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ORIGINAL PAPER

A newly identified myokine: irisin, and its relationship with chronic spontaneous urticaria and inflammation

Diler Us Altay[1] · Sevda Onder[2] · Fatma Etgu[2] · Abdullah Uner[3] · Tevfik Noyan[3]

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Abstract

Chronic spontaneous urticaria (CSU) is an important dermatological disease involving severe itchy urticaria lesions and/or angioedema. Urticaria and angioedema occur in the community at a rate of 25–30%. Many factors, such as inflammation, have been implicated in the etiology of CSU. Irisin is a newly identified adipocytokine shown by research to exhibit anti-inflammatory properties in addition to its many other effects. The aim of the study was to investigate, for the first time in the literature, the significance of serum irisin levels in patients with CSU. Seventy-eight individuals were evaluated. The study group included 44 patients diagnosed with CSU, and the control group consisted of 34 healthy individuals. Serum samples were collected, and serum irisin, Interleukin-2 (IL-2), Interleukin-3 (IL-3), Tumor Necrosis Factor-alpha (TNF-α), and Interferon-ɣ (IF-ɣ) levels were determined using the enzyme-linked immunosorbent assay (ELISA) method. Irisin was studied for the first time in patients with CSU and exhibited a significantly higher level in the control group than in the patient group ($p=0.020$). IL-2, IL-3, and IF-ɣ levels were higher in the CSU group than in the control group, although the results were not statistically significant. Only TNF-α results increased significantly. Correlation analysis was applied to determine the relationships between irisin and IF-ɣ and IL-3 levels. This revealed that the irisin parameter was significantly and positively correlated with IF-ɣ and IL-3 in patients with CSU ($r=0.518$, $p=0.016$ and $r=0.536$, $p=0.022$, respectively). This is the first report to evaluate irisin as an inflammatory biomarker in CSU. Irisin levels in patients with CSU were low, suggesting that irisin may pay a role in the pathogenesis of CSU and may be a marker showing the severity of the disease.

Keywords Irisin · Chronic spontaneous urticaria · Inflammation

Introduction

Irisin is a newly identified myokine regulated by fibronectin type III domain containing protein-5 (FNDC5) [1]. FNDC5 is a form of type 1 membrane protein proteolytically cleaved from the N-terminal domain by an unidentified enzyme, and 112 aa soluble irisin is then released into the bloodstream. Irisin is present in the blood at basal levels. Increased release from skeletal muscle to the blood has been reported with acute exercise (short and intense exercise); it binds to its hitherto unidentified receptor on adipose tissue, causing a significant increase in total body energy expenditure and weight loss [2, 3]. The anti-inflammatory, anti-apoptotic, and anti-oxidative properties of irisin have recently received considerable attention from researchers. Inflammation is closely related to various diseases, such as obesity, type 2 diabetes mellitus (T2DM), and dermatological diseases [4].

Chronic spontaneous urticaria (CSU) is characterized by the recurrence of itchy wheals, angioedema, or both for

✉ Diler Us Altay
surelid@hotmail.com; dilerusaltay@odu.edu.tr

Sevda Onder
drsevdaonder@gmail.com

Fatma Etgu
ftmyildirim@hotmail.com

Abdullah Uner
abdullahuner66.an@gmail.com

Tevfik Noyan
tevfiknoyan@hotmail.com

[1] Faculty of Health Sciences, Department of Nutrition and Dietetics, Ordu University, Ordu, Turkey

[2] Faculty of Medicine, Department of Dermatology, Ordu University, Ordu, Turkey

[3] Faculty of Medicine, Department of Medical Biochemistry, Ordu University, Ordu, Turkey

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longer than 6 weeks. The term is synonymous with "chronic urticaria (CU)" and "chronic idiopathic urticaria (CIU)" [5].

