Irisin: A Possibly New Therapeutic Target for Obesity and Diabetes Mellitus

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Abstract: Irisin, a newly discovered myokine that reduces obesity and improve insulin resistance via the browning of white adipose tissues. Irisin is expressed and secreted in response to exercise, providing a hormonal link between exercise and improved insulin sensitivity. Several studies reported low irisin level in diabetic patient as compared to control. Therefore, it has been assumed that irisin may be used as an injectable remedy for diseases, relating to metabolism and various other health disorders in which physical exercise leads to improvements, for example, obesity and type II DM. This review focuses on the therapeutic possibility of irisin in patients with obesity and type II DM.

Key words: Irisin • Myokine • Obesity

INTRODUCTION

In the recent era, muscle tissue, has been recognized as endocrine regulator of metabolism. Muscles released a novel hormone called risin. This hormone is named after Greek messenger goddess, Iris by researchers [1]. Its expression is induced by peroxisome proliferator-activated receptor-α coactivator 1á (PGC1á) and exercise. It has been reported that, irisin both in vivo and in vitro acts on white adipose cells stimulating UCP1 expression and alter expression of several molecules leading to brown fat like development [1]. 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 [1, 2]. Recent studies in humans have reported on the association between irisin levels and the expression of its precursor FNDC5 with exercise and PGC1á mRNA levels [3, 4]. More recent studies have shown that irisin is also released by adipocytes [5, 6] as it is also recognized as endocrine gland capable of metabolism and insulin resistance [7]. Under this context, irisin was rapidly postulated to be beneficial in the treatment of obesity, diabetes and a broadspectrum of pathological abnormalities which are considered by a variable energy imbalance expenditure and demand. This review explain the role of irisin in the control of type II diabetes mellitus and obesity.

Obesity: In both developed and developing countries, due to imbalance between energy expenditure and energy intake, the prevalence of type II diabetes and obesity is accelerating at an alarming rate. Probably, the consequences of this energy imbalance might be due to the combined effect of high supply of energy rich, tasty food supply at an affordable prices and reduced physical activity [8]. Worldwide the number of total obese peoples has reached about 2.1 billion, causing an outburst of obesity associated health issues with high morbidity and mortality [9]. In obese people there is resistance to the cellular actions of insulin, which are characterized by an impaired capability of insulin to inhibit glucose output from the liver and to promote glucose uptake in fat and muscle [10, 11]. For the
progression of type II diabetes mellitus, this insulin resistance is a vital etiological factor which has gotten epidemic proportions. For example, the current adult population in the United States diagnosed with this disease is approximately 6%. Similarly, about 41 million individuals are pre-diabetic, with a constellation of dyslipidemia, insulin resistance, hypertension, that puts them at high risk for cardiovascular morbidity and mortality [12]. Adipose tissues in obese individuals, releases high quantity of pro-inflammatory cytokines, hormones, glycerol, non-esterified fatty acids and other factors that have a key role in the progression of insulin resistance. When insulin resistance along with pancreatic islet β-cells dysfunction, the cells secreting insulin failed to control plasma glucose levels [13]. Most white adipocyte-derived cytokines such as, retinol binding protein 4, interleukin (IL)-6, tumor necrosis factor (TNF) have been described to induce insulin resistance by antagonizing insulin action especially in skeletal muscles and liver [14, 15] while adiponectin has been reported to have cardiovascular protective properties and insulin sensitizing activity [14].

Human brown adipose tissue (BAT) has been postulated as a major candidate for the treatment of obesity. It is important to note that less than 8% of humans appear to have active brown fat [16]. This is based on the fact that brown adipose cells can dissipate energy in the form of heat leading to weight loss. This process takes place through a specialized mitochondrial protein called uncoupling protein 1 (UCP1). The uncoupling activity of UCP1 is explained by its ability to transport protons across the inner mitochondrial membrane, avoiding ATP synthesis and dissipating energy as heat [17]. Regulation of UCP1 is mainly at transcriptional level, where peroxisome proliferator-activated receptor Y coactivator 1 α (PGC1 α) plays a key role [18]. Bostrom and colleagues demonstrated that irisin has potent effects on the browning of certain white adipose tissues, both in culture and in vivo. So, when they applied FNDC5 to primary subcutaneous white adipocytes during differentiation a great increase in oxygen consumption was observed which suggests higher energy expenditure [1]. This effects might be due to increased expression of mitochondrial DNA and gene expression of OXPHOS system (oxidative phosphorylation) in BAT [19, 20]. Although PGC1α??2 is mainly expressed in BAT, it is also expressed at higher levels in red, oxidative muscle. In fact, its expression is increased by exercise in human beings, in rats and in mice [21].

