Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

A Comprehensive Review on the Impact of Irisin on the Metabolic Regulation of Type 2 Diabetes Mellitus

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(Received: 27 September 2025 Revised: 05 October 2025 Accepted: 18 November 2025)

KEYWORDS

Irisin

FNDC5

Insulin resistance

Type 2 diabetes mellitus

ABSTRACT:

Irisin, a novel myokine cleaved off from the transmembrane protein FNDC5, is secreted primarily by skeletal muscle. It plays a significant role in energy homeostasis by promoting the browning of white adipose tissue, enhancing mitochondrial function, and improving glucose metabolism. Recent studies have highlighted its potential in modulating insulin sensitivity and reducing insulin resistance, making it a promising candidate for therapeutic strategies in the management in type 2 diabetes mellitus (T2DM). Given the rising global prevalence of T2DM and the limitations of current treatments, irisin emerges as a potential substitute or supplement to exercise, especially for individuals with limited mobility. This review summarizes the current understanding of irisin's biology, its interaction with various metabolic pathways in various organs, and its implications for the treatment, prevention and management of T2DM and its complications.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder marked by insulin resistance, impaired insulin secretion, and hyperglycaemia. It has become a major global burden, affecting over 500 million adults and imposing significant health and economic burdens on both developed and developing nations [1]. The International Diabetes Federation projects that the global prevalence of diabetes will surpass 640 million by 2030, with India alone contributing more than 100 million cases [2]. The disease is associated with long-term complications affecting the heart, kidneys, eyes, and nerves, and is a significant contributor to cardiovascular morbidity and mortality [3]. While pharmacological agents, insulin therapy, and lifestyle modifications remain central to diabetes management, their effectiveness is often limited by adverse effects, reduced patient adherence, and progressive β-cell dysfunction [4]. Therefore, identifying novel biomarkers and therapeutic targets is crucial for improving treatment outcomes.

Among non-pharmacological interventions, regular exercise has continually exhibited its benefits in reversing insulin resistance, improving glucose metabolism, and lipid profiles [5]. In recent years, there has been an increased interest in "exerkines," a class of exercise-induced peptides with systemic effects on energy homeostasis and metabolic regulation. One such molecule, irisin, discovered by Boström et al. in 2012, is cleaved from the fibronectin type III domain-containing protein 5 (FNDC5) and released into the circulation during physical activity [6]. Irisin has been shown to stimulate the browning of white adipose tissue, enhance mitochondrial biogenesis, and modulate inflammatory responses, all of which are relevant to T2DM pathophysiology [7]. Notably, irisin mediates these effects through the activation of PGC-1α, AMPK, and p38 MAPK signalling pathways, linking skeletal muscle activity to whole-body metabolic improvements [5], [8].

Emerging research indicates that irisin exerts pleiotropic effects across multiple tissues implicated in T2DM, including skeletal muscle, adipose tissue, pancreas, liver, and even bone and kidneys. It enhances insulin sensitivity by upregulating glucose transporter type 4

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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

(GLUT4), reducing pro-inflammatory cytokine levels, and promoting β-cell survival and proliferation [5], [9]. Moreover, irisin may offer therapeutic value for individuals unable to participate in regular exercise, serving as a pharmacological mimic of exercise-induced benefits [5], [10]. Despite promising animal model data, clinical validation remains a challenge due to difficulties in accurate measurement and variability in circulating levels among populations [7]. Nevertheless, irisin holds significant potential as a therapeutic target and biomarker for the prevention and management of T2DM. This review provides a comprehensive overview of irisin's biology, mechanisms of action, and its prospective role in combating insulin resistance and metabolic derangements in T2DM.

2. IRISIN / FNDC5

In 2002 Ferrer and Teufel al. first identified Fibronectin type III domain-containing protein 5 (FNDC5) and named as peroxisomal protein (PeP) or fibronectin type III repeat-containing protein 2 (FRCP2). [17,1815,16]. In 2012, Irisin gained extensive attention when Bostrom et al. proposed it as the extracellular portion of a type I membrane protein encoded by the FNDC5 gene [6].

