**The multitude of irisin’s essence in the body**

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**ABSTRACT**

Irisin is a novel peptide, discovered by Bostrom et al in 2012. It is a fragment of a cell membrane protein called ﬁbronectin type III domain-containing protein 5 (FNDC5). It is so named to highlight its role as a messenger, produced mainly from skeletal muscle and adipose tissue and acts on various parts of the body. This peptide is of major interest because of its therapeutic potential in various diseases. Some important aspects of the action and uses of irisin are discussed here, including its relation with the various physiological and pathological conditions of the body. Although upcoming and current research on irisin seems promising, further elaborate exploration is necessary to elucidate its full potential as a reliable therapeutic agent in treatment and prevention of many diseases.

**Keywords –** irisin; myokine; adipokine; exercise; diabetes

**I. INTRODUCTION**

Irisin is an adipomyokine, discovered by Boström and his colleagues in 2012. It is a fragment of a cell membrane protein called ﬁbronectin type III domain-containing protein 5 (FNDC5), composed of 209 amino acids (aa) residues. It contains an N-terminal signal sequence consisting of 29 aa, a fibronectin type III domain with 94 aa, an unidentified region consisting of 28 aa, a transmembrane domain having 19 aa, and a C-terminal part with 39 aa. The C-terminal fragment of FNDC5 is located in the cytoplasm, while the extracellular N-terminal portion is proteolytically cleaved to produce irisin which is ultimately released into the circulation.

Irisin reduces obesity and improves insulin resistance by the browning of white adipose tissues. It is expressed and secreted in response to exercise, providing a hormonal link between exercise and improved insulin sensitivity. Irisin is secreted mainly by skeletal muscles as well as subcutaneous and adipose tissues. Studies showed that traces of irisin are also produced by testes, liver, pancreas, brain, spleen, heart, and stomach. It usually serves to mediate interactions with other molecules (proteins, DNA, etc.) or cells. Hence, its name is derived from the Greek messenger goddess “Iris” like whom it serves as a powerful messenger for specific cells.The process of secreting circulating irisin is induced by the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). It has been reported to act on white adipose cells in vitro and in vivo to stimulate uncoupling protein 1 (UCP1) expression and to alter expression of several molecules leading to brown fat-like development. This conversion of white adipocytes to brown adipocytes and the resultant increase in thermogenesis promotes improved insulin sensitivity, reductions in body weight and improved glucose tolerance in mice.

It is said that Irisin, by the expression of β-trophin, promotes pancreatic β-cell proliferation and improves glucose tolerance.Therefore, irisin was speculated to promote insulin secretion by increasing the proliferation or reducing the apoptosis of β-cells. However, further studies are needed to clarify the molecular mechanisms underlying the correlation of irisin with β-cell function and its role in insulin secretion in normal glucose tolerance.Many studies have revealed that irisin improves insulin resistance and type 2 diabetes by increasing sensitization of the insulin receptor in skeletal muscle and heart, transforming white adipose tissue to brown adipose tissue, improving hepatic glucose and lipid metabolism and pancreatic β cell functions.Therefore, irisin poses as a potential new target to combat type 2 diabetes mellitus (T2DM) and insulin resistance.It was referred that irisin could be cloned through recombinant DNA technology, so that it might be isolated as a drug in the treatment of diabetes mellitus.

In healthy individuals,irisin levels were found to be lower in males than females after adjustment for lean body mass. The levels followed a day-night pattern with peak at 9 pm and increased after exercise. Irisin levels were not affected by the intake of a standardised meal and were not associated with caloric intake of diet quality. Studies indicated that girls had higher circulating irisin levels than boys and that irisin levels were independently associated with fasting blood glucose. Another study found that there was a statistically significant decrease in irisin levels in diabetic patients compared to controls and the levels were lower in patients with diabetic nephropathy (DN) than in those without complications. There was also statistically significant negative correlation between irisin and serum creatinine, systolic blood pressure, diastolic blood pressure, duration of diabetes, BMI, albumin/creatinine ratio, and HbA1c (glycated haemoglobin) in all type 2 diabetic patients.

