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10 YEARS OF BIOMEDICAL RESEARCH INTEREST REGARDING THE “EXERKINE” IRISIN: A BIBLIOMETRIC REVIEW

10 ANOS DE INTERESSE BIOMÉDICO ACERCA DA “EXERCINA” IRISINA: UMA REVISÃO BIBLIOMÉTRICA

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RESUMO

INTRODUÇÃO: A irisina é um peptídeo secretado pelo músculo esquelético após exercício físico que vem sendo amplamente estudado desde sua descoberta na última década. Embora um número robusto de estudos tenha avançado na compreensão dos efeitos desta miocina como uma molécula endócrina e potencial candidata para intervenção terapêutica para muitos distúrbios, não há dados bibliométricos catalogando seus principais avanços. O objetivo deste estudo foi analisar a produção científica de periódicos biomédicos sobre os efeitos da miocina irisina por meio de uma análise bibliométrica. **METODOLOGIA**: Uma busca foi conduzida nas bases de dados Web of Science e Scopus usando a palavra-chave “irisin" para identificar estudos entre 2001 e 2020. Os dados de todas as publicações foram exportados e analisados no pacote Bibliometrix usando o software R. **RESULTADO**: Um total de 1579 artigos foram incluídos, e a tendência de publicações anuais mostrou um crescimento significativo entre 2012-2020. China e Harvard Medical School (Estados Unidos da América, EUA) foram o país e a instituição mais produtivos no campo de pesquisa da irisina, e os EUA foram o país com mais manuscritos citados sobre o tema. Os atuais hotspots de pesquisa da irisina estão em “doenças metabólicas” e “doenças relacionadas ao sistema nervoso central”, e sugerem futuras aplicações e tendências de estudo para os próximos anos. **CONCLUSÃO**: O estudo da irisina têm ganhado visibilidade e aplicação em diversas áreas, com ênfase em tópicos de saúde secundários às adaptações corporais promovidas pelo exercício físico, que são dignos de maior exploração.

PALAVRAS-CHAVE: *Bibliometria; FNDC5; Irisina; Miocinas.*

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ABSTRACT

INTRODUCTION: Irisin is a peptide secreted by skeletal muscle following physical exercise that is being widely studied since its discovery over the last decade. Although a robust number of studies have advanced on understanding of the effects of this myokine as an endocrine molecule and a potential candidate for therapeutic intervention for many disorders, there is no bibliometric data cataloguing the main advances regarding this myokine and generating guidelines for future directions. The aim of this study was to analyse the scientific production of biomedical journals on the myokine Irisin effects by a bibliometric analysis. **METHODOLOGY:** A search was conducted in the Web of Science and Scopus databases using the keyword “Irisin" to identify studies between 2001 and 2020. The data from all publications were exported and analysed on the Bibliometrix package using R software. **RESULTS:** A total of 1579 papers were included, and the trend of annual publications showed a remarkable growth between 2012-2020. China and the Harvard Medical School (United States of America, USA) were the most productive countries and institutions in the Irisin research field, and the USA was the country with most cited manuscripts regarding Irisin. The current research hotspots of Irisin are in “metabolic diseases,” and “central nervous system-related diseases”. **CONCLUSION:** The authors summarize that Irisin is becoming frontier and focus on the health topics following the exercise adaptations in the upcoming years, which are worthy of further exploitation.

KEYWORDS: *Bibliometric analysis; FNDC5; Irisin; Myokines.*

INTRODUCTION

Skeletal muscle is one of the most dynamic and plastic tissues in the human body[1]. Besides the classic functions including protection for organs, ambulation, global energy metabolism, among others, recent evidence suggests that skeletal muscle could also be considered an endocrine organ, since it synthesizes and secretes multiple peptide factors[2,3]. These muscle-derived factors, known as myokines, exert beneficial effects on peripheral and remote organs, including brain, liver, bone and adipose tissue[4-7].

Irisin is a 112 amino-acid myokine synthesized after cleavage and glycosylation of the transmembrane protein fibronectin type III domain-containing protein 5 (FNDC5) that is produced and secreted by skeletal muscle following physical exercise intervention[8]. This myokine has been widely studied due to its capacity of modulating thermogenesis, neuroplasticity, immunological responses, and key metabolic pathways[9,10]. Moreover, the global biomedical interest in the endocrine function of Irisin and its role in organ crosstalk as an “exerkine”[11] has increased in the last two decades.