Irisin is a myokine derived from the fibronectin type III domain-containing protein 5 (FNDC5), which is a is a membrane-bound precursor protein first referred as a downstream effector of PGC-1α in skeletal muscle during physical activity that undergoes proteolytic cleavage to release irisin into circulation [1] [6] [20].

As a secreted peptide hormone, irisin has attracted notice for its diverse physiological roles, particularly its impact on energy metabolism and glucose homeostasis. Understanding the structure, synthesis, and regulatory mechanisms of FNDC5/irisin is essential to elucidate its function in metabolic tissues and its potential as a therapeutic target for type 2 diabetes mellitus (T2DM) [11], [12].

2.1 Structure

The FNDC5 locus contains six exons and encodes protein consists of 209 amino acid residues, featuring a 29-amino-acid signal sequence at the N-terminal end, followed by a fibronectin III (FNIII) domain of 94 amino acids (Irisin domain), a 28- amino-acid linking peptide, a 19-amino-acid transmembrane domain, and a cytoplasmic domain comprising 39 amino acid residues. Irisin, a 112-amino-acid peptide, includes the extracellular FNIII domain of 94 amino acids, cleaved from the C-terminal end of FNDC5 [19].

Crystallographic and Biochemical studies have revealed Irisin's existence as a homodimer, with the continuous ß-sheet interactions forming the core of the dimer, which is essential for receptor activation, signalling and communication with cell surface receptors like αV/β5 integrins have been identified as receptors in bone and adipose tissues [13]. Irisin is an endogenously produced peptide [20]. Glycosylation is a very common post-translational modification of proteins where the attachment of carbohydrates leads to greater heterogeneity in the structure of glycans [21]. There are two N-glycosylation sites in Irisin at the Asn-7 and Asn-52 positions [22]. The molecular weight of FNDC5/Irisin proteins ranges from 20 to 32 kDa [23], depending on the number and structure of glycan moiety attached to the molecule of protein during the process of post-translational modification. Deglycosylation lowers the molecular weight of Irisin to 12–15 kDa [20,24].

During proteolytic cleavage, the extracellular FNIII domain and adjacent linker region are released into circulation as irisin [9]. The cleaved irisin fragment is highly conserved across mammalian species, with nearly 100% sequence identity between human and rodent forms [12]. Interestingly, the human FNDC5 gene contains an unconventional ATA start codon in place of the canonical ATG, potentially reducing translational efficiency and contributing to some of the variability seen in circulating irisin concentration level in humans [2],[9]. These structural features provide the foundation for irisin's regulatory functions in various metabolic homeostasis.

2.2 Synthesis

FNDC5/Irisin is a downstream target gene of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α; PPARGC1A) [18], a versatile transcriptional coactivator that regulates numerous genes in response to nutritional and physiological signals. PGC-1α is highly expressed in tissues such as skeletal muscle, heart, brown adipose tissue, and liver, especially following exercise. It plays a significant role in mitochondrial biogenesis and energy metabolism [19],[20]. Additionally, the signalling pathways involving PGC-1α and peroxisome proliferator-activated receptor-alpha (PPARα) promote

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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

thermogenesis in adipose tissue, enhance glucose uptake in skeletal muscle, and help reduce insulin resistance. [21],[22].

The biosynthesis of irisin begins in skeletal muscle cells in response to physical activity, where the expression of the transcriptional coactivator PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) is upregulated [5],[6]. This, in turn, stimulates transcription of the FNDC5 gene, which encodes a type I membrane protein embedded in the endoplasmic reticulum (ER). FNDC5 contains a signal peptide, a fibronectin type III domain (FNIII), a transmembrane (TM) domain, and a short intracellular domain [9]. Once translated, FNDC5 undergoes post-translational modifications such as glycosylation before localizing to the plasma membrane. Proteolytic cleavage of FNDC5 by convertase enzymes releases a 112-amino acid segment into the bloodstream. This segment, known as irisin, circulates primarily as a homodimer and is considered the biologically active form [11]. While skeletal muscle is the Key area of synthesis of irisin, other tissues—such as adipose tissue, heart, brain, and liver—also express FNDC5 under certain conditions, contributing to systemic irisin levels [9],[12].

