Jordan Medical Journal, Volume 58, No.2 2024
DOI: https://doi.org/10.35516/jmj.v58i2.565

Irisin's Mechanism of Action and Levels in Physiological and Pathological Conditions

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Abstract

Background and Aims: The importance of establishing a universal baseline for irisin in healthy individuals has often been overlooked. Irisin is a recently identified adipomyokine messenger with proven diverse properties and functions in various parts of the body. In this review, published studies on irisin's structure, mechanism of action, and quantification are summarized, with a focus on its levels in relation to physiological and pathological conditions.

Materials and Methods: PubMed, ScienceDirect, and Web of Science were searched for studies on irisin's structure, mechanism of action, quantification, and effects in various tissues (no year restriction) using the following search terms: 'irisin', 'FNDC5', and 'PGC-1α', along with papers that discussed the levels of irisin in relation to physiological and pathological conditions.

Results: Most of the current research was found to focus on the study of irisin concentrations in fluids of individuals with various comorbidities relative to controls, for the purpose of assessing its role in disease progression and prevention. Few papers have been able to establish a reliable baseline for its levels in healthy individuals due to insufficient sample sizes, use of differing quantification methods, and factors involving racial, gender, and age variances.

Conclusions: Establishing a universal reference range for circulating irisin levels in healthy individuals has proven to be challenging. Despite being a potential biomarker for predicting illness, further investigation is still needed to overcome current limitations.

Keywords: Irisin, irisin levels, FNDC5, physical activity, review

(J Med J 2024; Vol. 58(2): 176–193)

Received *October 21, 2022* *Accepted* *February 13, 2023*

1. INTRODUCTION

Irisin, a recently identified adipomyokine messenger, acts as a signaling molecule between various body organs. It was named after the Greek goddess Iris, who was a powerful messenger of the gods. Boström et al. discovered irisin in 2012 [1] while researching the conversion of white to brown adipose tissue in adult mice. Their findings were later confirmed by mass spectrometry, showing comparable circulation levels to Insulin and proteins of similar function [2].

Irisin is considered significant due to its diverse properties and functions. The intramembranous protein fibronectin type III domain-containing protein 5 (FNDC5) is thought to be the original molecule from which irisin is directly cleaved and released into circulation [3]. The FNDC5 gene was found to be primarily expressed in skeletal muscles, but also in detectable amounts in the brain, lung, liver, kidney, and adipose tissue [4], which contributes to the many promising roles of irisin in various parts of the body. One primary benefit of irisin, which stands to be further validated, is its role in physical activity, through its enhancement of thermogenesis and glucose homeostasis, and suppression of appetite and insulin resistance.

This paper is an overview of irisin's discovery, structure, and mechanism of action in different tissues and contains a discussion of its levels of concentration in association with physiological and pathological conditions. Furthermore, it provides context for the potential use of irisin as a biomarker to predict illness, based on its methods of quantification and their limitations.

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2. DISCOVERY AND STRUCTURE

In 2002, Teufel et al. [5] decided to sequence and analyze the expression of two repeat-containing fibronectin type III genes, fibronectin type III repeat-containing protein 1 (Frcp1) and fibronectin type III repeat-containing protein 2 (Frcp2). The study found that Frcp1 was highly expressed in the brain and liver tissue of the adult mouse, while Frcp2 was expressed in the brain and heart, suggesting that these genes could possibly have specific functions in their respective tissues. It was then annotated as peroxisomal protein or FRCP2, now known as FNDC5.

FNDC5 regained attention in 2012 when Bostrom et al. reported that it is a target gene of Ppargc1α (also known as PGC-1α or PPARγ-co-activator-1α). The Ppargc1α gene encodes the transcriptional coactivator peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α), which is induced in muscles after exercise. PGC1 is involved in the regulation of several energy metabolism pathways. It interacts with PPAR-γ, a nuclear receptor, which activates the expression of FNDC5 [1]. In mice, FNDC5 is a 209-amino-acid transmembrane protein that is proteolytically cleaved, glycosylated, and modified, resulting in the release of the 112-amino-acid PGC1α-dependent myokine (**Figure 1**). The authors named this myokine irisin and concluded that its unexpected abilities could be attributed to some of the well-known positive effects of exercise with regard to metabolic control and overall health [1]. The theoretical molecular weight (MW) of the 112 amino acid-irisin peptide is 12.6 kDa without glycosylation, whereas the observed MW is 13 kDa [6].

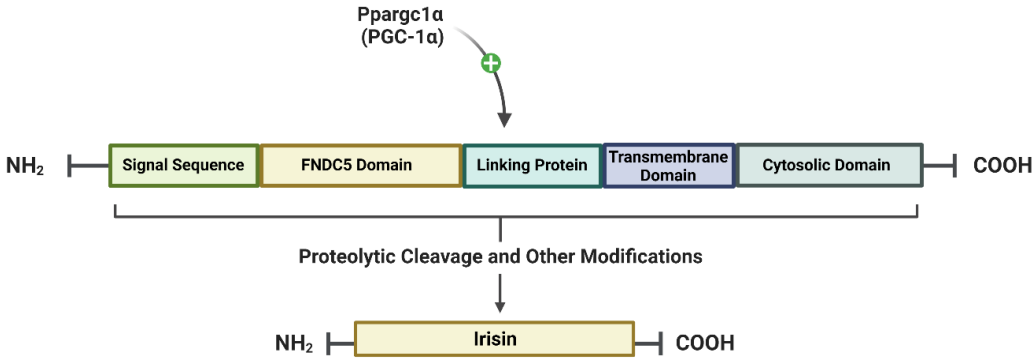

Figure 1: The structure of fibronectin type III domain-containing protein 5 (FNDC5) and irisin formation. Image created with BioRender (https://biorender.com/)

