



# Effect of nanocurcumin on serum levels of betatrophin and irisin in patients with metabolic syndrome; a clinical trial

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## Abstract

**Introduction:** Metabolic syndrome is a highly prevalent disease with combination of cardio metabolic risk factors. Insulin resistance is the most important reason of metabolic syndrome.

**Objectives:** The study aimed to evaluate the effects of nanocurcumin on insulin resistance and serum level irisin and betatrophin in patients with metabolic syndrome.

**Patients and Methods:** Sixty metabolic syndrome patients (30 males and 30 females) received 80 mg/daily nanocurcumin for three months. The samples of fasting blood were collected at the beginning of the study and after 90-days intervention to measure the biomarkers.

**Results:** comparing pre and post treatment with nanocurcumin values revealed a significant change in fasting plasma glucose (FPG), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and irisin ( $P > 0.05$ ), but there was no change in the amount of betatrophin ( $P > 0.05$ ).

**Conclusion:** According to the results, it seems that the use of nanocurcumin for 90 days may have positive effects on some metabolic components. However, more studies with larger sample sizes are needed to confirm the findings.

Trial registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20120215009014N214; <https://www.irct.ir/trial/30187>, ethical code; IR.UMSHA.REC.1396.859).

**Keywords:** Nano-curcumin, betatrophin, Irisin, Metabolic syndrome

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## Introduction

The metabolic syndrome is a collection of metabolic disorders that raises the risk of diabetes mellitus and cardiovascular disease. Increases in waist circumference among women, hyperglycemia, dyslipidemia, and hypertension are the main symptoms of this syndrome (1-4). According to the Joint Interim Statement (JIS), metabolic syndrome is characterized by the presence of three or more of the following risk factors (5):

1. Abdominal obesity with a waist circumference  $\geq 102$  cm (males) and  $\geq 80$  cm (females).
2. Fasting plasma glucose (FPG)  $\geq 100$  mg/dL or drug treatment.
3. Fasting triglyceride (TG)  $\geq 150$  mg/dL or drug treatment.
4. Fasting high-density lipoprotein cholesterol (HDL-c)  $< 50$  mg/dL in women and HDL-c  $< 40$  mg/dL in men.

5. Systolic blood pressure (SBP)  $\geq 130$  mm Hg, or diastolic blood pressure (DBP)  $\geq 85$  mm Hg, which indicates hypertension or antihypertensive drug treatment.

Insulin resistance that results in hyperglycemia is the pathophysiology of the metabolic syndrome that is most commonly recognized to explain it (6). Muscle, the liver, and adipose tissue all secrete the hormone irisin. This hormone promotes weight loss and reduces insulin resistance (7). A well-known circulating hormone generated by the liver and adipose tissue is called betatrophin (8).

The use of herbal medicines in the treatment of numerous disorders has recently received more attention. A phenolic substance called curcumin is obtained from the rhizomes of turmeric (9,10). Adipocytes, pancreatic cells, liver-shaped star cells, macrophages, and muscle cells are all directly impacted by curcumin, according

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### ■ Implication for health policy/practice/research/medical education

Insulin resistance is the most important reason of metabolic syndrome. This study evaluated the effects of nanocurcumin on insulin resistance and serum levels of irisin and betatrophin in 30 males and 30 females with metabolic syndrome. There was significant change in fasting plasma glucose (FPG), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and irisin after 90 days.

to earlier research. Its mode of action involves the stimulation of signaling pathways related to peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), and nuclear factor erythroid 2p45-related factor 2 as well as the inhibition of the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and STAT3, and Wnt-Catenin. Curcumin also lessens the control over adipokines such resistin, leptin, and interleukin-6. Contrarily, it raises the level of adiponectin. Thus, alterations brought about by curcumin ameliorate hyperglycemia, dyslipidemia, and other obesity-related issues (11,12). Because of its sensitivity to variations in the physiological pH of the body, curcumin is difficult to dissolve in water. The bioavailability of curcumin can be increased in a variety of methods. According to which the medical benefits of curcumin can be enhanced through the formation of nanoparticles and its incorporation in nanoemulsions (nanocurcumin) (13,14).

### Objectives

This study sought to ascertain how blood levels of irisin and betatrophin in individuals with metabolic syndrome were affected by nanocurcumin, taking into account the connection between irisin, betatrophin, and insulin resistance as well as the benefits of curcumin in reducing insulin resistance.

### Patients and Methods

#### Study design and population

The study comprised 60 patients with metabolic syndrome who were sent to the endocrine clinic in Hamadan, west of Iran (30 male and 30 females, and  $41.76 \pm 8.02$  years).

These people were hired following ethical board approval, an endocrinologist's confirmation of the metabolic syndrome, and patient-provided informed consent. Thyroid disease, known autoimmune diseases, cancer, cirrhosis, chronic kidney disease, undergoing diabetic therapy, receiving glucocorticoids, and failure to return for retesting were among the exclusion criteria.