Although Irisin is one of the most studied myokines, some points related to review studies that are being published in this area may compromise the understanding of the findings related to this myokine and need to be improved. Given their limitations to provide an overview of its applications in the fields of health promotion, we conducted a bibliometric analysis of the scientific literature on this molecule; including chronology, citations, keywords, authors, collaboration networks, institutions, countries, themes, journals, publishing patterns, and emerging trends. By doing so, we aim to provide health professionals and researchers with an up-to-date perspective on the current state of the field and future research directions. In the present study, we aimed to investigate the global literature regarding Irisin’s effects using a bibliometric approach of all publications since the first description of this myokine by Bostrom (2012).

METHODOLOGY

The bibliometric review was conducted by Biblioshiny through the Bibliometrix package in the software RStudio. The analysis was carried out through annual scientific production, authors, countries, publication sources (relevance, impact factor, citations) and keywords that provide insights of the research topics over the years. Furthermore, the ten most global cited articles related to Irisin were read in full and summarized. Figure 1 presents the flowchart of the methodology applied in this study.

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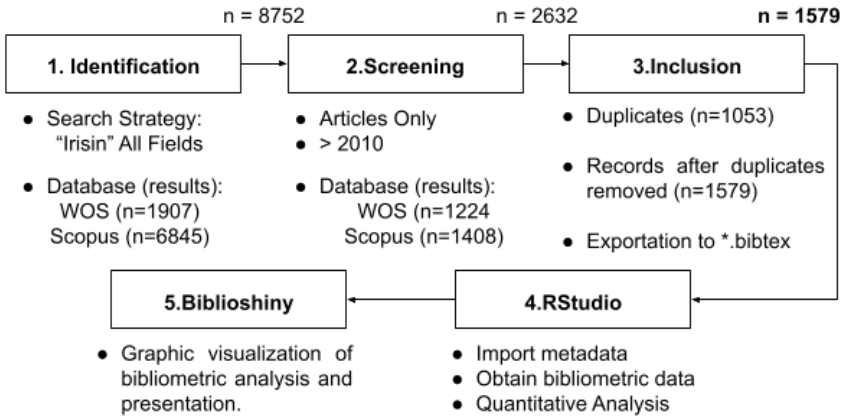
FIGURE 1. Flowchart of the methodology applied in this study.



Source: Authors (2024)

SEARCH STRATEGY OF STUDIES

The identification and screening were performed by two researchers (MSS and LCV) in Web of Science (Clarivate Analysis, Boston, USA) and Scopus (Elsevier BV Company, USA) databases on a singular day (April 4th, 2022) using the term "Irisin" (Title, Abstract, and Keywords). No language restrictions were imposed in order to reduce language bias.

ELIGIBILITY CRITERIA OF THE STUDIES

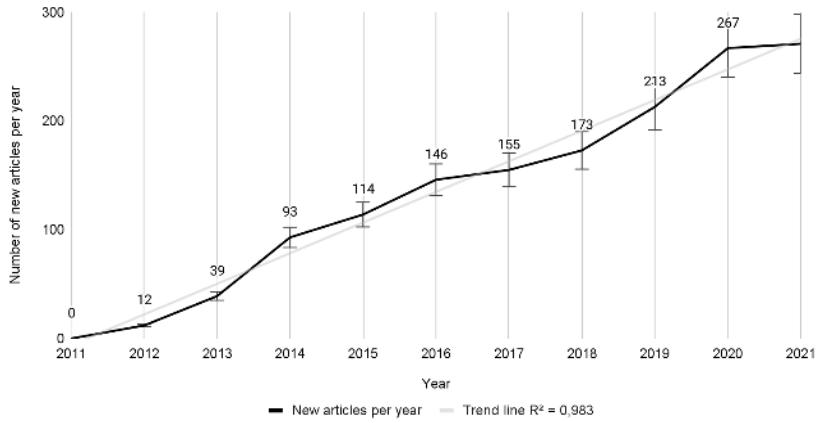
We included studies published in journals related to Medicine, Biochemistry, Sports Science, and Physical Activity. The results were filtered by "Only articles" and only publications after 2001. Duplicates were excluded automatically by RStudio Software.

