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Original Article

Investigating Atherosclerosis by Using Serum Irisin in Patients with Ankylosing spondylitis

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Abstract

Ankylosing spondylitis (AS) presents a considerable disease burden, largely due to its rheumatic nature and the increased risk of accelerated atherosclerosis, which raises the chances of cardiovascular disease (CVD). Identifying inflammatory biomarkers and cardiovascular risk factors in patients with axial spondylarthritis (axSpA) is critically important for clinical practice. Recent research has brought attention to the adipomyokine irisin, which is significant in regulating inflammatory responses and cardiovascular health. Our goal is to assess the viability of irisin as both a genetic and serological biomarker for detecting subclinical atherosclerosis, evaluating cardiovascular risk, and understanding the severity of disease manifestations in axSpA patients. By clarifying the connection between irisin levels and cardiovascular outcomes, we seek to deepen the comprehension of disease mechanisms and enhance risk stratification for this group. This understanding could lead to more focused therapeutic approaches and improved management of the comorbidities linked to AS, ultimately benefiting patient care and outcomes.

Keywords: **Ankylosing** Spondylitis, Atherosclerosis, serum Irisin

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Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory disorder primarily impacting the sacroiliac joints and the axial skeleton. Individuals diagnosed with axial spondylarthritis, such as AS, typically experience more favorable results compared to those suffering from diseases like rheumatoid arthritis. Nevertheless, AS is a long-term, progressive condition that can lead to significant health complications. [1]

Pathophysiology:

Enthesitis is the main pathophysiology of spondyloarthropathies with persistent inflammation, including macrophages and CD4+ and CD8+ T cells, that causing inflammation, fibrosis, and ossification at enthesitis sites, cytokines specifically, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-)also play a significant role in the inflammatory process. In spondyloarthropathies, the IL-23/IL-17 axis plays a significant role in Th17 cell activation and the generation of the proinflammatory cytokine IL-17. [2,3] Axial spondylarthritis has also been treated by therapeutically targeting TNF-α and IL-17.

Etiology:

Although the exact cause of AS is unclear, a confluence of environmental and genetic variables results in the clinical manifestation of the illness. [4]

Genetic predisposition:

The significance of genetic predisposition is directly demonstrated by the high correlation between AS and HLA-B27. HLA-B*2705 is the genotypic subtype of HLA-B27 that is most strongly linked to spondyloarthropathies. [5]

AS is linked to IL23R, which codes for the IL-23 receptor. Th17 CD4+ T cell survival is enhanced by IL-23.Th17 cells play a pivotal role in inflammatory and infectious disorders by producing various proinflammatory cytokines, such as IL-17, IL-6, and TNF-α, and by recruiting inflammatory cells, including neutrophils, to amplify the inflammatory response. [6]

Immunology mechanisms:

The development of ankylosing spondylitis (AS) may also involve the presentation of an arthritogenic peptide derived from enteric bacteria through specific HLA molecules. [7]

Environmental factors:

It is evident that environmental influences are significant since AS does not develop in all individuals who are HLA-B27 positive. Even HLA-B27-positive first-degree relatives do not always get the illness. The sickness only affects 15–25% of these people. [7]

Epidemiology:

White people are more likely than nonwhite people to have AS. It affects between 0.1% to 1% of the overall population, with sub-Saharan Africa having the lowest incidence and northern European nations having the highest. [8] About 1% to 2% of all HLA-B27-positive individuals go on to develop AS. If they have a first-degree family with HLA-B27 positive AS, this rises to 15-20% . [7]

Age-related demographics:

AS often first manifests between the ages of late adolescence and forty. Juvenile-onset AS is the term used to describe the condition in about 10%–20% of people whose symptoms appear before the age of 16. Although a moderate or asymptomatic diagnosis of AS may be made later in life. [9]

Sex-related demographics:

Both men and women exhibit similar rates of AS prevalence. Nevertheless, due to a male-to-female ratio of approximately 3:1, clinical AS is more common in men, who also tend to display more significant radiographic abnormalities in the hips and spine compared to women . [9, 10]

Presentation:

General symptoms

Inflammatory back pain, arthritis, peripheral enthesitis, and extra-articular manifestations unique to certain organs and constitutions are all symptoms of AS. Systemic characteristics are prevalent since AS is a systemic inflammatory illness. Patients with AS most frequently complain of stiffness and chronic discomfort. Over 70% of patients experience stiffness and discomfort on a daily basis. [11]

Another typical complaint is fatigue, which affects around 65% of individuals with AS. The majority of patients say they are fairly tired. Reduced functional ability and greater discomfort and stiffness are linked to higher degrees of tiredness. [12] Weight loss and fever might happen while the illness is active . [12]

There is recommended criteria for diagnosing inflammatory back pain. [13,14]. A 72.4% specificity and 79.6% sensitivity are achieved when four of the five criteria listed below are met [14].