Circulating irisin levels are temporarily elevated following acute bouts of exercise, especially high-intensity interval training (HIIT), though chronic training might produce inconsistent effects depending on physiological status and muscle adaptation [14]. The secretion of irisin is also modulated by age, sex, obesity, insulin sensitivity, and inflammatory states [15]. Interestingly, white adipose tissue may act as a secondary source of irisin in obese individuals, complicating interpretations of serum levels [16]. Once secreted, irisin targets multiple tissues. In skeletal muscle, it enhances glucose uptake; in white adipose tissue, it promotes the browning process, increasing thermogenesis and energy expenditure; and in the liver, it regulates gluconeogenesis and glycogenesis [6], [10]. These collective actions position irisin as a central modulator of systemic metabolic homeostasis and a promising therapeutic candidate for type 2 diabetes mellitus (T2DM).

Figure 1 illustrates how PGC-1α regulates FNDC5 expression, leading to translation, membrane integration, glycosylation, and cleavage of FNDC5 to release irisin. The secreted irisin dimer then exerts regulatory effects on peripheral metabolic tissues such as adipose tissue, skeletal muscle, liver, kidney, pancreas, bone, and brain.

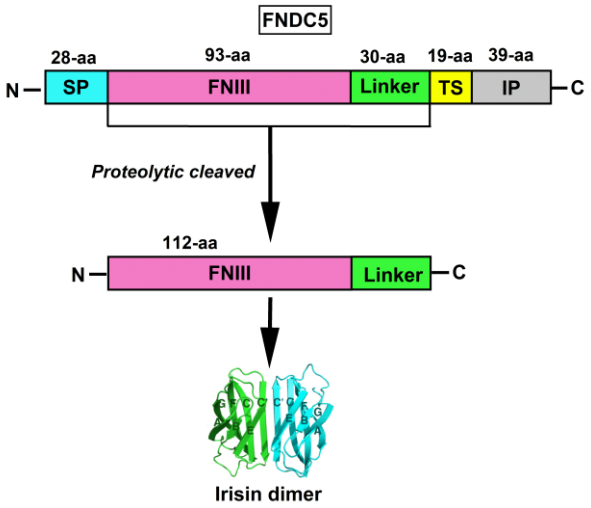

Figure 1: A schematic representation of irisin biosynthesis and secretion

3. Potential role of irisin in insulin sensitivity and type 2 diabetes

Since its discovery, irisin has appealed to researchers because of its important physiological function. Irisin exerts physiological effects by improving energy metabolic balance, enhancing cellular homeostasis through optimized autophagy, supporting mitochondrial quality control, lowering the production of reactive oxygen species (ROS), and reducing inflammation [25 - 27]. It has demonstrated beneficial effects in the management of various diseases, including cancer, diabetes, obesity, hepatic, renal and cardiovascular disorders. [22–24].

3.1 Insulin signalling

Glucose plays a pivotal role in providing energy for bodily functions. Dietary sugars are digested and absorbed by the mucosal layer of intestine into the bloodstream primarily as glucose. Once in circulation, glucose enters cells via the glucose transporter (GLUT) family. Inside the cells, glucose is either metabolized through glycolysis—producing lactic acid under anaerobic conditions—or via aerobic respiration in the mitochondria, generating carbon dioxide, water, and significant amounts of energy. Insulin, secreted by pancreatic β cells, plays a principal role in glucose

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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

metabolism by enhancing cellular glucose uptake, inhibiting glycogen breakdown in the liver, and promoting glycogen biosynthesis in the liver and muscles, thereby reducing blood glucose levels. Consequently, the pancreatic islets—particularly the β cells—are essential in diabetes, as insulin resistance (IR) or insulin deficiency can result in hyperglycaemia and related complications [25].

