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THE HORMONE-LIKE MYOKINES IRISIN AS NOVEL BIOMARKER FOR CARDIOVASCULAR RISK STRATIFICATION

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ABSTRACT

As a skeletal muscle cell-derived protein, Irisin regulates glucose and lipid metabolism, mitochondrial function, myogenesis, switching white adipocytes to brown fat-like cells, and thermogenesis and energy expenditure. The descriptive review aim is to summarize the knowledge regarding irisin as novel molecular mediators of energy metabolism of remote tissue with promising diagnostic and predictive values for CV risk in connection with a presence of metabolic conditions. The following database were used for searching of life science and biomedical information MEDLINE, the Web of Science, Medline (PubMed), the Cochrane Central, and EMBASE English publications to satisfy the keywords of this investigation.
Lowered concentrations of irisin were found in the patients with known CV disease including heart failure, Type 2 Diabetes Mellitus (T2DM), but the levels of circulating irisin were increased in obesity and pre-diabetes patients compared to healthy volunteers. In the general population, low levels of irisin have closely predicted T2DM, atherosclerosis, and coronary artery disease. Circulating levels of irisin in patients that have incident Heart Failure (HF) with reduced ejection fraction were related to the severity of the disease and can be a marker of cardiac cachexia. In contrast, in acute HF patients increased the levels of irisin in peripheral blood positively related to a one-year CV mortality rate. Large clinical studies are needed to determ the predictive role of irisin in the natural evolution of CV disease including HF, myocardial infarction, and cardiac cachexia.

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Introduction

During the recent decade, it has been shown that skeletal muscles secreting a wide spectrum of cytokines and proteins in response to muscle contraction could have a crucial role in autocrine/paracrine regulation of metabolism homeostasis and also, the endocrine and paracrine exertion of function on several tissues (white and brown adipose tissue) and organs (brain, liver, heart, and bones) [1, 2]. The secretome of skeletal muscles (known as myokines) includes a broad spectrum of active molecules, such as irisin, myostatin, myonectin, interleukin [IL]-1ra, IL-4, IL-6, IL-10, and Brain-Derived Neurotrophic Factor (BDNF), Insulin-like Growth Factor [IGF]-1, Fibroblast Growth Factor [FGF]-2, fetuin-A, and exerts anti-inflammatory ability and counteracts systemic low-grade inflammatory activation in physical inactivity, aging and numerous Cardiovascular (CV) and metabolic conditions, including coronary artery disease, atherosclerosis, cardiomyopathy, Heart Failure (HF), Type 2 Diabetes Mellitus (T2DM), and abdominal obesity [3, 4]. Although the biological effects of several myokines, such as BDNF, IGF-1, have been investigated, the mechanisms of the regulatory impact of irisin on the myocardium, adipose tissue, and vasculature are not still certain.

Irisin is a hormone-like molecule known as myokine that is secreted by skeletal muscle cells due to active deformation and stretching [5]. It regulates glucose and lipid metabolism, mitochondrial function, myogenesis, switching white adipocytes to brown fat-like cells, thermogenesis, and energy expenditure [5, 6]. Previously irisin-induced local and pleiotropic effects had been considered in the context of interplaying sedentary behavior and many chronic diseases, but nowadays there is a wide

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range of evidence regarding its possible association with adverse cardiac remodeling, Visceral Adipose Tissue (VAT) dysfunction, and poor clinical CV outcomes [6, 7]. Therefore, irisin plays an immunoregulatory role, stimulates angiogenesis, neovascularization, and reparation, whereas there are suggestions regarding its impact on cancer cell growth and modulation of pancreas function [8]. The present descriptive review aims to summarize knowledge regarding irisin as novel molecular mediators of energy metabolism of remote tissue with promising diagnostic and predictive values for CV risk in connection with a presence of metabolic conditions.

Materials and Methods

The following database were used to search biomedical information among English articles: the Web of Science, Medline (PubMed), the Cochrane Central, and EMBASE. The following keywords [diabetes mellitus], [type 2 diabetes mellitus], [cardiovascular risk factors]; [cardiac cachexia]; [cardiac myopathy]; [cardiovascular risk], [heart failure], [cardiac biomarkers]; [irisin]; [secretomics]; [myokines]; [circulating biomarkers]; [prognosis] were used. Both authors independently evaluated the articles' quality, coincidence to the initial hypothesis, and constructed the proof and final list of the references.

