ISSN 2449-8955 European Journal of Biological Research *Review Article*

DOI: http://dx.doi.org/10.5281/zenodo.3385065

Irisin - evidence for benefits resulting from physical activity

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Received: 22 June 2019; **Revised submission:** 16 August 2019; **Accepted:** 01 September 2019

http://www.journals.tmkarpinski.com/index.php/ejbr

ABSTRACT: Irisin is a myokine with wide metabolic action, which makes it very similar to a hormone. Its serum level depends on the expression of the genes FNDC5 and PGC-1α which, in turn, are induced, among others, by physical activity, especially aerobic exercises. According to many studies, aerobic training lasting for 45-60 minutes significantly increased the level of irisin in blood or muscles, and was considerably more effective than endurance training. Irisin shows protective properties against type 2 diabetes by decreasing insulin-resistance and against atherosclerosis by the improvement of lipid profile and anti-inflammatory action. It helps patients with overweight and obesity struggle with an excess of adipose tissue, and induces the conversion of white adipose tissue to brown. It also improves metabolic profile by the acceleration of metabolism and increase in thermogenesis. This myokine reduces the risk of occurrence of metabolic syndrome. Also, the neuroprotective effect of irisin has been confirmed, which would indicate a tremendous role of physical effort in slowing down the course of neurodegenerative diseases in seniors. In addition, irisin acts through many signal pathways exerting an anti-inflammatory, anti-oxidative, anti-apoptotic and anti-cancer effects, which is a potential therapeutic goal. Unfortunately, further studies concerning irisin are still needed before it can be clinically used. However, already now it may be the tool for psychologists working with persons suffering from overweight, obesity, diabetes, atherosclerosis, metabolic syndrome, neurodegenerative diseases, and many other disorders to motivate them for regular physical effort.

Keywords: Exercise; Metabolic syndrome; Diabetes type 2; Atherosclerosis.

1. INTRODUCTION

Physical fitness has always been considered as beneficial for the whole human organism - mind and body - the best example of which is in ancient culture; although since that time our knowledge has been considerably expanded, there is still a lack of a link which would directly combine physical effort with its supposed benefits. Many studies have shown a positive effect of physical effort on various aspects of the functioning of the organism; nevertheless, it was as late as in January 2012 when the specific gene was identified - FNDC5, regulated by PGC-1α and other undetermined kinases, and myokinase - irisin secreted under the influence of its activation [1]. A year later, physical activity was connected with PGC-1α, at the same time, adopting a sceptical approach to the possibility of the sole training exerting a direct effect on the

expression of FNDC5 [2]. In turn, the 2015 studies demonstrate that AMPK protein is also indispensable for normal FNDC5 expression, and thus to the production of irisin [3]. Knowing the specific causative agent, it was possible to investigate its effect on the functioning of individual systems of the human body, and also try to combine its levels and activity with particular clinical conditions. The presented study focuses primarily on the physiological effect of irisin related with changes in energy metabolism, and such clinical conditions as metabolic syndrome and its components, omitting the studies on the use of this myokine as a marker in the diagnostics of diseases such as hyperthyroidism and hypothyroidism. For in the effect of irisin on metabolism is sought a medicine for obesity and neurodegenerative changes in the central nervous system (CNS) taking place in elderly persons [4].

2. INCREASE IN SERUM IRISIN LEVEL UNDER THE EFFECT OF PHYSICAL EFFORT

The study conducted by Algul et al. [5] was aimed at assessment of changes in the serum levels of leptin, nesfatin-1 and irisin occurring after aerobic exercises. The results obtained by trained and untrained males were compared, and the trainings consisted in a 30 minute run with the achievement of individual maximum heart rate by each man in both groups. From among the examined proteins, only the results obtained for irisin were unequivocal. In both groups of males a statistically significant increase in the serum irisin level was observed, compared to the level from before the exercises [5]. Therefore, this study demonstrates that the level of irisin in the body increases after an intensive effort in both trained and untrained persons. This is of a great importance if we additionally assume that an untrained person is overweight or obese, because an increase in irisin level in these persons may in a special way illustrate its beneficial effect on the human body.