In humans, mice, rats, and cattle, irisin peptide is fully conserved, except for the signal peptide and segments from the C-terminal [7, 8]. Fish have a more divergent peptide, while amphibians lack the FNDC5 gene entirely [7]. Despite being a strongly conserved gene, the human FNDC5 gene has a mutated start codon, ATA, instead of the typical ATG codon, which is still found to be sufficiently active to generate plasma irisin at detectable levels, according to studies [7].

Regarding the proposed structure of irisin, Schumacher et al. revealed that irisin is a preformed tight dimer that has three beta-strands on one side and four on the other, which is the typical structure of an FNIII domain [8]. The two C´ strands associate antiparallel to form a beta zipper, resulting in an expanded 8-strand β-sheet that spans the two domains. Hydrophobic and Van der Waals interactions further stabilize the association and increase its affinity, with an area of 1,400 $Å^2$ [7].

3. EXPRESSION AND SECRETION

Irisin synthesis is thought to take place primarily in the perimysium, endomysium, and nuclear regions of skeletal muscle tissue [10]. Subsequent studies, however, have revealed that irisin is abundantly expressed and secreted in other locations throughout the body, such as in the myocardium of the heart muscle, as revealed through immunohistochemistry [10]. Irisin immunoreactivity can be detected in neuronal cells, sebaceous glands of the skin, salivary glands, and in smaller amounts in the liver, stomach, pancreas, testes, and spleen of rats [10, 11]. The fact that irisin is found in a variety of tissues in the body emphasizes its importance in maintaining normal body physiology.

4. EFFECTS AND MECHANISMS OF ACTION

Although irisin was first identified as a myokine involved in glucose homeostasis, it was later discovered to have a variety of effects on different parts of the body. The adipose and muscle tissues, heart, kidneys, bones, liver, and brain are some of the most important sites where irisin has been found to have a significant effect [12] (**Figure 2**).

