REVIEW ARTICLE

IRISIN AS A NOVEL DIAGNOSTIC BIOMARKER FOR INFLAMMATORY DISEASES: A REVIEW

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Background: Inflammatory biomarkers are molecules that can offer vital information on the intricate chain of happenings and molecular processes underpinning the pathophysiology of any inflammatory disease. They can be measured in various biological samples such as blood, urine, or saliva, and are used as indicators of the presence and severity of inflammation. Measuring salivary inflammatory biomarkers is a non-invasive and relatively easy way to monitor inflammation, and it has been shown to be a useful tool in the diagnosis and management of various oral and systemic inflammatory diseases. Irisin is a novel anti-inflammatory protein and its implication and diagnostic role in inflammation have been widely studied; however, not much have been studied in oral inflammation per se. Irisin is predominantly downregulated in several inflammatory conditions, including obesity, type 2 diabetes, periodontitis, and cardiovascular diseases. This suggests that irisin may be involved in the inflammatory process, but more research is needed, especially of salivary irisin to understand its precise role. Overall, the role of irisin as an inflammatory biomarker is still an area of active research, and more studies are needed to determine its diagnostic and therapeutic potential. This review highlights the diagnostic and therapeutic potential of irisin in various systemic and oral inflammatory conditions.

Keywords: Diagnostic biomarkers; Inflammatory diseases; Salivary irisin; Serum irisin

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INTRODUCTION

A biomarker is a molecule that is empirically measured and assessed as a gauge of biological and pathogenic developments, or pharmacologic responses to a therapeutic intervention. To diagnose a disease, monitor a patient's drug therapy, and assess a patient's response to an exposure or a therapy, biomarkers and diagnostics are crucial components and are also important for the development of medical therapeutics. They can be derived from histological, molecular, radiographic, or physiologic characteristic.[1,2] The detection of one or more biological biomarkers is the first step in diagnostic growth.[2] A diagnostic biomarker recognises or verifies the presence of a disease, a condition of interest, or identifies an individual with a subtype of the disease.[1] Numerous catalogued biomarkers are employed in diagnostic products and devices and are mentioned in the literature. Having this wide range of information and intricacy of developing and modifying prototypes, selection of biomarkers remains one of the most challenging aspects in designing and inventing diagnostic devices. This is the reason that there is always a need for new diagnostic biomarkers with improved sensitivity and specificity.[3] Numerous novel biomarkers are presently being researched to obtain better and improved tools in the diagnostics. In this regard, more research is emphasized on the discovery of new proteins that can be used as diagnostic biomarker, such as the novel protein irisin.

Many studies have established the multifunctional role of irisin and its advantageous effects on body homeostasis. Irisin depicts its therapeutic effects by decreasing systemic inflammation[4] and by keeping the balance between bone formation and resorption[5]. Many studies in the literature impart their role in understanding the molecular mechanism underlying the anti-inflammatory effects of physical activity, and further confirm the anti-inflammatory role of irisin in the development of illnesses associated with chronic inflammation.[6] However, no study has narrated the role of irisin in both systemic and oral inflammatory diseases. Majority of the studies depict research being done on serum irisin, especially in systematic diseases; less work has been done on salivary irisin. Thus, to have a better understanding of irisin as a diagnostic biomarker, this review explores the work done on irisin and its association with diseases, especially with

oral inflammatory diseases, and particularly of salivary irisin. Overall, the role of irisin as an inflammatory biomarker is still an area of active research, and more studies are needed to determine its diagnostic and therapeutic potential. Furthermore, this review highlights the diagnostic and therapeutic potential of irisin in various systemic and oral inflammatory conditions.

Irisin

Irisin is a novel protein which was discovered as an exercise-induced myokine in 2012. Fibronectin type III domain-containing protein 5 (FNDC5) is released from skeletal muscle during exercise via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). After the release of FNDC5, it is cleaved by an unknown protease and irisin is formed. PGC1-α activates many of the most well-known positive effects of exercise on muscle such as fibre type switching, angiogenesis, and mitochondrial biogenesis. Irisin initiates significant alterations in subcutaneous adipose tissue and promotes browning of white adipose tissues by inducing the increased expression of uncoupling protein-1 (UCP-1). Crucially, this results in a marked increase in total body energy expenditure and opposition to insulin resistance associated with obesity. The action of irisin thus mimics some of the most significant advantages of exercise and muscle activity.[7]