RESULTS

GENERAL CHARACTERISTICS OF COLLECTED DATA

A total of 2,632 publications, 1,408 (53,5%) from Scopus, and 1,224 (46,5%) from Web of Science were retrieved. In RStudio 1,053 duplicates were excluded and bibliometric analysis was performed with 1579 articles. The timespan for this collection started in 2012 when Bostrom and colleagues published the seminal manuscript about a novel PGC1-α-dependent myokine that drives brown-fat-like development of white fat ("browning") and thermogenesis[9], which is so far the most cited document concerning Irisin. Figure 2 showed that the annual scientific production (number of publications) remarkably increased within the last decade at a 22.72% annual growth rate between 2012 and 2022. The growth trend model between 2012-2021 ($R^2 = 0.983$) demonstrates that more research on the applications of Irisin in the health promotion domain is ongoing and that this field seems to be progressive and promising.

FIGURE 2. Number of scientific productions per year.



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MOST GLOBAL CITED DOCUMENTS

We reported on the 10 most cited documents for the search described. The “Cell Metabolism” journal (IF 2020 = 27,287) presents two manuscripts published in this top 10 list of most cited manuscripts in the field of Irisin. Among these manuscripts with the largest number of citations, the average impact factor of the journals in which these articles were published was 18.498 and median = 9.079, reinforcing the great scientific relevance given to this research topic.

The 10 most cited manuscripts were downloaded, read in full and their data were summarized in Table 1. The results showed that Irisin and its processing are associated with metabolic disorders and neurodegenerative diseases. Irisin produces a browning effect, since it increases the UCP-1 expression in the adipose tissues and browning of white fat tissues, suggesting physical exercise as a promising tool for obesity management. The browning effect induced by Irisin is dependent, at least in part, on the activation of extracellular signal–related kinase (ERK) and p38 protein kinase signaling cascades[12]. Furthermore, the study by Wrann et al. (2013) was included in the top 10 most cited manuscripts and suggested that Irisin induced by physical exercise could regulate the expression of BDNF in the hippocampus, a brain region implicated in learning and memory, as well as mood[5]. This study raised the possibility of this molecule acting as a neuroprotector and opened opportunities for future investigations of the effects of this myokine on the nervous system.

TABLE 1. Most global cited documents

#	Authors	Affiliation	Title	Study Type	Summary Findings	Journal	TC	TCPY
1	BOSTROM et al., 2012	Dana-Farber Cancer Institute, and Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, USA.	A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis	Animal and Human Studies	Irisin was identified as a new muscle-secreted polypeptide regulated by PGC1-α with endocrine action on adipose tissue inducing thermogenesis and regulating body energy expenditure in mice.	Nature IF = 49.962	2732	248.36
2	WU et al., 2012	Dana-Farber Cancer Institute, and Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, USA.	Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human	Preclinical	A subset of precursor cells from white adipocyte tissues (WAT) generates beige adipocytes which have an inducible thermogenic capacity upon stimulation, as well as are sensitive to Irisin.	Cell IF = 41.584	2132	193.82

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3	HUH et al., 2012	Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.	FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise	Clinical	FNDC5 gene is expressed in human skeletal muscle. Age, insulin, cholesterol, and adiponectin levels are negatively correlated with circulating plasma Irisin, while biceps circumference, body mass index, glucose, ghrelin, and IGF-1 levels are positively correlated. Both skeletal muscle FNDC5 mRNA levels and circulating Irisin levels are downregulated after bariatric surgery. Circulating Irisin levels is upregulated 30 min after acute exercise	Metabolism: clinical and experimental IF = 8.697	678	61.64
4	WRANN et al., 2013	Dana-Farber Cancer Institute, and Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, USA.	Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway	Preclinical	FNDC5 is elevated by endurance exercise in the hippocampus of mice and is regulated by PGC-1α. Peripheral delivery of FNDC5 to the liver via adenoviral vectors resulted in elevated blood Irisin and Bdnf gene expression upregulation in the hippocampus.	Cell Metabolism IF = 27.287	611	61.10
5	MORENO NAVARRETE et al., 2013	Department of Diabetes, Endocrinology, and Nutrition, Hospital of Girona Dr Josep Trueta, Girona, Spain.	Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance	Preclinical	FNDC5 gene expression in skeletal muscle of obese and type 2 Diabetes Mellitus participants was significantly decreased while circulating irisin levels were negatively associated with obesity and insulin resistance.	The Journal of Clinical Endocrinology & Metabolism IF = 5.958	522	52.20
6	LEE et al., 2014	National Institutes of Health, Bethesda, Maryland, USA.	Irisin and FGF21 Are Cold-Induced Endocrine Activators of Brown Fat Function in Humans	Clinical and preclinical	Shivering stimulates Irisin secretion in humans while non-shivering cold exposure increases FGF21, which may be a brown adipokine. Exercise may be a shivering mimic exemplifying muscle-fat thermogenic crosstalk.	Cell Metabolism IF = 27.287	503	55.89

