Review Article

THE ROLE OF PHYSICAL EXERCISE INTESITY TO IRISIN LEVELS ON OVERWEIGHT AND OBESE

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ABSTRACT

Physical exercise is a non-pharmacological therapy that can secrete various types of myokines to treat obesity problems. One of the myokines that play a role is irisin. Irisin is a polypeptide hormone with 112 amino acid residues that are synthesized in skeletal muscle after the proteolytic precursor cleavage of fibronectin type III domain-containing protein 5 (FNDC5). The release of irisin in the blood circulation will stimulate the browning process in white fat tissue by inducing the expression of uncoupling protein-1 (UCP-1) through signaling p38 mitogen-activated protein kinase (p38-MAPK) to increase energy expenditure, thermogenesis and reduce fat accumulation. This study described the differences in intensity of physical exercise mechanisms associated with the increased irisin secretion in overweight and obese subjects. This study was designed as a literature review that involved studies from research journals in the last 10 years concerning humans from some databases, such as Science Direct, PubMed, and Google Scholar. This study also discussed the relationship between the intensity of physical exercise and the synthesis, secretion, circulation, and regulation of irisin in preventing obesity.

***Keywords**: Irisin; physical activity; exercise; intensity; obesity*

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Highlights:

1. The differences in intensity physical exercise mechanisms associated with increased irisin secretion in overweight and obese subjects were determined.
2. The secretion of irisin in the right intensity blood on obesity can be reduced because the calories were balanced.

INTRODUCTION

Obesity is a factor in global problems that occur in both developed and developing countries (Norheim et al. 2014, World Health Organization 2019). Based on the data of World Health Organization in 2016, more than 1.9 billion people aged over 18 years were overweight, and 650 million of them were categorized as obesed. In Indonesia, data of the Ministry of Health in 2018 showed that obesity at over 15 years old in 2007 was 18.8%, while in 2018 it was 31.0%. Obesity could increase the risk of metabolic syndrome, such as stroke, type 2 diabetes, and heart disease (Grundy 2004, Gepstein & Weiss 2019). Therefore, we needed an appropriate intervention to reduce the potential rate.

One of the factors that plays a major role in obesity is excessive food intake and inadequacy of physical

activity (Global Burden of Disease 2015, Houben & Jansen 2017). This could increase various risks of metabolic syndrome (Ma et al. 2019). The risk of metabolic syndrome can occur due to the role of sympathetic nervous system activation which contributes to increased vascular and cardiac function which stimulates vasoconstriction of blood vessels, and causes blood pressure to increase. Besides, the metabolic balance is also disturbed, such as increased lipolysis which can drive fatty acid levels, so that it affects blood vessels and heart function (Ciccarelli et al. 2013). Thus, pathological symptoms will appear through an increase in blood pressure, an increase of triglycerides, glucose in blood and insulin resistance that can cause the increased risks of heart disease, stroke, and diabetes (Pescatello 2014, Han & Lean 2016).

As long as the conditions keep happening, it will have an impact on the low quality of public health, so that we needed an appropriate intervention; one of which was by doing physical exercise that could cause secreting various types of myokines to treat obesity problems. One of the myokines that play a role is irisin, but the intensity level of physical exercise can affect synthesis, secretion, circulation, and regulation of irisin in preventing obesity and negative impact.

In 2012, a myokine was identified and induced during physical exercise, known as irisin (Bostrom et al. 2012). This hormone can help to burn fat, so that it can inhibit obesity (Archundia-Herrera et al. 2017, Perakakis et al. 2017). Several studies have shown the many benefits of irisin secretion. A study by Huh et al (2014) showed that high intensity can increase acute response to irisin levels by 30% within 5 minutes after physical exercise in overweight men. However, Soori et al (2016) showed that moderate intensity-physical exercise was effective in increasing irisin secretion in the blood, so that the debate about the effective intensity in increasing irisin secretion was still being debated, as well as the effect of physical exercise intensity on irisin secretion in the overweight and obese categories that was still unclear. Therefore, this study examined differences in the intensity of physical exercise in increasing the secretion of irisin levels in order to find the right dose intensity to reduce the risk of obesity and avoid an increased risk of metabolic syndrome.

