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Research Article

Correlation between insulin resistance and serum irisin levels in polycystic ovary syndrome

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Abstract

Objectives: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age, often characterized by insulin resistance, hyperandrogenism, and metabolic disturbances. This study aimed to investigate the relationship between serum irisin levels, a myokine involved in energy regulation, and insulin resistance in women with PCOS.

Methods: A prospective study was conducted with 90 women diagnosed with PCOS, divided into two groups: 45 with insulin resistance and 45 without. Insulin resistance was evaluated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Serum irisin levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA). Statistical analyses, including correlation and regression tests, were used to assess the relationships between serum irisin levels and various metabolic and hormonal parameters.

Results: No significant difference in serum irisin levels was found between PCOS patients with insulin resistance (3.66±2.69 ng/mL) and those without insulin resistance (2.77±1.72 ng/mL) (p=0.065). Weak correlations were identified between serum irisin levels and insulin, HOMA-IR, free testosterone, and total testosterone levels. Significant positive correlations were observed with insulin (p<0.001) and HOMA-IR (p=0.008), while negative correlations were found with free testosterone (p=0.029) and total testosterone (p=0.013). Additionally, no significant differences in serum irisin levels were detected between patients with and without metabolic syndrome.

Conclusion: Although weak correlations between serum irisin levels and insulin resistance markers were observed, no significant difference was found between PCOS patients with and without insulin resistance. These findings suggest that serum irisin may not be a key factor in the pathophysiology of PCOS related to insulin resistance. Larger studies are needed to further explore the role of irisin in PCOS and its potential as a therapeutic target.

Keywords: Hyperandrogenism, insulin resistance, irisin, metabolic syndrome, Polycystic Ovary Syndrome (PCOS)

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Polycystic Ovary Syndrome (PCOS) is a complex endocrine illness affecting 4% to 12% of women of reproductive age, making it one of the most prevalent hormonal disorders in this demographic [1]. It is characterized by hyperandrogenism, chronic anovulation, and polycystic ovaries, and may be associated with irregular periods, hirsutism, and infertility [2]. Though PCOS is widespread, the underlying mechanisms of its development are not fully understood. Genetic, environmental, and lifestyle factors are thought to contribute to its development, with insulin resistance playing a central role in its metabolic manifestations [3].

An estimated 50% to 70% of women with PCOS exhibit insulin resistance, irrespective of their body mass index (BMI) [4, 5]. This insulin resistance exacerbates hyperinsulinemia, which in

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turn stimulates ovarian androgen production, further complicating the hormonal imbalance characteristic of PCOS [4]. Furthermore, the condition of insulin resistance makes women with PCOS more susceptible to the development of long-term problems, including type 2 diabetes, metabolic syndrome, and cardiovascular disease [4, 6].

Recent attention has turned to irisin, a myokine first identified in 2012, which is released during physical activity and plays a key role in energy homeostasis [7–9]. Irisin is synthesized by the breakdown of the membrane protein FNDC5 and stimulates the process of browning in white adipose tissue, increasing heat production and total energy expenditure [8, 10]. Additionally, irisin has been shown to improve glucose metabolism, reduce insulin resistance, and potentially mitigate obesity-related complications [10–12]. These effects suggest that irisin could be a crucial link between exercise and metabolic improvements in conditions such as obesity, diabetes, and PCOS [13].

Given the central role of insulin resistance in the pathophysiology of PCOS and the effects of irisin on metabolic regulation, we aimed to investigate the relationship between serum irisin levels and insulin resistance in women with PCOS. Gaining a comprehensive understanding of this correlation could offer fresh perspectives on the mechanisms that regulate PCOS and emphasize potential treatment targets for controlling its metabolic effects.

Materials and Methods

This study was performed prospectively from August 2017 to February 2018 at the Gynecology and Obstetrics Clinic of the Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital Perinatology Department. The first group consisted of 45 individuals diagnosed with both PCOS and insulin resistance, while the second group consisted of 45 patients diagnosed with PCOS but without insulin resistance.