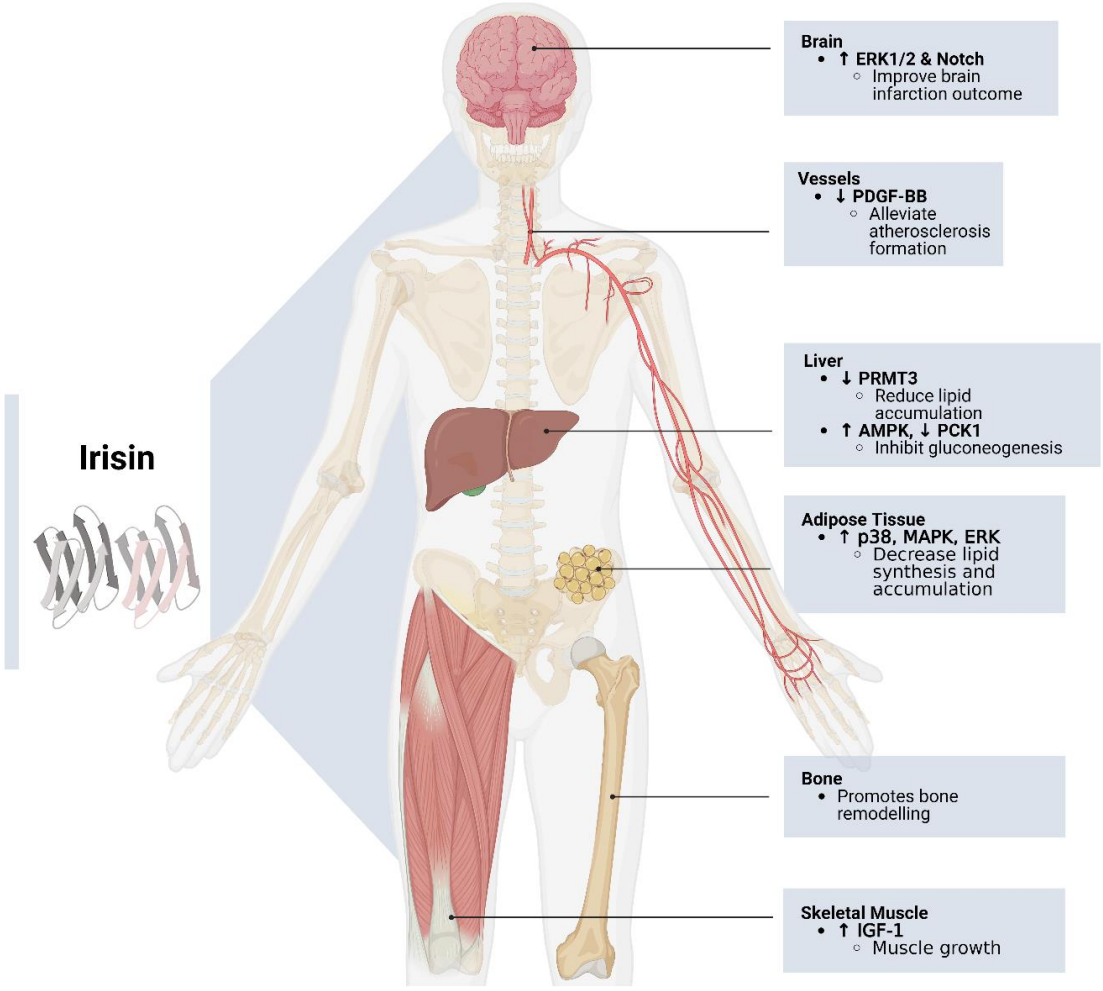

Figure 2: Effect of irisin on the body. Image created with BioRender (https://biorender.com/)

Adipose Tissue

The two types of adipocytes in our bodies are white adipocytes, which store fat, and brown adipocytes, which disperse stored fat as heat. Adipose browning is a process that transforms white adipocytes into thermochemically active adipocytes, also known as 'beige' adipocytes, by enhancing mitochondrial biogenesis through the upregulation of mRNA expression of the thermogenesis-mediating protein: uncoupling protein 1 (UCP1) [13]. Yuan Zhang et al. found that irisin-induced phosphorylation, and thus activation, of the p38 MAPK and ERK signaling pathways mediate UCP1 upregulation, and when these pathways were inhibited, UCP1 expression was abolished [14].

In a study conducted by Xiong et al. [15], irisin was found to reduce the size of subcutaneous adipocytes. The effect is likely mediated through upregulation of lipolysis-related genes, such as adipose triglyceride lipase, hormone-sensitive lipase, and the fatty acid-binding protein 4, resulting in decreased lipid synthesis and accumulation [16]. This suggests the potential advantage of irisin in the management of obesity and other metabolic disorders.

Skeletal Muscle

Exercise and irisin appear to be strongly connected through the process of 'browning' white adipose tissue, as PGC-1α expression is increased, in turn increasing that of FNDC5, an irisin precursor, downstream. Muscle contraction likely triggers FNDC5 cleavage via an unknown proteasome to produce irisin [1]. Irisin then stimulates mitochondrial biogenesis in myocytes, resulting in enhanced thermogenesis, through its upregulation of mitochondrial uncoupling protein 3 (UCP3), TFAM, and Ppargc1α genes [17].

According to one study, irisin, when induced by reactive oxygen species, stimulated glucose uptake in differentiated L6 muscle cells by translocating GLUT4 to the plasma membrane [17]. Another study, which used recombinant irisin (50 nM) to treat human skeletal myocytes, found that lowered ATP levels resulted in increased glucose and fatty acid uptake, phosphorylation of AMPK, and the consequent activation of its downstream pathway [18]. This activation is followed by an upregulation of genes involved in glucose transport and lipid metabolism (GLUT4, PPARA, and HK2) and suppression of those involved in glycogenolysis (PYGM) and gluconeogenesis (PCK1) [15].

Additional studies treating myocytes with irisin revealed irisin's role in muscle growth enhancement through the ERK pathway, showing increased expression of insulin-like growth factor 1, along with suppression of the myostatin gene [19].

Smooth Muscle

Phenotype modification of vascular smooth muscle cells (VSMC) towards a synthetic phenotype is regarded as a fundamental cause of cardiovascular disease [20]. The direct association between irisin and the phenotypic regulation of VSMC was unclear until Song et al. [21] investigated the relationship and identified the mechanisms involved. The results showed that irisin inhibited PDGF-BB-induced VSMC modulation via the STAT3 pathway, which is known to play a critical role in modulating VSMC dedifferentiation to a synthetic phenotype [22, 23]. These findings situate irisin as a promising pharmaceutical target for the treatment of cardiovascular disease.

Bone

After Kim et al. confirmed that irisin increases serum sclerostin levels [24], a bone formation inhibitor, researchers also discovered that FNDC5 knockout mice have decreased levels of a key mediator of bone resorption (RANKL) [19]. These generally unfavorable effects of irisin contrast with a previous study showing that irisin helps restore disuse-induced bone loss [24]. The main difference can be attributed to the mode of administration [24], as it seems that persistently high irisin levels can promote bone resorption by increasing sclerostin levels, whereas intermittently introduced high doses of irisin, such as during exercise, are capable of inducing bone remodeling [25].

According to a recent study, irisin acts on both osteoblast stimulation and osteoclast differentiation and resorption, promoting bone remodeling [26].

Liver

The liver is a vital organ in the body as it plays a critical role in modulating several key functions, including metabolism, digestion, and blood detoxification, among others [27]. The constitutive androstane nuclear receptor (CAR) is a metabolizing gene regulator in the liver that appears to promote fatty acid beta-oxidation while also suppressing lipogenesis and gluconeogenesis, and preventing hepatic steatosis, obesity, and insulin resistance. According to a study, CAR was linked to increased FNDC5 mRNA expression in the liver, which increased blood irisin levels. CAR appears to stimulate FNDC5 expression specifically in HepG2 cells by binding to a nuclear receptor-response element of the FNDC5 promoter [13,28].