Insulin resistance (IR) is defined by a diminished metabolic response of insulin-sensitive cells to insulin, resulting in a weakened regulation of blood glucose despite normal or elevated insulin levels. This condition can be triggered by a wide range of factors., including decreased insulin production by pancreatic β-cells, the presence of insulin antagonists in the plasma that interfere with insulin receptors or signalling pathways, or impaired responsiveness of target tissues to insulin. The liver plays a key role in maintaining glucose homeostasis by storing excess glucose as glycogen and generating glucose through gluconeogenesis—using substrates such as amino acids, lactic acid, and glycerol—or by breaking down glycogen (glycogenolysis) during periods of low blood glucose.

Recent studies suggest that Irisin may hold therapeutic potential in the diabetes therapy. Glucose transporter 4 (GLUT4), a membrane-bound protein expressed in myocardial, skeletal muscle, and adipose tissue, facilitates the initial step of glycolysis by transporting glucose from the extracellular environment into cells. Irisin enhances GLUT4 expression by activating the p38 mitogen-activated protein kinase (MAPK) signalling pathway, thereby promoting glucose absorption in conjunction with β-arrestin-2—a multifunctional adaptor protein involved in various physiological and pathological processes, including glucolipid metabolism [26]. As MAPKs regulate diverse cellular functions such as gene expression, cell division, metabolism, motility, survival, apoptosis, and differentiation [27], the p38 MAPK pathway plays a central role in Irisin-mediated signalling [28]. Additionally, Irisin activates both peroxisome proliferator-activated receptor alpha (PPARα) and the p38 MAPK/extracellular signal-regulated kinase (ERK) pathways, leading to increased expression of uncoupling protein 1 (UCP-1), induction of white adipose tissue browning, enhanced mitochondrial biogenesis, and elevated energy expenditure. These changes contribute to a reduction in glycosphingolipid dysmetabolism and improved metabolic health [29]. Furthermore, Irisin significantly enhances glucose uptake in brown adipose tissue (BAT), which exhibits a higher rate of glucose consumption upon activation than other metabolically active tissues, thereby reinforcing its contribution to sustaining glucose homeostasis [30].

Irisin, primarily through the PPAR signalling pathway—especially PPARα—stimulates the production of fibroblast growth factor-21 (FGF-21), which enhances insulin sensitivity and glucose uptake [31]. Additionally, Irisin plays a key role in regulating hepatic glucose metabolism. Research indicates that Irisin suppresses gluconeogenesis by downregulating phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) via the PI3K/Akt/FOXO1 signaling pathway. Simultaneously, it promotes glycogen synthesis through activation of glycogen synthase (GS) via the PI3K/Akt/GSK3 pathway in type 2 diabetes models, thereby significantly improving hyperglycemia and insulin resistance [32]. Furthermore, Irisin may support pancreatic β cell proliferation and function by activating the ERK and p38 MAPK signaling pathways, protecting these cells from apoptosis induced by high glucose levels through the regulation of key apoptotic proteins such as caspases [33,34, 35]. This new evidence further supports the idea that irisin may upregulate betatrophin expression, Facilitating the proliferation and regeneration of pancreatic β cells [36,37]. Whether by enhancing β cell function or proliferation, increased insulin secretion can help mitigate hyperglycemia in individuals with diabetes.

3.2 Irisin and skeletal muscles

Skeletal muscle is the primary site of glucose uptake with reference to insulin signalling and plays an inevitable role in the development of diminished insulin sensitivity. Irisin is one of the a key myokines, with approximately 75% of its circulating levels originating from skeletal muscle. Its release is regulated by the upregulation of PGC-1α expression, which is strongly stimulated by physical exercise. Exercise and associated muscle stimulation not only enhances PGC-1α expression but also activates AMPK signalling pathways. This activation leads to the phosphorylation of PGC-1α, which in turn promotes the production of FNDC5.

