AN OVERVIEW OF THE EFFECTS OF IRISIN ON METABOLIC DISORDERS

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ABSTRACT

Obesity and obesity-related diseases including insulin resistance and metabolic syndrome (MetS) pose a great risk for cardiovascular disease development. Skeletal muscle as an endocrine organ has pivotal role on secreting physiological factors such as hormones and myokines. Irisin that is one of these myokines also known as hormone is secreted mainly from muscle tissue in response to exercise. It is dependent to fibronectin type III-containing protein 5 (FNDC5) that is a membrane protein and encoded by FNDC5 gene. After discovering of FNDC5, metabolic effects of irisin have been investigated so far. Irisin has mainly effects on muscle, adipose tissue, pancreas, liver, nervous system and bone. In studies conducted to date, obtained findings regarding the relationship of irisin status with obesity, insulin resistance and MetS are contradictory. Although irisin concentration was found higher in individuals with metabolic disorders in some studies, lower irisin concentration were observed in some other studies. Additionally, any receptors for irisin molecule hasn't yet discovered. Therefore, it is thought that the discovery of irisin molecule receptors and the determining of the tissues where these receptors are localized will be useful in understanding the mechanism of action of the irisin. In this review, we aimed to investigate potential effects of irisin on obesity, insulin resistance and MetS and additionally to examine underlying mechanisms of the association between circulating irisin and metabolic disorders.

Keywords: Irisin, obesity, metabolic syndrome. FNDC5, metabolic disorders

İRİSİNİN METABOLİK BOZUKLUKLAR ÜZERİNDEKİ ETKİLERİNE GENEL BİR BAKIŞ

ÖZET

İnsülin direnci ve metabolik sendrom (MetS) dahil olmak üzere obezite ve obezite ile ilgili hastalıklar, kardiyovasküler hastalık gelişimi için büyük bir risk oluşturmaktadır. Bir endokrin organ olarak iskelet kası, hormonlar ve miyokinler gibi fizyolojik faktörlerin salgılanmasında çok önemli bir role sahiptir. Hormon olarak da bilinen bu miyokinlerden irisin, egzersize yanıt olarak başlıca kas dokusundan salgılanır. Bir membran proteini olan ve FNDC5 geni tarafından kodlanan fibronektin tip III içeren protein 5'e (FNDC5) bağımlıdır. FNDC5 keşfedildikten sonra, şimdiye kadar irisinin metabolik etkileri araştırılmıştır. Irisin esas olarak kas, yağ dokusu, pankreas, karaciğer, sinir sistemi ve kemik üzerine etkilere sahiptir. Bugüne kadar yapılan çalışmalarda, irisin durumunun obezite, insülin direnci ve MetS ile ilişkisine dair elde edilen bulgular çelişkilidir. Bazı çalışmalarda metabolik bozukluğu olan kişilerde irisin konsantrasyonu daha yüksek bulunmasına rağmen, bazı çalışmalarda daha düşük irisin konsantrasyonu gözlenmiştir. Ek olarak, irisin molekülü için herhangi bir reseptör henüz keşfedilmedi. Bu nedenle irisin molekülü reseptörlerinin keşfi ve bu reseptörlerin lokalize olduğu dokuların belirlenmesinin, irisinin etki mekanizmasının anlaşılmasında faydalı olacağı düşünülmektedir. Bu derlemede; irisinin obezite, insülin direnci ve MetS üzerindeki potansiyel etkilerini araştırmayı ve ayrıca dolaşımdaki irisin ile metabolik bozukluklar arasındaki ilişkinin altında yatan mekanizmaları incelemeyi amaçladık.

Anahtar kelimeler: İrisin, obezite, metabolik sendrom, FNDC5, metabolik bozukluklar

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INTRODUCTION

Obesity that is common today worldwide is defined by the World Health Organization (WHO) as excessive fat accumulation that deteriorates human health. In 2016, it is reported that 650 million adults over the age of 18 have obesity (1). Insulin resistance is defined as the secretion of more insulin than usual to keep the blood glucose level at normal levels as a result of the decrease in insulin sensitivity or the response of the tissues to insulin (2). Insulin resistance has been shown to be linked to increased obesity, Type 2 Diabetes Mellitus (T2DM), serum triglyceride level, cardiovascular disease, and decreased high-density lipoprotein cholesterol (HDL-C). In addition, insulin resistance is considered to be a major contributor of MetS pathogenesis (3). MetS is defined as the cluster of metabolic disorders including abdominal obesity, hyperlipidemia, hypertension and hyperglycemia. All these problems are associated with obesity and pose a risk for the development of cardiovascular diseases (4). The exact mechanism of MetS is not fully understood. However obesity, insulin resistance, ethnicity, genetic disposition and sedentary lifestyle are thought to be pivotal risk factors for MetS development (5).