• Pain at night.
• Insidious onset.
• Age of onset less than 40 years.
• No relief with rest.

Peripheral enthesitis and arthritis:

Arthritis accompanied by peripheral enthesitis affects 30–50% of individuals, leading to peripheral musculoskeletal issues. The primary pathological mechanism, referred to as peripheral enthesitis, involves inflammation at the sites where ligaments and tendons connect to the bone. This condition often progresses from osteitis and erosion to ossification, resulting in radiological signs indicative of new bone formation in the periosteum. [15]

The sites listed below are frequently involved:

• Plantar fascia insertion on the calcaneus or metatarsal heads.
• Achilles tendon insertion
• The tibial tuberosity.
• The base of the fifth metatarsal head

The patella's superior and inferior poles; the iliac crest Thirty-three percent of patients have involvement of peripheral joints, most frequently the hips.

Usually, bilateral hip involvement happens throughout the first ten years of the disease's progression.

The following additional joints might be affected:

• Costovertebral joints.
• Costosternal junctions.
• Manubriosternal joints.
•Shoulder girdle (glenohumeral, acromioclavicular, and sternoclavicular joints)
• The temporomandibular joint; symphysis pubis Rarely are peripheral joints affected. There is an asymmetric oligoarticular pattern when they are engaged. Extra-articular symptoms of AS (e.g., gastrointestinal [GI], cardiac, and ophthalmologic. [16]

Workup for gastrointestinal disorders, cardiovascular disease, pulmonary illness, renal disease, neurological disease, and uveitis,

Considerations for the Approach

The best way to diagnose ankylosing spondylitis (AS) is using radiographic investigations.

Although magnetic resonance imaging (MRI) and computed tomography (CT) may be helpful in certain individuals, they are usually not included in the regular examination due to cost . [17]

Laboratory Studies:

About 75% of patients have high levels of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), which can be used as indicators of therapy response and may correspond with disease activity in some individuals but not all of them . [18]

Diagnostic Considerations

Ankylosing spondylitis (AS) is often diagnosed by combining radiologic abnormalities with clinical criteria of enthesitis or arthritis and inflammatory back pain. [19,20]

The following are among the clinical and radiographic symptoms that form the basis of the modified New York criteria for the diagnosis of AS (21):

• The lumbar spine's restricted range of motion in all three planes
• Chest expansion limited to 1 inch or less, as measured at the fourth intercostal gap.
• Pain history or present at the lumbar spine or thoracolumbar junction

The following is the grading system for radiographic sacroiliac (SI) changes: Normal is grade 0, suspicious is grade 1, minimal sacroiliitis is grade 2, moderate sacroiliitis is grade 3, and ankylosis is grade 4. Grading is a little subjective, as the sickness progresses gradually.

A definitive diagnosis of ankylosing spondylitis (AS) can be established with grade 3–4 bilateral sacroiliitis accompanied by at least one clinical

criterion, grade 3–4 unilateral sacroiliitis, or grade 2 bilateral sacroiliitis along with clinical criterion 1 or both clinical criteria 2 and 3. Additionally, if grade 3–4 bilateral sacroiliitis is observed in the absence of clinical symptoms, AS remains the most likely cause.

Axial and peripheral spondyloarthropathy classification

Axial and peripheral SpA are classified using criteria created by the Assessment of Spondylarthritis International Society (ASAS). These criteria take into account the recently developed idea of non-radiographic axial SpA, which describes individuals who exhibit axial illness symptoms but do not have the sacroiliac joint radiographic damage required to satisfy the modified New York criteria. [21]

Classification of axial and peripheral spondyloarthropathy

Rudwaleit et al. evaluated the ASAS classification criteria for peripheral SpA and found them to be more effective than modified ESSG criteria, demonstrating a sensitivity of 77.8% and a specificity of 82.9%, compared to the modified ESSG's sensitivity of 62.5% and specificity of 81.1%.