Journal of Chemical Health Risks
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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

FNDC5 is then cleaved and released into the bloodstream as irisin [38,39].

Scientific research has demonstrated that irisin enhances glucose absorption by skeletal muscles through a pathway involving calcium/ROS and p38 MAPK-mediated AMPK activation (refer Figure 2). This indicates that irisin exerts beneficial effects on skeletal muscle by engaging AMPK-related signalling. In summary, irisin has been shown to encourage glucose uptake in skeletal muscle, likely through AMPK2 activation and subsequent p38 MAPK–GLUT4 translocation [40, 41]. These results help deepen our understanding of irisin's role in skeletal muscle glucose metabolism and suggest its potential as a target for future diabetes treatment research.

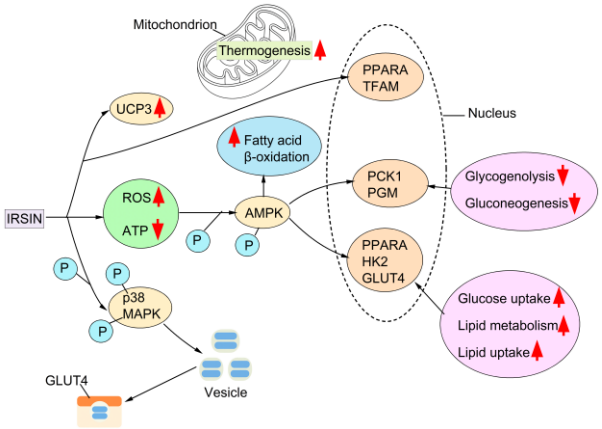

Figure 2: Biochemical actions of irisin in skeletal muscle

3.3 Irisin and adipose tissue

Adipose tissues exist in two forms white and brown. In humans, fat is predominantly made up of white adipose tissue (WAT), which plays a vital role in maintaining homeostasis. WAT communicates with other tissues and organs through autocrine, paracrine, and endocrine signalling pathways. It produces cytokines known as adipokines (or adipocytokines) that influence inflammation, angiogenesis, and various metabolic processes [42].

White adipose tissue (WAT) primarily functions as a storage site for triglycerides and fatty acids, serving as the body's largest energy reserve. It is made up of cells containing a single large (unilocular) lipid droplet and has relatively few blood vessels, giving it a white to yellow appearance. The cells typically have an eccentric nucleus and contain only a small number of mitochondria.

Brown adipose tissue (BAT) consists of multiples of iron-containing mitochondria and many multilocular lipid droplets. [43,44]. Uncoupling protein 1 (UCP1), also known as thermogenin, is a mitochondrial inner membrane protein, which transports protons from the mitochondrial matrix to the intermembrane space. When activated, UCP1 does not promote ATP production; instead, it generates heat, playing a crucial role in regulating body temperature, particularly in newborns [45,46]. BAT has a positive control over bodies metabolic processes and increases the total energy expenditure, ensuing reduction in body mass [43].

irisin induce browning of white adipocytes, under various stimuli such as cold, beta-adrenergic agonists, or hormone-like stimuli [47] which can be achieved by the upregulation of UCP1mRNA induction and expression of genes that uncouple respiration and heat production, which can be regulated through the p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-regulated kinase (ERK) [42]. Irisin mainly targets on white adipose tissue, enhancing energy expenditure and thereby helping to alleviate insulin resistance induced by a high-fat in the diet [43-45]. Some recent research findings also indicated that, irisin can enhance lipolysis via cAMP–PKA–HSL/perilipin pathway [46].

The conversion of white adipocytes to brown adipocytes leads to increase in energy expenditure and thermogenesis with subsequent improvement of insulin sensitivity, reductions in body weight, and improved glucose tolerance in mice [48-50].