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7	ZHANG et al., 2014	Center for Stem Cell and Regenerative Medicine, The Second Hospital of Shandong University, Jinan, People's Republic of China.	Irisin Stimulates Browning of White Adipocytes Through Mitogen-Activated Protein Kinase p38 MAP Kinase and ERK MAP Kinase Signaling	Preclinical	Irisin is a potential target for obesity and type 2 Diabetes Mellitus management by stimulating expression of “browning” genes via the p38 MAPK and ERK pathways.	Diabetes IF = 9.461	435	48.33
8	ROCA-RIVADA et al., 2013	Instituto de Investigación Sanitaria de Santiago de Compostela, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain.	FNDC5/Irisin Is Not Only a Myokine but Also an Adipokine	Preclinical	WAT (visceral and subcutaneous) expresses and secretes FNDC5, an putative adipokine. Obesity stimulates FNDC5 secretion while it is reduced in fasting animals.	Plos One IF = 3.240	386	38.60
9	NORHEIM et al., 2014	Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Norway.	The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans	Clinical	12 weeks of aerobic physical exercise had no effect or tended to reduce circulating Irisin levels.	FEBS J IF = 5.542	341	37.89
10	PARK et al., 2013	Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA	Circulating Irisin in Relation to Insulin Resistance and the Metabolic Syndrome	Clinical	Associations between high circulating irisin levels, metabolic syndrome, and insulin resistance can be explained by a physiological compensatory mechanism due to an underlying decreased sensitivity to irisin's effects or can be increased by muscle and fat tissue in obesity.	The journal of clinical endocrinology & Metabolism IF = 5.958	332	33.20

ID: Inclusion decision; TC: Total citations; TCPY: Total citations per year..

COUNTRIES INVOLVED IN THE IRISIN RESEARCH TOPIC

Most of the papers addressing “Irisin” were published by China (1º), Turkey (2º), and USA (3º). However, the countries of the authors of the most cited manuscripts in the research field are USA (n= 15362), China (n= 6118) and Germany (n=2471). When it comes to the relation, citation per article, USA has the highest average number of citations per article (n= 130.19) followed by

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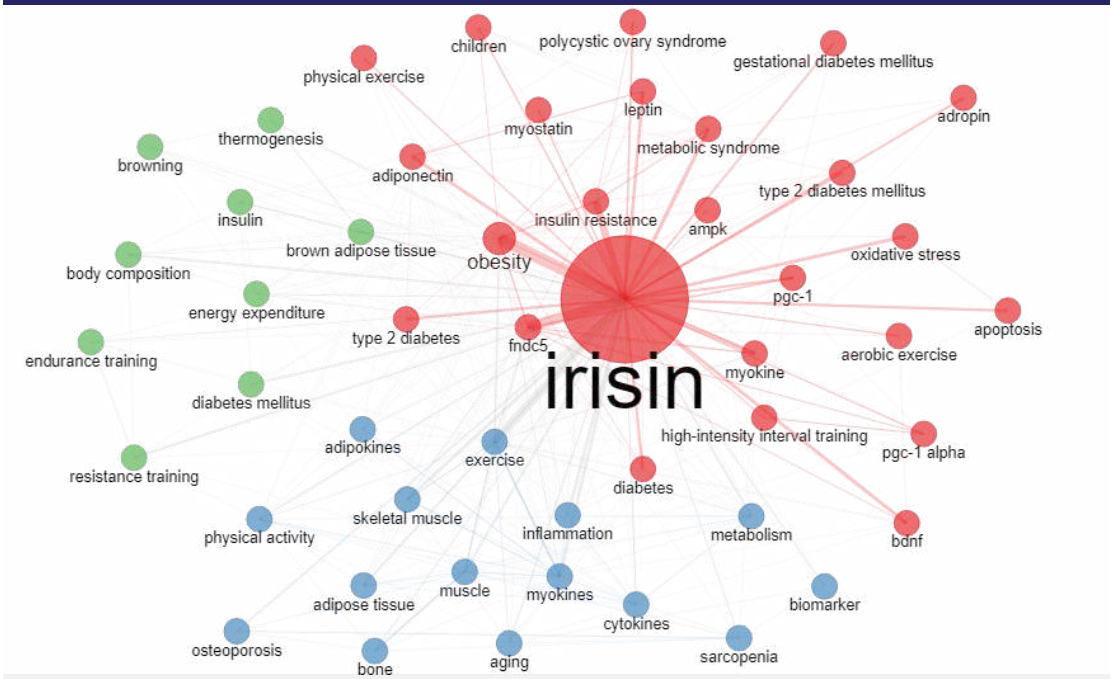
Norway (n= 109.33) and Lebanon (n= 108) which may indicate more relevance from these studies in comparison to the ones conducted in the countries with more publications and total number of citations.

