheral neuropathy [5].

GDF-8

GDF-8, belongs to the transforming growth factor β superfamily, is a key regulator of skeletal muscle mass. In 1997, McPherron et al. discovered GDF-8 in mouse muscle tissues by using PCR, and found the skeletal muscle in GDF-8-deficient mice was 2 to 3 times that in wild-type mice. After, GDF-8 was also known as MSTN because of its inhibitory effect on skeletal muscle growth. The existing research implied that GDF-8 is involved in the pathophysiological processes of cardiovascular diseases, kidney diseases, obesity and diabetes.

Amor M et al. found that GDF-8 is upregulated in the serum of obese patients and is positively correlated with the insulin resistance index, while negatively with the insulin sensitivity index. Insulin resistance is a key factor for the occurrence of T2DM [6]. When the function of pancreatic β cells cannot compensate for insulin resistance, abnormal rise of blood glucose level and impaired fasting glucose will occur, which finally lead to T2DM. A cross-sectional study involving 264 T2DM patients indicates that the level of GDF-8 is positively correlated with retinopathy and affects the progression and prognosis of diabetes. Down regulation of GDF-8 in T2DM patients can active the insulin signaling pathway, antagonizes the negative effects of on muscle mass, muscle strength and insulin signaling pathway partly in T2DM mice par, and thereby improve glucose homeostasis and relieve insulin resistance. In DM mice, metformin can significantly regulate GDF-8-mediated muscle dysfunction in skeletal muscle cells through AMPK-FOXO3A-HDAC6 pathway, providing a new idea for DM drug diabetes mellitus therapeutic development. Dapagliflozin, a T2DM therapeutic drug, can significantly down regulate the GDF-8 level, maintain skeletal muscle mass and relieve diabetes-related muscle tissue loss. Emerging diabetes exercise therapy showed excellent effect on diabetic rats. GDM attacks women with normal normal glucose metabolism or potential glucose tolerance reduction during pre-pregnant and is occurring or diagnosed during gestation. It is adverse to fetal growth and development. Early maternal serum marker GDF-8 increased in patients with GDM, highly GDF-8 has predictive value for the occurrence of GDM at late trimester of pregnancy [7]. T1DM, also called insulin-dependent diabetes mellitus, is related to the immunity-mediated destruction of β cells in late trimester of pregnancy. Clinical research implies that the serum GDF-8 level of T1DM children is significantly higher than healthy children at the same age and BMI (body mass index), which may be associated with impaired glucose tolerance. Interestingly, Dial A G et al. found the GDF-8 level was not fully related to clinical indices. The skeletal muscles of pigs can be enhanced and even the glucose ingestion in T1DM can be improved by controlling GDF-8 in vivo. Hence, the function of GDF-8 in T1DM may involve complex regulatory mechanisms, and exploring the mechanism of GDF-8 upregulation and its correlation with insulin dose in T1DM is extremely important.

FGF

FGFs are a structure-related polypeptide family and also called heparin-binding growth factors. FGFs in the form of paracrine or endocrine can mediate body development, tissue homeostasis or restoration, and relevant metabolic activities. Recent research shows that FGF-1, FGF-4, FGF-19, and FGF-21 can significantly act on diabetes mellitus and can be used as targets for early diagnosis, prevention and treatment of diabetes mellitus.

FGF1, the first discovered member in this family, is a strong angiogenesis factor and pro-mitogen that is a signaling protein encoded by the FGF1 gene. In vitro research demonstrates that all the subtypes of the FGF receptor as well as FGF1 are expressed at the mRNA level in the insular tissues and pancreas β cell INS-1E cell line of rats, and FGF1 can enhance the proliferation of INS-1E cells and improve the activity of insular cells. After the stimulus of islet cells by FGF1, the phosphorylation levels of extracellular regulated protein kinases are significantly increased, and blockage of ERK1/2 can destroy the exciting effect of FGF1 on islet cell proliferation, indicating ERK-related pathways are involved in the islet cell proliferation and regulation by FGF1 [8]. Experiments on T2DM and T1DM mice demonstrate that FGF1 can improve the rising blood sugar level in T2DM mice, but not in T1DM mice, suggesting the reduction of blood sugar level by FGF1 must be achieved with the presence of islet cells. This finding offers some theoretical basis for FGF1 to directly stimulate islet cells.

