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Low Irisin Levels in Patients with Type 2 Diabetes Mellitus without Current Treatment: a Systematic Review

REVIEW

Jaqueline Pinheiro de Alencar[1], Francisco Matheus Prado Luna[1], Matheus Barbosa Coelho[1], Raissa Maria Rolim Bem de Morais[1], José Antonio de Lima Neto[1], Messias Silvano da Silva Filho[2], Ivana Rios Rodrigues[3], Marcial Moreno Moreira[5], David de Sousa Gregório[5], Modesto Leite Rolim Neto[1,4,5]

1 Department of Medicine, Estacio/FMJ, Juazeiro do Norte, Ceará, Brazil.
2 Department of Medicine, Estacio/FM, Juazeiro do Norte, Ceará, Brazil. Scholarship of Scientific Initiation, Brazil.
3 Department of Clinical Care Nursing and Health, Ceara State University, UECE, Fortaleza, Ceara, Brazil.
4 Department of Medicine, Federal University of Cariri, Barbalha, Ceará, Brazil.
5 Department of Health Sciences, Faculty of Medicine of ABC, FMABC, Santo André, São Paulo, Brazil.

Contact information:

Messias Silvano da Silva.

Address: Faculdade de Medicina, Estácio FMJ.

messias_silvano@hotmail.com

Abstract

Background: The Irisin is a myokine associated with the improvement on insulin resistance caused by diet and increased physical energy expenditure. Recent studies have shown that patients with Type 2 Diabetes Mellitus (T2DM) have reduced levels of irisin, showing it as a potential marker for various endocrine and cardiovascular diseases. This study aimed to verify if T2DM patients never treated or without ongoing treatment have reduced levels of irisin when compared to individuals with other metabolic profiles.

Methods and Findings: Systematic review of the literature, considering the primary studies published in 2012 to 2016, with the outcome Irisin levels in patients never treated or without current treatment in the ambience of Type 2 Diabetes Mellitus. The search was conducted through the electronic database Scopus (Elsevier), using the key words: "Irisin", "Human" and "Diabetes Mellitus". From the 91 studies found, 8 met the eligibility criteria. Significant differences were found on levels of irisin in patients with T2DM compared to normoglycemic individuals, obese and/or pre-diabetic. On average, there was a reduction of 15 pg/ml in plasma levels of irisin in diabetics. However, a minority of studies says that this relationship does not exist.

Conclusion: Irisin reduced levels were found in patients with T2DM and is also related to lipid profile, with the risk of developing endocrine diseases, such as diabetes and obesity, and high risk for cardiovascular diseases because of its relationship with endothelial dysfunction. This

generates the need for research in order to explore the isolation and clinical use of irisin for treatment of disorders related to imbalance in energy demand, obesity and diabetes.

Keywords
Irisin; Human; Diabetes Mellitus.

Introduction

Diabetes mellitus is the most common chronic disease characterized by hyperglycemia resulting from defects in insulin secretion and/or activity [1].

Its incidence increases gradually each year. The worldwide prevalence of diabetes among adults was 6.4%, affecting 285 million people in 2010, and is expected to increase to 7.7% (ie, 439 million adults) in 2030 [2]. Obesity, especially visceral is one of the most important factors in the development of diabetes through various mechanisms, including increased circulating free fatty acids, secretion of cytokines by white adipose tissue, which ultimately exacerbates insulin resistance, and decreased adiponectin [3], a derived from white adipose tissue cytokine that has been linked to insulin sensitizing activity and cardiovascular protective properties [4]. The brown adipose tissue acts oxidizing chemical energy to produce heat as a defense against hypothermia and obesity [5], may alter insulin sensitivity [6, 7, 8, 9].

The reduction in physical activity has also been associated with an increase in the development of chronic diseases, including type 2 diabetes mellitus (T2DM) [10]. One possible explanation for this is the secretion of myokine by the muscular system [11]. Contraction of the skeletal muscle secretes a spectrum of bioactive molecules known as 'myokine', coordinating the flow of energy needed to sustain muscle activity and stimulating the adaptive plasticity of muscle and various organs and tissues in response to repeated exercise stimulus [12, 13].