Secretion and distribution of irisin

The cleavage and secretion of irisin are similar to some other transmembrane polypeptide hormone, such as transforming growth factor-alpha (TGF-α) and epidermal growth factor (EGF).[7] Irisin is secreted from the skeletal muscles specially in the perimysium, endomysium, and nuclear parts. Adipose tissues, sebaceous glands, and cardiac muscles also secrete irisin. Certain immunological studies have reported that it is also expressed in stomach, pancreas, liver, salivary glands, rectum, intracranial arteries, tongue, sweat glands, optic nerve, brain, oesophagus, and ovaries.[8,9] Irisin secretion is influenced by many factors, such as diet, exercise, drugs, temperature, and pathological conditions.[9] Serum irisin levels were significantly elevated in individuals engaged in exercise-induced activities as compared to those with less active and sedentary life style.[7]

Role of irisin

A myokine is a cytokine or a peptide which is secreted by skeletal muscle cells and is then released into the circulation. It exerts its endocrine or paracrine effects in other cells, tissues, and organs. Irisin being a novel myokine can play its role by several intracellular signalling pathways.[10] Irisin exercises its role in neural differentiation, white adipocytes browning, and osteoblasts proliferation. It can increase energy expenditure, promote weight loss, and reduce insulin resistance caused by food intake.[7] Salivary irisin has gained attention due to its non-invasive collection and correlation with serum levels.[11]

The therapeutic role of irisin is being studied in recent years. As an anti-inflammatory myokine, its role in therapeutics can open new horizon in the field of health and research. Table 1 provides a brief overview of therapeutic role of irisin in inflammatory diseases.

Table-1: Therapeutic role of irisin in various inflammatory diseases

Disease	Study sample type	Therapeutic role of irisin	Reference
Metabolic disorders	Serum irisin (humans)	Irisin converts WAT to BAT by increasing UCP-1, which increases thrombogenesis, improves lipid and hepatic glucose metabolism, and enhances glucose uptake. It plays beneficial role in hyperlipidaemia and hyperglycaemia	Chen *et al*., 2016[12]
Neurological disorders	Human CSF (ELISA) Human and mice brain tissue (immuno-detection)	- Low levels of irisin in CSF of AD patients - *In vitro* examination revealed an improvement in memory defects by increasing irisin levels in experimental mice model of AD - Peripheral administration of irisin amended memory damage in AD models	Lourenco *et al*., 2019[13]
Cancer	Tissue (cell culture)	Time- and dose-dependent irisin administration showed a decrease in cell proliferation and viability of both LNCaP and DU-145 cell lines in prostate cancer	Saeedi *et al*., 2022[14]
Post-menopausal osteoporosis	Affected bone in mice	Histological examination of irisin-treated group revealed appreciable normal bone architecture, numerous osteocytes and few osteoclasts, and demarcated lines of sub-periosteal bone formation, as compared to controls	Morgan *et al*., 2021[15]

AD: Alzheimer's disease, BAT: Brown adipose tissue, CSF: Cerebrospinal fluid, ELISA: enzyme-linked immunoassay, LNCaP: Lymph node carcinoma of the prostate, UCP-1: Uncoupling protein-1, WAT: White adipose tissue

Irisin and inflammation

Irisin has gained much attention since its discovery. It is reported that irisin plays an essential role in many processes, among them, inflammation. It suppresses vascular inflammation by inhibiting the chemotaxis of inflammatory cells into atherosclerotic lesions and by inducing the switch from pro-inflammatory phenotype of macrophages to the anti-inflammatory phenotype macrophages.[16] Irisin further downregulates pro-inflammatory pathways so that the secretion of pro-inflammatory cytokines is supressed.[17] Both *in vitro* and *in vivo* studies have shown noteworthy anti-inflammatory

properties of irisin as it moderates the production of cytokines, reduces oxidative stress, and induces mitogen-activated protein kinase (MAPK) cascade factors. Irisin inhibits the downstream pathway of toll like receptor-4 (TLR4), which in return supresses the MAPK phosphorylation and subsequently lowering the nuclear factor-kB (NF-kB) activation. All these changes lead to a reduction in the release and expression of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1β, high mobility group box-1 (HMGB-1), and monocyte chemotactic protein-1 (MCP-1).[18]

In summary, the primary role of irisin is related to metabolism and physical activity; there has been a lot of research suggesting a link between diagnostic potential of irisin and inflammatory diseases. Many studies have shown that irisin levels may be altered in certain inflammatory conditions; thus, establishing irisin as a potential diagnostic biomarker for inflammatory diseases.

