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The Role of Irisin in Type 2 Diabetes: Mechanisms and Therapeutic Implications

Ali Nosrati Andevari*
Department of Clinical Biochemistry, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran.

Abstract

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by decreased insulin sensitivity, impaired glucose homeostasis, and progressive pancreatic β-cell dysfunction. In addition to insulin and glucagon-like peptide-1 (GLP-1), the secretion of other hormones has emerged as a vital regulator of metabolic health, with potential implications for the prevention and treatment of T2DM. One of the hormones in question is irisin. It is a myokine substantially secreted by skeletal muscle during exercise. The aim of this study is to determine the roles of irisin in T2DM, along with its associated mechanisms and therapeutic implications. Irisin levels are declined in T2DM. Irisin enhances insulin secretion and sensitivity in T2DM, which is associated with improved glycemic indices. Medications such as sitagliptin, metformin, and simvastatin stimulate the release of irisin.

Keywords: T2DM, Irisin, Insulin, Glycemic

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Corresponding Author:
Ali Nosrati Andevari, Department of Clinical Biochemistry, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran.
Tel: (+98) 936 209 0578
Email: nosrati.ali70@gmail.com
Orcid ID: 0000-0002-8699-4688

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by decreased insulin sensitivity, impaired glucose homeostasis, and progressive pancreatic β-cell dysfunction. Furthermore, T2DM is an inflammatory disorder associated with cardiovascular, cerebral, renal, ocular, and neuronal complications. Despite advances in pharmacotherapy, the global prevalence of T2DM continues to elevate, necessitating novel therapeutic strategies that target substantial pathophysiological mechanisms (1-3). In addition to insulin and glucagon-like peptide-1 (GLP-1), the secretion of other hormones has emerged as a vital regulator of metabolic health, with potential implications for the prevention and treatment of T2DM. One of the hormones in question is irisin. It is a myokine substantially secreted by skeletal muscle during exercise. In recent years, irisin has become a major regulator of metabolic well-being, with possible implications for the prevention and treatment of T2DM (4,5).

The aim of this study is to determine the roles of irisin in T2DM, along with its associated mechanisms and therapeutic implications

History of Irisin

Before the official discovery of irisin, foundational research was conducted on this hormone. The gene that encodes the precursor protein of irisin, a type I membrane protein, known as Fibronectin Type III Domain-Containing Protein 5 (FNDC5), was first identified in 2002 (6). Initially, this protein was referred to as Fibronectin Type III Repeat-Containing Protein 2 (FRCP2), detected in the heart, brain, and skeletal muscle tissues of mice. Subsequent studies identified FNDC5 as a peroxisomal protein that plays a role in cellular metabolism (7). The FNDC5 comprises a 29-amino acid signaling peptide, a 94-amino acid domain, and a C-terminal section. The initial report on irisin was demonstrated in 2012 by Bostrom at Harvard University. Irisin is classified as a myokine, consisting of a 112-amino-acid peptide. There are many similarities between the structure and function of irisin in mice and humans. Irisin is mostly produced in skeletal muscle, particularly in the perimysium, endomysium, and areas around the nucleus, although other secretory tissues include adipose tissue, the pancreas, sebaceous glands, and cardiac muscle have also been identified (8,9). The research through mass spectrometry analysis verified the presence of irisin, yet at significantly lowered concentrations of approximately 3.6 ng/ml (10). Furthermore, Jedrychowski et al. used advanced mass spectrometry to vouch irisin's presence in humans, albeit at lower content than in mice (11).

Irisin and insulin secretion

It has been shown, irisin stimulates insulin secretion from pancreatic β-cells in a glucose-dependent manner, similar to glucagon-like peptide-1 (GLP-1) (12) (Table) (Figure). In a study published by Chen et al., a positive correlation was observed between serum irisin levels and fasting insulin levels in obese patients with acanthosis nigricans. Consequently, irisin exhibited a protective effect against beta-cell dysfunction in these patients (13). Zheng et al. stated that irisin effectively raised insulin secretion in high fat diet (HFD) mice (14).