Patients meeting two or more criteria, such as oligomenorrhea-amenorrhea, polycystic ovaries on ultrasound, and hyperandrogenism, were diagnosed with PCOS [14]. The exclusion criteria encompassed chronic illnesses (e.g., diabetes mellitus, thyroid dysfunction, kidney disease, hypertension), chronic drug usage, smoking, alcohol intake, and ovarian proliferation. Study participants were selected from women aged 18 to 45 who were still fertile. Demographic characteristics of the patients were recorded in the study. Insulin, glucose, free testosterone (F-TES), high-density lipoprotein (HDL), dehydroepiandrosterone sulfate (DHEA-S), low-density lipoprotein (LDL), white blood cells (WBC), hemoglobin, platelets, total testosterone (T-TES), sex hormone-binding globulin (SHBG), and prolactin levels were analyzed in venous blood samples from the patients.

The HOMA-IR approach, an acronym for Homeostatic Model Assessment of Insulin Resistance, was used to evaluate the insulin resistance of the patients. Blood glucose and insulin levels were measured after a fasting period of 8–10 hours. The study entailed the computation of HOMA-IR and Free Androgen Index (FAI) values for the patients, along with the implementation of Ferriman-Gallwey grading. HOMA-IR was calculated as follows: Fasting glucose (mg/dL) × Fasting insulin (uIU/mL) / 405. Patients with a HOMA-IR score ≥2.5 were classified as insulin resistant [15]. The Free Androgen Index (FAI) was calculated using the formula: total testosterone × 100 / SHBG [16]. The degree of hirsutism was assessed using the Ferriman-Gallwey scale, which is based on nine androgen-sensitive areas, with scores from 0 (no terminal hair growth) to 4 (severe hair growth). A score of >8 indicated a diagnosis of hirsutism [17].

Metabolic syndrome was diagnosed according to the American Heart Association (AHA) criteria, determined by the presence of three or more of the following: fasting serum glucose (FSG) ≥ 100 mg/dL, serum HDL<50 mg/dL, serum triglycerides ≥150 mg/dL, waist circumference ≥88 cm, and blood pressure ≥130/85 mm/Hg [18].

The study was conducted in compliance with the principles stated in the Declaration of Helsinki. Each patient was informed about the trial and gave informed consent. The local ethics commission granted ethical permission for this project, with approval number 849-22.08.2017.

Sample collection

The patients' venous blood samples were transferred into biochemical tubes fitted with separating gel. The biochemical tubes were spun in a centrifuge at +4°C, separating the blood cells and serum (4000 rpm, 10 minutes). The serum from the centrifuged blood samples was added to Eppendorf tubes, which were stored at -80°C until the irisin kits were obtained. The serum samples were slowly thawed the day before the test and homogenized by vortexing. The serums were prepared by keeping them at room temperature the day before the study.

Laboratory measurement and assay performance parameters

The spectrophotometric assay was used to analyze serum glucose, HDL, and triglyceride levels on a Roche Cobas c701 autoanalyzer (Mannheim, Germany). The LDL-C level was calculated using the Friedewald formula: [Total cholesterol - (HDL-C + (triglycerides / 5))]. An electrochemiluminescence assay (ECLIA) was used to analyze serum levels of F-TES, T-TES, prolactin, DHEA, SHBG, and insulin on a Roche Cobas e601 autoanalyzer (Mannheim, Germany). WBC and hemoglobin values were measured using a SYSMEX XT2000 Hematology Analyzer (Sysmex, Germany) via the fluorescence flow cytometry method.

The Enzyme-Linked Immunosorbent Assay (ELISA) was used to assess serum irisin levels. A Biotek ELX800 microplate reader was used to detect the absorbance of irisin (Human Irisin ELISA kit, catalog number: E-EL-H6120, www.elabsicience.com). Calculations were performed using Gen 5 software. Blood samples were analyzed in duplicate, with a dilution rerun procedure for values higher than the measuring range. The measurement range was 0.015–1 ng/mL. Three different mean values were used for intra-assay precision (0.04±0.002 ng/mL, CV%=5.34; 0.1±0.005 ng/mL, CV%=4.96; 0.47±0.23 ng/mL, CV%=5.02) and for inter-assay precision (0.04±0.002 ng/mL, CV%=5.1; 0.1±0.004, CV%=4.55; 0.4±0.02, CV%=4.56). All performance values were provided by the manufacturer's insert.