Subsequent studies aimed to elucidate candidate roles of irisin in hepatocytes, including oxidative stress reduction, gluconeogenesis, glucogenesis and lipid accumulation. Irisin's inhibitory role on PRMT3 expression may be responsible for the effects of reduced oxidative stress and lipid accumulation, along with supportive mechanisms involving reduction of inflammatory markers such as TNF and IL-6, nuclear factor-kB, cyclooxygenase-2, and the mitogen-activated protein kinase, p38. Irisin plays a part in inhibiting gluconeogenesis in the liver by activating the AMPK signaling pathway and downregulating PCK1 and G6PD [29-31].

Non-alcoholic fatty liver disease (NAFLD) is a condition where excess fat accumulates in the liver without being caused by alcohol consumption [32]. A recent study suggests that fluctuation patterns of circulating irisin levels can be used to track NAFLD progression in patients, as blood concentrations appear to change in accordance with disease severity, showing higher levels in patients with mild symptoms than those exhibiting moderate to severe cases [33].

Brain

Brain injury is considered a leading cause of morbidity and mortality worldwide, showing symptoms ranging from mild cognitive disruption to

comatose states and death [34]. Several studies on the neuroprotective effect of irisin against brain injuries and the resulting morbidities have been conducted. To test the neuroprotective potential of irisin, researchers used middle cerebral artery occlusion (MCAO) to cause brain infarction in mice, and this was followed by IV injections of recombinant irisin treatments. The findings showed that irisin improved brain infarction outcomes and neurological scores [35]. Its therapeutic roles ranged from reducing brain edema, infarct size, oxidative stress, and inflammatory responses, all through a variety of mechanisms, including upregulation of the ERK1/2 and Notch pathways, as well as suppression of the ROS/NLRP3 and TLR4/MYD8-8 pathways [36].

5. DETECTION AND QUANTIFICATION

Initially, three antibody-dependent methods were used to test circulating irisin levels in mice and humans: western blot, enzyme-linked immunosorbent assay (ELISA), and protein liquid chip assay [7]. Later, Jedrychowski et al. introduced a method for confirming the presence of irisin and quantifying its levels to a higher level of accuracy through combining mass spectrometry (MS) with other techniques. His methods demonstrated irisin to be present in equal or even higher levels than hormones, such as insulin, leptin, and resistin [37].

Western Blot

Initially, researchers used western blot to detect irisin bands at an MW of 20–22 kDa, which is higher than the predicted MW of irisin [10]. The experiments were then halted as the antibodies used were lacking specificity to any of irisin's domains [1,38]. Several antibodies used in western blot to detect irisin were evaluated and found to be ineffective since they appeared to bind unspecific serum and plasma proteins with a restrictive detection limit (>10 ng/mL), below which concentrations were undetectable [39]. In conclusion, there are still no reliable results for detecting circulating irisin in any species using western blot.

ELISA

During the years following irisin's discovery, many of the studies using ELISA to determine irisin levels were found to be fundamentally flawed in their methodological approaches, causing extremely divergent recordings of irisin levels. For instance, Huh et al. reported levels of 112.7 ± 32.2 ng/ml in a small group of obese individuals and 473.4 ± 36.4 ng/mL in athletic, young men [4], whereas the next study that used a different ELISA kit found levels of 770 ng/ml in normal-weight subjects and 917 ng/ml in severely obese persons [40]. Similar problems were found in rodent studies, having circulating irisin levels ranging from less than 1 pg/mL [41] to more than 1.5 μg/mL [42].

Inconsistency in the findings may be attributed to the nonspecific binding of irisin antibodies to non-target serum proteins, as seen in western blots, and the fact that irisin ELISA kits are often validated against the immunogen in artificial systems rather than in biological samples [39]. When Montes-Nieto et al. [43] compared two sets of an ELISA kit from the same producer, they found a weak correlation of only r = 0.22, indicating that even within a single assay, there were considerable problems.

Protein Liquid Chip Assay

Chen et al. tested serum irisin levels in healthy newborn infants using a Luminex bead-based multiplex detection system, showing levels of 1.1 ± 0.2 ng/mL [44]. More studies are needed to further validate the accuracy of this method.

Quantitative Mass Spectrometry

Jedrychowski et al. attempted to develop an accurate, unbiased assay for detecting irisin levels in human plasma, using MS as an antibody-independent approach [37]. The concentrations presented confirmed that irisin concentrations in humans corresponded to exercise levels, such that inactive individuals were detected to have 3.6 ng/ml of circulating irisin, while fitter individuals had significantly increased levels of 4.3 ng/ml.

Overall, irisin concentrations reported through the MS technique were found to be significantly lower than the detection limits of western blot antibodies, indicating that the bands detected by the blots were most likely not irisin. Furthermore, sample preparations themselves during studies were found to account for possibly a 10–30% loss of irisin, contributing additional inaccuracies.

Cost is a primary limitation of using MS [37]. Additional factors, such as repeated measurements of the same sample and successive sample preparations from the same person, result in pronounced measurement variations. This suggests high methodological inconsistency and raises serious concerns regarding the overall validity of any research interpretations made on the basis of minor recorded differences between sample groups, especially when also based on single measurements for each person [7].