Irisin promotes β-cell proliferation via activation of the extracellular signal-regulated kinases (ERK) and p38 MAPK pathways, improving β-cell mass and function. Also, Irisin promotes β-cell proliferation through activation of ERK and p38 MAPK signaling pathways, improving β-cell mass and function. In addition, irisin protects β-cells from apoptosis induced by high glucose or lipotoxicity by modulating Bcl-2/Bax balance and reducing caspase activity (Table). Liu et al. showed that irisin stimulated the proliferation of the rat insulinoma cell line

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(INS-1) through the ERK and p38 MAPK signaling pathways. Furthermore, the cells were safeguarded from apoptosis triggered by high glucose levels through modulation of caspases and the proteins Bad, Bax, Bcl-2, and Bcl-xl, which in turn enhanced the function of pancreatic beta cells. Also, irisin notably decreased blood glucose and improved serum insulin and glucose tolerance in diabetic rats (15). Chronic high blood sugar levels in T2DM trigger the β-cell pyroptosis of insulin-producing beta cells through an inflammatory process involving the NLRP3 inflammasome, resulting in lowered insulin production (16). The NLRP3 inflammasome activates caspase-1, which induces the production of active forms of IL-1β and IL-18 (16,17). Gasdermin D (GSDMD) acts as a crucial mediator to initiate pyroptosis. Programmed cell death, known as pyroptosis, exhibits a range of distinct characteristics, including membrane swelling and the formation of large bubbles on its surface, known as pyroptotic bodies, which ultimately leads to cell content leakage. The activation of the NLRP3 inflammasome serves as the first step in the standard pathway leading to pyroptosis. Following cleavage of pro-caspase-1, GSDMD is split into its GSDMD-C and GSDMD-N domains. GSDMD-N then relocates to the cell membrane, where it creates pores, resulting in cellular swelling accompanied by the formation of large bubbles (18). Irisin safeguards beta cells from pyroptosis and oxidative stress. Li et al. stated that irisin treatment substantially downregulated GSDMD and cleaved caspase-1, lowered caspase1 activity, and suppressed the secretion of interleukin 1β (IL-1β) and IL-18 in high glucose-induced Min6 cells. Irisin reduced oxidative stress and NLRP3 expression by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. Irisin also improved the functionality of islet cells in the T2DM mouse model (19).

Given that increased cholesterol and low-density lipoprotein cholesterol (LDL-C) levels negatively affect insulin secretion and sensitivity (20), we will discuss in the next section the studies that have demonstrated the relationship between irisin and these lipid factors.

Irisin and insulin sensitivity

AMP-activated protein kinase (AMPK) enhances insulin sensitivity by acting on various factors and pathways (21). AMPK mediates the transport of glucose transporter type 4 (GLUT4) to the adipose and skeletal muscle cell surface (Table). In a study published by Lee et al., irisin activated p38 MAPK in a manner dependent on AMPK, resulting in enhanced glucose uptake in L6 muscle cells (22). Zhi et al. stated, irisin notably lowered the enzymatic activity of phosphoenolpyruvate carboxykinase (PEPCK), enhanced the enzymatic activity of phosphofructokinase (PFK), and promote the production of liver glycogen in common carps. Regulation of glucose metabolism by irisin was via the PI3K/Akt pathway and AMPK. Furthermore, irisin elevated intracellular calcium levels, activating calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ), an upstream kinase of AMPK (23). Moreover, AMPK participates in stimulating insulin sensitivity by increasing fatty acid oxidation (24) (Table).

Irisin raises mitochondrial biogenesis via peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), improving oxidative metabolism and lowering lipid-induced insulin resistance (25) (Figure). PGC-1α is a transcriptional coactivator that collaborates with multiple transcription factors to boost the expression of genes associated with energy expenditure, the formation of mitochondria, and oxidative metabolism (26). It induces the expression of the FNDC5 gene (27). Hu et al. showed, knocking down PGC-1α led to a substantial decrease in irisin levels in mice with chronic unpredictable mild stress (CUMS) (28).Irisin induces browning of white fat, elevating energy expenditure, and decrease obesity-related insulin resistance (29).

