

**Role of serum Irisin in Early Detection of Subclinical Atherosclerosis and Endothelial Dysfunction in Patients with Behcet's Disease****Ola Mounir<sup>a\*</sup>, Esam Ahmed Abda<sup>b</sup>, Mohammed Ali Ismael<sup>a</sup>**<sup>a</sup>Rheumatology and Rehabilitation Department, Faculty of Medicine , Sohag University, Sohag, Egypt.<sup>b</sup>Rheumatology and Rehabilitation Department, Faculty of Medicine , Assuit University, Assiut, Egypt.**Abstract**

**Background:** Behçet's disease (BD) is a disease which affects vessels and cause inflammation and affects the function of the endothelium. Irisin is a hormone of metabolism which affects the function of the endothelium and has an effect on the resistance of insulin. The Main histopathological functions of BD are characterized via way of means of acute inflammatory process and persistent systemic vasculitis related to endothelial disorder.

**Objectives:** to, examine the connection among serum irisin and subclinical atherosclerosis in sufferers with Behçet's ailment. Also, evaluate serum irisin with different nicely modalities used to locate subclinical atherosclerosis and endothelial dysfunctions.

**Conclusion:** Irisin is an adipocytokine this is associated with energy metabolism and associated with release of insulin and its sensitivity. We determined that serum irisin ranges in sufferers with BD had a poor courting with thickness of the carotid intima, that is a famous indicator for the resistance of insulin . We need further studies in addition to assessment of irisin level and measurement of the carotid intima thickness

**Keywords:** Serum irisin; Subclinical Atherosclerosis; Endothelial dysfunction; Behcet's disease.

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## Introduction

Behçet's disease is an ailment which cause inflammation and affect vessels and heart with an incidence rate varying between 7% to 46%. (Gürkün et al., 2002).

The Main histopathological functions of BD characterized via acute inflammatory process and persistent systemic vasculitis related to endothelial disorder. (Hingorani et al., 2000).

The increased blood glucose level, the atherosclerosis and the hyperlipidemia which occur are great signs of the inflammatory process. (Haraoui et al., 2012).

Observational research have supported the data that sufferers with previous persistent inflammatory illnesses have a dramatically accelerated threat for CVD at earlier age onset, and associated with the truth that endothelial disorder is taken into consideration to be preliminary lesion in the occurrence of atherosclerosis. (Haraoui et al., 2012).

The impairment of the endothelium which known by measuring the thickness of the carotid intima help us to know the degree of atherosclerosis and the damage (Balta et al., 2013).

Recent researches have proven that an accelerated susceptibility to IR is associated with more damage to the endothelium and more disturbances in metabolism. (Erden et al., 2014).

. Irisin is released from different organs of the body and has an important role in the metabolism of energy (Moreno-Navarrete et al., 2013).

In cases associated with impaired glucose tolerance curve and those with high level of lipid profile, there was low level of serum irisin (Zhang et al., 2016).

With increased complications of blood vessels in those with high blood glucose level there was a low level of serum irisin (Liu et al., 2013).

Increased blood glucose level causes more lipid particles accumulation on the endothelium and more cytokine release and so more damage to the endothelium (Tabas et al., 2010).

Hyperglycemia, and persistent illness predispose to endothelial disorder and atherosclerosis in sufferers with BD. (Ozgen et al., 2011).

In diseases associated with disorders in metabolism and bad function of the endothelium, irisin may have a role in treatment. (Zhu et al., 2015)

Irisin, as a novel chemical like myokine which has an essential situation in energy consumption and metabolic guideline, is specifically emitted by skeletal muscle, kidneys, livers, heart, skin and nerves. (Xie et al., 2015).

Also there is an obvious relation between serum irisin level and with those on dialysis where there is affection of blood vessels especially the carotid arteries (Lee et al., 2015).

Interestingly, there are research specifying that there may be both poor and tremendous dating among irisin ranges and metabolic syndrome/HOMA-IR. (Yan et al., 2014) There is a contradiction on this regard.

Icli et al. (2016) pronounced that, the relation between serum irisin level and affection of blood vessels especially the carotid arteries may help in the strategies of therapeutic roles

**The intention of this examine have been to:** Evaluate the connection among serum irisin and subclinical atherosclerosis in sufferers with Behçet's ailment. Also, examine serum irisin with different known modalities used to diagnose subclinical atherosclerosis and endothelial dysfunctions.