An extensive review [7] providing an in-depth investigation of all currently available irisin methods of quantification concluded that calibrated MS has the highest potential for becoming the 'gold

standard' in quantifying irisin; however, an accurate method of measuring circulating irisin is still not available for all organisms. Considering the lack of consistency between ELISA-measured irisin levels, as well as the weak correlations between ELISA and MS values (r = 0.4), a reliable and precise detection method for irisin is yet to be determined. To date, there are no confirmed reference values for irisin levels in any species.

6. IRISIN CONCENTRATION IN PHYSIOLOGICAL CONDITIONS

For years, researchers have attempted to measure irisin concentration levels with respect to physiological conditions. Yet, owing to methodological problems and extreme variability in reported data, no reliable baselines have been established.

Age, Race, Sex, and Anthropometric Parameters

Few studies have investigated irisin level variations in different age and sex groups and those with varying body compositions. A study that addressed healthy lean individuals ranging in age from childhood to young adulthood [45] discovered a negative correlation of irisin with age.

Differences in hormonal levels between physiologically distinct categories pre-determine differing ranges for circulating irisin levels in different groups. The female sex hormone, estradiol, has been shown to be positively correlated with circulating irisin levels, and yet no significant correlation was observed with testosterone [4]. According to Löffler et al. [45], lean girls had higher serum irisin levels than lean boys, but irisin levels were higher in men overall than in women, implying a likely connection between irisin and hormonal levels. Moreover, plasma irisin levels were shown to be negatively associated with percentage of body fat (PBF) and body fat mass (BFM) in men but not in women [46]. Clearly, more research is needed to elucidate such differences.

Stengel et al. suggested that irisin may have an important regulatory role in adipose tissue with respect to the body mass index (BMI), reporting low plasma irisin levels in anorexic adults and a linear relationship between the irisin levels and BMI in adults [40]. In obese people, some studies have recorded higher levels of irisin [40, 47-49], while others have observed lower levels with increased weight or BMI [50-52]. Pardo et al. found that for every 1 kg increase in fat mass, irisin levels increased twofold [47]. Similarly, positive associations between the levels of plasma irisin and waist circumference (WC), fat mass (kg), and fat mass percent were shown in one study [53]. In the latter study, it was concluded that irisin was positively correlated with BMI, BMI percentile, WC, and fat-free mass, and negatively correlated with body muscle mass, but only BMI percentile showed a strong positive correlation after adjustment for age and sex [53]. Although it was never directly addressed, several recent studies highlighted the concerns about the potential impact of racial-ethnic differences on irisin levels and action [54, 55]. One meta-analysis [56] analyzed the relationship between circulating irisin levels and insulin resistance in non-diabetic individuals, and it appeared that there was a difference in the correlation between circulating irisin and insulin resistance in Asian, American, and European populations.

Physical Exercise and Browning

Physical exercise's importance in protecting against many diseases has long been established, the most important of which are those related to aging, such as CVDs, DM, dementia, depression, and cancer [57]. Myokines, released in response to muscle contraction during exercise, are under the spotlight when discussing mediators of those protective properties [58]. It has been postulated that irisin, being one of these myokines, could be responsible for moderating some of the beneficial metabolic effects of exercise.

There are two types of adipocytes in our body: white adipocytes, which store fat, and brown adipocytes, which disperse stored fat as heat. Adipose browning is a process of turning white adipocytes into thermochemically active adipocytes, referred to as 'beige' adipocytes, by indirectly inducing increased mitochondrial biogenesis and mRNA expression of UCP1 mediating thermogenesis [13]. Perhaps the most notable effect of irisin is that of being a key regulator, among other myokines, in stimulating the browning of white adipocytes through upregulating UCP1 in response to exercise [1,59]. However, later studies showed that significant browning was seen in rodent experimental studies, whereas very little evidence relating to humans supports this [7]. A slight increase in the UCP1 gene expression was seen in only one study following long-term exercise in obese subjects [60]. Interestingly, it was shown that human white adipose tissue (WAT) can only express small amounts of UCP1 [61].

Early on, it was proposed that PGC-1α activation increased the amount and cleavage of FNDC5 into irisin from skeletal muscles, consequently browning

WAT [10]. In 2020, Pillon et al. conducted a meta-analysis showing that acute exercise substantially increased the expression of PGC-1α but that this decreased with inactivity; in contrast, FNDC5 expression was affected by neither acute nor long-term exercise or inactivity [62]. Löffler et al. investigated the influence of various exercises on serum irisin levels in children and adults, finding that although acute vigorous activities of short duration increased serum irisin levels abruptly and transiently, long-term/chronic physical activity did not [45].

7. CONCENTRATION OF IRISIN IN PATHOLOGICAL CONDITIONS

Understanding the effect of pathological conditions and their impact on irisin concentrations shows how it can be of huge advantage in understanding and controlling many morbidities. Most of these pathologies appear to be associated with persistent and chronic inflammation. The effect of multiple morbidities on irisin levels was previously discussed in another review [63], and here we further discuss most of them.

