

Comparative Evaluation of Serum Irisin Levels in Rheumatoid Arthritis and Multiple Sclerosis

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ABSTRACT

Growing evidence indicates a close interaction between the autonomic nervous system and inflammatory processes. Irisin, a myokine primarily released from skeletal muscle, has recently been associated with immune regulation; however, data regarding its role in autoimmune diseases are limited. This study aimed to compare serum irisin levels in patients with rheumatoid arthritis (RA) and multiple sclerosis (MS) with those of healthy individuals.

The study included 45 patients with RA, 45 patients with MS, and 45 age- and sex-matched healthy controls. Blood samples were obtained and serum irisin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol. Patients were included under stable treatment conditions and low disease activity (DAS-28 <3.2 for RA; EDSS 2.0–5.0 for MS). Physical activity levels were not directly assessed and body composition parameters were not evaluated.

Mean serum irisin levels were 246.11±119.6 pg/mL in RA, 1898.5±187.6 pg/mL in MS, and 93.87±68.50 pg/mL in controls (p=0.001). Compared with healthy controls, both RA and MS patients exhibited elevated serum irisin concentrations. Moreover, irisin levels were significantly higher in patients with MS than in those with RA (p=0.001).

The findings suggest that increased serum irisin levels may be associated with autoimmune inflammatory conditions such as RA and MS. This elevation may be associated with inflammatory processes and could reflect a potential adaptive response. Further longitudinal and mechanistic studies are needed to clarify whether irisin primarily exerts anti-inflammatory or neuroprotective effects in autoimmune diseases.

Keywords: Multiple Sclerosis; Rheumatoid Arthritis; Irisin; Autoimmune Diseases

Introduction

Autoimmune disorders are organ-specific diseases in which antibodies and T cells respond to self-antigens localized in a particular tissue. It is also a spectrum of conditions ranging from non-organ-specific or systemic diseases characterized by reactivity to antigens that have spread to various tissues. Immune tolerance is the organism recognizing its antigens and not reacting to them. In cases where this tolerance is lost, autoimmune diseases occur by showing an immune response against the host's antigens. Autoimmune diseases (MS, RA) can have many causes. Recent evidence highlights a close relationship between the autonomic nervous system and inflammation(1). RA is an autoimmune disease of unknown etiology, characterized by inflammation and

proliferation of synovial tissue in the joints and tendon sheaths, sometimes with multisystem involvement(2). MS is an autoimmune disease considered a chronic inflammatory and neurodegenerative disorder affecting nerve conduction due to axonal damage in the central nervous system(3).

Myokines are peptides produced and released by myocytes of muscle fibers that affect the physiology of muscle and other organs and tissues. These myokines exert autocrine, paracrine, or endocrine effects both on surrounding organs and on organs distant from them. More than one hundred myokines have been identified(4, 5). Irisin, an important myokine, has been investigated in many tissues in human and animal studies in recent years. Since its discovery in 2012, irisin has been reported to have various functions

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in many organs. The mechanisms are unclear, and values vary. In addition, it showed significant differences in the measurements of the same samples used in the analysis of irisin, even with two series of the same kit(6, 7). In this regard, irisin data are valuable in the literature. Some myokines, especially irisin, are associated with many autoimmune diseases(5, 6). However, studies on this subject are limited(8). It is necessary to investigate irisin levels in autoimmune diseases such as MS, a neurodegenerative chronic inflammatory disease, and RA, characterized by chronic systemic inflammation, frequently encountered in recent years and the effects of irisin on the pathophysiology of these diseases. Despite growing interest in the immunomodulatory properties of irisin, its role in autoimmune diseases remains insufficiently characterized. Current evidence is primarily derived from single-disease studies, and direct comparisons between autoimmune conditions are notably lacking. In particular, serum irisin levels have not been adequately investigated in parallel in RA and MS, two chronic inflammatory diseases with distinct yet overlapping pathogenic mechanisms. This study directly addresses this gap by providing a comparative evaluation of serum irisin levels in these two autoimmune disorders (MS and RA) relative to healthy controls. Although rheumatoid arthritis and multiple sclerosis affect different organ systems, both are chronic autoimmune diseases characterized by persistent inflammation and immune dysregulation. Comparing these two conditions may provide insight into whether irisin reflects common inflammatory pathways or disease-specific mechanisms. Such comparative data are currently limited in the literature and may contribute to a better understanding of irisin's role across autoimmune disorders.

