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REVIEW

Serum Irisin: Pathogenesis and Clinical Research in Cardiovascular Diseases

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Abstract

Recently, muscular function/dysfunction has gained importance in the maintenance of metabolic homeostasis in cardiovascular diseases. Skeletal muscle plays a vital role in coordinating the activity and metabolism of endocrine organs by secreting many myokines, especially irisin. Irisin is a polypeptide hormone consisting of 112 amino acids secreted into the blood from muscle and adipose tissues. Serum irisin levels are associated with cardiometabolic risk factors such as obesity and insulin resistance as defined by homeostatic model assessment. Irisin reduces endothelial damage by inhibiting inflammation and oxidative stress, thus playing a key role in maintaining endothelial cell function. Unsurprisingly, low irisin levels cause endothelial dysfunction and increase the incidence of atherosclerosis. We aimed to summarize the studies on this issue since we have not found any review in the literature on the role of serum irisin levels in the process of atherosclerosis and other cardiovascular events in cardiovascular diseases.

Keywords: insulin resistance; irisin; cardiovascular diseases; body mass index

Introduction

Cardiovascular diseases (CVDs) are one of the leading causes of death and morbidity worldwide [1]. Diabetes mellitus (DM) increases the risk of CVDs by 1.5–2 times in men and 2–3 times in women. The risk of atherosclerotic disease in individuals with diabetes is 2–3 times higher than in individuals without DM [2]. In the last decade, muscle and adipose tissues have been described as regulators of endocrine metabolism in the body [3]. Skeletal muscle is considered to be an endocrine organ that secretes many myokines, including follistatin, myostatin, activin A, and irisin, which appear to play a vital role in coordinating the activity and metabolism of other endocrine organs [4].

Many biological processes related to energy metabolism are regulated by peroxisome proliferator–activated receptor γ (PPARγ) coactivator 1α, which also stimulates certain muscle gene products such as fibronectin type III domain–containing protein 5 (FNDC5) [5]. FNDC5 is a membrane protein released into the circulation after exercise and produces a derivative called *irisin* [5]. Irisin is a polypeptide hormone containing 112 amino acids secreted into the bloodstream from muscle and adipose tissues. Participates in the transformation of white adipocytes into brown adipocytes, both in vitro and in vivo, and stimulates the expression of thermogenic genes, including the gene encoding the mitochondrial brown fat separation protein 1 [5, 6]. Increased thermogenesis is a recommended

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mechanism by which irisin can increase insulin sensitivity and reduce blood glucose levels and body weight [5, 7]. Irisin, sirtuin, and vaspin have been proposed as regulators of PPARγ, and it appears all of these adipokines might be associated with PPARγ level [8].

In sedentary life, serum irisin levels are associated with cardiometabolic risk factors such as obesity and insulin resistance as defined by homeostatic model assessment [9]. Insulin resistance may result in microangiopathy and macroangiopathy, peripheral arterial disease, vascular dysfunction, hypertension, and endothelial cell and cardiomyocyte dysfunction. Directly related to insulin resistance and coronary artery disease (CAD), irisin increases the risk of coronary artery disease, myocardial infarction (MI), and heart failure [10].

Plasma irisin levels have been suggested to be positively correlated with body mass index. Irisin is a physiological protective factor against obesity, and its increased levels compensate for the increase in body weight. In obese individuals, physiological irisin cannot maintain the balance between stored and consumed energy, and thus the secretion of irisin is increased for the transfer of stored fat in skeletal muscle and adipose tissues [11].

Given the characteristics of irisin mentioned above, it may be considered a potential target for monitoring and intervention in people with type 2 (DM) and cardiovascular complications [12]. It can also be studied as a new target for the treatment of concomitant diseases such as obesity and diabetes and nonalcoholic fatty liver disease. However, despite this potential, many questions remain unanswered about the benefits of irisin as a therapeutic target. An important issue in this context is the role of irisin in metabolic syndrome and the associated complications, especially CVDs [10]. In this context, since there is no specific review of serum irisin levels and CVDs in the literature to our knowledge, we aimed to evaluate and synthesize research related to serum irisin levels in CVDs.

Khorasani et al. [12] reported irisin level was significantly higher in diabetic patients without CVDs than in diabetic patients with CVDs. To date, relations between irisin and DM [13, 14], obesity [15], and CVDs [16] have been reported. In some studies, irisin level was significantly lower in DM and MI patients than in control individuals [14, 16–18].