Although a trigger can be identified in 21–55% of children, the condition is largely regarded as a mast cell-mediated disease of unknown etiology. Autoimmunity, infections, and stress play a particularly important role in the etiology. Detailed history and physical examination are essential for diagnosis. Blood cell count, erythrocyte sedimentation rate, or C-reactive protein (CRP) measurement are recommended as initial tests. Standard dose oral second-generation antihistamine (H1AH) and omalizumab are recommended in all guidelines for first-line treatment. However, additional agents should now be developed taking advantage of the many promising targets recently identified and characterized [6, 7]. Studies of CSU have shown that inflammation plays an important role in the pathogenesis and clinical features of the disease [8]. Increased expression of TNF-α and IL-3 in both the lesional and non-lesional skin of patients with different types of urticaria compared to normal controls [9]. Another study reported serum IL-6 level elevation in patients with CSU, but no significant serum IFN-ϒ or TNF-α elevation [10].

We encountered no previous studies concerning the relationship between irisin and CSU. However, studies have investigated the relationship between irisin and some dermatological diseases (Behçet's, psoriasis, hidradenitis suppurativa, etc.) associated with inflammation, insulin resistance, and metabolic syndrome. However, the results of such studies are inconsistent. Baran et al. observed statistically insignificant higher irisin levels in patients with psoriasis compared to a control group [11]. In another study, patients with severe psoriasis exhibited lower irisin levels than a control group, suggesting that irisin may play a role in the pathogenesis of psoriasis and may be a potential marker showing the severity of psoriasis [12]. Statistically insignificant high irisin levels have also been detected in hidradenitis suppurativa, another dermatological disease associated with metabolic syndrome and insulin resistance [13]. Behçet's disease is a vasculitic condition characterized by inflammation. Significantly lower serum irisin levels have been detected in patients with Behçet's disease compared to healthy controls, with strong, negative correlation being shown between irisin levels and patients with Behçet's disease with high carotid intima–media thicknesses [14]. The Urticaria Activity Score (UAS) is used to evaluate disease activity in patients with chronic spontaneous urticaria. Urticaria manifests with wheals, rather than blisters, and the UAS, therefore, documents wheal numbers. The most commonly used UAS is UAS7, in which the patient evaluates the number of blisters and the severity of itching over a period of 7 days. The most important disadvantage of the UAS is that it does not evaluate the severity of angioedema, which often accompanies CSU or can be seen alone with puffiness. Angioedema scores should, therefore, also be checked. However, these tests are difficult to use in clinical practice. The most important factor in the approach to patients with CSU is time. Even if the number of blisters is low or itching is mild, patients with a disease duration over 6 weeks are considered to have CSU, and if these are resistant to antihistaminic therapies, systemic therapies should be initiated without loss of time, because the quality of life of these patients is significantly affected [15, 16].

The purpose of this study was to investigate, for the first time, irisin levels in serum samples from patients diagnosed with CSU. We planned to measure irisin, IL-3, TNF-α, IF-ɣ, and IL-2 parameters in serum samples from both sick and healthy individuals. In line with the data obtained, our intention was to add new information to the literature by determining whether irisin can be used as an inflammatory biomarker in illuminating the etiopathogenesis of CSU and in diagnosis.

Materials and methods

This prospective study was planned between May and August 2020 and involved patients who presented to the dermatology outpatient clinic for CSU treatment. The sample collection time was extended due to the COVID-19 pandemic.

Study population

The study protocol was approved by the Ordu University (ODU) Clinical Research Ethics Committee (Decision No: 2020/133). This investigation involved 44 patients previously diagnosed with CSU and 34 healthy individuals. The patients were recruited from the Ordu University Research Hospital dermatology clinics. All subjects provided written consent to participate. Patients not using any systemic medication and whose urticarial rash persisted during a follow-up period of at least 8 weeks were included in the study. The first-line treatment for CSU is antihistamine therapy, and the majority of our patients had received this, although some were not given any treatment. Antihistamines do not significantly affect inflammation. We, therefore, ignored this treatment. We excluded patients using systemic steroids, cyclosporine, and omalizumab, which are employed in the treatment of CSU and that may affect the inflammatory process. Patients with an inflammatory disease such as diabetes, hypertension, obesity, hyperlipidemia, rheumatological diseases, systemic inflammatory skin diseases, and cancer were also excluded. Patients and controls who exercised were also excluded from the study because of the effect of such exercise protocols on irisin levels. The study involved the collection of serum samples, the determination of Irisin, IL-2,

IL-3, IF-γ, and TNF-α levels in serum samples using the enzyme linked immunosorbent assay (ELISA) method, and statistical analysis. The methods and procedures employed are detailed below.