ANALYSIS OF KEYWORDS

A keyword map based on the Louvain algorithm was applied to present major objects and hot topics of research. The keywords were divided into major clusters with three different colors (red, blue, and green) presented in Figure 3. Red nodes illustrate the relationship between Irisin and several oxidative stress-related metabolic diseases, including type 2 diabetes Mellitus, polycystic ovary syndrome, obesity, metabolic syndrome, and Insulin resistance. In the blue nodes were demonstrated the relationship between Irisin and cellular signaling (paracrine or endocrine) in multiple tissues, including skeletal muscle, adipocytes, and bone modulating multiple processes including inflammation, and metabolism. Green nodes emphasize the great relationship between Irisin and adiposity (browning effect and thermogenesis).

FIGURE 3. Keyword map on topics of research.



Source: Authors (2024)

Upon observation, a higher frequency of co-occurrence was identified among terms associated with oxidative stress-related metabolic diseases, with a notable emphasis on "obesity". Regarding these strong relationships, the studies point out that the Irisin secretion induced by exercise is associated with increased energy expenditure through its ability to stimulate the browning of white adipose tissue. Interestingly, 9 manuscripts on the top 10 manuscripts more cited in the Irisin field are related to obesity-related investigations, suggesting new directions and research possibilities.

Since obesity is defined as abnormal or excessive fat accumulation that presents a risk to health[13], the studies revealed that exercise induces the synthesis and secretion of Irisin by skeletal muscle and at an endocrine level this myokine is able to induces the UCP-1 expression and content in the adipocytes driving the “browning” effect as described in Figure 4. This Irisin-induced mechanism could represent a promising therapeutic target for obesity management.

FIGURE 4. “Browning” effect of adipocytes.

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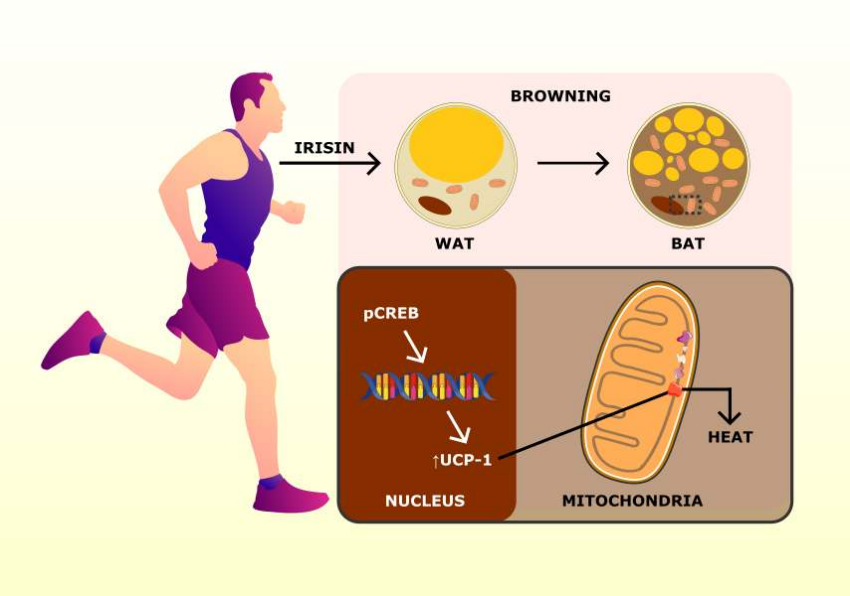

Source: Authors (2024)

Recent studies have also demonstrated that Irisin exhibits therapeutic potential in insulin resistance and type 2 diabetes mellitus by converting the white adipose tissue to brown adipose tissue ("browning effect"), promoting glucose use in skeletal muscle and heart, therefore improving hepatic glucose and lipid metabolism, and pancreatic β cell function homeostasis[14].