### Behçet's disease (BD)

**Definition:** It is a persistent autoimmune and multisystem vasculitis condition, unique with the aid of using a remitting and relapsing course, being specifically common in populations by the side of the Mediterranean Sea (Salmaninejad et al., 2017). It entails the skin, mucosa, joints, eyes, arteries, veins, CNS and the gastrointestinal tract (Hatemi et al., 2018a). It may be taken into consideration as a persistent systemic inflammatory illness with an unknown etiology; characterised with the aid of using manifestations together with mucocutaneous lesions, arterial aneurysms, venous thrombosis, arthritis, intestinal ulcers, CNS lesions, and pulmonary lesions (Gul, 2005).

### Epidemiology of BD

BD has enormous local differences, with maximum prevalence within the Mediterranean, the Middle East, and the Far East (Mendes et al., 2009).

BD happens maximum often among the latitudes 30° and 45°N in Eurasian populations. (Zeidan et al., 2016).

A more frequency has been recognized from maximum nations alongside the Silk Road but the sensitivity of the phenomenon is declining over time (Davatchi et al., 2011). The prevalence of BD varies in step with geographical location, and does not no longer observe Mendelian policies as proven with the aid of using own circle of relatives research. (Zeidan et al., 2016).

The maximum incidence is observed in Turkey, Iran, Israel, northern China, and Korea observe with the subsequent maximum incidence. The male-to-woman ratio in Egypt changed into 5.37 to one and could range throughout the globe to be 0.38 to one within the USA (Davatchi et al., 2010).

Newly mentioned instances were defined over the last decade in Russia, Australia, New Zealand, and many nations of the Central and South American continent. (Greco et al., 2018).

The onset of BD normally happens within the third decade of life, and it's far not often visible in earlier age onset or sufferers above the age of 50. The medical guides of childhood-onset BD and late-onset BD are incredibly benign (Nair and Moots, 2017).

#### **Prevalence of BD in Egypt:**

A preceding unmarried middle examine from Alexandria performed twenty years in the past stated a incidence of 7.6/100,000 population and a men: women ratio of 5.4:1 (Assaad-Khalil et al., 1997). In a current multicenter Egyptian examine; the general expected incidence of BD turned into 3.6/100,000 populace and the superiority over the united states governorates (Gheita et al., 2019).

#### ***BD and Cardiovascular manifestations***

Vascular manifestations are characterised via way of means of involvement of vessels of all sizes, each within the arterial and venous structures and venous events is higher than arterial events. Venous thrombosis happens in 30% of cases. The arterial events are visible in three to 5% of cases (Saadoun et al., 2012).

Cardiac involvement consists of pericarditis, myocarditis, endocarditis. Aneurysms and/or thrombosis of the coronary arteries are found complex via way of means of hemorrhage, myocardial infarction

and unexpected death (Seyahi, 2016).

#### ***BD and Peripheral arterial involvement:***

It occurs lately, growing after an average of 5-10 years of the disorder onset (Tascilar et al., 2014). Its frequency is much less than 5%. Male dominance is extra reported while in comparison to PAI. A large majority show aneurysms more than thrombotic occlusions. Commonly affected arterial sites are the infrarenal stomach aorta and iliac, femoral, popliteal, and carotid arteries (Seyahi et al., 2008).

Clinical symptoms and symptoms rely on the affected arterial site. Pulsatile and/or painful mass are the medical symptoms and signs. Lower extremity aneurysms might also additionally occur with leg ache and claudication and seldom with virtual ulcers. CT or MRI are used to visualise vascular lesions in detail. PET/CT can be additionally helpful (Seyahi, 2016).

The mortality in those sufferers reduced notably from 17% to 5% while in comparison to that done earlier than 1997 (Kechida et al., 2018).

#### **Irisin**

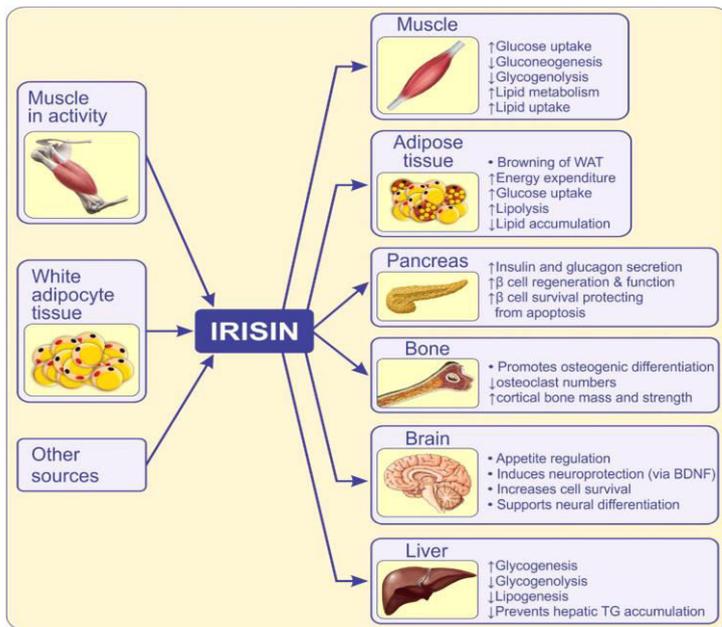
The adipose tissue and muscles are the sites of action of irisin where it uses white adipose tissue in energy processes (Rodriguez et al., 2017). Irisin produce energy as heat (Villarroya, 2012).