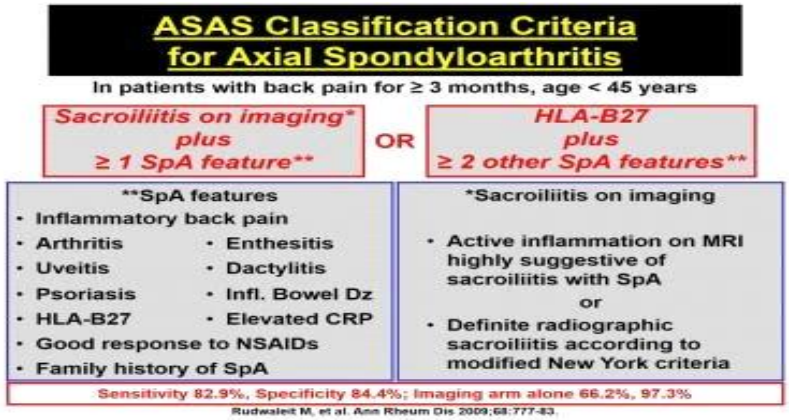

Fig (1) | ASAS Classification Criteria for Axial Spondyloarthropathy. [21]

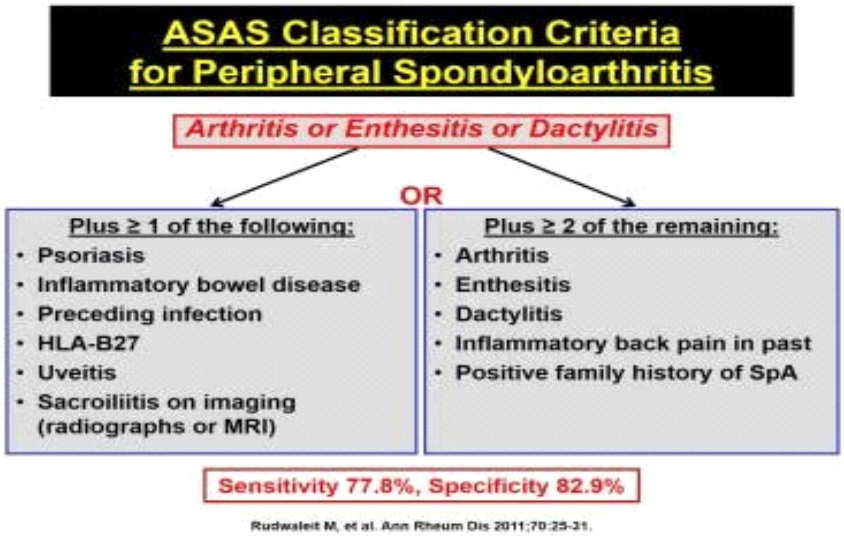

Fig (2) | ASAS Classification Criteria for Peripheral Spondyloarthropathy. [21]

Differential Diagnoses: [22]:

Imaging and Diagnosis of Diffuse Idiopathic Skeletal Hyperostosis (DISH), Diabetic Foot Ulcers, Herniated Nucleus, Degenerative Disk Disease, and Heterotopic Ossification Lumbar disc disease, kyphosis, lower cervical spine fractures, dislocations, and lumbar spine fractures Psoriatic arthritis, reactive arthritis, lumbar spondylosis, osteoarthritis, osteofibrous dysplasia, spinal stenosis, spondylolisthesis, and thoracic spine fracture.

Treatment:

Approach Considerations:

At present, there is no established cure for ankylosing spondylitis (AS), although biological treatments seem to show some benefits. Timely diagnosis leads to improved results. As with any long-term condition, educating patients is crucial for helping them understand the symptoms, progression, and management of the disease. Treatment options include medication, surgery, and physical therapy. However, no medication has been shown to alter the disease's progression, IL-17 inhibitors (IL-17i) and tumor necrosis factor-α (TNF-α) inhibitors (TNHi) show potential as disease-modifying therapies. [23]

Patients with AS typically do not require inpatient treatment. Patients who need surgery or have a comorbid or extra-articular illness are the exceptions to this rule.