A subsequent study examined whether irisin is related with metabolic changes taking place in obese individuals, by comparing two types of exercises - aerobic and endurance. For endurance exercises consisting in the maintenance of heart rate on the level of maximum 60-65% for 45 minutes, no statistically significant results concerning changes in the levels of irisin were obtained. For aerobic exercises, also lasting for 45 minutes, but with a higher intensity of training, a considerable increase in irisin levels was observed under the effect of exercises, obtaining even a several-dozen increase in its concentration. Nevertheless, it is an important fact that an increase in the level of irisin statistically significantly correlated with the Matsuda index, used for the determination of insulin sensitivity [6]. This study confirms that aerobic trainings may effectively counteract insulin-resistance, which is especially important for persons exposed or suffering from type 2 diabetes, very often including obese individuals.

Similar protective effects and probable increase in insulin sensitivity consisting in a decrease in glucose level, glycated haemoglobin (marker of diabetes), and insulin were observed in pregnant women. Young pregnant women, at approximately week 20 of pregnancy, performed a fitness programme for 8 weeks. After this period, the women who performed the programme at least 3 times a week on an appropriate intensive level determined by the researchers, a significant increase in serum irisin level was observed. Statistical analysis confirmed that the detected increase in the level of the examined myokine was closely related with the above-described changes in glucose metabolism [7]. The above-presented experiment shows that physical activity, e.g. riding a bicycle may, during pregnancy, become a cure for gestational diabetes or type 2 diabetes developing at that time, supplementing the therapeutic effect of a proper diet.

A specific form of aerobic training is the so-called High Intensity Interval Training (HIIT), which was compared with the classic form of aerobic exercises in the study conducted by Archundia-Herrera et al. [8] The first group of young overweight or obese women was given the task of maintaining their heart rate for 40

minutes on the level of 65% maximum (conditions close to endurance training described in the study by Blizzard LeBlanc et al. [6]), while the second group, in accordance with the HIIT principles, performed exercises in 6 rounds, consisting of effort lasting for one minute with heart rate on the level of 85-95% individual maximum, and a one minute break. The results of laboratory tests showed a statistically significant, considerable increase in irisin in muscles in the group exercising in accordance with HIIT, and a slight increase, which did not achieve statistical significance, in the group performing endurance exercises. This study failed to demonstrate an increase in serum irisin level under the effect of the exercises performed [8]. The study shows that a long-lasting training is not required in order to achieve an increase in irisin level in muscles, and it may be successfully replaced by an interval training lasting for several minutes. However, it is not known whether in this way it is possible to induce an increase in irisin level also in blood serum, which seems to be of a key importance for systemic changes in metabolism.

Also, population studies conducted in a very large group confirm the relationship between physical effort and an increase in serum irisin level. Buscemi et al. demonstrated that this level was higher in females than males, and also an increase in irisin level correlated with an increase in the level of HDL cholesterol [9].

Conclusions similar to those described above were drawn by Fatouros [10], who indicated that an intensive speed or strength training results in an increase in irisin in serum, under the condition that exercises have been sufficiently burdening and long-lasting. However, the researcher failed to select any sports discipline which would unequivocally satisfy the above-mentioned criteria. Nevertheless, Fatouros emphasizes that the analyzed data should be considered with a great caution, remembering that animal models do not ideally translate onto the model of the human organism, which may result in drawing incorrect conclusions concerning the physiology of irisin in the human body. Moreover, it should be kept in mind that the results of studies may also differ according to age of the examined persons and their being trained [10]. The difference frequently emphasized in studies is the constantly maintained level of irisin in mice with a regular, long-lasting training, whereas in humans an increase in the serum irisin level was observed in only short-term observations [11]. The to-date lack of the confirmation of a permanent increase in the level of myokine examined in humans regularly practicing sports considerably hinders a comprehensive investigation of its effect on the human body and, therefore, some researchers sceptically approach the effects ascribed to irisin based on studies on animal models.