THEMATIC EVOLUTION

The mapping of the research themes and areas enables the identification of research interests and their evolution across time, as well providing recognition of future directions[15]. We analyzed the thematic evolution of the inclusion index, weighted by occurrences of the authors' keywords, which analyzes the general diversification of themes over different periods. In the 2012-2019 period, the main research focuses were "Irisin" and "Exercise" and these same themes remained central in the 2020-2022 period. Notably, research in the Irisin field has evolved exercise, obesity, leptin and BDNF (brain derived neurotrophic factor).

It is important to note that the Biblioshiny tool allows for differentiated analyses depending on the selected parameters. For this study, five time slices were set, each covering the two-year period.

DISCUSSION

Chronologically, the discovery of circulating Irisin followed that of its precursor, FNDC5. In 2002, two independent research groups, during cloning studies in mice, identified FNDC5 as a peroxisomal protein and a fibronectin type III repeat-containing protein 2. Specifically, Ferrer-Martínez et al. found peroxisomal protein in the peroxisome matrix of various cell types, including skeletal muscle, heart, and brain, while Teufel et al. discovered the gene encoding fibronectin type III repeat-containing protein 2 in the liver, heart, and brain during embryonic development[16,17].

Interestingly, after the initial identification of these two molecules, researchers observed that both precursors, before hydrolysis, generated the same product. It was later confirmed that the molecules identified in different tissues were the same, leading to the unified nomenclature FNDC5.

Subsequently, a study reported that FNDC5 maturation involves at least two proteolytic cleavages: one between the signal peptide and ectodomain, and another between the ectodomain and transmembrane domain[18]. The remaining FNDC5 is believed to be Irisin, which can be secreted and detected in the bloodstream.

The amino acid sequence of Irisin was first described in 2012 by Boström et al. using mass spectrometry[8]. The Irisin peptide (KDEVTMKE) was identified in the N-terminus of FNDC5 (without the signal peptide) fused with the C-terminus of the Fc-domain of IgG construct[8]. This sequence corresponds to amino acids 133–140 of FNDC5 according to the UniProt entry Q8K4Z2. After cleavage, Irisin undergoes N-glycosylation, which stabilizes the peptide[19]. Irisin has two N-linked glycosylation sites, increasing its molecular weight. Based on its theoretical molecular weight, 1 nmol/L of glycosylated Irisin corresponds to a circulating level of ~20 ng/mL.

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Notably, FNDC5 synthesis is mediated, at least in part, by peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator 1-α (PGC1α), primarily in skeletal muscle[8,20]. PGC1α stability depends on phosphorylation induced by adenosine monophosphate-activated protein kinase (AMPK)[20]. Skeletal muscle stimuli, including exercise, increase PGC1α expression (Ca^{2+}-dependent) and AMP levels, leading to AMPK activation, PGC1α stabilization, and FNDC5 synthesis[20, 21].

The relationship between the most frequently associated keywords with Irisin highlights key contributions to this field. Since 2012, the keyword “FNDC5” has been closely linked to Irisin, reflecting its role as Irisin’s molecular precursor. Studies have established that Irisin is derived from the transmembrane glycoprotein FNDC5, which is cleaved in its extracellular domain by an as-yet unidentified enzyme, releasing a 112-amino acid polypeptide into the bloodstream—subsequently named Irisin[22].

IRISIN SECRETION INDUCED BY PHYSICAL EXERCISE

The role of Irisin in sports science is an emerging and attractive research area, as highlighted by the co-occurrence keyword map (Figure 3), which links Irisin to “Exercise.” Since the seminal study by Boström et al. (2012) demonstrated that Irisin is secreted by skeletal muscle in response to physical activity, this topic has gained significant attention in sports science research[8]. A growing body of literature has explored the effects of different exercise protocols on circulating Irisin levels in both animals and humans. In humans, Irisin levels were found to be significantly elevated 30 minutes after acute exercise[23].

