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Association between irisin and major chronic diseases: a review

M.C. GOUVEIA, J.P. VELLA, F.R. CAFEO, F.L. AFFONSO FONSECA, M.R. BACCI

General Practice Department, Faculdade de Medicina do ABC, Santo Andre, São Paulo, Brazil

Abstract. – OBJECTIVE: Irisin is a muscle-secreted protein released into the circulation by cleavage of fibronectin type III domain containing protein 5(FNDC5). Since its discovery in 2012, it has been the subject of many researches due to its physiological role. It is believed that understanding irisin's function may be the key to comprehend many diseases and their development. The aim of this study is to perform a systematic review in order to establish whether there is an association of irisin's levels with obesity, diabetes mellitus, non-alcoholic steatohepatitis, chronic kidney disease and cancer in terms of prognosis.

MATERIALS AND METHODS: The articles that support these findings were selected from Medline using the keyword "irisin" and filtered with "humans only". The selected articles were in English and with abstract.

RESULTS: Higher baseline irisin concentrations are associated with greater reductions in glycemia and insulinemia after weight loss in obese subjects. Besides, it was observed that macrovascular disease, a complication of diabetes, was developed when there were lower levels of irisin. In addition, although not statistically significant, high levels of irisin were associated with portal inflammation and severity of histological lesions. Its concentrations decreased with increasing chronic kidney disease stage, and they were not only independently and positively predicted by renal function and insulin resistance but also associated with sarcopenia and carotid atherosclerosis in patients undergoing peritoneal dialysis. Regarding cancer, irisin reduced the proliferation, viability and migration of malignant breast cells. Finally, it is also related to bone health once its concentration is associated with previous osteoporotic fractures.

CONCLUSIONS: In every condition studied, irisin's concentrations were related to the development of the disease.

Key Words:
Irisin, Chronic kidney disease, Biomarkers, Cancer.

Introduction

Irisin is a peptide hormone released into the circulation by cleavage of fibronectin type III domain containing protein 5 (FNDC5)[1]. Bostrom et al[2] were the ones who recognized this expression and suggested that although the full-length FNDC5 is a transmembrane protein, its extracellular N-terminal portion of FNDC5 could potentially be cleaved by a still unknown protease. The identification of the fragment was initially determined by antibody binding, confirmed by mass spectrometry. Their analysis also revealed that the secreted form of FNDC5 was highly homologous between mouse and humans, and they called this newly identified peptide irisin.

Since its discovery, irisin has been the subject of many studies due to its physiopathological role. It is believed that the understanding of how irisin works may be the key to discover how to manage many clinical conditions. The consolidation of this basic knowledge is essential so that other studies may be conducted and their findings may be implemented in the daily care of patients.

The aim of this work is to perform a review in order to establish whether there is an association of irisin's levels as a biomarker with the prognosis of major chronic conditions, namely obesity, diabetes, non-alcoholic steatohepatitis, chronic kidney disease, cancer and osteoporosis.

Materials and Methods

A systematic review was performed on Medline database in order to identify possible eligible studies. The MeSH descriptor "irisin" was used.

Inclusion criteria comprised the presence of the term in the title or abstract, articles with abstract in the English language that related irisin

Corresponding Author: Marcelo Rodrigues Bacci, MD; e-mail: mrbacci@yahoo.com

to major chronic diseases. Two researchers conducted the review independently, and a third party reviewed the final selection using the pre-established criteria.

Results

The final selection resulted in 22 out of 313 articles. The flow chart below shows the previously established inclusion and exclusion criteria until the final number was reached (Figure 1), and the Table I illustrates the relation between the selected articles and their objectives.

Discussion

Metabolic Disorders

Obesity, more specifically abdominal obesity, is one of the most important factors in the development of diabetes through various mechanisms, including increased circulation of free fatty acids, decreased adiponectin levels, decreased cytokine secretion by adipose tissue (such as tumor necrosis factor alpha [TNF-α] and interleukin-6) factors that exacerbate the insulin resistance. Besides that, the accumulation of fat in liver-due to obesity reduces its ability to metabolize glucose, promoting insulin resistance[3].

Once the relationship between the metabolic disorders has been exposed, it is necessary to associate them with irisin. Physical exercise seems to induce the increase of PGC-1 alpha (a transcriptional coactivator) in muscle, which is accompanied by improved FNDC5 levels in the membrane. FNDC5 is cleaved and released as a hormone: irisin. It goes into circulation and binds to receptors on the surface of certain white adipocytes to stimulate browning and UCP1 expression by an upregulation responsible for the resulting heat loss. Irisin acts as a signal that communicates directly with muscles and the adipose tissue, causing a phenotypic change in fat, which becomes similar to the brown adipose tissue. This mechanism leads to increased oxygen consumption and heat loss, thus increasing the energy expenditure during exercise. The effects of irisin are accompanied by increased oxygen consumption, decreased body weight, improved glucose tolerance and decreased insulin secretion[4].