Table 1. Demographic characteristics of all patients included in the study

	Group with insulin resistance n=45 Mean±SD	Group without insulin resistance n=45 Mean±SD	p
Age (year)	24.4±5.4	24±4.5	0.974
Weight (kg)	72.2±17.2	62.3±11.6	0.004*
Height (cm)	162.7±7.1	165.7±6	0.032*
BMI (kg/m^2)	27.2±5.8	22.7±4.1	<0.001*
Waist circumference (cm)	87.9±12.6	79.1±12	0.001*
Hip circumference (cm)	92.9±17.6	94±12.8	0.875

*: The group without insulin resistance. SD: Standard deviation; BMI: Body mass index.

Table 2. Laboratory values of all patients included in the study

	Group with insulin resistance n=45 Mean±SD/SEM	Group without insulin resistance n=45 Mean±SD/SEM	p
Hemoglobin (g/dL)	12.7±1.4[a]	12.6±1.1[a]	0.781
WBC (10^3/mm^3)	9.7±0.12[b]	8.3±0.05[b]	0.184
Platelet (10^3/mm^3)	305±85.6[a]	264.3±64.1[a]	0.012*
Glucose (mg/dL)	101.3±0.87[b]	85.7±1.90[b]	<0.001*
Insulin (uIU/mL)	21.5±0.26[b]	7±0.05[b]	<0.001*
HOMA-IR	5.8±0.14[b]	1.5±0.01[b]	<0.001*
HDL (mg/dL)	48.4±8.3[a]	54.4±11.9[a]	0.019*
LDL (mg/dL)	103.2±27.4[a]	102.8±28.4[a]	0.940
Triglyceride (mg/dL)	107.4±1.62[b]	97.3±1.86[b]	0.150
F-TES (pg/mL)	2.00±0.03[b]	2.44±0.02[b]	0.012*
T-TES (ng/dL)	2.54±0.03[b]	2.50±0.02[b]	0.460
Prolactin (µg/L)	22.5±0.22[b]	18.5±0.20[b]	0.045*
DHEA (µg/dL)	295.1±2.14[b]	311±2.65[b]	0.490
SHBG (nmol/L)	64.2±0.96[b]	53.9±0.81[b]	0.390
FAI	5.6±0.08[b]	7.4±0.14[b]	0.388
Ferriman gallwey score	4.3±0.15[b]	7.6±0.16[b]	0.008
Serum irisin (ng/mL)	3.66±0.06[b]	2.77±0.04[b]	0.065

*: No difference between the two groups. [a]: Standard deviation; [b]: Standard error of mean. SD: Standard deviation; SEM: Standard error of mean; WBC: White blood cell; HOMA-IR: Homeostatic model assessment of insulin resistance; HDL: High-density lipoprotein; LDL: Low-density lipoproteins; F- TES: Free testosterone; T-TES: Total testosterone; DHEA: Dehydroepiandrosterone; SHBG: Sex hormone binding globulin; FAI: Free androgen index.

Statistical analysis

The statistical analysis was conducted using SPSS 15.0 software for Windows. Descriptive statistics were presented as the mean, standard deviation, and standard error of the mean for numerical variables, and as numbers and percentages for categorical variables. Skewness and kurtosis values were initially used to evaluate normal distribution, followed by the Shapiro-Wilk test to confirm normality. The Student's t-test was used to compare two independent groups, as the numerical variables met the normal distribution requirement. Since the parametric test condition was met in all tests, Pearson correlation analysis was applied. Multivariate linear regression analysis was performed to determine if there were independent risk factors in the relationship between irisin and HOMA-IR. The statistical significance level was set at a p-value of less than 0.05.

Results

Table 1 presents the comprehensive characteristics of the individuals participating in the clinical investigation. The results showed no statistical difference in age and hip circumference between the two groups (p=0.974, p=0.875). The cohort with insulin resistance demonstrated significantly higher weight, BMI, and waist circumference compared to the cohort without insulin resistance. Conversely, the group without insulin resistance showed greater height (p=0.004, p<0.001, p=0.001, and p=0.032, respectively).