The skeletal muscle is known for its role in providing physical movement, but in recent studies there is increasing evidence that it may have important roles in the secretion of various physiological factors. Skeletal muscle is known as an endocrine organ because it secretes various hormones called myokines (6). Myokines are considered to have various functions such as myogenesis, fatty acid oxidation, endothelial function and turning the kind of adipose tissue from white to brown (6).

In 2012 Boström et al., (7) has discovered that exercise induces FNDC5 secretion from muscle tissue. This is a membrane protein and it is encoded by FNDC5 gene (8). In response to exercise, FNDC5 is synthesized from peroxisome proliferator-activated gamma coactivator-1α (PGC-1α) (7). While the C-terminal of FNDC5 is located in cytoplasm, N-terminal of FNDC5 is released into circulation during proteolytic cleavage as irisin (7). Therefore, irisin is formed from FNDC5, after proteolysis. As the proteolytic product of the FNDC5 protein, (9) irisin is expressed from skeletal muscle into the blood (10). Irisin which is an important factor for balancing body temperature (10) by causing white adipose tissue to browning, comprises 112 amino acids and its weight is 12 /kDa (7). Irisin increases energy expenditure by inducing thermogenesis (11). No any specific receptor for the irisin has been discovered yet (12). Although its main source is skeletal muscle and adipose tissue; it is also synthesized in tissues like heart tissue, in cranial arteries, kidneys, tongue, rectum were discovered (13). It can be regarded as a hormone due to its paracrine, autocrine and endocrine effects (14).

After the isolation of irisin from muscle tissue by Böstrom et al., (7) many studies have been carried out on this molecule until today. In these studies, important effects of exercise on health by increasing the concentration of the circulating irisin have been investigated. Irisin has effects on many tissues as adipose tissue, nervous system and bones. Its various effects on inflammation and carcinogenesis also have been described (12). Irisin has important roles in improving metabolic diseases by increasing mitochondrial density and metabolic rate in myocytes and adipocytes

(15). Irisin has positive effects on bones as it induces bone formation, decreases fracture risk and increases osteoblast differentiation (12). In addition, irisin has positive effects on the nervous system by maintaining neurogenesis, reducing some proinflammatory cytokines and preventing neuron damage by reducing oxidative stress (12). In the liver, it has important roles in modulating glucose homeostasis. It serves on regeneration and function of beta cells in pancreas, maintains beta cell survival and increases secretion of some hormones including insulin and glucagon (Figure 1) (11). In addition, it is considered to be of great importance in terms of the cure of obesity and various diseases associated with obesity (16). The irisin molecule is thought to be a potential agent for use in the treatment of many diseases (17). In this review, we aimed to examine the metabolic effects of irisin molecule on obesity, insulin resistance and MetS. Also underlying mechanisms of the association between irisin and obesity and obesity related metabolic disorders will be evaluated.

Irisin&Obesity

Slight elevated irisin levels with exercise leads to increased energy expenditure without any change in movement or food consumption. This has an important role in body weight control and balancing blood glucose level (18). Irisin activates mitochondrial uncoupling protein 1 (UCP1) (11) which is also called as thermogenin (12). Increased UCP1 expression also inhibits ATP synthesis (10) and increases thermogenesis by causing browning in white adipose tissue. All of these contribute to body weight control (11, 19, 20). The suppression of the gene expression of the irisin induces the development of adipogenesis by decreasing the UCP1 expression (11). Additionally it induces lipolysis via cAMP–protein kinase A (PKA)–hormone sensitive lipase (HSL)/perilipin pathway (21). Irisin decreases pro-inflammatory cytokine release from adipose tissue and increases anti-inflammatory cytokine release (11). Therefore, increasing anti-inflammatory cytokine levels suppress chronic inflammation resulting from obesity (22). Irisin also decreases the expression of monocyte chemoattractant protein-1 (MCP-1), impairs the release and expression of leptin which is related to proinflammatory state, and increases adiponectin, which is an anti-inflammatory cytokine (23). Increased serum leptin level in obese individuals pose an important risk factor in terms of MetS and insulin resistance (24) by causing excessive energy intake and decreased energy expenditure (25). Adiponectin increases the sensitivity of cells to insulin. Serum concentration of adiponectin is low in obese individuals and it is inversely related to insulin resistance (25).