3. PROTECTIVE AND REGULATORY FUNCTIONS OF IRISIN

A comprehensive analysis showed that irisin has relatively many systemic effects, and acts as a hormone, making muscles an endocrine organ. The effects of irisin include the reconstruction of the adipose tissue with activation of the precursor cells, resulting in the formation of brown adipose tissue and an increase in thermogenesis and total energy expenditure of the body [1, 12, 13]. The study conducted by Pérez-Sotelo et al. indicates that in obese individuals there occurs an attenuation of the FNDC5 gene, and a decreased PGC-1α and UCP1 activity, these changes resulting in the differentiation of adipocytes to the type FNDC5-KO with reduced thermogenesis and an increased adipose tissue deposition [13]. This study demonstrates the importance of a proper irisin level for the normal functioning of adipose tissue, and just how dangerous a reduction in its level may be. The latter change may lead to overweight and obesity, and may be related with metabolic syndrome, which has been described in a later part of the article.

In addition, irisin is ascribed an anti-inflammatory, antioxidative, antiapoptitic effect (with respect to the cells damaged by the inflammatory process), and proapoptotic effect (with respect to cancer cells), due to which its potential therapeutic use is indicated in the treatment of obesity, type 2 diabetes, nonalcoholic

steatohepatitis, cardiovascular diseases, as well as in the inhibition of processes damaging the lungs, nervous system, thyroid gland, and colon, taking its course accompanied by an inflammatory process [14]. Capabilities of irisin for the regulation of many metabolic pathways are due to such a wide action, comparable to hormone action. Its anti-inflammatory effect is expressed, among other things, by a decrease in the levels of: NF-κB, TNF-α, IL-6, and MCP-1, p-38, COX-2, PRMT3, ICAM-1, VCAM-1, Ox-LDL, as well as due to the change in macrophage phenotype from M1 (pro-inflammatory) into M2 (anti-inflammatory), decrease in T lymphocytes (CD3+) and macrophages (CD68+) recruitment in the atherosclerotic plaque, and protection of endothelial integrity via changes in their metabolism. Antioxidative properties may be related with a decrease in levels/activity of such particles as: iNOS, gp91 phox, PKC-β/NADPH oxidase, PRMT3, MDA, nitrotyrosine; the role of irisin in the decomposition of free radicals, and an increase in the activity of GPX-1, CAT and SOD. Antiapoptotic action results from the capabilities of irisin to reduce the activity of: caspases 3 and 9, BAX, annexin V and the stimulation of the activity of: Bcl-2, Bcl-xl, Bad, GSK-3β, eNOS, AMPKα, ERK1/2 (phophorylation in insulin-resistant hepatocytes and dephosphorylation in the ischemic heart muscle) and phosphorylated p38 [15]. Due to its ability to inhibit the ROS-NLPR3 pathway, irisin alleviates an already developed inflammatory condition, and exerts a protective effect on the vascular endothelium, stimulating is capability for synthesis of nitric oxide, which may be of importance in the treatment of atherosclerosis and arterial hypertension [16]. Epithelium-dependent vasodilatory effect induced by irisin is also related with TRPV4 protein. This is a subsequent metabolic pathway through which irisin protects endothelium and dilates blood vessels [17]. The above-mentioned mechanisms of antioxidative action are also of utmost importance in the case of ischemia and reperfusion in the lung tissue. In this situation, irisin interacts with the mitochondrial protein - UCP2, maintaining the function of the mitochondria and protecting these organelles against oxidative stress. It is interesting that in the case of the above-described lung damage, irisin level decreases in serum, while it increases in the pulmonary alveoli and the bronchial tree, which indicates its active transport to the destination site, and may partially explain the above-described difficulties in the unequivocal determination of the character of changes in serum irisin level in relation with physical activity [18].