The laboratory values of the participants are presented in Table 2. Analysis of the laboratory data indicated no difference in hemoglobin, WBC, LDL-C, triglyceride, total testosterone, DHEA-S, SHBG, and FAI values between the two groups (p=0.781,

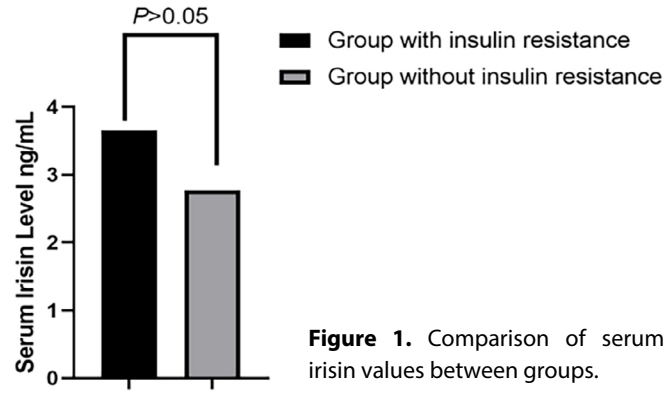

Figure 1. Comparison of serum irisin values between groups.

p=0.184, p=0.940, p=0.150, p=0.460, p=0.490, p=0.390, p=0.388, respectively). PCOS patients with insulin resistance had higher levels of platelets, insulin, glucose, HOMA-IR, and prolactin compared to PCOS patients without insulin resistance (p=0.012, p<0.001, p<0.001, p<0.001, p=0.045, respectively). The group with insulin resistance exhibited significantly lower levels of HDL-C, free testosterone, and Ferriman-Gallwey scores (p=0.019, p=0.012, p=0.008). Serum irisin levels were comparable between both groups. The concentration was 3.66±0.06 ng/mL in the group with insulin resistance and 2.77±0.04 ng/mL in the group without insulin resistance (p=0.065) (Fig. 1).

Table 3 displays the relationships between serum irisin concentration and the laboratory values of the study participants. Serum irisin levels were correlated with hemoglobin, insulin, HOMA-IR, F-TES, and T-TES levels (r=0.287, P=0.006; r=0.376, p<0.001; r=0.279, p=0.008; r=-0.230, p=0.029; r=-0.261, p=0.013, respectively). However, these relationships were weak and correlations were incomplete. Positive correlations were significant for hemoglobin, insulin, and HOMA-IR, while negative correlations were significant for F-TES and T-TES.

Table 4 shows serum irisin levels in the control and case groups with a Ferriman-Gallwey score >8. The average blood irisin level in PCOS patients with a high Ferriman-Gallwey score and insulin resistance was 3.70±0.06 ng/mL. In PCOS patients with a high Ferriman-Gallwey score but without insulin resistance, the average irisin concentration was 2.71±0.04 ng/mL. No substantial difference in irisin levels was found between the two groups (p=0.561).

The patients in the study had no prior chronic illness but were later diagnosed with metabolic syndrome. These patients were not excluded from the study. Among patients with insulin resistance, 12 (26.7%) were diagnosed with metabolic syndrome, compared to 3 (6.7%) in patients without insulin resistance. Serum irisin levels in patients with metabolic syndrome are shown in Table 5. The mean serum irisin concentration in PCOS patients with both metabolic syndrome and insulin resistance was 3.99±0.07 ng/mL, whereas in PCOS patients with metabolic syndrome but without insulin resistance, the mean was 2.37±0.02 ng/mL. There was no substantial distinction between the two groups (p=0.410).

According to multivariate linear regression analysis, age, BMI, and waist circumference were not identified as independent factors in the relationship between irisin and HOMA-IR (Beta=0.136, p=0.169; Beta=0.160, p=0.092; Beta=0.150, p=0.145, respectively).