**Link Between Irisin and Exercise:** Physical activities protects us against many types of disease including type II diabetes [22], cardiovascular disease [23], certain types of cancer [24], depression [25], osteoporosis [26] and sarcopenia [27]. These advantageous effects of physical activity might be due to reduced adiposity, a combination of improved energy balance and subclinical inflammation, potentially signaled via proteins released from skeletal muscle (myokines) [28]. Both in humans and mice, after endurance exercise training, concentrations of irisin increases significantly. Further, irisin mRNA levels in muscle tissue and irisin levels in the blood plasma are correlated [1]. Irisin along with increasing total energy expenditure also, mitigates diet induced insulin resistance, prolongs life expectancy and reduces body weight in animal models, thus reducing insulin resistance and obesity [1]. In human, 10 weeks of aerobic exercise increases serum irisin level by 2 fold [1]. In general, serum irisin levels increase acutely after exercise in young and otherwise healthy individuals [29, 30-33]. Similarly, Bostrom et al. [1] demonstrated that 7 days of swim training could induce UCP1 mRNA expression in inguinal white adipose tissue when compared to 7 days of rest in mice. However, injection of an anti-irisin antibody prior to exercise blocked this increase in UCP1. This implies that irisin is a critical signal to white adipose tissue to increase UCP1 expression after exercise [1]. Brenmoehl et al. demonstrated a near doubling of serum irisin levels in mice after acute submaximal treadmill exercise [34]. Fain et al. also demonstrated that exercise training could increase serum irisin levels by 42% [35]. Huh et al. found that serum irisin increases after 30 minutes of sprint training [36]. Similarly, Kraemer et al. found an over 20% increase in serum irisin levels in the first 54 minutes of treadmill exercise in healthy young individuals [37]. Thus, irisin secreted in response to exercise can reduces obesity and increases insulin sensitivity.

Bostrom et al. [1] demonstrated that overexpression of irisin at 3-4 fold of normal serum levels through the use of adenoviral delivery to murine liver could decrease fasting insulin and improve oral glucose tolerance in mice fed a high fat diet. This was accompanied by an increase in UCP1 expression in the adipocytes of these mice, as well as an increase in metabolic rate as evidenced by increased oxygen consumption. The effect of irisin on myocytes has also been investigated in vitro [38]. In myocyte culture, irisin increases oxidative metabolism and mitochondrial uncoupling in myocytes, as well as increasing PGC1α levels and GLUT4 mRNA and protein
levels. Such a discovery suggests a positive feedback loop whereby increased circulating irisin increases PGC1α levels, which in turn induces further irisin secretion. PGC1α is in fact the master regulator capable of increasing UCP1 protein in brown adipose tissue [39]. Although no downstream irisin receptor has been since identified, the effects of irisin are hypothesized to be mediated by increased peroxisome proliferator-activated receptor alpha (PPARα) [1].

**Type II Diabetes Mellitus:** Various studies reported that in type II DM, plasma irisin levels are lower as compared to nondiabetic controls [40-42]. Furthermore, serum irisin concentrations are also negatively correlated with BMI [41] and with the triglyceride contents in the liver and liver enzymes in obese adults [43]. Overall, plasma level of irisin may reveal the metabolic status of patients suffering from metabolism disorders. Though assurance should be taken, as the discovery of irisin opens novel promises, as its application may prove advantageous not only in monitoring and/or treatment of diabetes and obesity [44] but also for a lot of pathological disorders that are characterized by a variable imbalance of energy demand and expenditure [45, 29]. Irisin is involved in DM, as significantly low levels were reported in 104 individuals with newly diagnosed and untreated T2DM as compared to age, gender and BMI matched controls [40]. Similarly, decreased serum irisin levels were also reported in 96 individuals with T2DM receiving various medications when compared to 60 individuals with normal glucose tolerance [42]. Even, in normal pregnancy, serum irisin levels are altered. Garces et al. found serum irisin levels to be higher in pregnancy [46]. Kuzinicki et al. reported a significant decrease in irisin levels 3 months postpartum in both women with gestational diabetes mellitus (GDM) and controls with normal glucose tolerance. These two studies suggest that the placenta and the pregnant state may contribute to an increase in circulating irisin levels. Irisin has been localized via immunohistochemical staining to the cytoplasm of decidual, cytotrophoblast and syncytiotrophoblast of the placenta [47]. Yuksel et al. reported lower mean serum irisin levels in GDM compared to controls [48].

**Use of Recombinant Irisin for Therapy:** It has been assumed that irisin could be used as an injectable remedy for both metabolic disease and various other disorders for which physical exercise may cause improvements, such as obesity and type II DM [1]. A lot of compounds have been evaluated and discovered, that may act to improve such disorders. For example, exercise-mimetic drugs such as 5€-aminoimidazole-4-carboxamide-1-b-d-ribofuranoside (AICAR) and GW1516 (a modulator of peroxisome proliferator-activated receptor d) were suggested as potential treatments for obesity [49]. In the media, these drugs led to questionable announcements such as ‘exercise in a pill’ [50]. However, the adverse effects of AICAR are contentious [51] and a particular disease application for this compound has not been investigated so far [45]. The discovery of irisin had opened new possibilities as, it is an endogenous hormone which using recombinant DNA technology can be easily cloned. A lot of recombinant human proteins such as, erythropoietin, growth hormone, insulin etc. are used widely in modern therapeutics. Still, a lot of work is needed, the administration of irisin may show positive effects not only in the treatment of obesity and diabetes, but also for a wide range of pathological conditions that are characterized by a variable imbalance of energy demand and expenditure [45].

**CONCLUSIONS**

Irisin, secreted by muscles and adipocytes in response to exercise 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. Due to its anti-diabetic and anti-obesity property, there is a hope that, this endogenous hormone can be use as injection for treatment using recombinant DNA technology. Further studies are needed both in animal and human models to test the efficacy of recombinant irisin in obese and diabetic patients.

**REFERENCES**


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