Recently Boström et al. [14] identified the Irisin, an energetic metabolism-related myokine. Its secretion involves the increase of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1 alpha) in the muscle, inducted by exercise, promoting the expression and proteolytic cleavage of Fndc5, a type 1 membrane protein fibronectin type III domain-containing protein 5, with the release of the Irisin fragment for the blood flow [14, 15]. This hormone promotes a browning process on the white adipose tissue, a programming for the thermogenesis in the tissue cells, through the increase of the mitochondrial uncoupling protein 1 (UCP1). The final effect of the hormonal signaling promoted by the Irisin is an increase on the physical energy expenditure, with the reduction of the obesity and improvement on the insulin resistance caused by diet [14].

Some recent studies have shown that the Irisin levels are lower in patients with T2DM when compared to non-diabetics [16, 17] possibly for a deficient expression of PGC1 alpha in the muscle [16]. Therefore, part of the diabetic subjects from the researches used various medications. This discrepancy also has been found on other forms of diabetes, like the type 1 diabetes mellitus (T1DM) [18] and gestational diabetes mellitus (GDM) [19]. Furthermore, increased levels of Irisin are also associated with other metabolic parameters such as BMI, 2 h plasma glucose after OGTT (oral glucose tolerance test), HbA1c and triglycerides [6]. Other studies have related Irisin levels with endothelial dysfunction, assessing the flow-mediated dilatation (FMD) in patients with type 2 diabetes [20, 21], and with betatrophin, a cytosine expressed on the liver and on the adipose tissue that rises the proliferation of the β-cells from the pancreatic islets [22].

Bostrom et al. [14] suggested that the increased levels of irisina resulted in improvement on obesity and on glucose homeostasis and it may be used as a therapeutic protein for human metabolic disease and other disorders that are improved with exercise. The applying of this myokine is hopeful. Sanchis-Gomar et al. [23] referred that we are in front of a endogen peptide that can be cloned through recombining DNA technology such as some modern treatments like insulin, opening the way so irisin may be isolated as a drug on the treatment of metabolic disorders such as diabetes mellitus. Before that, this study is based on the following questioning: Do diabetic patients that have never been treated or without ongoing treatment have reduced levels of plasmatic irisin when compared to non-diabetic individuals? This research was made through a systematic review aiming to answer this question to evidence the irisin action on the energetic metabolism as well as in the physiopathology of the diabetes mellitus, searching the possibility of isolating this hormone to the treatment of metabolic disturbs.

Methods

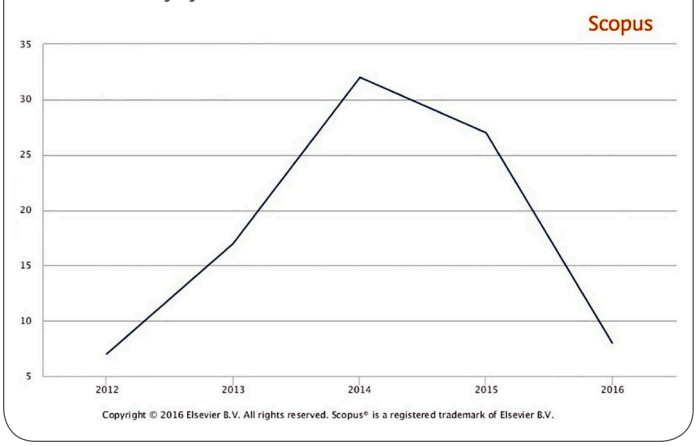
This systematic review has regarded primary studies having as denouement the irisin levels on patients never treated or without treatment on course in the ambience of T2DM. A PICO strategy was formulated to guide the studies selection (Table 1) and, for the search of the articles, the following descriptors indexed on Medical Subject Headings (MeSH) were used: "Irisin, Human" and "Diabetes Mellitus". These were combined through Boolean operator "AND". To know: "Irisin, Human" AND "Diabetes Mellitus". **(Table 1)**

Studies published on the period from 2012 January to 2016 March were included on this article. The temporal cutting is justified by the discovery made for Boström et al. [14] of the hormone irisin in 2012 and the following rise of original publications about the theme **(Figure 1)**, earning therefore relevance on the scientific community.

Table 1. The PICO Strategy.