Obesity

BMI is the most widely used criteria for categorizing obesity, ranging from underweight (<18.5 kg/m^2) to morbidly obese (≥40 kg/m^2) [64]. As of 2016, 13% of the world's adult population was classified as obese [65]. Obesity acts as a huge burden on the quality of life and is associated with increased risk of developing major non-communicable diseases, most notably diabetes, cardiovascular diseases and cancer, and thus making any means of significant therapy targeting this morbidity a highly sought-after goal worldwide. Knowing that brown adipocytes use fat to produce heat rather than store it shows the great potential of irisin as an anti-obesity agent, considering its role in the 'browning' of white adipocytes. A significant correlation was validated between circulating irisin levels and many obesity markers, including body mass index, body adiposity index, waist circumference to height ratio, waist to hip circumference ratio, and others [66].

Irisin levels in lean and obese individuals were investigated. Chung-Ze Wuin et al. found that irisin levels in children had different responses to obesity in the two sexes, with obese boys having slightly higher irisin levels than those who are normal or overweight, while overweight and obese girls had lower irisin levels compared to normal, despite no significant difference between the groups [67].

Diabetes Mellitus

In diabetes mellitus (DM), irisin has been found to increase insulin receptor sensitization in the skeletal and cardiac muscles through many mechanisms, some of which promote pancreatic β cell functions and adipocyte browning [68]. A negative association was clinically proven in many studies between circulating irisin levels and insulin resistance in cardiomyocytes, skeletal muscles, and adipose tissue [69-71].

Insulin resistance is a primary accelerator in the development of Type-2 DM [72] and, as discussed before, irisin contributes to reducing insulin resistance; therefore, it is a potential target of therapy in diabetic patients [69]. Furthermore, a positive association was found between the amounts of irisin and the efficiency of glycemic control in Type 1 DM patients [51]. According to Zhang et al., in obese diabetic patients, circulating irisin levels were lower than non-diabetic obese adults, but greater than diabetes patients of normal weight, signifying that the rise in irisin levels associated with obesity appears to be a physiological reaction to enhance glucose tolerance. However, it appears that, once diabetes develops, the compensatory secretion of irisin ceases [72].

Diabetes has been linked to a number of microvascular (e.g., nephropathy and retinopathy) and macrovascular (e.g., cardiovascular disease and stroke complications) in diabetic patients, all of which are associated with increased disease and mortality [73]. A total of 60 patients with Type 2 DM took part in a study [74] to determine whether serum irisin is linked to diabetes complications in diabetics. Diabetic neuropathy patients had lower irisin levels than those without neuropathy. However, there was no statistically significant difference in irisin levels between diabetic retinopathy (DR) patients and those with a healthy fundus. Another study [75], on the other hand, found that Type 2 DM patients with DR have significantly lower levels of irisin than those without DR. The findings also revealed a significant negative relationship between irisin levels and the various stages of DR, implying that irisin could be used to predict its formation and progression.

Increased levels of vascular endothelial growth factor (VEGF) in the serum have been linked to DR and its stages, indicating that this biomarker could be used as a DR predictor [76]. In Jordanian patients, the association between levels of vascular endothelial growth factor (VEGF) and irisin has been explored, and it was revealed that the levels of VEGF and irisin had a negative relationship [77].

The link between irisin and retinopathy and

neuropathy in diabetics could be related to the effect of irisin on inflammation and endothelial dysfunction, which are both important risk factors for microvascular complications [78], suggesting that irisin may protect against DR through potential anti-interleukin-17A effects [79].

Cardiovascular Diseases

Cardiovascular diseases (CVDs) are one of the most common causes of mortality and morbidity, which have a major impact on quality of life. Irisin appears to approach issues with CVDs in multiple ways, such as by improving glycemic control, lipid profile markers, and even direct protective effects on endothelial cells [80]. It was determined that irisin levels were lower in diabetic patients with complicated CVDs vs uncomplicated, showing the potential role of irisin in CVD prognoses [81]. Many studies have been conducted to investigate the association between irisin levels and different CVDs, as it was discovered that irisin levels gradually decreased in a rat model of myocardial infarction (MI) [82] and chronic heart failure [83] compared with the control group.

The therapeutic effect of irisin post-MI in adult mouse models was explored [84], and it was discovered that irisin treatment reduced infarct size and improved heart function, which was related to irisin's pro-angiogenic activity via an ERK-dependent pathway. Furthermore, in a hypertensive rat model, irisin therapy led to lower blood pressure through the AMPK-Akt-eNOS-NO pathway [85].

Irisin's specific role in vascular function modulation remains unknown. One study [86] revealed that irisin causes vasodilation in a dose-dependent manner in both an endothelium-dependent and -independent manner, with the latter appearing to act by inhibiting Ca^{+2} influx via voltage-gated calcium channel blocking. Ye et al., however, discovered that irisin only caused endothelium-dependent vasodilation in rats in response to extracellular Ca^{+2} influx through TRPV4 channels [87].

Chronic Kidney Disease

The gradual deterioration of kidney function over months to years is known as chronic kidney disease (CKD), a form of kidney disorder. According to data collected between 2014 and 2018, 37 million adults in the United States have CKD [88]. In order to determine how irisin serum levels correlate with CKD stages, Ebert et al. conducted a study in which serum irisin concentrations were measured in 532 subjects with varying degrees of renal function. Irisin levels were found to decrease significantly as CKD stages progressed, indicating that irisin is not cleared by the kidneys and that it can predict CKD progression [89]. Supporting these findings, irisin circulating levels were measured in 90 patients with stage 2 or stage 4 CKD. It was determined that, as CKD progressed from stage 2 to stage 4, the amount of irisin decreased; however, the underlying mechanism for this decrease remains unknown [90].