The following are examples of extra-articular manifestations that may require a referral to a specialist for the proper management. [16]

Conduction abnormalities, pulmonary fibrosis, amyloidosis, acute anterior uveitis, aortitis, neurologic deficiencies, including cauda equine, and related inflammatory bowel illness.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are valuable laboratory markers for monitoring disease progression and assessing treatment response. [18]

The goal of surgical therapy is to address the issues associated with AS; it is seldom used to fix spine abnormalities due to the high morbidity rate and is only sometimes utilized to repair injured peripheral joints. When patients with AS-related spinal fusion report a shift in their spine's position, they should be treated with caution and treated as though they may have had a spinal fracture. Stabilizing the fracture and preventing a brain injury may need surgery**.** [24]

Atherosclerosis:

The natural history of atherosclerosis, a chronic and progressive inflammatory disease that begins early in life, is marked by a protracted subclinical period. [24]

All arteries are impacted by atherosclerosis, an inflammatory condition that can cause ischemia in the heart, brain, or limbs. Plaques arise as a result of interactions between environmental and genetic variables that cause the artery wall to react to stimuli through the action of platelets, inflammatory cells, smooth muscle, and endothelial cells. [25]

The first phases, which are quiet and develop gradually, start in childhood and adolescence and often present clinically around middle life. But the initial atherosclerosis-induced incident can be lethal.

There has been a growing recognition of the significance of subclinical atherosclerosis. For example, older adults suffering from this condition tend to have a worse prognosis compared to those who do not exhibit early signs of the disease. [26]

Signs & symptoms:

Atherosclerosis often remains asymptomatic for decades, as the arteries can expand at all plaque sites, resulting in no immediate impact on blood flow. Even when plaque ruptures occur, they typically do not lead to symptoms until significant narrowing or blockage of an artery, caused by clots, takes place. Symptoms and signs generally emerge only after severe narrowing or blockage restricts blood flow to various organs sufficiently to trigger noticeable effects . [27]

Patients typically don't become aware that they have the illness until they suffer from other heart-related conditions like a heart attack or stroke. However, these symptoms continue to differ according to the damaged organ or artery .[28]

Clinically, men in their 40s and women in their 50s to 60s are usually linked to symptomatic atherosclerosis due to decades of artery expansion. Subclinical, the illness seldom manifests at birth and usually first manifests in childhood. At puberty,

noticeable symptoms may start to appear. Early screening for cardiovascular illnesses in children may benefit the kid and his or her family, even if symptoms are uncommon in young patients. Men are more likely than women to have coronary artery disease, although both sexes are equally susceptible to stroke and cerebral artery atherosclerosis.

Epidemiology of cardiovascular events in ankylosing spondylitis

Patients with AS have higher standardized mortality ratios (SMRs) than the general population (1.6–1.9), and cardiovascular events frequently cause early mortality. [29, 30] Patients with AS had a greater risk of cardiovascular morbidity in addition to higher SMRs. [30, 31] There are little and inconsistent data on the prevalence of cardiovascular disease in AS patients. Peripheral artery disease, cerebrovascular accidents, and ischemic heart disease are more prevalent in AS patients than in the general population, according to much research. [32] As of right now, the majority of research (though not all of them) have found that AS patients are at a higher risk for a number of cardiovascular problems than people without AS. In a cohort research, Eriksson et al. [32] showed that individuals with AS had a 30–50% increased risk.

Compared to the general population, there is an increased risk of cerebrovascular and thromboembolic events that cannot be fully attributed to traditional cardiovascular risk factors such as diabetes, smoking, obesity, hyperlipidemia or dyslipidemia, and arterial hypertension.

The connection between ankylosing spondylitis patients increased cardiovascular risk and atherosclerosis is an inflammatory, persistent, progressive illness that first shows no symptoms for a long time. It has been demonstrated that atherosclerosis, the primary source of increased cardiovascular risk and one of the major causes of cardiovascular system mortality and morbidity, is influenced by mechanisms related to systemic inflammation [33] Atherogenesis starts at the sites of endothelial damage, and endothelial dysfunction represents an early, initially reversible stage in the development of atherosclerosis . [34] and endothelial damage sites are where atherogenesis starts. Furthermore, all phases of atherosclerosis—from plaque development to instability and ultimately plaque rupture—are influenced by inflammation and compromised endothelial function [35] This process involves numerous proinflammatory molecules, including fibrinogen, TNF-α, IL-1, IL-6, IL-10, IL-17, and IL-23 cytokines, as well as CRP. Consequently, Biomarkers indicative of inflammation and endothelial dysfunction are utilized as surrogate markers for subclinical atherosclerosis.[36, 37]