4. IRISIN AS A POTENTIAL MEDICINE CONTROLLING OBESITY AND TYPE 2 DIABETES

In the light of the data according to which the number of overweight or obese children and adults constantly increases, it becomes extremely important to impress upon the consciousness of society the positive aspects of enhanced physical activity which, apart from an appropriate diet, is the basis for the struggle with an excess of adipose tissue [19]. Statistical data show that in Poland 62.8% of adult males and 54.7% of females are overweight, while obesity concerns 23.8% and 26.7%, respectively [20].

Thus, the role of irisin in counteracting obesity and type 2 diabetes through the enhancement of energy metabolism and reduction of insulin dependence deserves special mention. Obese individuals in whom a higher activity of the FNDC5 gene and higher serum irisin level are observed, are characterized by a better metabolic profile. Bonfante et al. [21], in their study found that the irisin level significantly correlated with sensitivity to insulin expressed by the HOMA-S and QUICKI indices, and lower values of the levels of insulin, triglycerides, insulin-resistance expressed by HOMA-IR. Also, the above-mentioned team of researchers confirmed that a high serum level of irisin is related with a decreased risk of the occurrence of type 2 diabetes, better lipid profile, and lower LDL cholesterol in these patients [21, 22]. Changes in the lipid profile described by Bonfante et al. undoubtedly exert a beneficial effect on the treatment of cardiovascular diseases, including atherosclerosis, in which a high level of LDL cholesterol is one of the risk factors.

Studies conducted by Shim et al. [23] allowed the development of a method of diagnostics of the

metabolic syndrome in children at prepuberty age suffering from overweight or obesity, based on the level of irisin. In children with the level of irisin below 15.43 ng/ml, metabolic syndrome was diagnosed with a sensitivity of 75% and specificity of 94%. Thus, a decreased level of irisin is associated with the systemic disorder of energy metabolism, and consequently very often with obesity [23]. Further studies would probably allow an artificial increase in the level of irisin in persons afflicted with obesity and metabolic syndrome, increasing the chances of recovery. The sole increase in physical activity may extremely positively affect organisms of these persons if an enhancement of FNDC5 expression and increase in the level of the examined myokine can be successfully achieved. Such an action should also protect these patients against the development of type 2 diabetes, very often related with metabolic syndrome and obesity [24].

One more effect of irisin on the life of persons suffering from overweight and obesity should be emphasized. It is a direct evidence for the improvement of the quality of life and overall health through physical effort, connecting it directly with the outcomes of exercises. Due to the motivation resulting from the possibility to achieve specific goals, providing effects possible to predict with a high probability, irisin is not only the key connecting physical activity with its long-known advantages, but is a powerful weapon for psychologists working with overweight and obese patients [25].

5. PROTECTIVE EFFECT OF IRISIN ON THE CARDIOVASCULAR SYSTEM

Many effects which have been already discussed in this article contribute to the protective action within the cardiovascular system, such as: protection of the endothelium and vasodilatory effect [15-17], decrease in the level of LDL cholesterol and elevation of HDL cholesterol, decrease in the level of triglycerides [9, 21], anti-inflammatory effect slowing down the development of atherosclerosis [15, 16], as well as prevention of the occurrence of obesity, metabolic syndrome, and type 2 diabetes [6, 7, 14, 21, 23, 24].

Another action of irisin which has not yet been discussed is its cardioprotective effect expressed by its ability to penetrate the blood-brain barrier, allowing an interaction with the nucleus ambiguus which, via the vagus nerve, slows down the heart rate [26]. Thus, its action may occur to be extremely beneficial in patients with heart failure. Moreover, it would seem that irisin is responsible for the known effect of the lower resting heart rate in sportsmen.