Irisin as diagnostic inflammatory biomarker

Inflammatory response to any injury or infection is a very crucial survival mechanism. Chronic inflammatory disorders are linked with the activation of detrimental signal transduction pathways and release of many inflammatory mediators, all of which impart their roles in disease development.[19] At the inflammatory sites, various inflammatory mediators act in a limited manner and support the process of inflammation. Among these mediators are different anaphylatoxins of complement cascade, some prostaglandins, leukotrienes, kinin proteins of the coagulation system, and various other lipid mediators. These mediators are found in serum or tissue fluids and are released by degenerating cells. They can also be secreted by some inflammatory cells or endothelial cells upon stimulation. There are many immunoregulatory cytokines, such as IL-6, IL-8, cyclooxygenase, C-reactive protein (CRP), and TNF-α, which are termed as anti-inflammatory cytokines. They neutralize various aspects of inflammation, namely the cell stimulation or the synthesis of pro-inflammatory cytokines. In this way, they control the magnitude of the inflammatory responses,[20] and can be effective diagnostic biomarkers[21].

The potential of irisin as a biomarker has promoted much research in different pathological conditions, including cardiovascular diseases (CVD), different types of cancer, chronic inflammatory diseases, metabolic disorders, osteoporosis, and autoimmune diseases.[6,22,23] Higher levels of serum irisin were observed in patients with severe inflammation. These results suggested an association between the high irisin levels and an inactive or bed-ridden lifestyle of the patients. However, the mechanism through which irisin levels are increased or decreased in inflammatory diseases is still not fully understood. More studies with increased sample size are needed to answer this query.[24]

In metabolic diseases such as diabetes, low serum irisin levels are noted.[25] It can be speculated that preventive measures taken before a major drop in irisin levels may have a greater impact on halting or stabilising the progression of pre-diabetes. This would highlights irisin's capacity to restore glucose metabolism until a certain threshold of metabolic failure and turn irisin into a helpful parameter in metabolic research.[26,25] A study[26] proposed that decreased irisin levels are correlated with development of insulin resistance and diseases related to insulin inefficiency such as type 2 diabetes mellites (T2DM). However, the study did not consider some potential confounding factors such as physical activity and dietary habits, which can affect the results.[27]

In addition to the inflammatory disorders listed above, psoriasis is another frequent inflammatory skin disease. A slight increase in the irisin level was seen in patients with psoriasis compared to controls. Moreover, a significant difference was seen between mild and severe psoriasis.[28] Another skin inflammatory lesion is acne vulgaris. Decreased serum irisin levels were seen in patients with acne vulgaris as compared to the controls and a negative correlation was seen with the severity of the lesion. Irisin was reported as a diagnostic and prognostic indicator of acne vulgaris.[29]

Most of the studies show serum irisin levels in various diseases, which can be a limitation of these studies. Other body fluids such as saliva, must be considered for the evaluation of irisin levels, to have a better understanding of irisin as a diagnostic biomarker. Salivary proteins have earned a trustworthy place in diagnostics for the detection of various human ailments such as episodes of acute myocardial infarction, asthma, chronic obstructive pulmonary disease, and autoimmune immunodeficiency syndrome (AIDS). Salivary biomarkers can be of more importance, especially regarding the oral inflammatory diseases. It was assumed that increased salivary irisin levels in recurrent aphthous stomatitis (RAS) were due to the anti-inflammatory role of irisin as a compensatory process to recover from the inflammation.[30] A positive association was observed between salivary irisin and salivary IL-6 levels in patients with grade B periodontitis, where both biomarkers were raised in periodontitis group as compared to controls.[31] Even though studying inflammatory biomarkers in blood has become a ritual, their detection in saliva is more accessible and non-invasive. Role of irisin as a diagnostic inflammatory biomarker in various inflammatory diseases is summarised in Table 2.