Materials and Methods

This study commenced with the approval of the University Non-Interventional Research Ethics Committee meeting, dated 16 September 2021, and numbered 2021/09-40. In this study, a total of 175 individuals were initially assessed for eligibility. Of these, 30 participants were excluded during the recruitment phase: 12 declined to participate, and 18 did not meet the predefined inclusion criteria. Consequently, 145 participants were enrolled and underwent baseline assessment. During the evaluation phase, biological samples from 10 participants were excluded due to hemolysis, including five from the

RA group, three from the MS group, and two from the healthy control group. After these exclusions, the final analysis comprised 135 participants, evenly distributed across three groups: 45 patients with rheumatoid arthritis, 45 patients with multiple sclerosis, and 45 healthy control participants in the Physical Medicine and Rehabilitation Department at University Hospital. Patients participated in the study after signing a voluntary, fully informed consent form (Figure 1). All patients received detailed information about the study, and informed consent was obtained from each patient. We conducted this research in accordance with the principles of the Helsinki Declaration.

Participants were recruited in accordance with predefined inclusion criteria. Patients with rheumatoid arthritis were eligible if they had been diagnosed according to the American Rheumatology Association classification criteria, were between 18 and 65 years of age, had not experienced any change in medical treatment during the preceding three months, and exhibited low disease activity as indicated by a DAS-28 score below 3.2. Patients with multiple sclerosis were included if they were aged between 18 and 65 years, had a confirmed diagnosis of relapsing–remitting multiple sclerosis or secondary progressive multiple sclerosis, demonstrated Expanded Disability Status Scale scores ranging from 2.0 to 5.0, and were not receiving corticosteroid therapy or had discontinued such treatment at least three months before study initiation. Healthy control participants were required to be between 18 and 65 years of age and to be matched to the patient groups with respect to age and sex. Patients were selected under stable treatment conditions to minimize treatment-related confounding effects.

Participants were excluded from the study based on the following criteria. Patients with rheumatoid arthritis were excluded if they were pregnant, had a diagnosis of malignancy, exhibited severe neurological involvement, immobility, or impaired cooperation that could limit physical activity, or had cardiac symptoms classified according to the New York Heart Association functional classification criteria. Patients with multiple sclerosis were excluded if they had experienced an acute MS relapse or had a history of relapse within the preceding month, had concomitant orthopedic or systemic conditions, had a known neuromuscular disorder other than MS, had initiated immunomodulatory therapy within the previous six months, or presented with visual involvement or diplopia. In addition, patients with moderate to severe spasticity of the upper or lower extremities, defined as an Ashworth score of 3 or 4, as well as those with persistent severe fatigue or

depression (given the potential confounding effects of these conditions and related pharmacological treatments on study outcomes), were excluded.

Blood samples were collected, and whole blood samples were stored at room temperature for one h and centrifuged at 3000g for 5 min at 4°C. The sera were collected and held at -80°C until analyses using the ELISA method. The concentration of irisin in the serum of participants was determined using commercially available high-sensitive ELISA kits (Elabscience Biotechnology Inc., Houston, TX, USA). The assays were performed based on the manufacturer's recommendations.

Statistical Analysis: Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using skewness and kurtosis values, which indicated normal distribution (between -2 and +2). Descriptive data were expressed as mean \pm standard deviation. Comparisons among the three independent groups (RA, MS, and control) were performed using one-way analysis of variance (ANOVA). When a significant difference was detected, post hoc pairwise comparisons were conducted using Tukey's test. A priori power analysis was performed using G*Power 3.1.9.4 software, indicating that a sample size of at least 130 participants would provide 95% power at a 95% confidence level. A p-value ≤ 0.05 was considered statistically significant. The same statistical approach was consistently applied to all continuous variables, including age, BMI, and serum irisin levels.

Results

Thirty-one (68.9%) of the individuals with RA included in the study were female, 29 (64.4%) of the individuals with MS were female, and 31 (68.9%) of the healthy individuals were female. Other demographic data are shown in Table 1.

Age and body mass index among the demographic data analyzed in all groups were not statistically significant ($p > 0.05$, Table 1). Serum irisin levels were higher in all groups of male individuals. In addition, irisin was found at a very low level in the control group. MS serum irisin levels were found to be higher than RA. When serum irisin levels in all groups were compared, statistically significant differences were found ($p = 0.001$, Table 1). Post hoc analysis revealed that serum irisin levels were significantly higher in MS compared to RA and control groups, and in RA compared to controls ($p = 0.001$ for all comparisons).