The subsequent study discusses again the effect of the reduced irisin level compared with normal, this time related with coronary heart disease. This study confirmed that in patients suffering from coronary heart disease the level of irisin is considerably lower than in healthy individuals. Therefore, this is another example where irisin could show its therapeutic effect as a medicine reducing also the risk of coronary heart disease, and consequently, minimizing the risk of myocardial infarction, or a diagnostic effect indicating, sufficiently in advance, an increased risk of the development of coronary disease [27].

6. PROTECTIVE EFFECT ON THE NERVOUS SYSTEM

In their study, Tanhaei et al. [28] showed that physical effort, through the miRNA encoded signal, stimulates an increase in the expression of the FNDC5 gene and expression of irisin. Also, the researchers pointed to irisin as a protein necessary for the normal function and differentiation of neurons [28]. Therefore, it may be concluded that physical effort, through elevation of the irisin level also in the brain would ensure an efficient function of neurons, whereas the lack of proper physical activity would lead, especially in older individuals - most susceptible to such changes - to a gradual degeneration and loss of function of the CNS neurons [12].

The above-mentioned action is confirmed by specific cases. Gmiat et al. [29] observed changes in cognitive abilities taking place under the effect of daily physical activity in the form of Nordic walking in

elderly women. After 12 weeks of trainings, a significant improvement was obtained in the results concerning cognitive abilities among the examined women. A statistically significant increase in the level of irisin and BDNF (brain-derived neurotrophic factor) was also observed, supposed to be directly related with the progress achieved, as well as a decrease in the level of glucose and tryptophan in blood, which could also contribute to these changes [29].

In another study conducted by Kim et al., [30] elderly women participated in aerobic training in a pool. After 16 weeks of exercises, a considerable increase was observed in the levels of irisin and BDNF [30]. Thus, both these studies indicate that even at an advanced age one cannot forget about physical activity because, especially during this period of life, it is of great importance in the protection of neurons against degenerative processes. Therefore, physical activity should be promoted among seniors.

A study in a large group of patients with ischemic stroke also indicated a neuroprotective effect of irisin. In patients with a low level of irisin, a risk of negative functional effects increased by 94% was observed, and by 66% higher risk of death, compared to patients with a normal irisin level [31]. Determination of the serum irisin level in patients with ischemic stroke could potentially gain a prognostic importance. In addition, appropriately frequent and intensive physical activity, through the secretion of irisin, should reduce the risk of severe complications and death due to ischemic stroke.

7. CONCLUSION

An analysis of the latest scientific literature indicates that an intensive, regular and properly long-lasting physical activity, and optimally aerobic training, with the achievement of possibly the highest individual heart rate, significantly increase serum and muscle levels of recently discovered myokine - irisin. Muscle irisin level was also considerably elevated by the interval training (HIIT); however, it could not be discovered how it affects the serum levels. The described effect of physical exercises was observed in patients of different gender and age. An increased FNDC5 and PGC-1α expression is responsible for the enhanced secretion of irisin.

Irisin shows a considerable regulatory activity in human metabolism, which allows its comparison with a hormone. Its increased level was related with anti-inflammatory, antioxidative, antiapoptotic, and anti-cancer effects. While acting through many various pathways, irisin exerts a protective effect, among others, on the cardiovascular, nervous, and respiratory systems, and also counteracts obesity, type 2 diabetes and metabolic syndrome. This constitutes a direct evidence for the advantageous effect of physical effort on the human body, and provides an argument for psychologists motivating people with an excessive body weight to undertake physical effort.

Taking into account the considerable benefits which result from a full understanding of irisin action and its potential therapeutic and diagnostic uses, i.e. a chance to obtain an effective weapon with the most common civilisation diseases of the 21st century - atherosclerosis, coronary disease, metabolic syndrome, obesity, type 2 diabetes, and neurodegenerative diseases, it appears evident that there is a need for its further studies.

Conflict of Interest: The author declares no conflict of interest.

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