Population	Subjects with type 2 diabetes mellitus newly diagnosed or with no current treatment and healthy patients or with other metabolic profiles
Intervention	Dosage of irisin levels
Comparison	Comparing the levels of irisin among diabetics and other subjects of the sample
Outcome	Diabetic patients have lower levels of irisin

Figure 1: Evolution on the number of publications by year related to Irisin.

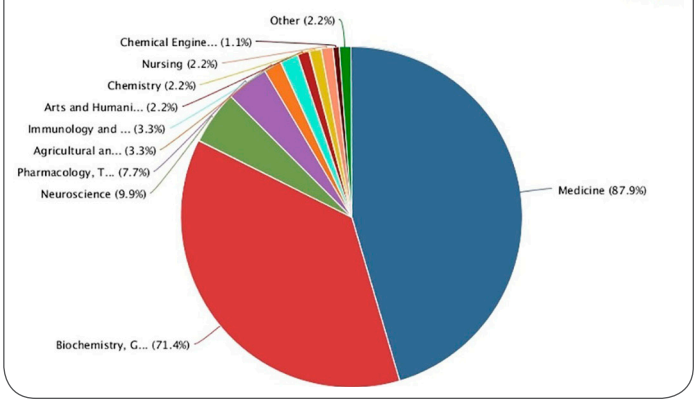


The strategy of sample selection was made through 3 steps: electronic research on database, selection and identification of the eligible articles by applying the inclusion criteria and data extraction from included studies. Original articles on english language, full texts available online and studies that work with adults on its sample were adopted as eligibility criteria. Researches that did not approach the proposed theme, reviews, editorials, letters to the editor, notes, conference articles, brief communications and those related to gestational diabetes were deleted from this work.

Results

91 (N) studies were found using the descriptors **(Figure 2)**. It can be seen a predominance of original studies followed by systematic reviews, showing

Figure 2: Distribution of the publications by type of studies.



the relevance of the theme to the scientific community.

Adding the inclusion and exclusion criteria to the refinement mechanism only 53 articles remained. From these, 19 studies were selected by title and abstract and 8 (n) were elect to compose the sample **(Figure 3)**.

All the studies measured the irisin levels using ELISA kits commercially available. Three studies (Choi et al. [6], Xie et al. [22], Tang et al. [25]) used the criteria defined by the World Health Organization (WHO) to characterize the cases of diabetes mellitus; other three (Sanchis Gomar et al. [26], Wang et al. [20], Zhang et al. [27] used the American Diabetes Association criteria, and two of them (Kurdiova et al. [12], Xiang et al. [21]) did not explain the chosen parameters.

Seven studies (Choi et al. [6], Kurdiova et al. [12], Wang et al. [20], Xiang et al. [21], Xie et al. [22], Tang et al. [25], Zhang et al. [27]) included on its sample only patients newly diagnosed and just Sanchis Gomar et al. [26] applied as selection criteria the absence of current treatment like insulin and/or statins to compose the sample. The main results found on the review are listed on the **(Table 2)**.

Figure 1: Flowchart of the selected studies (adapted from the PRISMA protocol [24]).