Discussion

RA is a multisystemic, chronic, inflammatory autoimmune disease characterized by erosive synovitis and symmetrical polyarthritis, the most common in the world and our country, with a prevalence of approximately 0.8% (8). Since there are findings that negatively affect the quality of life, such as significant pain, fatigue, functional disability, and depression in RA patients, the scientific world is looking for ways to eliminate them. There is a need for surrogate biomarkers that can be measured in patients with RA that show their life improvement. Based on literature data, irisin may be a surrogate parameter in the inflammatory activity of RA (11, 12).

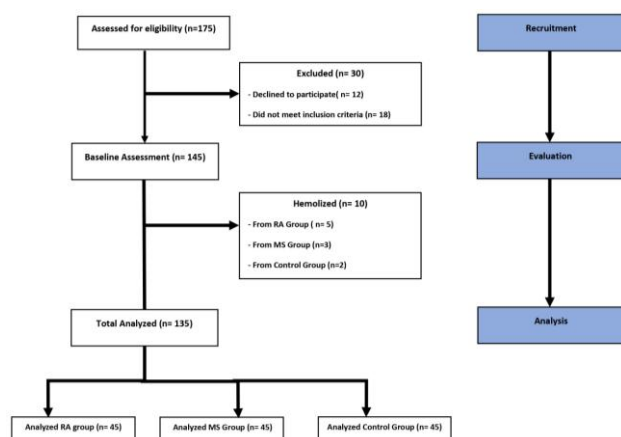
Irisin was first reported by Boström et al., defined as a myokine secreted from skeletal muscles after exercise (13). Irisin exerts its effects in different ways, including anti-inflammatory, anti-apoptotic, and anti-oxidative mechanisms (12). In a study, irisin was shown to inactivate inflammatory cytokines by reducing inflammatory cell infiltration (14). Many studies have focused on irisin's anti-inflammatory properties (15-18). Lavrova et al. (19) investigated the relationship between serum irisin levels and the presence of low traumatic bone fractures in RA patients. They found increased irisin levels in 63% of individuals with RA. Another study showed that serum irisin levels were increased in psoriatic patients compared to the control group (20). Gamal et al. (11) have also demonstrated lower irisin levels in RA patients with poor sleep quality compared to RA patients with good sleep quality and healthy controls. However, although studies on irisin levels in RA are very few in the literature, their effects on the pathophysiology of the disease need to be investigated. We believe that our study, in which we compared serum irisin levels in RA and MS, which is autoimmune diseases, with healthy individuals, will be among the first in the literature to the best of our knowledge. In this study, irisin showed a significant increase in RA patients compared to the control group. It is thought that this increase may be associated with a potential adaptive response; however, this interpretation remains speculative and should be interpreted with caution.

MS is a chronic autoimmune-mediated, inflammatory, and neurodegenerative disorder that affects nerve conduction due to axonal damage in the central nervous system. It is more common in women than men, mainly in the young population. MS is the most common demyelinating disease

Table 1: Demographic Data and Post Hoc Comparisons Among Groups

		RA (n=45) Mean(±SD)	MS (n=45) Mean (±SD)	Control (n=45) Mean (±SD)		P	
					RA-MS	RA- CONT	MS- CONT
AGE	Female	44.19±8.40	47.40±9.74	44.55±5.10			
	Male	41.86±4.13	42.60±3.97	46.63±4.64	0.261	0.440	0.932
	Total	43.47±7.37	45.80±8.53	45.29±4.99			
BMI	Female	25.23±3.02	26.71±3.86	26.14±1.75			
	Male	24.47±2.44	28.02±5.67	26.26±2.03	0.060	0.200	0.340
	Total	25.01±2.85	27.15±4.52	26.18±1.83			
IRISIN pg/ml	Female	236.48±115.38	1877.23±191.46	77.03±60.93			
	Male	267.43±130.45	1941.27±178.37	124.37±72.75	0.001	0.001	0.001
	Total	246.11±119.64	1898.58±187.66	93.87±68.50			

RA: rheumatoid arthritis; MS: multiple sclerosis; BMI: body mass index. Data are presented as mean ± standard deviation. Group comparisons were performed using one-way ANOVA followed by Tukey post hoc test. Exact p-values are reported