3.4 Irisin and liver

The liver helps to maintain normal glucose homeostasis by maintaining a balance between hepatic glucose production (gluconeogenesis and glucogenolysis) and glucose storage. Rate of gluconeogenesis are primarily determined by transcriptional levels of two gluconeogenic enzyme genes phophoenolpyruvate carboxykinase (pepck) and glucose 6 phosphatase (G-6-pase). Glycogenesis is modulated by the activity of GSK-3 and glycogen synthase, while inhibition of GSK-3 promotes glycogen synthase activity and glycogen synthesis. Generally, it improves glucose homoeostasis

Journal of Chemical Health Risks
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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

by reducing gluconeogenesis via PI3K/Akt/ FOXO1-mediated PEPCK and G6Pase down-regulation and increasing glycogenesis via PI3K/Akt/GSK3- mediated GS activation [51]. Hepatic system plays a significant role in conversion of glucose into fat by de novo lipogenesis pathway, when its intake exceeds storage and oxidation capacities. But excess hepatic lipid deposition promotes inflammatory responses and hepatic insulin resistance [52].

Hepatic endoplasmic reticulum stress facilitates elevated glucose output, lipid synthesis, and the development of insulin resistance in the context of obesity and diabetes mellitus. Action of hepatic AMPK exerts anti diabetic actions through downregulation of lipogenesis and gluconeogenesis as well as promotion of lipid oxidation and glycolysis [53]. Irisin also activates AMPK in skeletal muscle. Whether irisin regulates hepatic AMPK – FOXOl signaling pathways and thus ameliorates hepatic ER stress and regulates glucose and lipid metabolism [54].

3.5 Irisin and kidney

Renal impairment is frequently associated with Type 2 diabetes. Diabetic kidney disease (DKD) is a major long-term complication of type 2 DM and is the primary causes of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide [55]. Serum irisin levels are reduced in patients with Type 2 diabetes, with an even more marked decrease observed in those with diabetic nephropathy [56].

There is increasing evidence supporting the role of signalling crosstalk connecting skeletal muscle and kidney, and many molecules secreted by skeletal muscle contribute to, or exacerbate a variety of physiological processes in the kidney [57].

For instance, Hu et al. observed that serum irisin levels were markedly decreased in T2DM patients with albuminuria and negatively correlated with albumin-to-creatinine ratio and serum creatinine levels [58]. Experimental studies support a reno-protective role for irisin in diabetic mouse models, irisin supplementation attenuated renal fibrosis, suppressed TGF-β/Smad and β-catenin signalling, and improved histological markers of kidney injury [59,60]. Furthermore, irisin seems to mitigate insulin resistance and systemic inflammation, which may indirectly reduce the progression of Diabetic Nephropathy [61,62]. Despite these promising findings, the mechanistic pathways linking irisin to renal outcomes in T2DM remain incompletely understood, and additional longitudinal studies are needed to evaluate its potential as a biomarker or therapeutic target in diabetic kidney disease.

3.6 Irisin and pancreas

Irisin is an insulin-regenerating hormone, and many animal studies shows that irisin can promote the neogenesis of mouse beta cells and enhance the number of mouse beta cells [63-65]. According to these studies, p38-PGC-1α -irisin beta cell signal pathway, a novel hypothesis of signalling pathway, is proposed. This pathway explains, during skeletal muscle stimulation, the expression of PGC-1β significantly increases, which in turn promotes the synthesis and proteolytic processing of FNDC5 to produce irisin. Irisin then activates UCP1 expression, enhancing the browning of white adipose tissue (WAT), boosting energy expenditure, supporting insulin regeneration, and contributing to the restoration of pancreatic beta cells (refer Figure 3) [66-67].