**II. ASSOCIATION OF IRISIN WITH VARIOUS PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Physiological Conditions** | | **Pathological Conditions** | |
| **Condition** | **Relation with irisin** | **Condition** | **Relation with irisin** |
| Exercise | Increases irisin secretion | Type 1 Diabetes Mellitus (T1DM) | Increases irisin concentration |
| Gender | Lower concentration in men | Type 2 Diabetes Mellitus (T2DM) & Gestational Diabetes Mellitus | Decreases irisin concentration |
| Body Mass Index (BMI) | Positive correlation | Metabolic syndrome | Increased level |
| Pregnancy | Higher levels in pregnancy | Cancer | Lower levels of irisin |

**III. ASSOCIATION OF IRISIN WITH VARIOUS SYSTEMS OF THE BODY**

|  |  |  |  |
| --- | --- | --- | --- |
| **Cardiovascular system** | | | |
| **Condition** | **Relation with irisin** | **Condition** | **Relation with irisin** |
| Vascular Endothelium | Increases Proliferation | Coronary Artery Diseases | Predicts adverse coronary events |
| Angiogenesis | Proangiogenic Effect | Vascular Diseases | Therapy & Prevention |
| **Bone Metabolism** | | | |
| Bone formation | Osteoblastogenic effects | Osteoporosis & Osteopenia | Therapeutic effect |
| **Brain/Central Nervous System** | | | |
| Neurogenesis | Enhances | Neurodegenerative disorders | Therapeutic potential |

**A. Irisin in Exercise**

During muscle contraction, myokines are secreted that can possibly protect against chronic diseases.Studies have reported that there is a correlation between aerobic activities and the expression of FNDC5 and PGC-1α genes. This results in the secretion of the myokine irisin by muscles and adipocytes in response to exercise, which converts white adipocytes to brown adipocytes. This conversion of white adipocytes to brown adipocytes and the resultant increase in thermogenesis promotes improved insulin sensitivity, improved glucose tolerance and reductions in body weight.

**B. Irisin and gender**

The gender differences might be explained by the differences in the distribution of fat (white and brown) in males and females. Another plausible explanation may be the hormonal differences in males and females. Estradiol, a primary female sex hormone, has been shown to be positively correlated with circulating irisin levels, while there was no significant relationship with free testosterone levels.

**C. Irisin with BMI**

Positive association of irisin with BMI was reported in various studies which could be explained partly by the muscle mass and percentage of fat mass. This could support the theory of a possible resistance to irisin in case of obesity. However, both positive and negative correlations with BMI and WHR have been reported, depending on the studied population.

**D. Irisin in pregnancy**

Serum irisin levels are found to be higher in normal pregnancy. Studies have suggested that the placenta and pregnant states may contribute to the increase in circulating irisin levels. Immunohistological staining has localized irisin to the cytoplasm of decidual, cytotrophoblast and syncytiotrophoblast of the placenta.

**E. Irisin in Type 1 Diabetes Mellitus**

Increased irisin levels are found in children and adolescents with T1DM compared to controls by certain studies. In patients with continuous subcutaneous insulin infusion, better metabolic control was seen with elevated irisin levels and there was association of irisin and better glycemic control. A negative correlation was also observed between irisin and insulin requirement. betatrophin is a hormone secreted by adipose tissue and liver that has the capacity to improve metabolic control in mice by inducing β cell proliferation in response to insulin resistance. Studies have reported positive correlation between irisin and total betatrophin in T1DM patients.

**F. Irisin in T2DM and Gestational Diabetes Mellitus**

Compared with non-diabetic controls, circulating irisin concentrations were significantly lower in patients with Type 2 Diabetes Mellitus (T2DM) and Gestational Diabetes Mellitus (GDM). Reduced PGC-1α activity in the muscle tissue of patients with T2DM can explain the decreased irisin level in patients with T2DM. Reduced activity of PGC-1 in muscular tissue results in reduced FNDC5 synthesis and reduced irisin production. In addition, insulin resistance leads to hyperglycemia and an increase in circulating free fatty acids, which also leads to a decrease in PGC-1α activity.