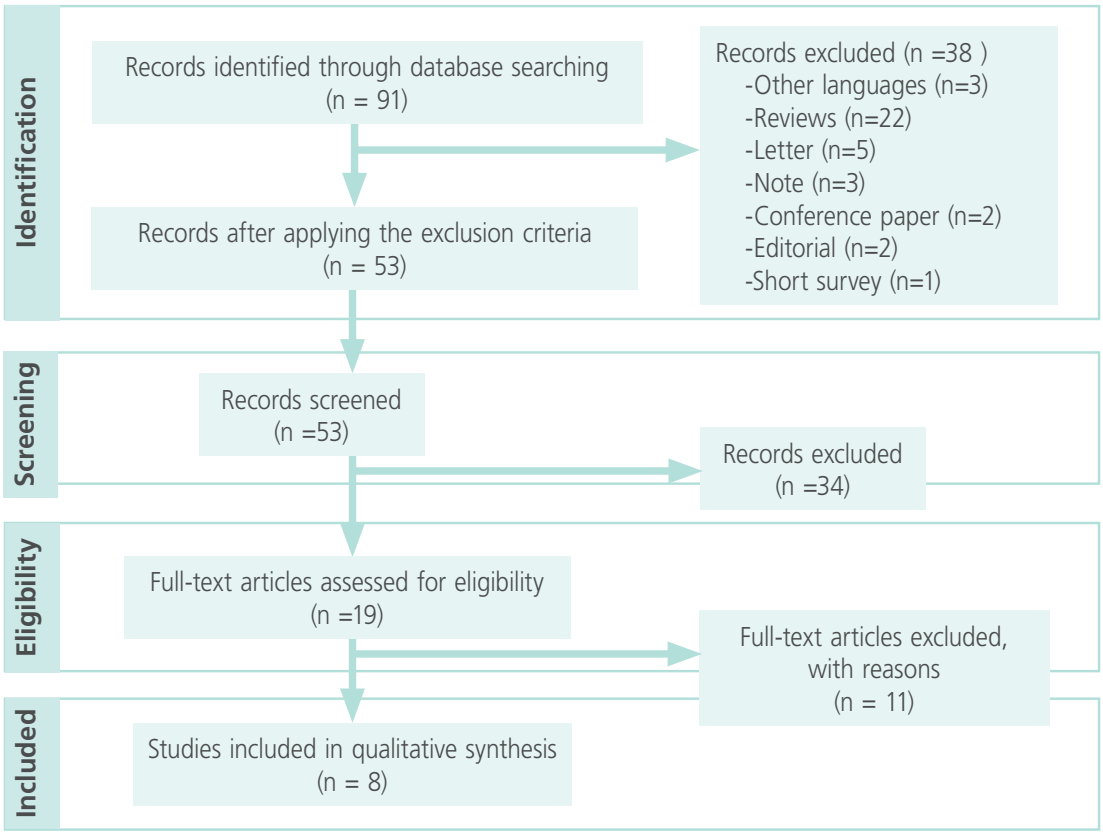


Table 2. Studies and main findings.

Authors	Year	Title	Journal	Sample	Main Findings
Chun Zhang [27]	2016	Lower irisin level in patients with type 2 diabetes mellitus: A case-control study and meta-analysis.	Journal of Diabetes	50 healthy and 50 newly diagnosed T2DM subjects.	Irisin levels in patients with newly diagnosed T2DM were significantly lower than in the matched healthy controls.
Xie [22]	2015	Associations of betatrophin levels with irisin in Chinese women with normal glucose tolerance	Diabetology & Metabolic Syndrome	50 newly diagnosed T2DM and 50 with normal glucose tolerance (NGT).	There were no significant differences in irisin levels between the NGT and T2DM groups.
Shanshan Tang [25]	2015	Circulating irisin levels are associated with lipid and uric acid metabolism in a Chinese population	Clinical and Experimental Pharmacology and Physiology	72 newly diagnosed T2DM subjects, 63 with impaired fasting glucose and 68 healthy controls.	There were no significant differences in circulating irisin levels among the three groups.
Hao-hua Wang [20]	2015	Relationship between serum irisin levels and urinary albumin excretion in patients with type 2 diabetes	Journal of Diabetes and Its Complications	100 newly diagnosed with T2DM and 100 healthy controls.	Serum irisin levels in patients with type 2 diabetes were significantly lower compared to control subjects.
Lin Xiang [21]	2014	Circulating irisin levels are positively associated with endothelium dependent vasodilation in newly diagnosed type 2 diabetic patients without clinical angiopathy	Atherosclerosis	188 newly diagnosed T2DM patients and 40 healthy controls.	Irisin levels were significantly lower in diabetic patients.
Timea Kurdiova [12]	2014	Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: in vivo and in vitro studies.	Journal of Physiology	29 healthy subjects, 29 patients with overweight/obesity, 25 pre-diabetic and 16 with T2DM.	Circulating levels of irisina were reduced almost 40% in subjects with T2DM.
Sanchis-Gomar [26]	2014	Circulating irisin levels are not correlated with BMI, age, and other biological parameters in obese and diabetic patients.	Endocrine	153 subjects divided into 64 T2DM, 69 Patients morbid obese (BMI>40) and 20 control subjects.	There were no significant differences in irisin levels when comparing the morbid obese groups and individuals T2DM with control subjects.
Choi [6]	2013	Serum irisin levels in new-onset type 2 diabetes.	Diabetes research and clinical practice	104 subjects with NGT and 104 with new-onset T2DM.	Serum irisin levels were significantly decreased in the new-onset T2DM group compared with the NGT control group.