Results and Discussion

Biological Role and Function of Irisin

Irisin belongs to the heterogeneous contraction-induced myokine family and it is synthesized from fibronectin type III domain-containing protein 5 in response to an effect of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). Secretion of irisin is regulated by N-linked oligosaccharides attached to the PGC-1α. After synthesis, irisin transfers to the muscle cell membrane to be proteolytically cleaved on the extracellular surface and then released into circulation. Both secretion and function of irisin in physiological and pathological conditions are under strong regulation of several myokines (follistatin, myostatin, adropin), adipocytokines (fibroblast growth factor 21, leptin, adiponectin, resistin, chemerin, and visfatin), and cytokines with pro-inflammatory capabilities (i.e., tumor necrosis factor [TNF]-alpha) [9, 10].

The main biological function of irisin is to influence white adipose tissue to induce the browning response and subsequently activates non-shivering thermogenesis. The N-linked oligosaccharides molecules are part of the irisin glycoprotein act as regulators of the energy homeostasis of adipocytes. In some tissues, irisin probably affects through integrins, which are widely expressed on the surface of a wide range of cells as transmembrane receptors [10]. Therefore, in both physiological state and pathological conditions, irisin is produced during physical exercise and further regulates biological functions of the musculoskeletal system. Besides, it has a central role in bone mass retain control, has several positive effects on bone geometry and mineral densityof bones [10]. The potential biological effects of skeletal muscle secretome are presented in **Figure 1**.

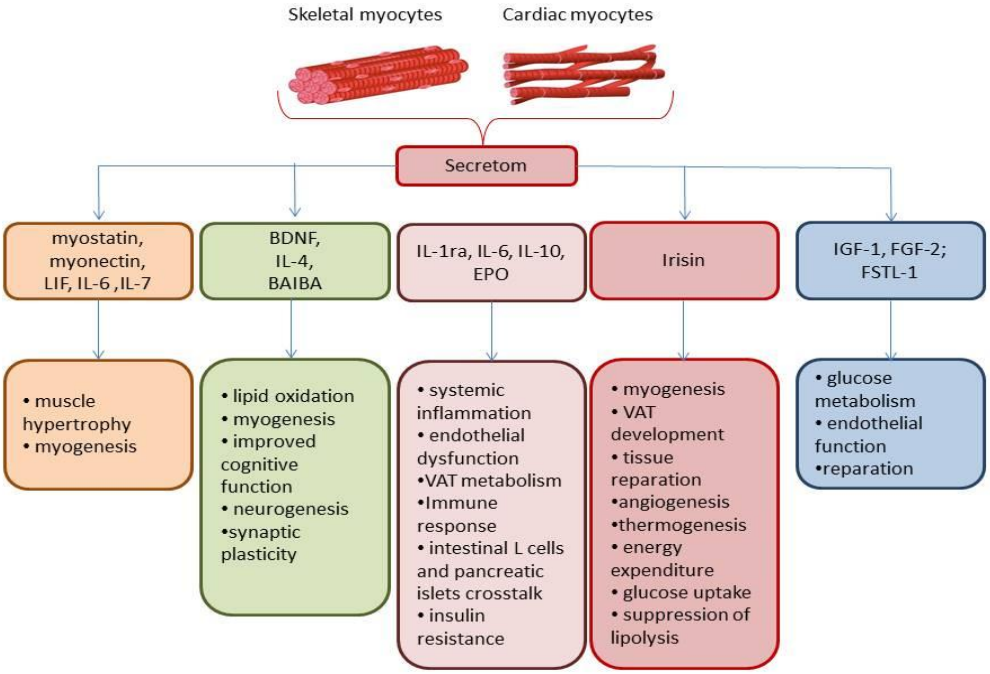

Figure 1. The Potential Biological Effects of Skeletal Muscle Secretome on Target Cells and Tissues
Abbreviations: BAIBA: β-Aminoisobutyric Acid, BDNF: Brain-Derived Neurotrophic Factor, IL: Interleukin, EPO: Erythropoetin, IGF-1: Insulin-like Growth Factor, FGF-2: Fibroblast Growth Factor, FSTL-1: Follistatin-Related Protein-1, and LIF: Leukaemia Inhibitory Factor