#### ***Discovery and nomenclature of irisin***

Irisin is a protein which is composed from 112 amino acids and discovered first in animals and then in human (Bostrom et al., 2012) and its name originate from the word iris which is a greek word which is related to the function of serum irisin (Grimal and Maxwell-Hyslop, 1986).

The adipose tissue, the skeletal muscles, pancreas and cardiac muscles are the main sites where irisin is secreted and irisin reactivity was found in salivary glands, testes and ovaries (Aydin, 2014).

Irisin helps in regulation the process of energy by affecting the expression of the receptors which is activated by peroxisome (Vaughan et al., 2014; Chen et al., 2015) irisin help in decreasing weight and increase energy expenditure and also decrease the resistance of insulin. (Zhang et al., 2014b) and (Bostrom et al., 2012).



**Fig.1.** Sources and actions of irisin

### *Irisin and exercise*

Secretion of myokines is related to muscle contraction and so has a role in protection against chronic illness (Pardo et al., 2014).

It is known that changing life style and improving physical activity has an important role in protection against type 2 DM (Moreno et al., 2015). Since irisin has a relation to muscle contractions and exercise but the investigations that link it to physical exercise show non conclusive results (Pekkala et al., 2013).

### *Irisin and obesity*

Obesity is a condition which is associated with accumulation with fat and increased in the resistance of insulin and possible metabolic abnormalities and there may be heart affection (Meiliana et al., 2015). The modifications within the irisin stages have been determined within the serum of overweight people. Earlier research mentioned the decreased attention of irisin in overweight individuals (Moreno-Navarrete et al., 2013), at the same time as a number of the latest research confirmed the other outcomes in which the irisin stages have been located to be expanded in overweight conditions. A condition of irisin resistance can be observed throughout the direction of weight problems improvement (just like leptin resistance) which can give an explanation for the extended stages of irisin in those topics (Sahin-Efe et al., 2018).

There is a relationship between the change of fat

mass and the change in irisin level, at the same time as different research verified that weight reduction in overweight topics results in a decreased in serum irisin (Pardo et al., 2014), Obesity is frequently associated with the occurrence of central inflammatory condition (Meiliana et al., 2015), additionally called meta-inflammation, that is referred to condition of persistent inflammatory process precipitated in non-immunocompetent tissues, inclusive of muscles, intestines, adipose tissue, or liver, attributable to the activation of resident macrophages. Meta-infection can also additionally bring about diverse metabolic abnormalities, and throughout the direction of weight problems, a big inflow of macrophages into fats tissue is determined (Roger and Calder, 2018).

Irisin has an effect on monocyte chemotactic protein expression which lead to affection of macrophage inflow and so affect leptin expression (Mazur-Bialy et al., 2017). Leptin level has an effect on meals consumption and so the metabolic process (Choi and Cohen, 2017). Leptin is related to the resistance of insulin and the improvement of metabolic syndrome (Martins Mdo et al., 2012). Leptin has an intimate effect through its action on adipose tissue (Gutierrez-Repiso et al., 2014). Adiponectin, is an anti inflammatory adipokine, which increase the sensitivity to insulin and so has a role in weight reduction, (Choi and Cohen, 2017). Irisin thru heme oxygenase 1 (HO-1)/adiponectin axis improves perivascular adipose tissue (PVAT) feature in diet-precipitated overweight mice and attenuates the anti-contraction impact of PVAT (Hou et al., 2016). Irisin decrease tumour necrosis factor alpha (Hou et al., 2016). the antiinflammatory effect of irisin by its effect on macrophages and adipocytes ask us to search for factors that increase the sensitivity to irisin (Korta et al., 2019).

### *Irisin and glucose homeostasis*

Irisin has a role in the metabolism of glucose by increasing its uptake by skeletal muscles and so improve the function of the liver in glucose metabolism and so improve the sensitivity to insulin receptors and decreasing insulin resistance (Chen et al., 2016).. It is thought that irisin affect organs like liver and pancreas through changing of insulin resistance also it modulates the function of pancreatic islets (Palermo et al., 2015).