Discussion

Irisin levels on patients with T2DM and additional findings

Five studies [6, 12, 20, 21, 27] of this review showed reduced levels of irisin on patients with T2DM. Other three researches [22, 25, 26] did not evidence significant differences between diabetic patients and control groups.

Choi et al. [6] found an inverse correlation between the irisin and the development of T2DM and, according to these authors, it characterizes the irisin as an independent marker to the newly diagnosed DM. The results also suggest that the dysfunction on the hormonal signaling of the irisin may be involved on the onset of the disease. As well as on that study, Kurdiova et al. [12] also found reduced levels of irisin on diabetics and the-

se values remained virtually unchanged both in the state of euglycemic hyperinsulinemia and fasting, being inferred that insulin has no effect on the levels of irisin in vivo.

Comparing diabetics and patients with impaired glucose tolerance (prediabetics), Kurdiova et al. [12] found lower levels on diabetics. These results were not supported by Tang et al. [25] research which did not notice any significant differences between these groups.

Sanchis-Gomar et al. [26] divided the group of diabetics of the study on subgroups of obese and non-obese, based on BMI, and they did not find out differences on irisin levels by comparing diabetics and controls and neither between the diabetic subgroups. In addition, Xie et al. [22] did not find differences between diabetics when comparing gender subgroups.

Zhang et al. [27] aimed on their study to stablish a confidence interval of the irisin levels on patients with T2DM, using a case-control study and a meta-analysis. In the case-control study, the irisin concentrations were lower on newly-diagnosed diabetic patients when compared to healthy controls. In the meta-analysis, the obtained data indicated that the concentrations were lower on patients with T2DM then on the healthy controls (irisin 24,46 ng/mL (95% confidence interval [CI] of 9,31, 39,60; P = 0,002).

Beyond the findings about the serum irisin, the Kurdiova et al. [12] work assessed the in vivo and in vitro expression of the Fndc5 gene in the skeletal muscle of his sample, finding divergent results between both assessment methods, with higher levels on the group of diabetics only in vitro. On behalf of that, it was simulated a diabetic hyperglycemic state in the cultivated myocytes to the in vitro study, evidencing decrease of Fndc5 levels. The authors suggested that the irisin secretion was probably regulated by endogen factors related to DM.

Irisin and the mycrocirculation on diabetics

Xiang et al. [21] concluded that the irisin levels are associated to endothelial dysfunction and could to be a marker for precocious detection of the angiopathy phase in the T2DM after finding a significant positive correlation between the irisin levels and arterial dilatation dependent of the endothelium in a sample of individuals without clinical angiopathy and systemic arterial hypertension. This association was also found in a posterior study of Wang et al. [20], being added to this finding a decrease of urinary excretion of albumin between the diabetics according to the plasmatic irisin levels, with serum values of this hormone significantly lower in diabetic groups with macro and microalbuminuria. Given that, it is believed that the irisin may play a role over the pathophysiological process of albuminuria on diabetics, by a direct or indirect effect about the endothelial dysfunction presented by the patients.

Furthermore, other studies not included on this review also assessed the relation between irisin and kidney function, showing that markers like glomerular filtration rate (GFR) are independently associated with the irisin levels [16, 18].

Irisin levels on patients with T1DM and Gestational Diabetes

Our review limited itself by assessing the irisin levels on studies that approached patients with T2DM without current treatment, but other studies [18, 19] analyzed the dosage of this hormone and its relation with other diabetes types. Espes et al. [18] decided to characterize the irisin levels on T1DM carriers. They presented rise values of the hormone, especially the women, diverging with some studies already presented that find lower plasmatic levels of irisin in individuals with T2DM [16, 28]. Also it was evidenced negative correlations between irisin levels and age presented at the onset of the T1DM [18]. Studying women with gestational diabetes, they found lower levels when compared to healthy

pregnants [15, 29, 30]. Ebert et al. [19] also found in their study, irisin levels significantly higher in patients with gestational diabetes mellitus in comparison to postpartum controls.