Collection of patient and control serum samples

Detailed histories were taken from all patients, and all underwent physical examinations and routine biochemical tests. Five-milliliter (5 ml) 13 × 100 mM blood samples were collected from the peripheral veins of all participants and kept for approximately 30 min in Vacutainer® tubes before being stored at 4 °C. Serum specimens were obtained by centrifuging the blood samples at 3000 rpm for 10 min. Serum specimens were then stored at − 80 °C until biochemical analysis.

Determination of irisin, IL-2, IL-3, TNF-α, and IF-γ levels in serum samples using the elisa method

Human irisin, IL-2, IL-3, TNF-α, and IF-γ serum levels were determined using ELISA kits (Catalog nos. SL2020Hu, SL0987Hu, SL0993Hu, SL1761Hu, and SL0960Hu; Sunlong Biological Technology, Zhejiang, China) in line with the manufacturer's instructions. Absorbance was measured at 450 nm using a BioTek Instrument EL800 microplate reader (Winooski, VT, USA). The results were expressed as ng/mL, pg/mL, pg/mL, ng/L, and pg/mL, respectively.

Statistical analysis

The test results were analyzed on SPSS 13.0.1 statistical software (license number 9069727) (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range) in case of non-normal distribution. The distributions of irisin, IL-2, IF-γ, IL-3, TNF-α, WBC, NEU, PLT, MPV, PDW, and LYM levels in each group were calculated using the Kolmogorov–Smirnov test. Comparisons of the groups were performed using Student's *t* test in case of normal distribution and the Mann Whitney U test in case of non-normal distribution. Statistical significance was set at $p < 0.05$.

Results

Forty-four patients and 34 controls were enrolled in the study. No significant age difference was observed between the groups. Distributions of CBC test results and biochemical parameters are shown in Tables 1 and 2. Irisin levels were studied for the first time in patients with CSU, and were found to be significantly higher in the control group than in the CSU group ($p = 0.020$). IL-2, IL-3, and IF-γ levels were higher in the CSU group than in the control group, although the differences were not statistically significant. Only TNF-α results increased statistically significantly in the CSU group. Correlation analysis was applied to determine the relationships between irisin and IF-γ and IL-3 levels. This revealed significant and positive correlation between irisin and IF-γ and IL-3 in patients with CSU ($r = 0.518$, $p = 0.016$ and $r = 0.536$, $p = 0.022$, respectively) (Fig. 1).

Table 1 CBC test results

Parameters	CU group ($n = 44$)	Control group ($n = 34$)	*p* value
WBC ($\times 10^3$/mm^3)	7.20 ± 0.29	7.14 ± 0.29	0.879
NEU ($\times 10^3$/mm^3)	4.41 (3.48–5.23)	3.76 (3.20–4.67)	0.067
LYM ($\times 10^3$/mm^3)	2.00 (1.64–2.89)	2.30 (1.86–2.55)	0.378
PLT ($\times 10^3$/mm^3)	269 ± 9.65	258 ± 12.2	0.480
MPV	10.0 ± 0.11	9.89 ± 0.12	0.462
PDW	11.2 ± 0.21	11.1 ± 0.26	0.590

Data were expressed as: mean ± SEM for parametric tests, median (inter quarter range for 25–75%) for nonparametric tests. *P* according to student *t* test for WBC, PLT, MPV, PDW the Mann Whitney *U* test for NEU, LYM, $p < 0.05$ is considered statistically significant