There are serious controversies regarding the irisin levels in peripheral blood in age and among patients who ~~that~~ have metabolic syndrome, T2DM, abdominal obesity, and CV disease. Most findings confirm significantly lowered levels of irisin in patients with metabolically active central obesity, metabolic syndrome, and T2DM in comparison with healthy volunteers. While there is evidence that irisin serum levels have demonstrated a tendency to increase in patients that have metabolic syndrome, abdominal obesity, CV diseases, and decrease in patients that have chronic kidney disease in comparison with healthy volunteers [9]. In fact, it was revealed that irisin levels in peripheral blood were markedly increased in non-T2DM patients with abdominal obesity, while they were decreased in T2DM obese individuals [10]. Additionally, lowered irisin levels have been determined in patients with T2DM in comparison to non-T2DM individuals, but they were non-significantly higher than in healthy volunteers. Irisin serum levels were also lower in the serum of pregnant women with gestational diabetes mellitus than in non-diabetics [10]. Nevertheless, the serum levels of irisin were significantly higher in young athletes than in women with abdominal obesity. In addition, the levels of irisin were positively correlated with strength in athletes and bone mineral density and inversely associated with low-energetic fractures in female with overt postmenopausal osteoporosis [10]. Interestingly, some findings have demonstrated increased irisin levels in pre-diabetes patients in comparison with healthy volunteers before and after acute physical exercise [11]. Moreover, chronic exercise did not strongly relate to a significant decrease in circulating levels of irisin during chronic physical training [12]. Additionally, mRNA expression of PGC1A did not demonstrate a significant correlation with irisin plasma levels in both healthy volunteers and pre-diabetes individuals. However, circulating irisin levels in chronic training in subjects with metabolic syndrome / T2DM were reported by several studies to be enhanced as well as reduced [13]. The discrepancy in these results is explained by the evidence of endogenous production of irisin in remote skeletal muscle organs, and maybe important determinant of plasma irisin levels independent of PGC-1α, as well as insulin sensitivity, high-density lipoproteins, ATP concentration in muscle, fasting glucose, and adiposity [14].

Previous preclinical and clinical investigations have indicated an important role of irisin in white-to-brown adipose tissue trans-differentiation called browning and thermogenesis [15-17]. Indeed, energy expenditure is closely related to the thermogenic regulation in White Adipose Tissues (WAT) and classical brown adipose tissue (BAT). Importantly locally synthesized fibronectin type III domain-containing protein-5 rather than circulating irisin mediated turn-over of WAT to BAT during regular exercise training [17]. It has been suggested that subcutaneous browning WAT could be an alternative regulatory mechanism, which reduces thermogenic capacity beyond irisin effects, while the irisin-derived impact on adipose tissue browning has been established [18].

Then irisin was discovered exercise-induced myokine that has been attributed to the autocrine and paracrine effects on skeletal muscles and remote tissues **(Figure 2)**.