This study was designed as a literature review that involved studies from research journals in the last 10 years. We searched for data sources from the Science Direct, PubMed, and Google Scholar database with some keywords, namely irisin, physical exercise, intensity, overweight, and obesity with the inclusion criteria of physical exercise, irisin levels, and one subject with a Body Mass Index (BMI)> 25 kg/m^2. The exclusion criteria included the absence of physical exercise interventions, animal subjects or in vivo studies, meta-analyses, reviews, books, book chapters, editorials, and letters to the editor. According to prior keywords searching, it found 69 articles from science direct, 123 articles from Pubmed, and 42 articles from Google Scholar. However, all articles still needed to be further reviewed to get results according to the specified criteria. After reviewing the results of the review, the final results of the search for the appropriate database resulted in 45 article journals.

OVERVIEW

Irisin

Irisin is a hormone that was discovered in 2012. Initially studied in mice and secreted from mouse muscle expressing Ppargc1a or encoded by transcription cofactor peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) which enters the energy metabolism pathway (Huh et al. 2012). PGC1α stimulates the expression of fibronectin type III domain-containing protein 5 (FNDC5) and synthesizes membrane protein FNDC5 consisting of 212 amino acids to 209 amino acids in mice and mice (Bostrom et al. 2012). This protein sequence is included in the peptide signal located in the cyto serum (Perakakis et al. 2017). After proteolytic cleavage, glycosylation, and possibly a dimerization process from FNDC5, a new protein structure consisting of 112 amino acid chains was called irisin.

The highest irisin in humans was produced in skeletal muscle, so that it was known as a myokine, apart from those several other organs, such as heart, tongue, and rectum also produced it, although not significant (Huh et al. 2012). In contrast, the lowest expression of FNDC5 was in the pancreas and liver. Roca-rivada and Castelao et al (2013) also found FNDC5 / irisin in adipocytes. Yet of course, the expression was 100-200 times lower than the expression in human skeletal muscle (Huh et al. 2012, Perakakis et al. 2017).

When irisin has been secreted from muscle, irisin will communicate with several cells and organs in the body, one of which is fat cells or adipocytes. When irisin enters adipocytes it stimulates the expression of UCP1 via the p38 mitogen-activated protein kinase (MAPK) pathway and extracellular-signal regulated kinase (ERK) which then causes a thermo-genetic reaction in the mitochondria. The increase in thermogenesis causes the white adipose tissue (WAT) to turn brown / Brown Adipose Tissue (BAT). The process of converting WAT-type fat into BAT will cause an

converting WAT-type fat into BAT will cause an increase in the burning of energy reserves stored in the body, so that fat deposits can be burned and used as energy. A more detailed explanation can be seen in Figure 1.

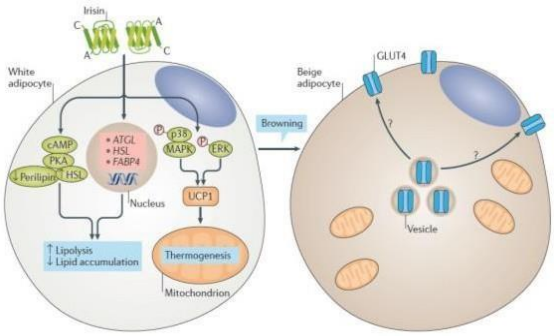

Figure 1. Irisin and communication on adipocyte cells (Perakakis et al. 2017)

In several studies conducted on animals or humans, irisin had also been shown to be strong in secretion during physical exercise. For example, in the study of Löffler et al (2015) on children and adults shown in Figure 2, there was an increase in irisin levels both in Figures A and B of 1.2 fold.