Metabolic Syndrome

Metabolic syndrome refers to a combination of diabetes, hypertension, abdominal obesity, and dyslipidemia, putting the patient at higher risk of developing many disorders [91]. While its exact cause is not yet well understood, many of its features relate to insulin resistance. Many studies have considered the link between irisin levels and metabolic syndrome and found conflicting results, with some finding that irisin levels were higher in adults with metabolic syndrome [55] and others that irisin levels were lower [50]. It can thus be reasonably speculated that irisin levels are influenced by a variety of factors, such as body composition in different races, age, and physical activity. Unfortunately, no clear conclusion on the association between irisin and metabolic syndrome has yet been reached.

Cancer

In 2018, cancer, with an estimated 9.6 million deaths, was the second world-leading cause of death [92]. Irisin's role in tumor diagnosis and prognosis was explored in one review. Increased irisin appears to be able to differentiate thyroid cancer oncocytic variants, non-small cell lung cancer (NSCLC), gastric adenocarcinoma, colon adenocarcinoma, and renal cancer [93]. According to Provatopoulou et al., irisin can be used as a biomarker for early detection and prognosis of breast cancer. A one-unit rise in irisin levels seems to reduce the risk of breast cancer by approximately 90% [94]. Aside from positive and negative correlations between irisin and various types of cancer and stages, irisin was discovered to have the ability to suppress tumors. Shao et al. found that irisin substantially inhibited lung cancer cell proliferation and invasion in a time-based scenario [95]. Irisin also appears to play a role in decreasing pancreatic cell growth and may even be able to suppress malignant breast cells without affecting healthy cells [96-99]. These findings suggest that irisin could be a viable treatment option for lung cancer metastasis, pancreatic cancer, and breast cancer.

Neurological Diseases

A vast range of studies have centered on the role of irisin in the pathogenesis of many neurodegenerative diseases, including Alzheimer's

and Huntington's diseases. Increased irisin levels, along with brain-derived neurotrophic factor (BDNF), improved cognition in Alzheimer's patients. Furthermore, in one study conducted by Wang et al., an irisin and Aβ peptide conditioned astrocytes media increased neuronal survival after a marked decrease in inflammatory factors, such as COX2 and IL-6 [100]. Huntington's disease is characterized by hyperkinesia and cognitive decline. Irisin was found to ameliorate its neurological manifestations through increased delivery of BDNF [101]. Astrocyte-derived ATP demonstrates a critical role in the pathophysiology of major depressive disorders as they induce antidepressant-like effects in animal models [102]. Interestingly, irisin proved to have a potential role in inducing these antidepressant-like effects when injected into rats exposed to chronic stress, as it was found that it significantly increased the enzymes and transporters (GLUT-4) required for glucose metabolism in astrocytes [103].

Depressive disorders are common and disabling in patients with chronic neurological diseases, although their causes are often complicated and multifactorial. Regular physical activity has been shown to reduce the risk of depression and anxiety, among other mental diseases [104]. According to Jodeiri Farshbaf et al., irisin may reduce the consequences of acute stress. When they directly injected irisin into the hippocampus, they discovered that it partially prevented stress-induced neurobehavioral deficits in male mice but not in females [105].

In a six-month follow-up study in Chinese patients, one study [106] investigated irisin level associations with post-stroke depression and found that serum irisin levels were lower in patients with depression than in patients without, which implies that lower serum irisin levels can be a potential biological marker of post-stroke depression risk.

Immune Dysfunction and Chronic Inflammation

Low-grade inflammation and immune dysfunction appear to be linked to a variety of chronic diseases. Type 2 DM [107], atherosclerosis [108], and neurodegenerative diseases (e.g., Parkinson's disease [109] and Alzheimer's disease [110]), for example, are all closely related to the inflammation of the tissues. Physical activity and moderate exercise appear to reduce the inflammation level [111], which is reflected after the discovery of myokines such as IL-6, IL-8, and IL-15 [112]. Furthermore, findings strongly link PGC1α, which is induced by exercise, to the release of inflammatory cytokines. PGC1α's role in inflammation has previously been established, with PGC1 -/- mice showing increased encoding of inflammatory cytokines like IL-6 and TNF-α [113, 114]. This shows that individuals who exercise, particularly those who engage in chronic exercise, experience a reduction in systemic inflammation. Inactivity, on the other hand, results in a chronic systemic inflammatory state due to low levels of PGC1α in skeletal muscles [115].

One study used murine macrophages cultured in an irisin-enriched medium to consider the role of irisin, specifically in inflammation. It was discovered that irisin reduces the intensity of reactive oxygen species (ROS) production in macrophages, implying that it may have anti-inflammatory properties [116]. Added to this, another study examined the protective effect of irisin against oxidative stress in vitro, finding that irisin reduced the harmful effects of H_2O_2, a ROS, via increased expression of antioxidative stress enzymes like SOD and GSH-Px [117]. According to Mazur-Bialy et al. [118], the beneficial anti-inflammatory and potential protective effects of irisin from the development of obesity-related illnesses may, at least partially, be associated with the fact that irisin inhibited the downstream pathway of TLR4/MyD88, which consequently lowers NF-κB activation.