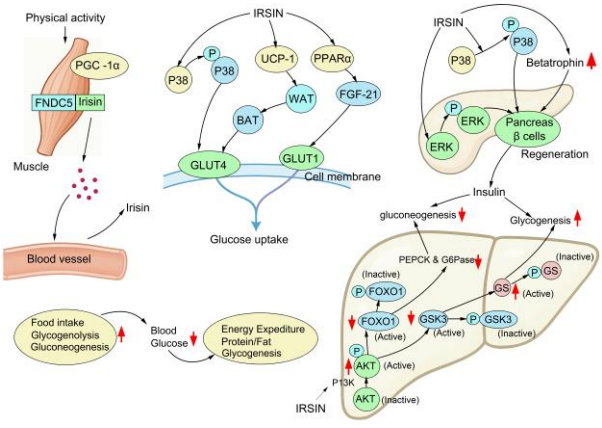

Figure 3: The action of irisin on various organs for the effective regulation of glucose dysmetabolism and insulin resistance

Generally, many experimental studies proved that irisin has anti-apoptotic actions on pancreatic beta-cells and drives beta-cell proliferation endogenous insulin generation, and insulin secretion. So, Increased circulating irisin has been shown to improve glucose tolerance and mitigate insulin resistance, suggesting a promising new approach for diabetes treatment [66-68].

Journal of Chemical Health Risks
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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

3.7 Irisin and bone

Diabetic bone disease, a form of secondary osteoporosis, is characterized by weakened bones and an increased risk of fractures, especially seen in type 2 diabetes patients [69] and it is found that they have low circulating level of irisin [70].

A study from Behera et al found out that exercise increases the secretion of irisin by bone cells and muscle. Here in this study bone is acting as a main source of circulating irisin. In bone irisin promotes osteoblast precursor survival by protecting them from pyroptosis. Irisin indirectly reduces osteoclast differentiation. The net effect of irisin on bone is to increase bone mass. Irisin and exercise also increases the expression of uncarboxylated osteocalcin (ucOCN) improves insulin sensitivity (refer Figure 4), improves energy consumption and reduces blood glucose level [71]. Irisin fosters osteoblast proliferation, differentiation, and mineralization predominantly through the ERK, p38, and AMPK signalling pathways. Concurrently, it regulates osteoclast differentiation and maturation via the JNK, Wnt/β-catenin, and RANKL/RANK/OPG signalling pathways (refer Figure 5) [72-73].

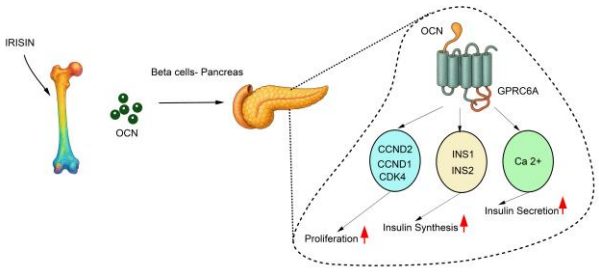

Figure 4: Action of irisin on bone osteocalcin

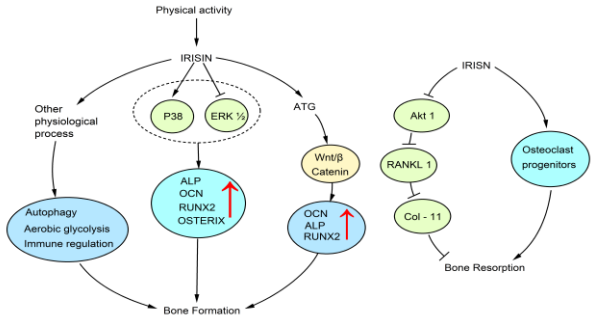

Figure 5: Action of irisin in bone formation and bone resorption

3.8 Irisin and brain

Type 2 diabetes mellitus (T2DM) is increasingly recognized not only as a metabolic disorder but also as a condition that adversely affects the central nervous system (CNS). Patients with T2DM are at greater risk for cognitive decline, depression, and neurodegenerative diseases such as Alzheimer's disease (AD) [74]. Chronic hyperglycemia, insulin resistance, increased pro-oxidant production, and neuroinflammation are believed to the root cause to these complications [75]. Recent attention has turned to irisin, a myokine secreted by skeletal muscle in response to exercise, for its potential neuroprotective effects, especially in the context of metabolic disorders such as T2DM [76].