Irisin was independently related to reduced risks of metabolic syndromes. Raised fasting plasma glucose concentration and insulin resistance indicators were negatively associated with circulating irisin levels, which, in turn, were positively associated with a 10-year-risk of general CVD. This suggests that irisin plays a protective role in the pathophysiology of insulin resistance and its related conditions, such as type 2 diabetes mellitus (T2DM) and metabolic syndromes[5,6].

Circulating irisin's level is lower in T2DM when compared to non-diabetic controls[7].

Obesity

Apparently irisin's levels are related to the prognosis of this disease. In a study that compared irisin's concentrations before and after a calorie restriction diet, it was shown that the high levels of irisin in early intervention could be associated with greater reductions in blood glucose levels and insulin concentrations. As a result of this effect, triglyceride levels also decreased in larger proportions. Furthermore, irisin is involved in increased energy expenditure; therefore, high levels of triglycerides start to provide energy substrates for the body. It is suggested then that irisin levels are increased in situations of metabolic abnormalities, and these levels are lowered with weight loss, resulting in improved metabolic parameters[8].

Type 2 Diabetes

Irisin is believed to act through the stimulation of glucose transporter expression of adipocyte

Figure 1. Established inclusion and exclusion criteria.

Table I. Selection of studies relating irisin and chronic diseases.

Author	Year	Study design	Objective
Teufel A et al	2002	Descriptive analysis	Expression of fibronectin and irisin genes in brain and liver
Bostrom P et al	2012	Experimental	Irisin and its role in white adipose cells and thermogenesis
Sanchis-Gomar F et al	2012	Review	Irisin and treatment of obesity and T2D
Pyrzak B et al	2015	Review	Association between browning agents and the development of obesity
Park KH et al	2013	Cross-sectional	Irisin and the risk of metabolic syndromes, cardiometabolic variables and CVD
Yan B et al	2014	Cross-sectional	Irisin and metabolic syndrome in obese Chinese adults
Liu JJ et al	2013	Cross-sectional	Association between circulating irisin and type 2 diabetes mellitus
Lopez-Legarrea P et al	2014	Case-control	Irisin levels and glucose homeostasis in obese subjects with metabolic syndrome
García-Fontana B et al	2015	Case-control	Relationship between serum myostatin and irisin and inflammation in T2DM patients and controls
Zhang M et al	2014	Prospective	Irisin and expression of inflammation-related factors in elderly T2DM patients
Polyzos SA et al	2013	Cross-sectional	Irisin levels in patients with nonalcoholic fatty liver disease and controls.
Choi ES et al	2014	Cross-sectional	Irisin levels and non-alcoholic fatty liver disease
Kobayashi S et al	2005	Cross-sectional	Irisin and insulin resistance in chronic kidney disease
Ebert T et al	2014	Cross-sectional	Irisin and CKD stage and insulin resistance
Yang S et al	2015	Cross-sectional	Irisin and body composition in chronic kidney disease
Liu JJ et al	2015	Cross-sectional	Relationship between renal function, body composition and irisin
Lee MJ et al	2015	Cross-sectional	Irisin and sarcopenia and cardiovascular disease in peritoneal dialysis patients
Gannnon NP et al	2014	Prospective	Irisin and evolution of breast cancer
Moon HS et al	2013	Cross-sectional	Irisin and obesity-related cancer cell lines
Kawao N et al	2015	Cross-sectional	Search bone interacts with skeletal muscle via signaling from local and humoral factors in addition to their musculoskeletal function.
Palermo A et al	2015	Cross-sectional	Investigate the relationship between irisin and body composition in postmenopausal women with osteoporosis and the impact of irisin levels on fragility vertebral fractures.
Choi HY et al	2014	Cross- sectional	To assess the association of circulating irisin concentrations with brown adipose tissue (BAT) and/or sarcopenia in humans.
Anastasilakis AD	2014	Cross sectional	Evaluate predictors of circulating irisin in postmenopausal women with low bone mass and to assess a potential effect of denosumab or teriparatide treatment for 3 months.

mitochondrial biogenesis and the formation of a phenotype, with the activation of brown adipose tissue thermogenesis and lipid consumption. Under these conditions, glycolysis and oxidative phosphorylation increase energy consumption and improve glucose and lipid metabolism[9].

In a study, Zhang et al, a significant decrease in serum irisin in T2DM patients was found, which

further confirmed the potential role of irisin in glucose metabolism regulation and diabetes occurrence. Moreover, when serum concentrations of irisin were compared between T2DM patients, with and without macrovascular disease (MVD), irisin's levels decreased more significantly when MVD was present. The findings suggest that irisin could be a potential target for monitoring and intervention of T2DM and its vascular complications, thus improving prognosis[10].