Conflicting results were obtained in studies examining the relationship of irisin with obesity. Studies showing an inverse relationship between adiposity and the concentration of circulating irisin have been reported in the literature (26, 27). Tang et al., (16) have shown that the irisin concentration decreases in overweight and obese individuals compared to individuals with normal body weight. This is attributed to the impaired PGC-1α expression in muscle in obese individuals. Similarly, there was an inverse relationship between the circulating irisin and Body Mass Index (BMI) in other study (22).

Some studies have shown that serum irisin levels are positively associated with BMI and adiposity. In two studies, it was shown that the serum irisin concentration of morbid obese patients was higher than that of normal and anorexic individuals (28, 29). This is explained by the fact that irisin resistance may have developed in obese individuals (29). Irisin resistance is defined as the increased irisin level in obese individuals to modulate the energy balance and maintain glucose homeostasis. Therefore, it is thought that hyperiricinemia seen in obese individuals may be a mechanism to maximize the anti-obesity and anti-hyperglycemic effects of the irisin hormone (30). Serum irisin level was positively associated with BMI in other studies (31, 32). There is also a study showing that the concentration of the irisin is not related to adiposity (33).

It has been reported that the level of circulating irisin decreases due to weight loss and causes a decrease in muscle mass (34). After bariatric surgery, it has been shown that the serum irisin level also decreases with body weight loss, which has been attributed to the decrease in lean body mass and FNDC5 mRNA levels (11, 35). However, decreased serum irisin status returned with the regain of body weight (11).

Irisin&Insulin Resistance

Böstrom et al. discovered that irisin molecule has beneficial effects on glucose tolerance and reduces fasting insulin level in mice. After these findings other studies have been conducted to understand the association between irisin and insulin resistance and diabetes mellitus all over the world (20). In addition to the role of the irisin in maintaining the energy balance, it is also linked to obesity-related metabolic disorders such as insulin resistance and T2DM (36).

Irisin molecule acts as an insulin sensitizer since it increases glucose uptake into skeletal muscle and improves hepatic glucose and lipid metabolism (11). Irisin is considered to be an important option for the treatment of diabetes, as it increases insulin sensitivity, increases glycogenesis and decreases gluconeogenesis (Figure 1) (12).

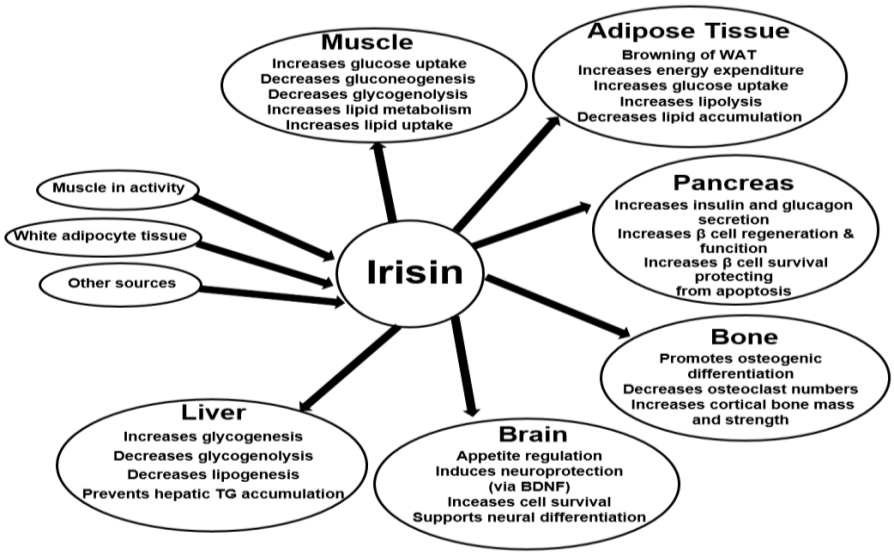

Figure 1. Functions of irisin molecule in various tissues and organs. WAT: White adipose tissue, BDNF: Brain derived neurotrophic factor. Adapted from 13th reference.