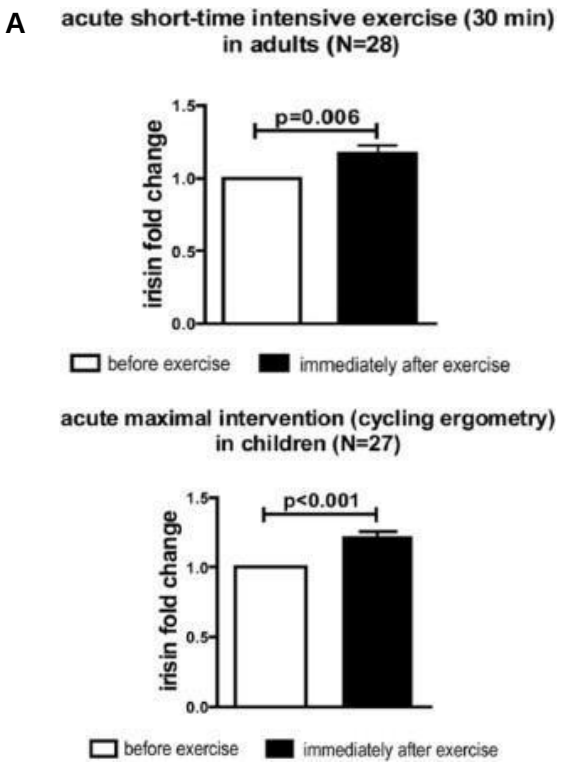

Figure 2. Serum irisin levels induced during physical exercise (Löffler et al. 2015)

In addition, a study by Bostrom et al (2012) showed that plasma irisin levels in mice increased by 65% after 3 weeks of running intervention, while in humans, irisin levels doubled after a 10-week intervention with aerobic-type physical exercise. In addition to increasing lipolysis, the increase in irisin can also create a state of glucose homeostasis in the blood.

Perakakis et al (2017) explains that irisin could activate the AMP-Activated Protein Kinase (AMPK) pathway by reducing intracellular ATP levels, increasing reactive oxygen species (ROS) or intracellular calcium concentrations. Activation of the AMPK pathway would stimulate the expression of Glucose transporter 4 (GLUT4). High GLUT4 expression, combined with the increased translocation of the GLUT4 protein from the cytoplasm to the membrane, induces glucose uptake by cells. In addition, irisin induction in cells will cause an increase in fat metabolism, a decrease in glycogenolysis, and a decrease in gluconeogenesis. In brief, it could be seen in Figure 3 regarding the role of irisin in stimulating the activation of various metabolisms in cells.

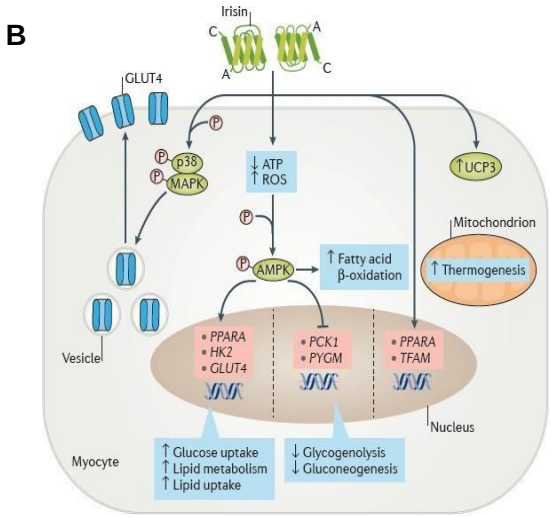

Figure 3. Irisin signal pathways inside the cell (Perakakis et al. 2017)

In the Fukushima et al (2016) study conducted on 22 women and men with the obesity category, physical exercise for 6 months with a diet setting showed a decrease in body weight and BMI. Irisin levels also showed an increase associated with decreases in the percentage of body fat, subcutaneous fat, triglycerides, and fasting blood sugar.