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Table 1. Summary of key mechanisms in the relationship between irisin and type 2 diabetes

Target cell	Irisin's action	Outcome
β-cell	Insulin secretion, β-cell proliferation, ERK, p38 MAPK, and Nrf2 pathways activation, modulation of caspases and the proteins Bad, Bax, Bcl-2 and Bcl-xl, reduced oxidative stress and NLRP3.	Fasting insulin level ↑ Inflammation ↓ Apoptosis ↑
Muscle cell	AMPK and PI3K/Akt activation, GLUT4 translocation	Glucose uptake ↑
Adipocyte	AMPK and PI3K/Akt activation, GLUT4 translocation, browning of white fat, UCP1 and PGC-1α upregulation, NF-κB inhibition	Glucose uptake ↑ Energy expenditure ↑ inflammation ↓
Liver cell	FoxO1 and gluconeogenesis inhibition	Fasting glucose ↓

ERK: extracellular signal-regulated kinases, Nrf2: nuclear factor erythroid 2–related factor 2, UCP1: uncoupling protein 1, PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1α, FoxO1: forkhead box protein O1

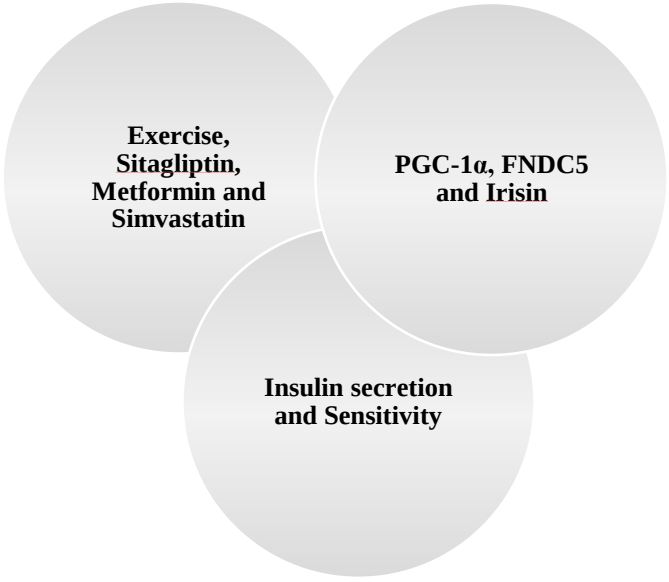


Fig 1. Schematic of the relationship between irisin-related factors and type 2 diabetes.

PGC-1α induces the expression of the FNDC5 gene, FNDC5 is the precursor protein of irisin. Irisin and PGC-1α have reciprocal functions. As a result of the action of these three factors, insulin secretion and sensitivity increase. Exercise, sitagliptin, metformin, and simvastatin have positive effects on FNDC5, PGC-1α, and irisin. Impaired insulin secretion and sensitivity lead to type 2 diabetes, which can be managed using therapeutic approaches such as exercise, sitagliptin, metformin, and simvastatin.

Shi et al. showed, the browning of white fat in circulating extracellular vesicles (EVs) was enhanced by irisin, which is associated with AMPK and mitochondrial uncoupling protein 1 (UCP1) (30). In a study reported by Luo et al., irisin triggered the activation of the AMPK pathway, thereby facilitating the browning of white adipose tissue by upregulating UCP1 and PGC-1α expression (31) (Table).

Since AMPK is an inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (32), irisin may participate in the downregulation of IL-1β and tumor

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necrosis factor alpha (TNF-α), both of which decrease insulin sensitivity. Chen et al. demonstrated that irisin downregulated TNF-α through the ERK signaling pathway in IL-1β-induced rat chondrocytes (33). Wang et al. reported the values of IL-1β and TNF-α were substantially reduced by irisin in C57BL/6 mice with intracerebral hemorrhage (ICH) (34).