Table 2 Irisin, IL-2, IL-3, IF-γ, TNF-α concentrations of CU and control groups

Parameters	CU group ($n = 44$)	Control group ($n = 34$)	*p* value
Irisin (ng/mL)	12.8 (11.3–17.1)	17.5 (12.7–19.7)	0.020
IL-2 (pg/L)	42.9 ± 2.46	38.2 ± 3.97	0.297
IF-γ (pg/L)	34.5 (28.9–41.1)	33.1 (30.2–38.9)	0.716
IL-3 (pg/L)	37.8 ± 2.83	30.2 ± 3.30	0.083
TNF-α(ng/L)	52.5 ± 2.09[a]	42.0 ± 4.45	0.041

Data were expressed as: mean ± SEM for parametric tests, median (inter quarter range for 25–75%) for nonparametric tests. *P* according to student *T* test for IL-2, IL-3, TNF-α, the Mann Whitney *U* test for Irisin, IF-γ; $p < 0.05$ is considered statistically significant

[a]Significantly different from the control group

Discussion

CSU is a common allergic skin disease that requires long-term pharmacological therapy, as described above. Some patients with severe CSU experience poor quality of life. The pathogenic mechanisms of CSU are not yet clearly and fully understood [17]. However, autoimmunity, inflammation, and coagulation disorders have been implicated in the pathogenesis, making the treatment of the disease particularly difficult [17]. Serum irisin levels have previously been investigated in obesity, chronic kidney disease, T2DM, metabolic syndrome, inflammatory disease, and various types of cancer [3,