The difference in intensity also affects the secretion of irisin in the blood. This was evidenced from several previous studies that had been conducted. The study of

Cialowicz et al (2020) showed that High Intensity Interval Training (HIIT) caused an increase in irisin levels in the blood by 30% after 8 weeks of intervention.

The increase in irisin can occur, because the body experiences hypoxia and an increase in the glycolytic rate during intense and short physical exercise. This anaerobic process contributes to mitochondrial biogenesis causing increased oxygen and fat burning. Figure 4 shows the differences in irisin secretion in HIIT before and after intervention and their comparison with the control group in a clearer manner.

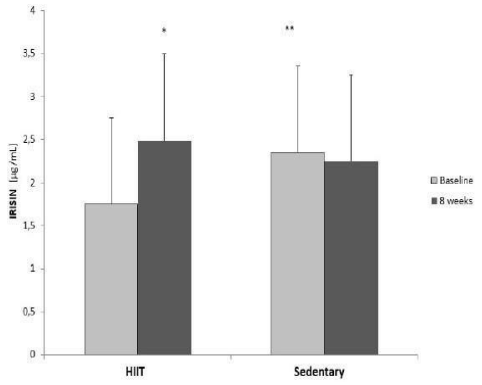

Figure 4. Differences in irisin secretion in the HIIT and control groups (Cialowicz et al. 2020)

This was in line with the research of Huh et al (2014) by involving 78 people divided into two groups, namely 38 adolescents and 40 elderly people. Each group was given physical exercise treatment which was divided into two groups, namely Continuous Moderate Exercise (CME) and High Intensity Interval Exercise (HIIE) which would be observed to increase levels of irisin regularly, namely before intervention, shortly after intervention (10-15 minutes), one hours, and 24 hours. In the results of this study, HIIE had the highest increase in irisin secretion after the intervention compared to CME.

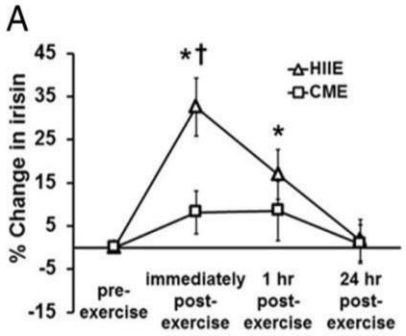

Figure 5. Irisin circulation response between HIIE and CME (Huh et al. 2014)

Obesity is a condition of body weight due to excess fat accumulation (American College of Sports Medicine 2018). This happens, because there is an imbalance of calories in and calories out (Sahoo et al. 2015). In this case, the adipose tissue has a role as a form of body mechanism to store energy reserves in the form of fat. The network was divided into two types, namely White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT). WAT stores excess energy in the body, forming triglycerides, and releasing energy in the form of free fatty acids and glycerol. Meanwhile, BAT oxidizes the stored fat to be readily used as energy for physical activity (Lo & Sun 2013).

According to Cui and Chen (2017), WAT has two main storage depots, namely visceral white adipose tissue (vWAT) and subcutan white adipose tissue (scWAT). WAT has a percentage of about 20% of normal adult body weight. Meanwhile BAT is involved in metabolism, especially during heat generation. A study by Saely et al (2012) showed that BAT functioned as an energy homeostasis in the body. Apart from WAT and BAT, there were also beige/ brite/ brownlike adipose tissue (bAT) (Cedikova et al. 2016). BAT has mixed characteristics of WAT and BAT. During the homeostatic state or basal state, BAT will be similar to WAT morphologically, but when stimulated by exercise or physical activity, the morphological appearance will change to BAT, thus transforming stored fat (Cedikova et al. 2016).