Table-2: Diagnostic role of irisin in various inflammatory diseases

Disease	Study methodology	Sample type	Irisin profile/conclusion	Reference
Metabolic diseases				
i. Gestational DM	*In vivo*	Serum	↓ irisin levels	Kulhan *et al*., 2019[26]
ii. Myocardial injuries in severe hypothyroid disease	*In vivo*	Serum	↓ irisin levels	Yao *et al*., 2021[25]
Cardiovascular diseases (CVD)				
i. CAD and ACS	*In vivo*	Serum	- ↓ irisin levels in patients with ACS - ↑ irisin levels exhibited higher survival rate in both SCAD and ACS after successful percutaneous coronary intervention	Pan *et al*., 2021[16]
ii. CAC	*In vivo*	Serum	- ↑ baseline serum levels are associated with lower prevalence of CAC - ↑ serum levels are associated with better cardiometabolic profile including obesity, lipids, and diabetes - Irisin has the potential role in predicting occurrence and development of CAC	Hisamatsu *et al*., 2018[32]
Cancers				
i. Prostate cancer	*In vivo*	Serum	- ↓ levels of irisin compared to controls - No relationship between irisin levels, cancer staging, and Gleason scores - Irisin can be used as a diagnostic biomarker with or without PSA as adjunct biomarker	Aslan *et al*., 2020[33]
i. CRC	*In vitro*	Cell culture	- ↑ irisin expression in CRC cells compared to control cells - Significant difference of irisin expression in stage I as compared to stage III and IV of CRC, where irisin was ↓ in advanced stages	Wozniak *et al*., 2022[34]
Neurological disorders AD	*In vivo*	CSF	Positive correlation between irisin levels, BDNF, and cognition in AD	Lourenco *et al*., 2020[35]
Oral inflammatory diseases				
i. RAS	*In vivo*	Saliva	↑ levels of irisin, IL-2, and IF-$_\gamma$ levels compared to controls	Altay *et al*., 2021[30]
ii. Generalised periodontitis	*In vivo*	Saliva and serum	- ↑ levels of salivary irisin and IL-6 compared to controls - No significant difference of serum irisin in periodontitis and control groups	Turkmen *et al*., 2023[31]

AD: Alzheimer's disease, ACS: Acute coronary syndrome, BDNF: Brain-derived neurotropic factor, CAD: Coronary artery disease, CAC: Coronary artery calcification, CRC: Colorectal carcinoma, CSF: cerebrospinal fluid, DM: Diabetes mellitus, IF-$_\gamma$: Interferon-Gamma, IL-6: Interleukin-6, IL-2: Interleukin-2, PSA: Prostate specific antigen, RAS: Recurrent aphthous stomatitis, SCAD: Stable coronary artery disease.

Salivary irisin as diagnostic inflammatory biomarker

Irisin is usually measured in blood; however, blood collection exposes patients to potential dangers such as needle discomfort, infection at the venipuncture site, and bruising.[11] Furthermore, it is less desirable in research involving youngsters, the elderly, and individuals who do not have good venous access. As a result, an alternative method for detecting irisin appears desirable. There are only a few studies which have investigated salivary irisin.[11] The potential role of saliva to detect irisin changes induced by physical exercise was studied. In serum and saliva samples of all participants, increased levels of irisin 24 hours post-exercise were observed, which was restored to baseline levels after 48 hours of rest.[11] Therefore, it was suggested that collecting saliva samples may be a valid strategy for quantifying changes in irisin level because of exercise, and that it can be employed especially in the elderly or when a time course study is necessary.

Moreover, salivary irisin has not been studied for oral diseases. Due to the local influence, salivary irisin can be a potential diagnostic biomarker for oral diseases. Table 2 shows a couple of studies done on salivary irisin as diagnostic biomarker for oral diseases.[30,31]

CONCLUSION

Irisin has a potential as a therapeutic myokine and diagnostic biomarker for inflammatory diseases, as summarised in Figure 1. Saliva, being an easy to collect diagnostic tool, can be used to study irisin in oral inflammatory conditions. Further investigations into the role of salivary irisin in inflammatory diseases is warranted and may ultimately lead to new diagnostic and therapeutic strategies for improving patient outcomes.