Studies comparing circulating irisin levels with levels in a control group have shown that irisin has a protective effect against the development of CVDs [16–19]. Several potential mechanisms have been proposed in this regard. Irisin plays a key role in maintaining endothelial cell function, and low levels of irisin lead to endothelial dysfunction and increase the incidence of atherosclerosis [20, 21]. In addition, irisin reduces endothelial damage by inhibiting inflammation and oxidative stress [22]. Hyperhomocysteinemia (which increases the risk of heart disease) has an inverse correlation with irisin levels [23]. Circulating irisin levels may be an indicator of increased heart muscle damage in patients with myocardial lesions [24]. In addition, low circulating irisin levels may increase the accumulation of advanced glycation end products, which lead to vascular complications in DM patients [21]. Irisin also plays an important role in lipid metabolism, and decreased irisin levels may lead to hyperlipidemia in CAD [25]. Despite these findings, the explanation of the function and mechanism of irisin in CVDs is not yet satisfactory.

Calan and Demirpence [26] found that circulating irisin levels were higher in patients with acromegaly. High levels of circulating irisin in patients with acromegaly were associated with increased epicardial adipose tissue and carotid intima-media thickness. Increased irisin levels may be a useful marker for cardiovascular risk in patients with acromegaly, but further research is needed to clarify the findings.

The relationship between metabolic syndrome and irisin in the pediatric population has been described [27]. The results suggest that overweight and obese children with metabolic syndrome have significantly lower irisin levels than those without metabolic syndrome.

Shim et al. [28] found an inverse relationship between glucose and triglyceride levels and irisin levels in overweight/obese children. Irisin is negatively associated with metabolic syndrome parameters (central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL)) also in adult populations [29]. Interaction of irisin with lipids and glucose may result in cell dysfunction and metabolic syndrome [30].

Fan et al. [31] demonstrated the protective effects of irisin in the presence of hyperglycemia

stress in reperfusion-treated cardiomyocytes. Irisin treatment supported survival of cardiomyocytes by modulating mitochondrial function via adenosine 5′-monophosphate–activated protein kinase (AMPK). The findings suggest that irisin is a promising therapeutic agent in the treatment of cardiac muscle damage in DM patients.

Elizondo-Montemayor et al. [32] conducted the first study showing reduced irisin levels in children and adolescents with type 2 DM compared with healthy controls. On the basis of experimental evidence, the reduction of circulating irisin levels in the pediatric population with type 2 DM can be attributed to the reduction of muscular secretion of FDNC5. The mechanism that may demonstrate that irisin has a potential protective mechanism against endothelial damage and vascular disease is the relationship between irisin and high-sensitivity C-reactive protein. They observed that the level of high-sensitivity C-reactive protein was higher in the type 2 DM group and positively correlated with anthropometric and metabolic markers, indicating that type 2 DM was a systemic inflammatory condition in the pediatric population. Low concentrations of irisin in this population may potentially increase the metabolic and inflammatory components of type 2 DM [32].

It is well known that physical exercise benefits human health at any age. However, the exact mechanism by which physical exercise improves health is unknown. Recent studies of exercise-related FNDC5/irisin have begun to illuminate this mystery. Exercise-induced FNDC5/irisin has been shown to be protective against cardiovascular damage after an ischemic event, to improve neuronal function in patients with Alzheimer's disease, and to play a role in macrophage and adipocyte regulation. Experiments have shown that FNDC5/irisin reduces cardiac regeneration, neovascularization, and cardiac fibrosis due to the interaction of Nkx-2.5-positive cardiac progenitor cells. It has also improved macrophage functions that can provide protection against defects in the cardiac conduction system [33].

Similarly, in a mouse model of Alzheimer's disease, FNDC5/irisin has been shown to alleviate memory impairment in mice with reduced memory performance [33]. In the same study, FNDC5/irisin was shown to be associated with regulation of osteocytes and adipocytes by signaling through the cytoplasmic membrane–integrated protein αVβ5 integrin receptor. Although these recent discoveries have strengthened the importance of FNDC5/irisin, many details about how FNDC5/irisin contributes to exercise physiology are unknown and deserve further research.

Irisin level is reduced in patients with heart failure following MI. It is negatively correlated with high troponin I, creatine kinase MB (CK-MB), TNF, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels. In contrast, it is positively correlated with left ventricular ejection fraction (LVEF) and high-density lipoprotein cholesterol level. Troponin I and CK-MB are useful biomarkers in the diagnosis of MI and are useful in predicting the incidence of post-MI complications [34]. Higher irisin concentration results in greater ATP loss due to its uncoupling property. With a gradual decrease in serum and tissue irisin levels, it is aimed to protect myocardial cells by saving the energy required for ischemic myocardial cells. This causes more uncoupling with higher levels of irisin, leading to loss of ATP and more heat generation. The increased irisin levels cause more damage to myocardium and cause a decrease in ventricular function in MI [18].