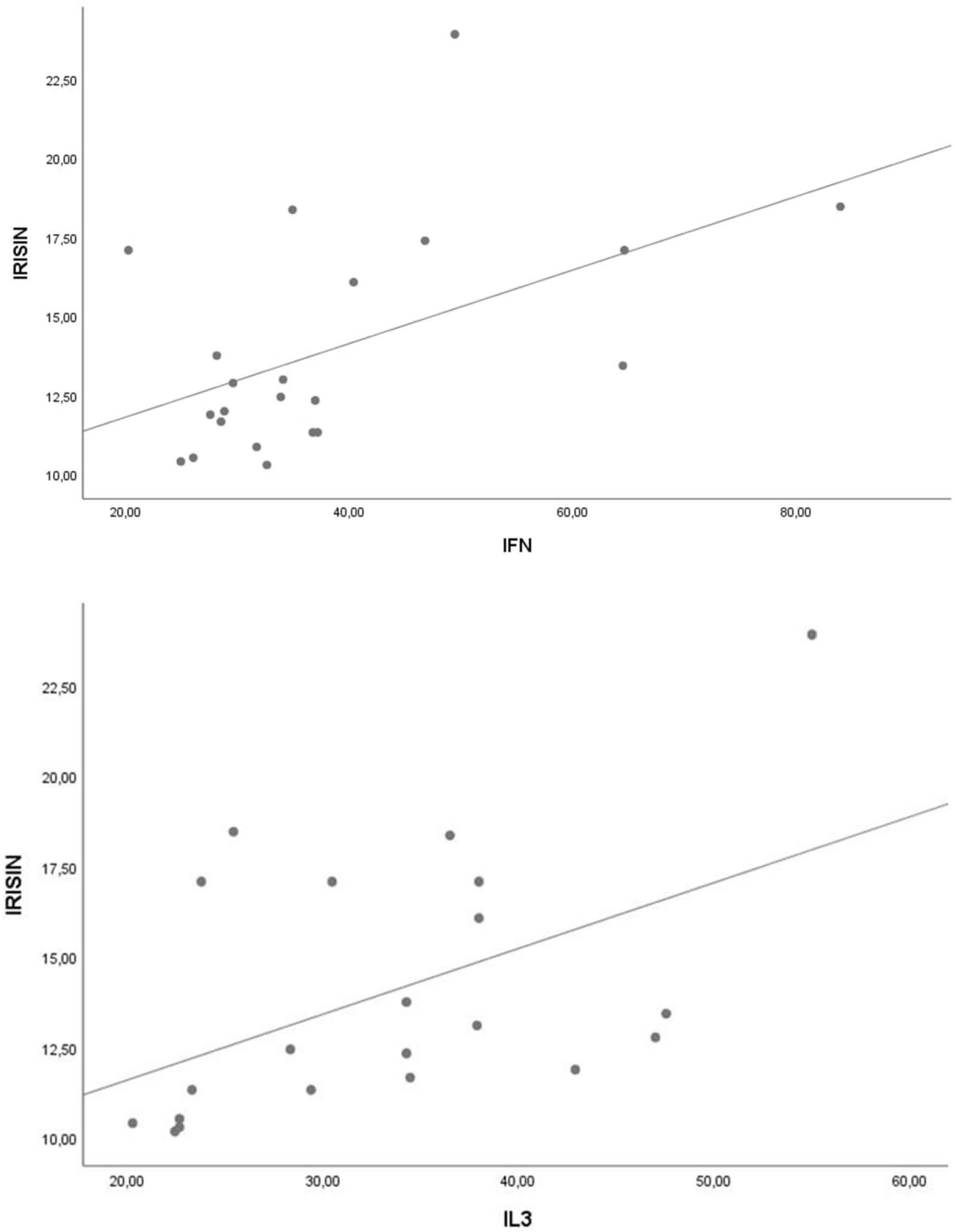

Fig. 1 Graph illustrating the correlation between (**A**) Irisin and IFN levels and (**B**) Irisin and IL-3 levels

19–25]. Ataseven et al. showed significantly higher WBC, NEU, and PLT counts in groups with CSU than in healthy controls, although CRP levels were higher in the healthy control group [26]. NOD-like receptor protein 3 (NLRP3) mutation was detected and Muckle–Wells syndrome (MWS) was diagnosed in a man with a 15-year history of CSU in a recent case report study. MWS is an inherited autoinflammatory disease caused by CIAS1/NLRP3 mutation and characterized by intermittent fever, urticaria, progressive sensorineural deafness, and renal amyloidosis. The rashes

resolved following canakinumab therapy, and both CRP and urine protein levels normalized [27]. TNF-α is a proinflammatory cytokine synthesized, stored, and released by mast cells during allergic inflammation. It can be found at the site of urticarial lesions, and a number of studies have reported upregulation of TNF-α expression in patients with CSU [17]. Mean platelet volume (MPV) is the most commonly used measure of platelet size and is a potential marker of platelet reactivity. Recent studies have reported correlation between high MPV values and active inflammatory response. MPV has been used as an inflammatory marker in various inflammation-related diseases, including CSU. Some studies have reported high MPV levels, others low MPV levels, and some no changes. Alicja et al. observed higher platelet counts in patients with CSU [28]. Onder and Ozturk determined no significant change in MPV values after treatment [18]**.** No statistically significant difference was observed between the control and CSU groups in the present study.

No significant differences were found in the present study between the CSU and control groups in terms of NEU, PLT, LYM, MPV, or PDW parameters (Table 1), although irisin levels were significantly higher in the control group than in the CSU group, while IL-2, IL-3 and IF-γ levels higher in the CSU group than in the control group, although these results were not statistically significant. Only TNF-α results increased significantly, as shown in Table 2. A decrease in irisin levels is as important as an increase. A decrease in irisin levels may be decisive in the serum of patients with CSU, and in patients with T2DM [29]. The pathogenesis of CSU is not yet fully understood, but has been associated with several complex mechanisms. Although it is generally regarded as a mast cell-mediated disease, conditions such as autoimmunity, inflammation, and coagulation disorders have also been implicated in the pathogenesis, making treatment problematic.

Conclusions

This study is the first to investigate the relationship between inflammation and irisin in serum samples from patients with CSU. We observed lower irisin levels in the CSU group. Analysis of the results suggests that a decrease in irisin levels may be decisive for CSU.

The principal limitation of this investigation is the relatively small number of patients and controls involved**.** More comprehensive studies with higher numbers of patients and controls are now needed. UAS values were also not evaluated. During the planning of this study, our intention was to compare only healthy controls with a CSU group. Studies investigating the relationship between patients' irisin levels urticaria activity scores might usefully be planned in the future.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest All the authors of this original research article declare that they have no conflict of interest.

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