Table 3. The relationship between laboratory findings and serum irisin in all patients included in the study

	Serum Irisin	
	r	p
Hemoglobin (g/dL)	0.287	**0.006**
WBC (10^3/mm^3)	0.104	0.328
Glucose (mg/dL)	0.141	0.183
Insulin (uIU/mL)	0.376	**<0.001**
HOMA-IR	0.279	**0.008**
HDL (mg/dL)	-0.161	0.130
LDL (mg/dL)	0.143	0.179
Triglyceride (mg/dL)	0.061	0.567
F-TES (pg/mL)	-0.230	**0.029**
T-TES (ng/dL)	-0.261	**0.013**
Prolactin (µg/L)	0.052	0.627
DHEA (µg/dL)	0.009	0.934
SHBG (nmol/L)	0.149	0.160

Student t-test was used to examine whether there was a significant difference between the means of two groups. WBC: White blood cell; HOMA-IR: Homeostatic model assessment of insulin resistance; HDL: High-density lipoprotein; LDL: Low-density lipoproteins; F- TES: Free testosterone; T-TES: Total testosterone; DHEA: Dehydroepiandrosterone; SHBG: Sex hormone binding globulin.

Table 4. Serum irisin levels of the control and Case groups with Ferriman-Gallwey score>8

	Ferriman gallwey score>8	
	Serum Irisin Mean±SEM	p
Insulin resistance		
Yes n=17	3.70±0.06	0.561
No n=29	2.71±0.04	

SEM: Standard error of mean.

Table 5. Serum irisin levels diagnosed in patients with metabolic syndrome

	Metabolic syndrome	
	Serum Irisin Mean±SEM	p
Insulin resistance		
Yes n=12	3.99±0.07	0.410
No n=3	2.37±0.02	

SEM: Standard error of mean.

Discussion

Our study investigated the relationship between the hormone irisin and insulin resistance in PCOS patients. While the serum irisin level in PCOS patients with insulin resistance was 3.66±0.06 ng/mL, it was 2.77±0.04 ng/mL in PCOS patients without insulin resistance, with no significant difference between them. Insulin, HOMA-IR, F-TES, and T-TES levels were weakly correlated with serum irisin levels. Hemoglobin, insulin, and HOMA-IR values showed a positive correlation with irisin levels, whereas F-TES and T-TES values were negatively correlated.

Insulin resistance affects 50–70% of women with PCOS and is strongly linked to metabolic syndrome, hypertension, dyslipidemia, diabetes mellitus, and long-term cardiovascular disease [5]. The complexity of these comorbidities highlights the importance of understanding and managing insulin resistance in PCOS patients. The hormone irisin has been shown to improve hepatic glucose metabolism by promoting glucose uptake in skeletal muscle [19]. Due to its association with improved glucose tolerance and reduced insulin resistance, irisin is an attractive molecule to study in PCOS patients.

Chang et al. [20] conducted a comparison of serum irisin levels between PCOS and control groups, finding abnormally elevated serum irisin levels in PCOS patients. Additionally, PCOS patients exhibited elevated BMI and insulin levels. Increased serum irisin levels were linked to the development of insulin resistance and hyperandrogenemia. Bayraktar et al. [21] observed elevated serum irisin levels in individuals with PCOS compared to control patients; however, insulin resistance and HOMA-IR levels were similar in both the PCOS and control groups. Conversely, Masaeli et al. [22] found that in patients with PCOS, blood irisin levels were significantly elevated compared to those without the condition. They also noted a reduction in insulin resistance and serum irisin levels following three months of metformin therapy in PCOS patients. Similarly, Farhan et al. [23] examined serum irisin levels in PCOS patients before and after therapy, observing a reduction in serum irisin levels and insulin resistance following four months of metformin treatment compared to pretreatment levels in the control group.

Since not all PCOS patients exhibit insulin resistance, we selected participants from both groups of PCOS patients to allow for a more controlled comparison of serum irisin levels within a similar patient population, minimizing potential confounding factors. Serum irisin levels were not significantly different between PCOS patients with and without insulin resistance. Given that insulin resistance is not the only determinant in PCOS development, further research with larger patient cohorts is necessary.