SARS-CoV-2

The membrane receptor angiotensin-converting enzyme-2 (ACE2) is found in the lungs, adipose tissue, cardiovascular system, kidneys, gastrointestinal tract, and central nervous system [119]. The pathogenic effects of SARS-CoV-2 are caused by the virus targeting ACE2 receptors, which are found primarily on the alveolar epithelium, causing damage to the lungs as well as other organs such as the heart [120]. According to one study, SARS-CoV-2 infection raises ACE2 levels via pathological pathways, resulting in adverse complications, whereas ACE2's physiological response to physical activity improves health [121].

In human cells, various genes appear to regulate ACE2, increasing (TLR3, KDM5B, RAB1A, FURIN, HAT1, HDAC2, SIRT1, and ADAM10) or decreasing (TRIB3) virus replication. Irisin was discovered to modulate genes involved in the replication of the novel coronavirus in human cells by a three-fold increase in TRIB3 transcription, while decreasing the levels of other genes, according to researchers at Sao Paulo State University (UNESP) [122]. This demonstrates that irisin may be useful in the prevention and possibly the

treatment of SARS-CoV-2 infection.

Osteoporosis

Osteoporosis is a global disease marked by a loss of bone mass and change in bone architecture, leading to increased bone fragility and fracture risk. Increased age, female sex, and low bone mineral density (BMD) are some of the known risk factors of osteoporosis [123]. Following the discovery of the physiological role of irisin in bone metabolism, a meta-analysis [124] was conducted to determine the link between irisin and osteoporosis, including seven studies with a total of 1,018 participants. It was concluded that middle-aged and older adults with osteoporosis had lower circulating irisin levels. Moreover, irisin serum levels were positively correlated with BMD.

8. SUMMARY

In the early years following the discovery of irisin, the focus remained on conducting numerous comparative studies of irisin concentration levels in the fluids of individuals with various comorbidities relative to controls, to assess its role in disease progression and prevention. However, few papers have established a reliable baseline for irisin concentrations in healthy individuals. Some of the primary issues included insufficient sample sizes and variations due to ELISA kits, the main method of quantification, thus inconsistently targeting different epitopes [125]. Other factors include polymorphic and multi-factorial variations across different races, genders, and age groups. As a result, establishing a universal reference range for circulating irisin levels in normal healthy people has proven challenging [126]. Consequently, to qualify irisin as an effective biomarker for disease prediction, a reliable standardization method remains to be established.

9. ACKNOWLEDGMENTS

None

10. DATA AVAILABILITY

All data analyzed during this study are included in the data repositories listed in the References.

11. FUNDING

This research received no external funding.

All authors contributed equally to this work.

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آلية عمل الأيريسين ومستوياته في الظروف الفسيولوجية والمرضية

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الملخص

الخلفية والأهداف: غالبًا ما يتم تجاهل أهمية تأسيس قاعدة معيارية عالمية لهرمون الأيريسين في الأفراد الأصحاء. الأيريسين هو هرمون خاص للدهون والعضلات، الذي تم تحديده حديثًا، ذو خصائص ووظائف متنوعة مثبتة في مختلف أنحاء الجسم. في هذا الاستعراض، يتم تلخيص الدراسات المنشورة حول هيكل الأيريسين، وآلية عمله، وكميته مع التركيز على مستوياته بالنسبة للظروف الفسيولوجية والمرضية.

منهجية الدراسة: تم البحث في قواعد بيانات PubMed، ScienceDirect، و Web of Science عن الدراسات التي تتضمن دراسة هيكل الأيريسين، آلية عمله، تركيزه، وتأثيراته في الأنسجة المختلفة (بدون قيود سنوية) باستخدام مصطلحات البحث التالية: "Irisin"، "FNDC5"، و"PGC-1α"، بالإضافة إلى الأوراق التي ناقشت مستويات الأيريسين بالنسبة للظروف الفسيولوجية والمرضية.

النتائج: تبيَّن أن معظم الأبحاث الحالية تركز على دراسة تراكيز الأيريسين في السوائل للأفراد ذوي الأمراض المصاحبة المختلفة مقارنة بأفراد في مجموعات الضوابط، بهدف تقييم دوره في تقدم ووقاية الأمراض. قليلة هي الأوراق التي استطاعت إنشاء نطاق مرجعي موثوق به لمستوياته في الأفراد الأصحاء نظرًا لحجم العينات غير الكافية، واستخدام طرق القياس المتباينة، والعوامل المتعلقة بالتباينات العرقية، الجنسية، والعمرية.

الاستنتاجات: لقد ثبت أن تأسيس نطاق مرجعي عالمي لمستويات الأيريسين في الدورة الدموية للأفراد الأصحاء يعد تحديًا. على الرغم من كونه علامة حيوية محتملة لتوقع المرض، إلا أن البحث المزيد ما زال مطلوبًا للتغلب على القيود الحالية..

الكلمات الدالة: الأيريسين، مستويات الأيريسين، FNDC5، النشاط البدني، استعراض.