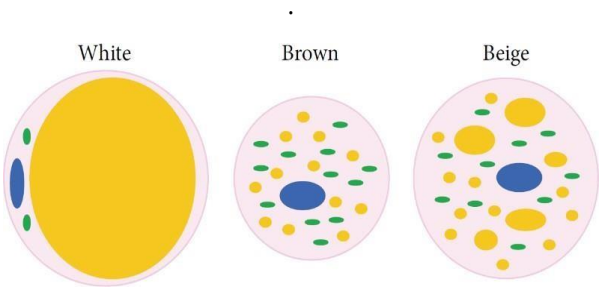

Figure 6. Morphological characteristics from WAT, BAT, and bAT (Cedikova et al. 2016)

There were several measurements that could be done to identify the body was included in the obesity category. These measurements included waist circumference, hip circumference, waist to hip circumference ratio (WHR), and Body Mass Index (BMI) (Ahmad, 2016). The easiest way to do the calculation at BMI. The BMI category of obesity has a value range of 25-29.9 (World Health Organization 2000). However, BMI has disadvantages, such as not being able to differentiate between muscle mass and fat, so that if it is done in a trained person, further measurements are needed.

Table 1. Classification of body weight based on BMI in adults in Asia

Classification	BMI	Risk of Disease
Underweight	<18.5	Low (but may increase the risk of other clinical diseases)
Normal	18.5-22.9	Average
Overweight Risk	≥23	Risk increases
Obesity I		
Obesity II	23-24.9	Moderate
	25-29.9	
	≥30	Severe

Source: World Health Organization (2000)

Several disease risks can arise due to excess weight gain, especially in the obesity category, such as cardiovascular disease, high blood pressure, cholesterol, glucose tolerance to diabetes mellitus type 2, and other musculoskeletal diseases (Global Burden of Disease 2015, American College of Sports Medicine 2018). This weight regulation is of course influenced by the energy put into the body and the energy released (Pescatello 2014). For someone with obesity, the energy released is lower than that which it enters, and it causes food not to be processed as energy, but stored as energy reserves in the form of fat.

Gender differences will also differentiate fat distribution in each individual (American College of Sports Medicine 2018). In general, there are three types of fat distribution, namely android, gynoid, and intermediate patterns. For females, fat distribution will be spread over the hips and thighs, or commonly known as the gynoid pattern. Meanwhile, in men, the distribution of fat is spread over the neck, shoulders and stomach which is known as android pattern. There is also another form, namely the intermediate pattern; the distribution of fat located in the upper and lower areas of the body, so that it forms a shape like a square appearance (Plowman & Smith 2011).

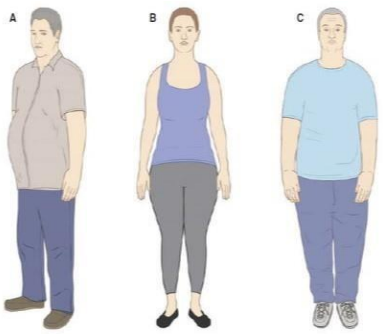

Figure 7. Fat distribution A) Android, B) Gynoid, C) Intermediate pattern (Plowman & Smith 2011)

Effects of physical exercise intensity on irisin levels

Based on the results of several studies, irisin can be improved with acute physical exercise interventions (Tsuchiya et al. 2014, Huh et al. 2015, Löffler et al. 2015, Herrera et al. 2017, Winn et al. 2017). Conversely, several studies had also succeeded in proving that chronic physical exercise interventions could also increase irisin secretion (Bluher & Panagiotou 2014, Kim et al. 2016, Bonfante et al. 2017, Leblanc et al. 2017, Tofighi et al. 2017), so that irisin is a myokin influenced by physical exercise. In overweight and obese subjects, they were able to prove that irisin was secreted higher than the pre-intervention level. One of the changes in the increase in irisin is affected by the intensity of physical exercise. The high intensity of physical exercise can increase irisin secretion more than low intensity (Tsuchiya et al. 2014, Huh et al. 2015, Löffler et al. 2015), but high intensity physical exercise will immediately cause irisin to return to basal value at 15 minutes after physical exercise. Meanwhile, at moderate intensity with continuous type irisin secretion looks more stable, where it can increase up to 2-3 hours after the intervention (Winn et al. 2017).