Irisin, derived from the cleavage of fibronectin type III domain-containing protein 5 (FNDC5), crosses the blood-brain barrier and has been demonstrated to promote neuronal survival, synaptic plasticity, and hippocampal neurogenesis, largely via activation of brain-derived neurotrophic factor (BDNF) pathways [77,78]. These mechanisms are highly relevant in T2DM, where hippocampal atrophy and reduced BDNF expression are commonly observed [79]. Preclinical studies demonstrate that irisin administration can ameliorate cognitive impairment and reduce markers of oxidative stress and inflammation in diabetic rodent models [80,81].

Clinical studies have also linked low circulating irisin levels with cognitive dysfunction and poor metabolic control in T2DM patients. For instance, a study by Yang et al. found significantly lower plasma irisin levels in T2DM patients with mild cognitive impairment (MCI) compared to those without, and irisin positively correlated with performance on memory and executive function tests [82]. Furthermore, irisin has been found to reduce amyloid-β accumulation and tau hyperphosphorylation in mouse models of Alzheimer's disease, suggesting a potential safeguard role against neurodegenerative processes that are accelerated by diabetes [78,83].

Irisin can serves as a molecular link between exercise, metabolism, and brain health. Given the shared pathways between T2DM and neurodegeneration particularly mitochondrial dysfunction, insulin signalling, and neuroinflammation. Irisin may represent emerging drug target for mitigating CNS complications in diabetes.

Journal of Chemical Health Risks
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JCHR (2025) 15(6), 1042-1054 | ISSN:2251-6727

However, further research is needed to establish causal relationships, optimal dosing, and long-term effects in humans.

3.9 Irisin and inflammatory response

Irisin has demonstrated remarkable anti-inflammatory effects in type 2 diabetes mellitus. Chronic inflammation is a major contributor to insulin resistance, fueled by the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which disrupt insulin signalling pathways [85]. Irisin is known to downregulate these cytokines by inhibiting the NF-κB signalling pathway, a central mediator of inflammation [4]. In macrophages, irisin suppresses the expression of pro-inflammatory genes, reduces oxidative stress, and promotes an anti-inflammatory phenotype [86,87].

Furthermore, irisin may play a protective role in the preservation of pancreatic β-cell function. Inflammatory stress is known to impair β-cell viability and insulin secretion. Studies suggest that irisin can attenuate cytokine-induced apoptosis in β-cells, potentially supporting insulin production and glycemic control in T2DM [88].

Clinically, circulating irisin levels are often reduced in patients with T2DM, particularly among obese or sedentary individuals [89,90]. This deficiency may exacerbate metabolic dysfunction and inflammation. However, exercise-induced increases in irisin have been consistently associated with improved glucose metabolism and decreased systemic inflammation, suggesting that irisin may mediate some of the metabolic benefits of physical activity [84,90].

It has dual role in modulating energy balance and suppressing inflammation, irisin holds promise as a biomarker and therapeutic target in T2DM. Future research should focus on the development of irisin-based therapies or mimetics, and the precise mechanisms underlying its regulatory effects on immune and metabolic pathways.

4. Conclusion

Irisin can be used as a promising effective strategy for downgrading metabolic derangements in type 2 diabetes mellitus and associated insulin resistance. It has positive impact on stimulating browning of white adipose tissue, promoting glucose uptake from skeletal muscle and heart, improving hepatic glucose and lipid metabolism, boosting pancreatic β cell function, improves bone strength, alleviate CNS complications in diabetes and it has an eminent role in anti-inflammation. So, Irisin can provide even a more promising approach to the therapy of type 2 diabetes mellitus or prevention of Insulin resistance.

Abbreviations

1. FNDC5 - Fibronectin type III domain-containing protein 5
2. T2DM - Type 2 diabetes mellitus
3. IR - Insulin resistance

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