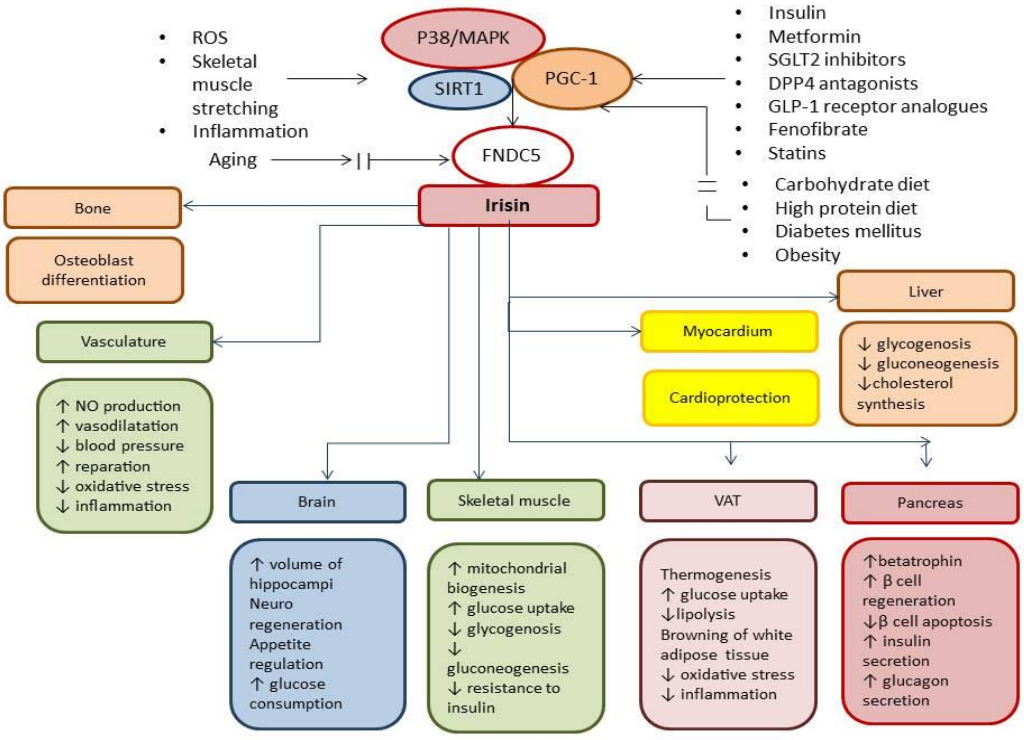

Figure 2. Autocrine and Paracrine Effects of Irisin on Skeletal Muscles and Remote Tissues
Abbreviations: DPP4: Dipeptidyl Peptidase-4, GLP-1: Glucagon-Like Peptide 1, MAPK: Mitogen-Activated Protein Kinase, PGC-1α: Peroxisome Proliferator-activated Receptor γ Coactivator 1α, SGLT2: Sodium-dependent Glucose Cotransporters, ROS: Reactive Oxide Species, NO: Nitric Oxide,VAT: Visceral Adipose Tissue.

Although there are several controversial reports regarding the association between serum irisin levels and physical activity, [19] it has yielded a positive effect of irisin on the metabolism of skeletal muscle, hepatocytes, bone, kidney, and adipose tissue [20]. In fact, irisin has increased glucose uptake, suppressed lipolysis, gluconeogenesis, glycogenolysis, and insulin resistance, stimulated mitochondrial biogenesis, lowered synthesis of cholesterol in hepatocytes, as well as decreased oxidative stress and inflammation leading to improve endothelial function, reparation, angiogenesis, and a mild decrease in blood pressure [21, 22]. There is strong evidence concerning the irisin's role in an inhibition of the expression and transcriptional activities of key master regulators of lipogenesis (LXRα and SREBP-1c) and several pro-inflammatory genes that were responsible for the expression of a wide spectrum of the inflammatory markers, such as nuclear factor κB, COX-2, p38 MAPK, TNF-alpha, and IL-6 [23]. The resistance training in animals had yielded an increase in the serum levels of irisin, which were significantly and positively correlated with circulating levels of betatrophin, insulin, and inversely correlated with fasting blood glucose, and low-density of lipoprotein cholesterol. Finally, irisin has shown an ability to regulate appetite, food behavior, stimulate neuroregeneration, and trigger beta-cell regeneration in the pancreas [24].

The most molecular mechanisms regarding improved functions of multiple organs have contributed to stimulation of p38 AMP-activated protein kinase/phosphatidyl Inositol 3 kinase signaling and calmodulin-dependent mechanism in concordance with an expression of IL-6 receptor on the target cells [25]. Additionally, the increase in sensitivity to insulin and oxidation of fatty acids were associated with promoting intracellular signaling systems, such as TLR4/D88, Janus Kinases/signals, and activators of transcription (STAT) pathways [26]. Numerous findings received in pre-clinical and clinical stidies have yeilded evidence for anti-inflammatory effects of irisin, which influence transcriptional regulators that are involved in inflammation, as well as anti-inflammatory protective impact that is in favor of various tissues [27, 28]. Angiopoetic effects of the irisin are related to reducing oxidative/nitrative stresses via suppression of the PKC-β/NADPH oxidase and NF-κB/iNOS signaling pathways in vascular smooth muscle cells and progenitor / mature endothelial cells affecting their ability to release secretome [29].

Thus, irisin was recently recognized as a beneficial metabolic modulator in the physiological state (aging and physical exercise), as well as in obesity, metabolic syndrome, and T2DM, for which imbalance in the expression and secretion of several pro-and anti-inflammatory cytokines had determined [30]. However, the beneficial role of irisin in the CV and metabolic diseases has been widely discussed, but the cardiac protective effect of irisin remains uncertain and requires to be elucidated.

Irisin and CV Risk in T2DM and Non-T2DM Populations

Previous clinical studies have revealed that the lowered circulating levels of irisin in T2DM patients and patients without established CV disease significantly correlated with HbA1c, HOMA-IR, triglycerides, and body mass index, as well as with 1.6-fold increased CV risk [31, 32]. In the meta-analysis that was performed by Zhang *et al*. (2016), [33] the cut-off point for irisin concentrations that predicted T2DM in the general population were 24.46 ng/mL ($P = 0.002$). In the T2DM female population, the irisin levels were lower than in the volunteers regardless of the presence of atherosclerosis, while negative associations between serum irisin levels and fasting blood glucose were noticed in T2DM patients with established atherosclerosis compared with the diabetics group without atherosclerosis [34]. There is evidence that the reduced serum levels of irisin powerfully predicted developing depression in patients at very high CV risk after stroke [35].