In addition, the type of weight training with high intensity can also increase irisin secretion than the aerobic type of physical exercise at both moderate and high intensity (Huh et al. 2015, Löffler et al. 2015). It is possible that the higher the intensity, the higher the load on the muscle contraction that occurs so that it can increase the microscopic muscle damage. The microscopic muscle damage will be positively associated with increased production of lactate and creatine kinase as biomarkers of muscle damage (Huh et al. 2015). Other factors (gender and fitness status) had not affected irisin secretion (Löffler et al. 2015, Nygaard et al. 2015). There were also studies that showed the occurrence of irisin levels remained from baseline with aerobic and resistance-type physical exercise interventions (Pekkala et al. 2013). However, these differences may occur due to differences in the methodology.

The difference in results in each study can be determined from the type of sample observed and the sampling time. In most studies, samples to measure irisin levels were observed in serum and blood plasma, and there were those who took samples using saliva (Aydin et al. 2013). The results obtained from the types of serum and saliva samples also showed different results. In saliva, the irisin concentration increased after the intervention of aerobic exercise sessions, while the serum irisin concentration before and after

the intervention did not show any difference (Aydin et al. 2013). However, it is difficult to certainly observe the difference between serum and saliva, because two different methods are used. Saliva is easier to sample without non-invasive action, while serum and plasma use invasive measures using Elisa kits. The most common measurements using these elisa kits are the types EK-067-29 and EK-067-52: Phoenix Pharmaceuticals, Burlingame, CA, USA with a detection range of 0.1-1000 ng/ml and 0.328-204.9 ng./ml (Bluher & Panagiotou 2014, Norheim et al. 2014, Tsuchiya et al. 2014, Huh et al. 2015, Herrera et al. 2017).

The role of optimal physical exercise intensity in increasing irisin secretion occurred at high intensity and resistance exercises. Both were more effective in increasing the concentration of irisin in the blood. However, studies on this effect are still limited and there remains a variety of approaches among studies, so that it is not sufficient to develop a suitable protocol. However, this is sufficient to prove that physical exercise is a non-pharmacological therapy that has a potency to solve the problem of overweight and obesity by increasing irisin secretion, so that it can increase the thermogenesis process.

Strength and limitation

The study is highly relevant and up-to-date. The study provides a detailed explanation of the structure and function of irisin and how it induces the browning of white adipose tissue. The findings could have important implications for the design of exercise interventions for individuals who are overweight or obese, as well as the development of non-pharmacological therapies for the treatment of obesity. This study is a valuable contribution to the field of exercise physiology and obesity research, providing important insights into the mechanisms by which physical exercise can promote the secretion of irisin, and its potential therapeutic benefits for preventing obesity.

CONCLUSION

Obesity is a global problem that occurs today. The increasing prevalence of obesity will lead to various risks of metabolic syndrome which can increase the risk of diseases, such as type 2 diabetes, heart disease, and stroke. In overcoming these problems, physical exercise is a non-pharmacological therapy that can be done to prevent obesity, so that various risk factors for the disease can be reduced. Physical exercise can stimulate irisin that can help the process of converting WAT to BAT, so that it helps to increase lipolysis activation.

The secretion of irisin in the blood with the right intensity is expected to be able to balance calories in and calories out, so that it can reduce the incidence of obesity. The most proven intensity to increase irisin secretion is higher at high intensity. In addition, the type of physical exercise with resistance exercise is also quite high in increasing irisin secretion compared to other types. Therefore, it is important to know the dosage of physical exercise, especially at intensity, which is necessary to prevent overweight and obesity as well as to get health and fitness benefits in a sustainable manner.

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Conflict of interest

None.

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None.

Author contribution

INA-conceptualized the study and wrote the manuscript. S-reviewed, validated, and finalized the manuscript. PSR-Revised, collected, validated and finalized the manuscript.

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