Hyperandrogenism, although not necessarily present in every patient, is one of the diagnostic criteria for PCOS and can influence the treatment modality to be planned. This consideration has prompted the examination of the correlation between irisin and hyperandrogenemia. Among PCOS patients, Li et al. [24] examined the correlation between hyperandrogenism, the FAI index, and serum irisin. PCOS patients with a high FAI exhibited elevated serum irisin levels compared to both PCOS and control patients with a low FAI index. Additionally, these patients had a higher incidence of insulin resistance when hyperandrogenemia was present. Zhang et al. [25] observed elevated serum irisin levels in individuals with PCOS compared to a control group. They further analyzed these levels based on PCOS characteristics. While serum irisin levels in patients with a normoandrogenic phenotype were nearly equivalent to those in control participants, patients with a hyperandrogenic phenotype had higher serum irisin levels. Based on these findings, it has been shown that therapy with insulin sensitizers is not effective for PCOS patients with a normoandrogenic phenotype.

The results of our investigation indicated that PCOS patients without insulin resistance had higher FAI rates and lower serum irisin levels, though this difference did not reach statistical significance. In the studies mentioned above, patients with hyperandrogenemia were not divided into groups with and without insulin resistance for comparison. In our study, we had the opportunity to compare patients with hyperandrogenemia in two groups: those with and those without insulin resistance. We also investigated the relationship between hirsutism, a clinical manifestation of hyperandrogenemia, and serum irisin. In our comparison of patients with hyperandrogenemia, the group with insulin resistance had elevated serum irisin levels; however, there was no statistically significant difference observed between the group with insulin resistance and the group without it.

While commonly referred to as a myokine, irisin is also secreted from adipose tissue [11, 12]. A study by Arhire et al. [26] revealed a significant correlation between blood irisin levels and both obesity and metabolic syndrome. Furthermore, Elizondo-Montemayor et al. [27] demonstrated that an elevated serum irisin concentration is associated with a twofold increase in the risk of metabolic syndrome. To investigate the correlation between serum irisin and metabolic syndrome, the study included patients who were not initially diagnosed with metabolic syndrome but were subsequently diagnosed with it. The serum irisin levels of these patients were then compared. No statistically significant difference in serum irisin levels was observed between patients with PCOS and insulin resistance diagnosed with metabolic syndrome and patients without insulin resistance diagnosed with metabolic syndrome.

A primary limitation of our study is the restricted sample size. Additionally, we were unable to evaluate changes in serum irisin levels post-treatment for PCOS. However, our study provided an opportunity to compare serum irisin levels in patients who were diagnosed with metabolic syndrome after their PCOS diagnosis and who had elevated Ferriman-Gallwey scores due to hyperandrogenemia.

Conclusion

The objective of this study was to investigate the correlation between serum irisin levels and insulin resistance in women diagnosed with PCOS. Our findings revealed no statistically significant difference in serum irisin levels between PCOS patients with and without insulin resistance. While modest correlations were found between serum irisin and insulin, HOMA-IR, free testosterone, and total testosterone levels, these relationships were not sufficiently robust to establish conclusive findings on the involvement of irisin in the pathogenesis of PCOS.

In the metabolic complications of PCOS, insulin resistance remains a crucial determinant. Although irisin may play an essential role in enhancing insulin sensitivity and glucose metabolism, our results suggest that insulin resistance alone may not have a direct impact on serum irisin levels in PCOS patients. This underscores the complexity of the condition, in which various factors, such as hyperandrogenism and metabolic syndrome, likely interact to influence clinical outcomes.

Further research is necessary to elucidate the role of irisin in PCOS and its potential as a therapeutic target. Future studies should include larger patient cohorts and carefully evaluate the impact of treatment on serum irisin levels to gain a deeper understanding of its therapeutic significance in the management of PCOS.

Ethics Committee Approval: The study was approved by The University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (No: 849, Date: 22/08/2017).

Authorship Contributions: Concept – G.K., U.K., D.A., S.C., A.E.Y.; Design – G.K., U.K., D.A., S.C., A.E.Y.; Supervision – G.K., U.K., D.A., S.C., A.E.Y.; Funding – G.K.; Materials – S.C., D.A., G.K.; Data collection &/or processing – G.K., D.A.; Analysis and/or interpretation – G.K., U.K.; Literature search – G.K., U.K.; Writing – G.K., S.C.; Critical review – A.E.Y., G.K.

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