Irisin and its relation with other metabolic parameters

Countless metabolic parameters were assessed in patients with T2DM, as well as their relation to irisin levels. Choi et al. [6] assessed the relation between this hormone and the adiponectin, a cytocin that has demonstrated sensitizing activity to insulin and protective cardiovascular properties, evidencing that the adiponectin and the irisin have a significantly inverse association to type 2 diabetes mellitus (T2DM). Sanchis-gomar et al. [26] did not find significant correlation between irisin and BMI, while Choi et al. [6] showed a negative association between these parameters. Additionally, 2 hours serum glucose after OGTT, HbA1c and triglycerides also showed negative correlation in this study. Sanchis-gomar et al. [26] also observed other inverse correlations with HbA1c.

Xie et al. [22] searched the relation between betatrophin and irsin on half-age chinese with normal glucose tolerance (NGT) and T2DM. It was demonstrated that plasmatic betatrophin levels were significantly higher on newly-diagnosed with T2DM then in the individuals with NGT. Other studies also found that same association [18, 31]. Tang et al. [25] observed that plasmatic irisin was significantly associated with the total cholesterol, LDL-c and uric acid in a chinese population. This finding was supported by Wang et al. [20] that also found a tendency to the LDL-c levels decrease with the rise of irisin levels on diabetics.

Limitations of the studies

The analyzed studies on this review made clear the limitations found during their researches, except Zhang et al. [27]. A common limitation to all the articles was the reduced size of the samples. Xiang et al. [21] bring like one of the limitations the fact that they did not regard the relation of cause and effect in the pathology of angiopathy in the T2DM [21]. Choi et al. [6] and Kurdiova et al. [12] considered the transversal drawing of the studies as being one of the limiting factors of the research for not allowing the analysis of changes in the assessed parameters. Xie et al. [22] considered the absence of data after oral glucose tolerance test the final limitation of his study, given financial constraints. Wang et al. [20] bring still like limiting factor the inability to investigate other features that can to influence the irisin secretion, like physical activity.

Conclusion

Type 2 diabetes mellitus carriers without current treatment or never treated have reduced irisin levels when compared to non diabetic individuals in the most part of the studies [6, 12, 20, 21, 27] in contrast to those who did not show this relation [22, 25, 26].

The irisin seems to act beyond the energetic metabolism, like in the improvement of cognitive function for the rise of FNDC5 expression in the brain induced by the exercise [32], showing itself as a finding of big importance to the scientific community, contributing in a positive way to the working of the human organism. Beyond the relation to the lipid profile and the risk of developing endocrine pathologies like diabetes and obesity, reduced levels of this hormone are also associated to high cardiovascular risk for its direct or indirect relation with the endothelial dysfunction. It brings the hypothesis that the irisin may be used as a marker of atherosclerosis, given that the genesis of this disease is related to the vascular changes provided by the endothelial dysfunction, but there is need of future studies that confirm or not this hypothesis.

Despite the existent discrepancies between some studies and the controversies about the real role

of the irisin, the improvement in the sensibility to insulin induced for PGC1 alpha muscular make the possibility of clinical exploration of this hormone in the treatment of T2DM and other energetic metabolism-related diseases that get better with exercise [14], given that it is about a endogen peptide that can to be cloned through recombining DNA technology, like some current modern treatment as insulin [23].

Therefore, it has been questioned the possible therapeutic action of this hormone in the treatment of these pathologies for its effect already known to stimulate the thermogenesis in the adipocytes promoting the browning of the white adipose tissue that improves the metabolic profile and increases the body energy expenditure. The isolating and formulation of drugs based on irisin would be especially interesting for patients that, because of some physical limitation, cannot make activities regularly, contributing to the prevention and treatment of metabolic disorders. Studies that explore this possibility of therapeutic action may represent big advances for treating these pathologies.

There is still need for more researches about this hormone, mainly because the existent divergences between the studies, that involved heterogenic populations and with samples in numbers and different proportions between them. A future meta-analysis involving researches with populations in more similar proportions and studies about the influence of pharmacological therapy for diabetes over the irisin secretion will contribute to elucidate the pathophysiological mechanisms present in the disorder.

Conflict of interest

The authors do not have any conflicts of interest to report.

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