Another compelling argument is that inflammation itself might worsen lipid profiles. The acceleration of atherosclerosis has been demonstrated to be caused by alterations in lipid levels, particularly a decrease in serum HDLc and an increase in triglyceride and LDLc concentrations. HDLc decrease was more common in AS than in health controls in a number of investigations. [37] The increased cardiovascular risk in AS people may be caused, at least in part, by this phenomenon. Furthermore, the available evidence suggests that vasa vasorum neovascularization is exclusively linked to rapid atherogenesis and is inhibited by inflammatory processes in the vascular wall. [37]

In patients, several endogenous regulators of endothelial integrity and angiogenic factors, such as ET-1, EPCs, proinflammatory cytokines, and adhesion molecules, show alterations. These biomarkers offer an opportunity to explore the link between the development of asymptomatic atherosclerosis and increased cardiovascular risk. They may also help identify individuals at high risk who could benefit from targeted therapies aimed at preventing further cardiovascular events.

Prevalence of subclinical atherosclerosis

It is noteworthy that 50% of men and 64% of women in the USA who die suddenly from coronary heart disease (CHD) have no prior symptoms of the disease, and most of these individuals were not considered to be at high risk according to Framingham risk stratification, despite the fact that the exact prevalence of subclinical atherosclerosis is unknown, According to an evaluation of almost 5000 persons 65 and older who took part in the Cardiovascular Health Study, the prevalence of subclinical atherosclerotic disease rose with age, reaching 36% for women and 38.7% for men . [38]

In a subsequent investigation, 318 asymptomatic participants were chosen at random from the Framingham Offspring Study cohort according to age, sex, and Framingham Risk Score strata. According to cardiovascular MRI, aortic atherosclerosis was evident in 38% of women and 41% of men, and plaque load rose with age group. (39)

Diagnosis:

Techniques for measuring subclinical atherosclerosis.

Atherosclerosis and subclinical atherosclerosis may be measured using a range of invasive and non-invasive methods. These methods can determine factors including plaque volume, vascular wall thickness, luminal diameter or stenosis, and the precise location and distribution of atherosclerotic disease. As a result, atherosclerosis may be recognized and measured within certain vascular distributions even if it may not cause any symptoms.

Non-invasive techniques:

- B-mode ultrasonography:

The combined thickness of the arterial medial and intimal layers, which is typically tested in the common carotid artery, may be ascertained using B-mode ultrasonography.

Carotid intima-media thickness (IMT) serves as a marker for cardiovascular event risk and the extent of atherosclerotic disease, reflecting the diffuse thickening of the intimal layer seen in atherosclerosis. (40)

- High-resolution MRI:

This non-invasive technique assesses lesion type, fibrous cap integrity, and plaque volume and composition. As a result, it offers a gauge of plaque burden and rupture vulnerability.

High-resolution MRI and B-mode ultrasonography are now exclusively utilized in clinical trial settings and are not yet sufficiently advanced for diagnosing individual patients. The reproducibility of IMT measurements outside of core laboratory conditions is still up for debate.

Ankle-Brachial Index (ABI) Measurement The ankle-brachial index (ABI) is a noninvasive, straightforward, reproducible, and cost-effective diagnostic test that compares blood pressures in the upper and lower limbs to assess resistance to blood flow in the lower extremities, often due to arterial lumen narrowing from atherosclerosis. Its simplicity and low cost make ABI measurement an ideal tool for the early detection of peripheral arterial disease (PAD) or acute arterial damage . (41)

Invasive techniques

- **Coronary angiography**

A 'lumenogram' is produced by coronary angiography, which locates plaque and shows the extent of coronary luminal stenosis. Angiography is unable to detect culprit lesions that are prone to rupture and result in acute coronary syndromes (ACS), despite the fact that the quantity and presence of high-grade stenoses are linked to an elevated risk of subsequent coronary events . (42)

- **Intravascular ultrasound (IVUS)**

Another experimental method, intravascular ultrasonography (IVUS), is an invasive operation that may be performed at the tip of a coronary catheter because of the downsizing of ultrasound transducers. IVUS can measure the size and composition of plaque across the artery wall's thickness, which offers information on the location of lesions and the extent of plaque load, in contrast to coronary angiography, which determines the effect of atherosclerosis on the vessel lumen. (43)