Whether serum concentrations of irisin had been attributed by the complicated T2DM is not yet clear, while there was a strong negative association between T2DM duration and the levels of irisin in patients with both known CV disease and without it [36, 37]. However, elevated irisin serum levels in T2DM patients in some studies have shown a positive correlation with indices of adiposity, soluble E-selectin, insulin, apolipoprotein B / apolipoprotein A-I ratio, subclinical hypothyroidism, Framingham risk score, and conventional CV risk factors [38]. Perhaps, obesity is the main factor contributing to the increase in circulating irisin levels in T2DM and non-T2DM patients regardless of CV disease presence.

Although there is a wide range of evidence regarding the positive impact of various antidiabetic drugs on the adipocytokine profile, there are not strong findings confirming CV risk modification in connection with up-regulation of irisin expression in target tissues (including VAT, liver, and myocardium) and peripheral blood among T2DM patients [39, 40]. Interestingly, serum levels of irisin in the non-diabetic population were inversely associated with conventional CV risk factors and biomarkers of metabolic phenotype, while T2DM patients did not show these associations [41]. Moreover, higher irisin levels in obese patients positively correlated with a better metabolic profile (lower HOMA-IR, triglycerides, and low-density lipoprotein levels) and a lower risk of T2DM development [42]. Finally, additional larger clinical studies are required to determine whether irisin may play a predictive role in monitoring CV risk in diabetics who are treated with antidiabetic drugs and among drug-naïve patients with T2DM.

Discussion Around the Role of Irisin as Predictor of Cardiac Remodeling and Clinical Outcomes

Previous animal and clinical studies have shown that there were negative correlations between serum irisin levels and both collagen deposition and caspase-3 expression in the myocardium after acute ST-Elevation Myocardial Infarction (STEMI) [43, 44]. Moreover, over-expression of irisin in the myocardium of animals with experimental STEMI was associated with reduced cardiac myocyte apoptosis, augmentation of protective autophagy, and alleviation of myocardial hypertrophy induced by pressure overload and angiotensin II-induced injury [45]. In humans circulating levels of irisin were negatively correlated with MB-creatine kinase, and troponin I in the early STEMI period [44]. It has been suggested that irisin could be a protector from myocardial ischemia/necrosis in acute myocardial infarction. Moreover, lowered circulating irisin levels were inversely

associated with adverse CV outcomes after acute STEMI [46]. The concentrations of irisin higher than the 75th percentile of the overall distribution are related to a 4-fold soaring in the risk of combined endpoint included CV mortality, stroke, HF, and revascularization (hazard ratio=3.96, P<0.01) [46]. Patients with STEMI and HF had reduced serum irisin, which positively correlated with Left Ventricular (LV) Ejection Fraction (EF), and inversely associated with troponin-I, CK-MB, TNF-alpha, and high-density lipoprotein cholesterol [47]. There was no significant correlation between circulating levels of irisin and Body Mass Index or HOMA-IR for both HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) groups, while irisin levels have demonstrated a remarkable association with incident HFpEF (OR = 1.76; p < 0.01) [48]. Among HFrEF patients with cachexia, the levels of irisin were positively correlated with New York Heart Association functional class and Brain Natriuretic Peptide (BNP) levels and inversely associated with body mass index and serum albumin levels [49]. Thus, circulating levels of irisin exhibited a close relation to the severity of chronic HFrEF/HFpEF and can be a powerful prognosticator marker of cardiac cachexia among HFrEF patients. Probably, irisin has acted as a component of the endogenous repair system that prevents muscle atrophy through attenuating energy homeostasis and browning of adipocytes. Shen *et al*. (2017) [50] have reported that irisin serum levels were discovered to be substantially higher in acute / acutely decompensated HF patients who were died over one-year follow-up and they have strongly predicted mortality risk comparably to NT-pro-BNP. Overall, irisin appears to be an important independent predictive factor for CV risk, CV mortality, and HF-related clinical outcomes.

Conclusion

Irisin circulating levels in patients who have established CV and T2DM disease were found to be lowered when compared with healthy volunteers, but patients with metabolic syndrome have demonstrated higher levels of one than in diabetics. Post-STEMI period and chronic HF were associated with remarkably decreases in serum levels of irisin, whereas, acute HF patients have revealed an increase in the concentration of the biomarker. The majority of collected findings have confirmed the participation of irisin in attenuation of cardiac and vascular remodeling through several tissue-protective effects including anti-oxidative, anti-inflammatory, and anti-apoptotic impacts. Large clinical studies are required to elucidate the predictive role of irisin in the natural evolution of CV disease including HF, myocardial infarction, and cardiac cachexia.

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