Yu et al. [35] demonstrated increased FNDC5/irisin expression in hypertrophic hearts, cardiomyocytes, and angiotensin II-treated skeletal muscle cells. Administration of recombinant irisin alleviated pathological cardiac hypertrophy and improved cardiac function both in vivo and in vitro. Irisin application activated AMPK–mammalian target of rapamycin signaling, which further reduces cardiac hypertrophy. Irisin was initially described as a skeletal muscle–derived protein [5]. However, an increasing number of studies have found expression of irisin in a variety of other organs, including heart muscle, brain, liver, and the gastrointestinal tract [36, 37]. Irisin expression appears to be relatively high in muscle-rich organs. Studies also show that heart muscle may have higher irisin expression than skeletal muscle [38].

Chen et al. [39] reported that irisin reduces angiotensin II-induced cardiac fibrosis due to inhibition of redox-sensitive transforming growth factor β1–SMAD2/3 signaling via NRF2. As an inference, irisin therapeutics are thought to be useful to reduce

cardiac fibrosis related to angiotensin II. Bi et al. [40] demonstrated that exogenous irisin attenuates hepatic ischemia-reperfusion damage by limiting mitochondrial division, supporting mitochondrial biogenesis, and reducing oxidative stress. Irisin treatment seems to be a new and promising treatment approach for ischemia-reperfusion injury in liver.

Bashar et al. [41] recommended recombinant irisin treatment and regular exercise to protect people at risk of acute MI. They made this suggestion on the basis of a negative correlation between serum irisin and lipid peroxidation, CK-MB, troponin I, collagen deposition, and the percentage of caspase 3 expression in a trial with rats. They also showed a positive correlation between serum irisin and total antioxidant status.

On the other hand, Ho et al. [42] showed that overexpression of irisin resulted in reactive oxygen species production and hypoxia-induced apoptosis in mice and cardiomyocytes. Irisin may have a double-edged sword effect on energy metabolism and tissue repair. Excessive irisin expression may increase energy wastage during the heart healing process. Prevention of overexpression of irisin after MI may be important. Further studies are needed to determine the exact mechanisms of the irisin/mitochondrial pathway in the myocardium and whether modulation of irisin levels may have therapeutic benefits in MI.

Asadi et al. [43] showed that irisin causes dose-dependent neuroprotective effects in stroke-induced brain injury. This effect is achieved by suppressing apoptosis and enhancing brain-induced neurotrophic factor expression in the ischemic area. Tu et al. [44] claimed that irisin is a new and independent prognostic marker that improves the risk classification currently used in stroke patients.

Kalkan et al. [45] reported that serum adropin and irisin levels were significantly increased in cachectic heart failure patients with reduced ejection fraction, and were significantly correlated with low-LVEF-related markers such as brain-type natriuretic peptide level and New York Heart Association class. The results show that adropin and irisin levels are correlated with the severity of heart failure and are reasonable candidates to be new markers for cardiac cachexia in patients with low-LVEF heart failure.

Moreno-Perez et al. [46] demonstrated higher irisin concentrations were associated with higher insulin resistance, nonalcoholic fatty liver, and subclinical atherosclerosis in HIV-positive men without DM. Waist-hip ratio is the strongest predictor of insulin homeostasis, and plasminogen activator inhibitor 1 levels and lipodystrophy are the main determinants of subclinical atherosclerosis, but the study asserts that irisin is also positively associated with other cardiovascular risk factors and may be considered as a marker of subclinical atherosclerosis. Among the factors associated with HIV infection, only the duration of exposure to nucleoside reverse transcriptase inhibitors was associated with higher concentrations of irisin. At present, primary and secondary prevention of CVDs are by the management of traditional cardiovascular risk factors, and only extensive studies with clinical outcomes to clarify the role of irisin in cardiovascular and metabolic risk in the HIV-positive population will provide a definitive answer [46].

He et al. [47] first proved a relationship between serum irisin levels and vascular calcification in hemodialysis patients. Lower irisin levels, long-term hemodialysis, and advanced age were independent risk factors for vascular calcification in hemodialysis patients.

Deng [25] showed that a decrease in serum irisin concentration was associated with the presence and severity of CAD. Likewise, Hisamatsu et al. [48] demonstrated that higher serum irisin levels were associated with lower coronary atherosclerosis burden in the Japanese male population. This relationship was different from the traditional cardiometabolic pathways. Hsieh et al. [49] demonstrated that higher serum irisin levels were associated with increased major adverse cardiovascular events (MACEs) and outcome rates in patients after ST-elevation MI. As confidence in new myokines continues to increase for the treatment of obesity, identification of the myocardial effects of myokines will become more important. Whether pharmaceutical agents that increase or decrease irisin levels may be applicable to the treatment or prevention of MI has yet to be determined. Further studies are needed to determine the exact mechanisms of the irisin/mitochondrial pathway in the myocardium and whether modulation of irisin levels may have therapeutic benefits in MI.

Conclusions

Irisin is a recently discovered molecule produced by muscles. It has been shown to be associated with different metabolic markers. Current studies suggest that irisin is a promising therapeutic agent in diseases such as DM, metabolic syndrome, and CVDs. Further studies are needed for the use of irisin in clinical practice.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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