Prevention and treatment of atherosclerosis:

Treatment for the diagnosed condition may necessitate the administration of antihypertensive medication., anti-clotting- drugs like aspirin, or cholesterol-lowering drugs like statins. A number of treatments, including carotid endarterectomy, coronary artery bypass graft, and percutaneous coronary intervention, may also be performed. (44)

Symptom relief is a common goal of medical interventions. Nonetheless, strategies that target the reduction of underlying atherosclerosis rather than just its symptoms are more successful. (45)

The initial line of therapy is typically non-pharmacological, such as quitting smoking and engaging in regular exercise. (46)

Medications are often the next line of treatment for cardiovascular disorders if these approaches fail, and with advancements, they have progressively

emerged as the most successful approach in the long run.

Statins

Statins are a class of drugs that are frequently administered to treat atherosclerosis. With little adverse effects, they have demonstrated advantages in lowering cardiovascular disease and death in those with elevated cholesterol. (47)

Multi-society guidelines recommend secondary prevention therapy, which includes aspirin and high-intensity statins, for all patients with a history of atherosclerotic cardiovascular disease (ASCVD) in order to prevent the recurrence of peripheral arterial disease, coronary artery disease, or ischemic stroke. (48)

When it is in the subclinical phase. Significant variations in the rates of development of coronary and carotid atherosclerotic disease are linked to statin therapy's reduction of atherogenic lipoprotein load.

Aggressive statin treatment can reduce LDL-C and show some degree of plaque reversal.

Aggressive LDL-C lowering is associated with substantially greater reductions in the risk of acute cardiovascular events, the need for revascularization, and hospitalization for unstable angina pectoris, compared to more moderate lipid-lowering approaches. This was demonstrated in the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 trial. The critical importance of significant cholesterol reduction with statins in individuals with established atherosclerotic disease is further reinforced by recent clinical outcome studies . (49)

Serum Irisin:

Irisin: A Novel Molecule

Bostrom at Harvard University released the first report on irisin in 2012. Irisin was defined as an exercise-induced myokine having a 112-amino acid peptide structure. Fibronectin type III domain containing 5 (FNDC5) genes encode the type I membrane protein cleavage that produces irsin. (50)

In particular, the FNDC5 structure is made up of a 94-amino acid domain, a 29-amino acid signaling peptide, and a C-terminal that is thought to be the location that performs lysis prior to being released into the bloodstream as irisin.

This molecule has been identified in other animals, where it may have extremely similar structures and activities; for example, it is 100% comparable in humans and mice . (51)

The primary secretory tissues of irisin are skeletal muscle, particularly the perimysium, endomysium, and nuclear portions; other secretory tissues include adipose tissue, the pancreas, sebaceous glands, and cardiac muscle.

Salivary glands, ovaries, testes, rectum, cerebral arteries, tongue, optic nerve, stomach, neuronal cells, and sweat glands have all been shown to exhibit irisin immunoreactivity. (51)

The potential control of thermogenesis is among irisin's most significant roles. This mechanism was studied in vitro in muscle by Vaughan et al. (52)

Irisin increases the expression of the receptor activated by peroxisome and its coactivator-1α (PGC-1α), which in turn promotes the production of intracellular factors such mitochondrial uncoupling protein mRNA 1 (UCP1) . (53) which have specialized roles in mitochondrial biogenesis . (52)

In their investigations to clarify the molecular processes of irisin, Zhang et al. discovered that r-irisin therapy increases UCP1 via increasing the phosphorylation of regulatory kinases and p38 mitogen-activated protein kinase (p38 MAPK) . (54)