In addition, it has an important role in improving insulin resistance and maintaining glucose homeostasis by causing the browning of fat tissue (20). Also, it induces the continuation of the functions of beta cells in the pancreas by reducing the endoplasmic reticulum stress (11). Also irisin induces glucose uptake in skeletal muscles via AMPK-related pathways, which reveals the positive effects of irisin on glucose metabolism. Therefore, it is estimated that irisin may have possible effects on diabetes in the future (21). Additionally, irisin contributes the beta cell formation and induces increased beta cells number. It has been suggested that circulating irisin may play role in maintaining homeostasis, improving insulin resistance and diabetes mellitus (21).

Moreno et al., (26) have found that irisin concentration was negatively associated with insulin resistance in men. In studies conducted on individuals with T2DM (37) and gestational Diabetes Mellitus (38), it has been shown that serum irisin concentration was inversely related to the development of diabetes, considering that impairment of PGC-1α expression may result in this in individuals with T2DM. Fasting insulin, HOMA-IR were inversely associated with irisin concentration (16, 39). Shoukry et al., (40) has found that serum irisin concentration was lower among individuals with new onset T2DM compared to healthy counterparts. Therefore, modulation of the irisin level has pivotal role on controlling obesity and various diseases associated with obesity (16).

Also positive association of irisin concentration and HOMA-IR, fasting insulin and blood glucose levels were reported in some studies. Studies have shown that insulin resistance is positively associated with serum irisin concentration (41, 42). In other study, it is reported that children with impaired glucose tolerance, had higher circulating irisin levels (43). Additionally, it has been considered that higher irisin concentration is because of the impairment of insulin sensitivity, lipid and glycose metabolism, suggesting that a potential feedback mechanism between irisin and adiponectin for higher energy consumption in the adipocytes (32).

Irisin&Metabolic Syndrome

The results of the studies that examine the associations between irisin and MetS appear to be contradictory. It has been demonstrated that serum irisin levels decrease in children diagnosed with MetS (44, 45). It has been suggested that the irisin molecule may be a biomarker for the diagnosis of MetS in children in prepubertal period (44) and lower irisin concentration may worsen the metabolic disturbances among children with obesity and MetS (45). Decreased irisin concentration was associated with the emerge of increased MetS and fasting blood glucose level in obese adults (46, 47). On the other hand, Tabak et al., (15) have shown that there is a positive association between irisin level and MetS components including BMI, waist circumference and waist/hip ratio. It has also been suggested that the serum irisin concentration may be a biomarker for the development of MetS. In addition, there are studies showing that the level of circulating irisin is positively associated with total cholesterol (48) and inversely associated with HDL-C (49). It has been reported higher irisin concentration in children with MetS (50). In addition, it was shown that the serum irisin concentrations of individuals in the group with a diagnosis of MetS were

higher compared to control group; this is attributed to the increased irisin resistance in adipose tissue (31). In the study of Tang et al., (16) a positive relationship was found between irisin and triglycerides; however, no relationship was found between total cholesterol and HDL-C and irisin.

CONCLUSIONS

Irisin which is expressed mainly from muscle tissue in response to exercise is PGC-1α dependent, and its most important function is to increase energy expenditure by inducing thermogenesis via turning of white adipose tissue to brown adipose tissue. Although it is a new discovered hormone, various studies have been conducted on irisin until today. The irisin molecule is thought to be a potential therapeutic agent for treatment of many diseases, especially obesity and T2DM. Irisin is considered to be an important option for the treatment of diabetes as it increases insulin sensitivity, increases glycogenesis and decreases gluconeogenesis. In addition to regulating insulin resistance and maintaining glucose homeostasis, it also reduces endoplasmic reticulum stress thereby it provides the continuation of the functions of beta cells in the pancreas. In this review, the potential effects of the irisin molecule on metabolic disorders including obesity, insulin resistance and MetS were evaluated and the studies on this subject are reviewed. Even though there are contradictory results about irisin status in individuals with obesity, insulin resistance or MetS, irisin may have an important therapeutic target in the treatment of these metabolic abnormalities. It is also considered that the receptors of the irisin molecule, which have not been discovered and the knowing of the tissues where these receptors are located may be an important finding to understand underlying mechanisms of the association between circulating irisin concentration and metabolic disorders associated with obesity. There are still need for prospective or randomized controlled clinical trials involving large case series to elucidate the potential mechanisms and causal relationships to develop the new therapeutic approaches.

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