A study by Jedrychowski et al.[24] reported that plasma Irisin levels increased following 12 weeks of high-intensity aerobic training in young, healthy participants, compared to a sedentary group (~3.6 ng/mL in sedentary individuals vs. ~4.3 ng/mL in trained individuals). However, a meta-analysis revealed that chronic exercise training was associated with a significant reduction in circulating Irisin levels in randomized controlled trials (RCTs), while findings remained inconclusive in non-randomized studies [22]. Notably, 26 individuals undergoing 12 weeks of endurance training exhibited a decrease in circulating Irisin levels, from 160 ng/mL to 143 ng/mL[21].

The discrepancies in human studies examining the impact of chronic exercise on circulating Irisin levels may be attributed to variations in exercise protocols (type [aerobic vs. anaerobic], intensity [low vs. high], volume [sessions per week]), population characteristics (age, pathology, ethnicity, lifestyle), and Irisin detection methods (ELISA kits, Western blot with different antibodies, mass spectrometry).

In this study, we analyzed the methodologies for Irisin detection and the populations assessed in the 10 most cited manuscripts on Irisin research (Table 2). Our findings indicate that study populations, exercise protocols, and Irisin detection techniques vary considerably, warranting further discussion on these aspects.

TABLE 2. Summary of methods used in articles that evaluated the level of circulating irisin after physical exercise.

#	Authors	SP	AM	IP	TE	Sample	IL
1º	Bostrom et al. (2012)	12 Week Old B6 Mice	WB	3 Weeks Free Wheel Running	Chronic	Plasma	↑*
		8 Male Non-Diabetic Individuals	WB	10 Weeks Endurance Training	Chronic	Plasma	↑*
3º	Huh et al. (2012)	Fifteen Healthy Young Male Moderately Trained (20.5±1.5 Years Old)	ELISA	30 min	Acute	Serum	↑***
		Fifteen Healthy Young Male Moderately Trained (20.5±1.5 Years Old)	ELISA	8 weeks	Chronic	Serum	↑*
6º	Lee et al. (2014)	4 Healthy Females (27±5 Years Old)	WB	Cycloergometerat VO_2max	Acute	Serum	↑

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		4 Healthy Females, (27±5 Years Old)	WB	Submaximal Exercise Test at 40% VO_2max for 1 hour	Acute	Serum	↑*
8º	Roca-Rivada et al. (2013)	Male Sprague Dawley Rats (160 g)	WB	1 Week Free Wheel Running	Chronic	Plasma	↑**
			WB	3 Weeks Free Wheel Running	Chronic	Plasma	↑*
9º	Norheim et al. (2014)	Healthy and Physically Inactive Men (40–65 Years)	ELISA	12 weeks Combined Endurance and Strength Training	Chronic	Plasma	↓**

*The asterisks indicate the statistical significance of the result when compared to control (before intervention): *(p<0.05), **(p<0.01), ***(p<0.001). # = Position on top 10 most cited articles; SP = Study population; AM = Analysis Method; IV = Intervention Protocol; TE = Type of Exercise; IL= Irisin level after intervention.*

The manuscripts show great variability in the population sample (gender, age, lifestyle and metabolic profile) used to verify the effects of physical exercise on the circulating Irisin levels. The population profile analysed in the studies presents a pivotal importance for Irisin circulating levels, since: i) circulating Irisin levels is decreased with age; ii) Irisin levels is increased in puberty, in comparison to the prepubertal stage; iii) Irisin levels is higher in men than in women, and iv) obese subjects had significantly higher circulating Irisin levels than leaner subjects[26].

CONCLUSION

This study presents a bibliometric analysis of myokine research, with a specific focus on Irisin. We analyzed 1,579 publications indexed in the Scopus and Web of Science (WoS) databases, providing insights into potential research collaborations, key topics, influential journals, and emerging trends. Additionally, we explored the historical development and future perspectives of Irisin research and its applications in health promotion. Over the years, obesity, inflammation, and insulin resistance have emerged as prominent research themes. Current hotspots in Irisin research include metabolic disorders, cardiovascular diseases, neurological diseases, and musculoskeletal conditions. Our findings suggest that Irisin is becoming a central focus in health-related research, particularly in relation to exercise-induced adaptations, a field that is expected to receive increasing attention in the coming years.

COMPETING INTERESTS

The authors report there are no competing interests to declare.

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