FGF4 plays an indispensable role in embryonic development, including implantation, morphogenesis, and organogenesis. FGF4 was found to be an effective anti-hyperglycemic factor with hypoglycemic effects comparable to FGF1. This study also validates that the endocrine FGF21 and FGF19 regulate hypoglycemic activities mainly in the liver, but not in muscles. Hence, FGF19 and FGF21 cannot stimulate the glucose ingestion by skeletal muscles, which explains the fact that FGF secretion in skeletal muscle is worse than paracellular secretion.

FGF19 was first discovered in the brain at the human fetal development stage, but was later found to be mainly expressed in the ileum. FGF19 not only plays a role as a physiological regulator of bile acid homeostasis, but also plays an insulin-like role in promoting

glycogen synthesis and reducing blood glucose levels in diabetic mice. It is important to note that lateral ventricle injection of FGF19 can decrease the blood sugar levels of diabetic mice, without affecting insulin secretion or systemic insulin sensitivity, indicating FGF19 can reduce the blood sugar level in an insulin-independent way.

FGF21 is mainly expressed in the liver and slightly expressed in extrahepatic tissues, such as white and brown fat tissues, skeletal muscles, the heart, kidney and pancreas. FGF21 has an insulin-like effect and can improve the function of islet β cells by regulating the protein kinase B signaling pathway, thus regulating fat and glucose metabolism, which has varying degrees of elevation in patients with diabetes, coronary heart disease, obesity and metabolic syndrome. Hence, FGF-21 may also be a biomarker to indicate the higher risk of developing metabolic syndrome [9].

Altogether, the occurrence and development of diabetes mellitus are regulated by multiple factors in various signaling pathways. However, the heterogeneity among races, origin heterogeneity among tissues from different parts, and differences in microenvironment call for abundant experiments for data collection and research, which will theoretically underlie clinical applications.

Irisin

Irisin is negatively correlated with fasting plasma glucose, insulin level, homeostasis model assessment-insulin resistance, retinol binding protein4, and hemoglobin in diabetic patients. The Irisin level is low in T2DM patients accompanied with vascular complications. The above findings indicate irisin has certain relieving effect on diabetes mellitus. Tarboush et al. found that irisin level in plasma was not only correlated with DR stage of diabetic retinopathy, but also significantly different in irisin level between DR stages, which has great guiding value for studying irisin as a potential associated marker of diabetic complications. Irisin can also relieve myocardial microvascular injuries, cell apoptosis, insulin resistance and blood sugar level rise through activating the ERK1/2/Nrf2/HO-1 pathway in diabetic patients. In streptozotocin (STZ) induced diabetic mice, intraperitoneal injection of recombinant Irisin significantly reduced the daily water intake, food intake and blood glucose [10].

In all, irisin is closely related to sugar metabolism and has been shown to have a certain degree of therapeutic effect in alleviating diabetes in cells, animals and clinical experiments However, studies on the correlation between irisin and diabetes and metabolic syndrome also have different results One study shows that there is no significant correlation between serum irisin and glucose metabolism related indicators in T2DM patients. As a result, the definite mechanism of irisin in diabetes mellitus calls for further research.

Conclusion

Taken together, the myokines released during skeletal muscle contraction play important regulating roles involved in the development of diabetes, which may become potential targets for diagnosis, monitoring, prevention and treatment of diabetes mellitus. Diabetes patients lacking a specific muscle factor can be improved by targeting specific muscle factors, or as a new test indicator or a combination of indicators for the diagnosis of the disease. Moreover, exercise therapy can also be an effective way to treat diabetes or adjunctive therapy. Although myokines are closely related to the occurrence of diabetes mellitus, the underlying mechanism of how they play a role in the pathogenesis and target organ injury is still unclear and needs to be further explored. The results of cell, animal and even the clinical trial are a degree of heterogeneity or even fully opposite, which may be related to different sample sizes, selected population ethnicity, clinical characteristics of the disease, and measurement criteria and methods of myokine. Given the extensive applications of myokines in medicine and exercise medicine, exploring the role and mechanism of exercise or myokines in alleviating diabetes mellitus will be conducive to better playing the health promotion role of exercise.

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