As mentioned, cholesterol and LDL-C levels are related to insulin secretion and sensitivity. The accumulation of cholesterol in lipid domains of cell membranes impairs insulin receptor function and attenuates insulin sensitivity (35). In a study published by Tang et al., irisin injection into high fat diet-induced obese (DIO) mice lowered plasma and hepatic cholesterol values via activation of AMPK and inhibition of sterol regulatory element-binding transcription factor 2 (SREBP2) (36). SREBP2 upregulates the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA-R) in the cholesterol synthesis pathway (37). Moreover, Tarboush et al. reported a negative association between irisin and LDL-C in T2DM patients (38).

Studies on irisin relationship with glycemic indices and drugs in t2dm conditions

In a study published by Xuan et al., serum irisin levels in the T2DM group were significantly lower than in the control group. Since irisin improves insulin secretion and sensitivity, its levels declined in T2DM (39). Wang et al. showed that individuals with T2DM had lower irisin levels compared to those without the condition. Sitagliptin therapy resulted in a notable rise in serum irisin concentrations among patients with T2DM versus baseline levels (Fig.1). This increase in irisin values correlated with a reduction in both fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c). Sitagliptin is a typical example of dipeptidyl peptidase-4 (DPP-4) inhibitors, which are commonly used in the treatment of T2DM (40).

In a study by Tarboush et al., comparative research between healthy subjects and those with T2DM demonstrated that patients with T2DM condition possessed substantially lower plasma levels of irisin. Research indicated that irisin has a negative correlation with HbA1c levels (38).

Li et al. showed the values of FNDC5 mRNA and protein expression in skeletal muscle, as well as blood irisin content, were found to be lower in diabetic mice in comparison to wild-type mice. Metformin elevated intramuscular FNDC5 mRNA and protein levels and blood irisin concentrations (Figure). In contrast, glibenclamide did not show a notable effect on irisin levels. The reductions in blood glucose levels observed in metformin-treated mice were correlated with increased blood irisin concentrations. Furthermore, metformin enhanced the expression of intracellular FNDC5 mRNA and protein in C2C12 cells and stimulated the release of irisin (41).

One of the factors associated with insulin sensitivity and gluconeogenesis is forkhead box protein O1 (FOXO1). FOXO1 upregulates key gluconeogenic genes such as PEPCK and glucose-6-phosphatase (G6Pase), which are essential for glucose production in the liver. Insulin hinder FOXO1 function (42). Liu et al. showed irisin hindered gluconeogenesis through PI3K/Akt/FOXO1 pathway, resulting in lower FBG in diabetic mice (43) (Table). Moreover, Liu et al. showed that irisin notably decreased the blood glucose in rats with T2DM. Results from an oral glucose tolerance test (OGTT) demonstrate that irisin also raised the glucose tolerance of rats (15).

Statins and ezetimibe are drugs that attenuate cholesterol and LDL-C levels in T2DM patients (44). In a study reported by Gouni-Berthold et al., patients with mild hypercholesterolemia, who have no apparent cardiovascular disease, were given a 14-day treatment regimen consisting of simvastatin 40 mg and ezetimibe 10 mg. Irisin levels in the blood rose notably in participants taking simvastatin but not in those taking ezetimibe.

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Furthermore, simvastatin substantially elevated irisin release in addition to upregulating the mRNA expression of its precursor peptide hormone, FNDC5, in human skeletal muscle cells (HSKMCs) (45) (Figure).

Conclusion

The mechanisms by which irisin enhances insulin secretion and sensitivity and improves glycemic indices were through regulation of the levels or activities of GLP-1, ERK, p38, caspases, Bad, Bax, Bcl-2, Bcl-xl, GSDMD, IL-1β, IL-18, NLRP3, Nrf2, AMPK, PEPCK, PFK, PI3K/Akt, CaMKKβ, UCP1, PGC-1α, TNF-α, cholesterol, SREBP2, LDL-C and FOXO1. However, further studies in preclinical phase and clinical trials should investigate the association of irisin with T2DM-related factors. It was shown, medications such as sitagliptin, metformin, and simvastatin stimulate the release of irisin. Furthermore, the effects of other medications used by T2DM patients need to be investigated in preclinical and clinical trial studies.

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Conflict of Interest

There is no conflict of interest.

Authors' contributions

A.N contributed to the design and writing of the article, figure and table.

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