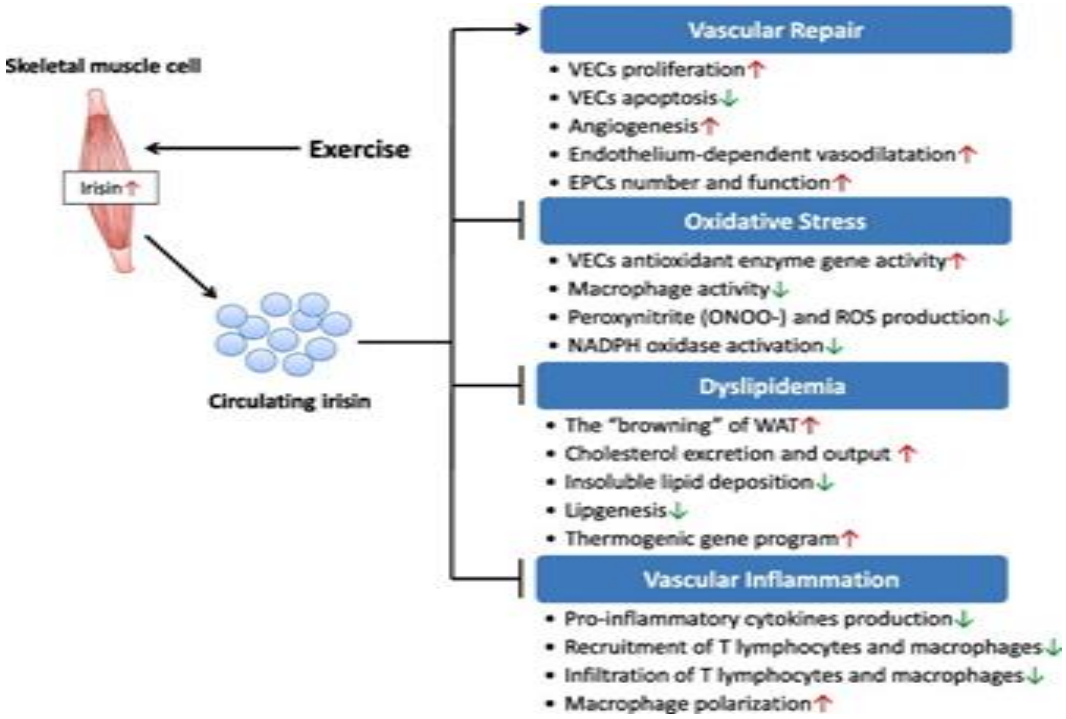

Fig (3) | Irisin, an exercise-induced myokine, is synthesized in skeletal muscle and released into the bloodstream, enhancing vascular repair, inhibiting inflammation, dyslipidemia, and oxidative stress. (63)

Thus, irisin is suggested as a hormone that can boost energy expenditure, encourage weight reduction, and reduce diet-induced insulin resistance. (55)

The expression of Fndc5 mRNA or enzyme-linked immunosorbent tests in plasma or serum (ELISA) are used to assess irisin. (56)

In muscle, it is also expressed in the heart, rectum, and pericardium; it may also be identified in the kidney, liver, lungs, and adipose tissue, according to Huh et al. (57)

Irisin participates in the regulation of numerous physiological and pathological processes and mediates energy metabolisms in muscle and other organs, including the liver and AT, by facilitating the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) through a network of paracrine, autocrine, and endocrine pathways. (58)

At first, research mostly concentrated on irisin's connection to lipid and glucose metabolism. (59)

Low serum irisin levels may be intimately linked to the increased risk of CVD in T2DM patients, and subsequent clinical investigations have demonstrated relationships between greater serum irisin levels with a reduced burden of coronary atherosclerosis in the Japanese male general population . (60)

Serum irisin levels were also shown to be considerably lower in individuals with myocardial infarction and coronary artery disease, and they were believed to be an independent predictor of the severity of the illness. (61)

Additionally, it was demonstrated that in peritoneal dialysis patients, reduced irisin concentrations were negatively correlated with carotid intima-media thickness and strongly associated with carotid atherosclerosis. (62)

Irisin may help cure atherosclerosis by suppressing endothelial damage, neointima development, inflammation, and oxidative stress in the atherosclerotic vasculature, according to some current research. *(63)*

Relevant clinical studies on the thorough assessment of the particular development of related diseases within irisin intervention are currently underway, while the majority of current research on irisin's regulatory role during atherosclerotic lesions has been carried out using animal models and cells in culture.

There are connections between irisin and important pathological processes of atherosclerosis, such as

vascular repair, oxidative stress, dyslipidemia, and vascular inflammation, since recent studies have neatly defined irisin and its antiatherosclerosis activities. Novel insights into therapeutic targets for the prevention, diagnosis, and treatment of atherosclerosis should surface as our understanding of the role of irisin activities deepens. [62]

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