Irisin improves insulin sensitivity, reduces fast blood glucose and improves glucose homeostasis by reducing gluconeogenesis and the increase of glycogenesis[6].

Nonalcoholic Fatty Liver Disease (NAFDL)

Levels of serum irisin are related to the prognosis of fatty liver disease as they tend to be significantly lower in obese controls and NAFDL patients than in lean controls. It suggests that irisin may be associated with the presence of portal inflammation and the severity of histological lesions (degrees of steatosis, fibrosis stages, lobular inflammation, cytological ballooning). However, these differences did not reach conventional levels of statistical significance and they have to be further explored[11]. The hypothesis that in the initial stage of NAFDL serum irisin increases as a defense mechanism and only afterwards it decreases with the progression of the disease must be taken into consideration[12]. The prognosis of development could be determined with further studies, depending on the level of irisin, which would establish a pattern between the lesions and the concentrations.

Chronic Kidney Disease (CKD)

Patients with CKD have a high cardiovascular incidence of morbidity and mortality. This is explained by common risk factors for both conditions. Besides, CKD itself predisposes to cardiomyopathies due to volume overload, interference in bone mineral metabolism, inflammation, oxidative stress and uremia. All these mentioned factors cause insulin resistance and hyperinsulinemia and play an important role in the physiopathology of CKD and its consequent cardiovascular morbidity and mortality. The fact that irisin improves glucose homeostasis and insulin resistance points out a possible potential therapeutic and prognostic factor because irisin's levels in CKD patients without diabetes were lower when compared with healthy patients[13]. Although the causes are still unknown, some hypotheses suggest that since irisin is associated with sarcopenia, CKD patients may have lower muscle volume, or even because such individuals may be less physically active. However, the most reasonable theory is that uremic toxins contribute to irisin decrease as the administration of indoxyl sulfate decreased FNDC5 (irisin precursor) expression levels[14].

According to Yang et al[15], body fat percentage was independently associated with CKD, a fact that is sensibly explained once the amount of adipose tissue is considered a risk factor for insulin resistance as well. Ebert et al[13] concluded that irisin's serum concentrations adjusted for age, gender and BMI significantly decreased with increasing CKD stage, and they were independently and positively predicted by renal function and insulin resistance. This tends to confirm the speculation about the role of irisin in the development of CKD.

Moreover, irisin lower levels were associated with renal function in type 2 diabetes patients, mainly in those who presented some level of insufficiency, thus indicating an association with prognosis[16]. Therefore, irisin could be involved not only with the prevention of chronic kidney disease in patients who already have diabetes, but also with its prognosis as a preventive tool for onset of complications[17].

Cancer

Irisin significantly decreased the proliferation, viability and migration of MDA-MB-231 and MCF-7 breast cancer cells without affecting non-malignant cells. Furthermore, irisin potentiated the cytotoxic effect of doxorubicin (DOX) and stimulated caspase activity that leads to apoptotic death. These observations imply that irisin can provide therapeutic benefits for prevention, treatment and prognosis of breast cancer, probably by an anti-inflammatory response, induction of cell death by apoptosis, or by improved sensitivity of the tumor to common antineoplastic agents such as DOX[18].

Although there seems to be an association between irisin and breast cancer, further studies are necessary to determine if there is a practical use for irisin in breast cancer patients and whether other types of cancer are related to irisin. A research showed that irisin had no effect on cell proliferation, on cell adhesion or on colony formation when compared to control in human and mouse endometrial, colon, thyroid and esophageal cancer cell lines[19].

Osteoporosis

A large number of data has indicated that increased muscle mass is related to increased bone mass and reduced fractured risk[20]. A study[21] showed that serum levels of irisin were lower in patients with previous osteoporotic fractures when compared to controls with significant values after adjustment for creatinine, vitamin D, lumbar and femoral BMD and lean mass. This information speculates that irisin has a protection role on bone health. Nevertheless, it is not known whether this association is independent or whether it is due to low muscle mass as sarcopenia was not related to irisin's levels[22,23].

Conclusions

Higher baseline irisin's concentrations are associated with greater reductions in glycemia and insulinemia after weight loss in obese subjects. Macrovascular disease, a complication of diabetes, was seen when there were lower levels of irisin.

Irisin serum concentrations adjusted for age, gender and BMI significantly decreased with increasing chronic kidney disease stage, and they were independently and positively predicted by renal function and insulin resistance. Besides, serum irisin was significantly associated with sarcopenia and carotid atherosclerosis in patients undergoing peritoneal dialysis, also indicating a worse evolution of the disorder.

Regarding cancer, it was shown that irisin significantly decreased the proliferation, viability and migration of malignant breast cells. It means that higher levels of irisin tend to be associated with a better disease outcome and probably a superior prognosis.

Finally, irisin has a protective role in bone health because serum levels of irisin were lower in patients with previous osteoporotic fractures. However, some authors prefer not to believe in this information yet; they say that further studies on the subject are still required.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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