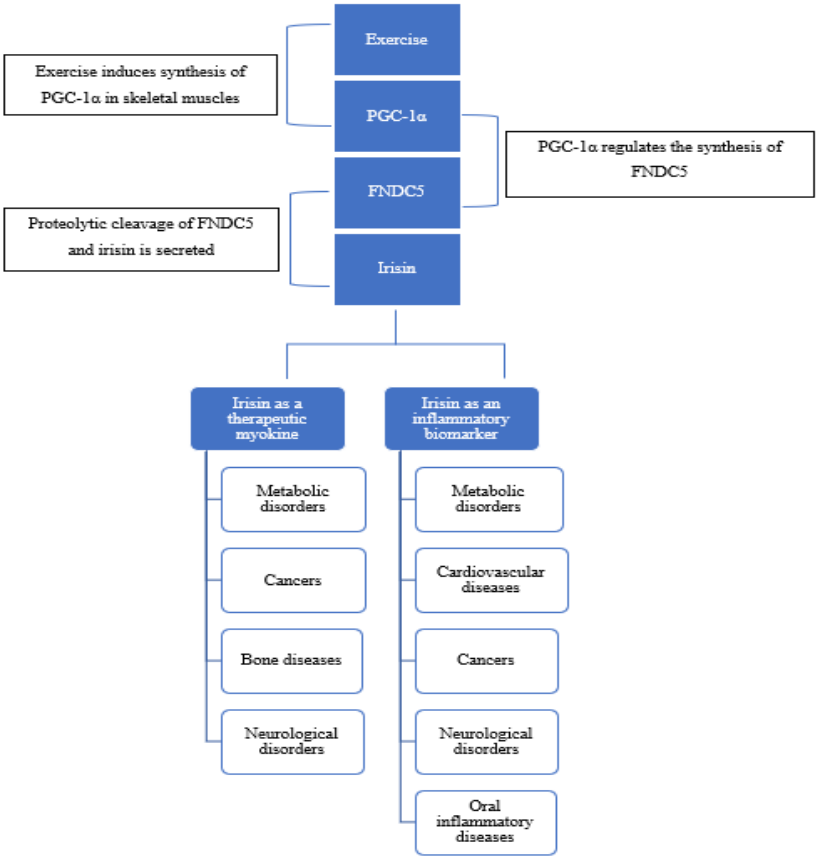

Figure-1: Overview of secretion of irisin and its promising roles as therapeutic myokine and biomarker in some conditions.

REFERENCES

1. Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood) 2018;243(3):213–21.
2. Srinitha B. Biomarkers and Disease Diagnosis. Prim Health Care Open Access 2021;11(4):1–2.
3. Byrnes SA, Weigl BH. Selecting analytical biomarkers for diagnostic applications: a first principles approach. Expert Rev Mol Diagn 2018;18(1):19–26.
4. Mazur-Bialy AI. Irisin acts as a regulator of macrophages host defense. Life Sci 2017;176:21–5.
5. Mazur-Bialy AI, Kozlowska K, Pochec E, Bilski J, Brzozowski T. Myokine irisin-induced protection against oxidative stress in vitro. Involvement of heme oxygenase-1 and antioxidazing enzymes superoxide dismutase-2 and glutathione peroxidase. J Physiol Pharmacol 2018;69(1):117–25.
6. Korta P, Pochec E, Mazur-Bialy A. Irisin as a Multifunctional Protein: Implications for Health and Certain Diseases. Medicina (Kaunas) 2019;55(8):485.
7. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, *et al*. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481(7382):463–8.
8. Aydin S, Kuloglu T, Aydin S, Eren MN, Celik A, Yilmaz M, *et al*. Cardiac, skeletal muscle and serum irisin responses to with or without water exercise in young and old male rats: cardiac muscle produces more irisin than skeletal muscle. Peptides 2014;52:68–73.
9. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, *et al*. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab 2013;18(5):649–59.
10. Khan SU, Ghafoor S. Myokines: Discovery Challenges and Therapeutic Impediments. J Pak Med Assoc 2019;69(7):1014–7.
11. Missaglia S, Tommasini E, Vago P, Pecci C, Galvani C, Silvestrini A, *et al*. Salivary and serum irisin in healthy adults before and after exercise. Eur J Transl Myol 2023;33(1):11093.
12. Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. Diabetes Metab Res Rev 2016;32(1):51–9.
13. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, *et al*. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 2019;25(1):165–75.
14. Saeedi Sadr A, Ehteram H, Seyed Hosseini E, Alizadeh Zarei M, Hassani Bafrani H, Haddad Kashani H. The Effect of Irisin on Proliferation, Apoptosis, and Expression of Metastasis Markers in Prostate Cancer Cell Lines. Oncol Ther 2022;10(2):377–88.
15. Morgan EN, Alsharidah AS, Mousa AM, Edrees HM. Irisin Has a Protective Role against Osteoporosis in Ovariectomized Rats. Biomed Res Int 2021;2021:5570229.
16. Pan JA, Zhang H, Yu Q, Zhang JF, Wang CQ, Gu J, *et al*. Association of Circulating Irisin Levels and the Characteristics and Prognosis of Coronary Artery Disease. Am J Med Sci 2021;362(1):63–71.