Irisin affect liver and pancreas islets and so help in improving hepatic metabolism by affect endoplasmic reticulum stress and so decrease the occurrence of diabetes (**Briganti et al., 2018**).

Irisin act as insulin sensitizing hormone so it plays an important role in glucose haemostasis and so improving insulin resistance (**Sesti et al., 2014**). The strong relation between irisin and endothelial dysfunction help us to use it as a biomarker for the disease (**Rana et al., 2017**).

#### *Irisin and cardiovascular diseases (CVD)*

The presence of the metabolic syndrome has a role in heart diseases and so decreasing body weight is important to protect against stroke (**Han and Lean, 2016**). There are researches that CVD is associated with irisin level where decreased concentrations of irisin on this population have association with decrease expected time for life (**Aronis et al., 2015**).

Some researches detect a relation between irisin level and LDL level but other researches failed to detect any relation (**Liu et al., 2013**). Also some researches show that decrease in irisin level is associated with decrease HDL level but other researches detect no relation (**Wen et al., 2013**).

#### **Relationship of serum Irisin, atherosclerosis, endothelial dysfunction in BD**

Past exploration found the association among coursing irisin degrees, endothelial impairment and subclinical atherosclerosis in adult patients who are not diabetic (**Kwasniewska et al., 2015**). It became validated that serum irisin stage became considerably correlated with carotid atherosclerosis (detected through carotid intima thickness "cIMT") in sufferers receiving dialysis (**Lee et al., 2015**). Patients suffer from macrovascular affronts caused by diabetes have lower levels of serum irisin when contrasted with patients without diabetes and without macrovascular affronts (**Zhang et al., 2015**).

A former analyze validated that BD patients have serum irisin degrees which had inverse relation with thickness of carotid intima media, that is a famous procedure for detection of IR and subclinical atherosclerosis (**Icli et al. 2016**). The authors concluded that BD patients with low levels of serum irisin are at risk for atherosclerosis.

Endothelial disorder, a known method for identifying subclinical atherosclerosis which is detected

through measuring the thickness of intima-media of common carotid artery by sonographic techniques, is the first occasion in insults which affect vessels in patients with BD, also, contributes significantly to the commencement and progression of the disorders which affect blood vessels in explicit regions of the human core, causing disorders of the metabolism (**Balta et al., 2013**).

IR is pathognomonic situation described through a lowering sensitivity of insulin managing levels of glucose in blood. Past research found that there is association among levels of serum irisin, impairment of the endothelium and subclinical atherosclerosis in patients who are not diabetic (**Xie et al., 2015**).

Low levels of serum irisin play a vital position in lowering the amount of secretion of insulin, causing IR and disorders affecting the metabolism of glucose and fatty acid (**Liu et al., 2013**). Lower levels of serum irisin occur in patients who are diabetic and have events affect large vessels in compare to patients without diabetes and have no macrovascular insults (**Zhang et al., 2014**). Hyperglycemia, boost up the Atherosclerosis can be fastened by increased blood glucose levels, IR and advanced cease products which is -glycosylated, through inflicting endothelial disorder directly, enhancing endothelial cytokine launch, lipid peroxidation and inflicting oxidative harm (**Tabas et al., 2010**).

Hyperglycemia, IR and continual irritation motive endothelial disorder and atherosclerosis in sufferers with BD (**Zhang et al., 2016**). Irisin, glucose, insulin, C- reactive protein and blood sugar levels is elevated in BD patients in comparison to healthy ones, while the serum irisin show lower levels when determined in BD in comparison to healthy ones. There became high correlation among age, serum level of creatinine, insulin, HOMA-IR and thickness of carotid intima media, while an inverse relation became detected among thickness of carotid intima media and level of serum irisin levels. Also, there is inverse relation between serum levels of irisin and HOMA-IR. Assessment outcomes affirmed that decreased serum level of irisin turned into a powerful and prescient for HOMA-IR and cIMT (**Icli et al. 2016**).

**Lee et al.(2015)** distinguished significantly decline irisin levels in suffers getting dialysis for the peritonium while when contrasted with the normal

ones, and decided a strong connection among serum level of irisin and thickness of carotid intima media. In any case, it got said of their inspect that level of serum irisin is likely identified with diminished muscle gatherings. (Sesti et al., 2014).

### Conclusion

Irisin is an adipocytokine associated with metabolic process, insulin affectability and launch. The serum level of irisin in sufferers with BD have inverse relation to thickness of carotid intima media, that is a known pointer for IR and subclinical atherosclerosis. There is relation between decreased level of serum irisin in sufferers with BD and atherosclerosis..

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