**Fig. 1.** Flowchart of the study.

with its prevalence. With the growing knowledge base of MS pathology, the Committee (supported by the US National Multiple Sclerosis Society [NMSS] and the European Committee for Treatment and Research in MS) in 2012; re-examined original clinical phenotypes to provide improved terminology while including imaging, liquid biomarkers, and other assays, made additions(3, 21). Although the etiology of MS is not known precisely, it is a complex and multifactorial disease in which viral, genetic, and immunological factors are thought to play a role. Immune reactions are carried out with a particular order of pro-inflammatory and anti-inflammatory cytokines in lesions mainly managed by T cells in MS. In MS; the disease occurs due to cellular and humoral immune responses against autoantigen(22). The Irisin hormone, widely used in recent years, has also been defined as a new

hormone-like myokine, that plays a vital role in central nervous system diseases(23). It has been observed that the irisin is deactivated in neuronal precursors, impairing the development of mature neurons. In light of these results, it is thought that the hormone irisin plays a developmental role in neurons. In addition, it has been argued that irisin inhibits inflammation and plays a role in protecting mitochondria. In addition, irisin has effects against oxidative stress, neuroprotective effects, and anti-inflammatory properties the literature(24, 25).

There are very few studies on MS and irisin in the literature. Zhang et al.(23) investigated irisin hormone levels in serum and cerebrospinal fluid of 23 MS patients and 16 healthy controls. They found that serum irisin levels of MS patients were higher and statistically significant compared to healthy controls ($p<0.05$). In light of these findings, it has been suggested that irisin may have a protective effect on the central nervous system, and that increased peripheral serum irisin levels may represent a potential adaptive response or reflect disease severity; however, no direct evidence supporting these interpretations was provided in the present study(23). Our study compared serum irisin levels of healthy controls and MS patients; MS, an autoimmune inflammatory disease, and irisin levels, thought to be a new anti-inflammatory myokine in the literature, were examined. In our study, similar to the study by Zhang et al.(23), serum irisin levels were found to be significantly increased in MS patients compared to healthy controls ($p<0.05$). In addition, in our study, by the literature, serum

irisin levels of male subjects were found to be higher than female subjects in all groups(26).

Several potential confounding factors should be considered when interpreting the findings. Physical activity is a major determinant of irisin secretion and was not directly quantified in this study. Additionally, sex differences, disease severity, and treatment regimens may influence circulating irisin levels. Although efforts were made to include patients with stable treatment and low disease activity, residual confounding cannot be excluded. In addition, body composition parameters such as muscle mass and fat distribution may also influence circulating irisin levels and should be considered in future studies.

This study has several limitations that should be acknowledged. First, the study population consisted of a relatively specific subgroup of patients with RA and MS, which may limit the generalizability of the findings. Future studies including patients with different disease subtypes and varying levels of disability may provide more comprehensive insights. In addition, physical activity levels were not directly measured, although they are known to significantly influence irisin concentrations. Similarly, body composition parameters were not assessed and may represent an additional confounding factor. The cross-sectional design of the study also precludes causal interpretation. Furthermore, no correlation analyses were performed between irisin levels and clinical parameters such as disease duration or disability scores; therefore, interpretations regarding potential compensatory mechanisms should be considered with caution. Despite these limitations, the study has several strengths, including providing evidence suggesting a potential link between irisin levels and inflammatory processes in autoimmune diseases, as well as a relatively large and adequately powered sample size.

In conclusion, irisin levels may be associated with autoimmune inflammatory conditions and could reflect a potential adaptive response. Elevated irisin levels in RA and MS patients may be linked to inflammatory processes; however, the underlying mechanisms remain to be elucidated. Further studies are required to determine whether irisin plays an anti-inflammatory or neuroprotective role and to clarify its potential as a biomarker in autoimmune diseases.

Ethical Approval: This research has been approved by the IRB of the authors' affiliated institutions.

This study has compliance with ethical standards. The study was approved by the local ethical committee, Ethics Committee of University (16.09.2021 and numbered 2021/09-40.)

Declaration of Competing Interest: The authors declare no conflict of interest.

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Informed Consent: Informed consent was obtained for each participant prior to their involvement in the study.

Credit authorship contribution statement

GD: Conceptualization, Investigation, project administration, review & editing. **ZE:** Writing, original draft, methodology, visualization. **FB:** Investigation, writing, original draft, methodology, conceptualization. **SBY:** Conceptualization, data curation, software, investigation, review & editing. **GA:** Investigation, writing, review & editing.

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