**G. Irisin in Metabolic syndrome**

Irisin levels were significantly higher in cases with Metabolic syndrome (MetS) than those without MetS. Irisin was associated with increased risk of MetS, indicating either increased secretion by adipose or muscle tissue or a compensatory increase of irisin to overcome an underlying irisin resistance. Increased irisin maybe due to deterioration of insulin sensitivity and lipid and glycolytic metabolism, considering a positive feedback mechanism between irisin and adiponectin to increase energy consumption in the adipocytes.

**H. Irisin in Cancer**

Significantly lower levels of irisin have been reported in cancer patients especially in breast cancer. Irisin has the ability to decrease the number of malignant mammary cells by inducing apoptosis. Moreover, it decreases the viability and migration of these cells. Irisin sensitizes malignant mammary cells for chemotherapeutic treatments without altering nonmalignant cells. Therefore, it could be a useful adjuvant treatment for some neoplasias.

**I. Irisin in Cardiovascular system**

Irisin administration is known to significantly increase the proliferation of endothelial cells via the extracellular signal-regulated kinase (ERK) pathway. Proangiogenic effects of irisin have also been demonstrated specifically in the process of cell migration and stimulation of capillary structures. It also protects endothelial cells in vivo with the activation of ERK signaling pathway. Many studies have suggested that phosphorylation of the ERK signaling pathway is one of the molecular mechanisms of irisin action. Irisin is found to predict adverse coronary events in patients with coronary artery diseases. It has also been proposed as prevention and therapy for vascular diseases.

**J. Irisin in Bone Metabolism**

Irisin has been demonstrated to promote osteoblast differentiation. It was found that osteoblastogenic effects are attributed to an irisin-dependent mechanism. Administration of low doses of irisin showed anabolic actions in the bone mass and mineral density of the cortical tissue of bones, reported a decrease in osteoclasts and an increase in the expression of osteoblastic genes and a decrease in the expression of osteoblastic inhibitory genes. Irisin was demonstrated to exert its osteoblastic effects by means of the signal pathway where there is activation of p38 mitogen-activated protein kinase (p38 MAPK) and ERK. Decreased levels of irisin were found in women with osteoporotic fractures. This can be attributed to probable positive effects of irisin on bone quality. Thus, irisin has been proposed as a myokine with a probable therapeutic effect for bone mass gain in osteopenia and prevention of osteoporosis.

**K. Irisin in Brain/Central Nervous System**

Irisin and FNDC5 are reported to be expressed by Purkinje cells in rodent cerebellum. It was also found in cerebrospinal fluid of humans, and its expression was detected in the neurons of the paraventricular nucleus, where the neuropeptide Y, which is related to appetite regulation, is also expressed, suggesting that it has central metabolic functions. It is reported that irisin is possibly responsible for the neuroprotection of physical exercise for the diseases such as cerebral ischemia through the activation of ERK1/2 and Akt pathways in brain tissue as well as protection against brain damage. Administration of irisin has found to increase neurogenesis via the STAT3 signalling pathway. Since irisin promotes favourable processes in the nervous system, its therapeutic potential should be explored in neurodegenerative disorders.

**IV. FUTURE PROSPECTS**

Irisin, a novel peptide secreted by muscle, has been demonstrated to relate to various metabolic conditions. It has been regarded as a possible treatment, where it could be used as injection using recombinant DNA technology, for diabetes and therapy in many disease conditions. However, there has been some controversial results in the many studies conducted on irisin especially regarding studies on humans. Moreover, it is presently unclear about the precise impact of irisin as a possible therapeutic target for diseases such as diabetes, metabolic syndrome etc. Therefore, the future poses a challenge to conduct deeper research for identification of a possible clinical application.

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