17. Liu L, Guo J, Chen X, Tong X, Xu J, Zou J. The Role of Irisin in Exercise-Mediated Bone Health. Front Cell Dev Biol 2021;9:668759.
18. Mazur-Bialy AI, Pocheć E, Zarawski M. Anti-Inflammatory Properties of Irisin, Mediator of Physical Activity, Are Connected with TLR4/MyD88 Signaling Pathway Activation. Int J Mol Sci 2017;18(4):701.
19. Liu CH, Abrams ND, Carrick DM, Chander P, Dwyer J, Hamlet MRJ, *et al*. Biomarkers of chronic inflammation in disease development and prevention: challenges and opportunities. Nat Immunol 2017;18(11):1175–80.
20. Ansar W, Ghosh S. Inflammation and Inflammatory Diseases, Markers, and Mediators: Role of CRP in Some Inflammatory Diseases. Biol C React Protein Health Dis 2016;2016:67–107.
21. Dieterle MG, Putler R, Perry DA, Menon A, Abernathy-Close L, Perlman NS, *et al*. Systemic Inflammatory Mediators Are Effective Biomarkers for Predicting Adverse Outcomes in Clostridioides difficile Infection. mBio 2020;11(3):e00180.
22. Byun K, Lee S. The Potential Role of Irisin in Vascular Function and Atherosclerosis: A Review. Int J Mol Sci 2020;21(19):7184.
23. Fu J, Li F, Tang Y, Cai L, Zeng C, Yang Y, *et al*. The Emerging Role of Irisin in Cardiovascular Diseases. J Am Heart Assoc 2021;10(20):e022453.
24. Buscemi S, Corleo D, Vasto S, Buscemi C, Barile AM, Rosafio G, *et al*. Serum Irisin Concentrations in Severely Inflamed Patients. Horm Metab Res 2020;52(4):246–50.
25. Yao Z, Ding X, Gao X, Yang N, Jia Y, Liu J, *et al*. Irisin as a Potential Biomarker Associated with Myocardial Injuries in Patients with Severe Hypothyroidism. Int J Endocrinol 2021;2021:3116068.
26. Kulhan NG, Kulhan M, Turkler C, Ata N, Kiremitli T, Kiremitli S. Could serum levels of irisin be used in gestational diabetes predicting? Taiwan J Obstet Gynecol 2019;58(3):434–7.
27. Shim YS, Kang MJ, Yang S, Hwang IT. Irisin is a biomarker for metabolic syndrome in prepubertal children. Endocr J 2018;65(1):23–31.
28. Ambrogio F, Sanesi L, Oranger A, Barlusconi C, Dicarlo M, Pignataro P, *et al*. Circulating Irisin Levels in Patients with Chronic Plaque Psoriasis. Biomolecules 2022;12(8):1096.
29. Mustafa AI, El-Shimi OS. Serum irisin: A prognostic marker for severe acne vulgaris. J Cosmet Dermatol 2018;17(5):931–4.
30. Altay DU, Korkmaz M, Ergun S, Korkmaz H, Noyan T. Salivary irisin: potential inflammatory biomarker in recurrent apthous stomatitis patients. Eur Rev Med Pharmacol Sci 2021;25(5):2252–9.
31. Turkmen E, Uzun EV, Bozaba F, Balci N, Toygar H. Salivary irisin level is higher and related with interleukin-6 in generalized periodontitis. Clin Oral Investig 2023;27(6):3001–8.
32. Hisamatsu T, Miura K, Arima H, Fujiyoshi A, Kadota A, Kadowaki S, *et al*. Relationship of serum irisin levels to prevalence and progression of coronary artery calcification: A prospective, population-based study. Int J Cardiol 2018;267:177–82.
33. Aslan R, Alp HH, Eryılmaz R, Huyut Z, Sevim M, Araz Ş, *et al*. Can the Irisin be a Biomarker for Prostate Cancer? A Case Control Study. Asian Pac J Cancer Prev 2020;21(2):505–9.
34. Wozniak S, Nowinska K, Chabowski M, Dziegiel P. Significance of Irisin (FNDC5) Expression in Colorectal Cancer. In Vivo 2022;36(1):180–8.
35. Lourenco MV, Ribeiro FC, Sudo FK, Drummond C, Assunção N, Vanderborght B, *et al*. Cerebrospinal fluid irisin correlates with amyloid-β, BDNF, and cognition in Alzheimer's disease. Alzheimers Dement (Amst) 2020;12(1):e12034.

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