Before and after the trial, participants got a thorough evaluation that included a medical history, physical exam, and anthropometric measurements. 10 ml of patient blood was drawn while they were fasting, and the serum from the blood sample was then separated. The subjects took 80 mg of nanocurcumin every day for 12 weeks from Exir Nano Sina Company in Iran (IRC: 1228225765). Following the

course of treatment, 10 ml of blood were again drawn from the patients, and the serum was once again separated. A CONSORT diagram of study participation is presented in Figure 1.

### Biochemical measures

Fasting plasma glucose (FPG), total cholesterol, triglyceride (TG), LDL-c, and HDL-c were assessed using commercial enzyme reagents. Irisin, betatrophin, and insulin serum levels were measured using enzyme-linked immunosorbent assay (ELISA) commercial kits (My BioSource, San Diego, United States and Mercodia, Uppsala, Sweden, respectively) in accordance with the manufacturer's instructions. The homeostasis model assessment of insulin resistance (HOMA-IR) model was computed to assess insulin resistance using the following formula;

$$HOMA-IR = [(fasting\ insulin\ level\ (mU/L)) \times (FPG\ (mmol/L))]/22.5\ (15).$$

### Statistical analysis

SPSS version 22.0 (SPSS Inc., Chicago, USA) and GraphPad Prism version 6.0 were used for data analysis

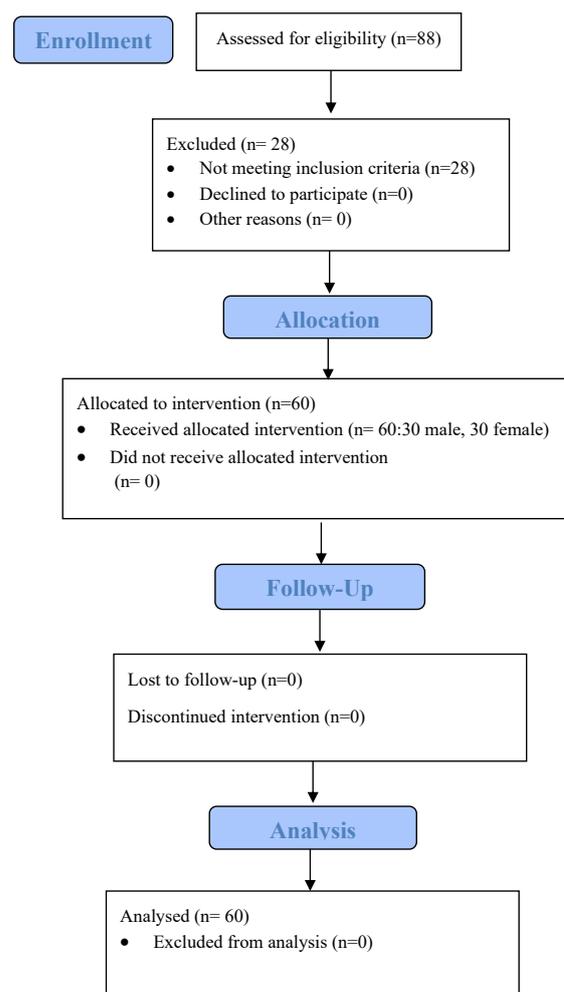


Figure 1. CONSORT diagram of study participation.

(GraphPad Software, San Diego-USA). Kolmogorov-Smirnov test was conducted to check the normality of the variables. The findings are presented in terms of number, percentage, mean, and standard deviation. The data were analyzed using a two-tailed, paired Student's t-test and Pearson's correlation analysis. A *P* value below 0.05 were regarded as significant.

## Results

30 men and 30 women participated in this study, with a mean age of  $46.77 \pm 8.02$  years. The results show that at the start of treatment and 12 weeks later, no significant difference in body mass index, waist circumference, systolic blood pressure, or diastolic blood pressure were detected ( $P > 0.05$ ; Table 1).

After receiving treatment with nanocurcumin, there was no significant difference in total cholesterol (TC), triglycerides (TG), LDL-c, and HDL-c ( $P > 0.05$ ; Table 1).

After treatment with nanocurcumin, the levels of FPG, fasting insulin, and HOMA-IR were significantly lower than pre-treatment values ( $P < 0.05$ ; Table 1).

Additionally, individuals receiving nanocurcumin therapy had considerably greater levels of irisin ( $P = 0.047$ ). The levels of betatrophin before and after the intervention, however, did not differ ( $P = 0.068$ ; Figures 2 and 3).

The level of serum irisin and betatrophin were positively and insignificantly correlated, according to Spearman's rank correlation coefficient ( $P = 0.757$ ; Figure 4).

## Discussion

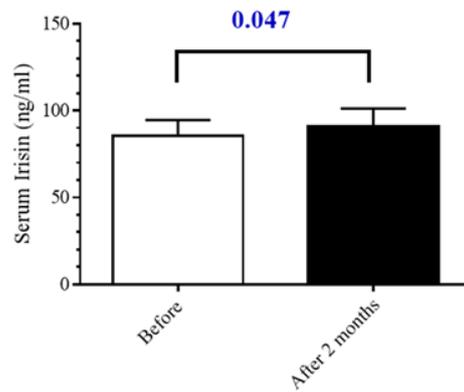
Our research revealed that taking nanocurcumin for 12 weeks significantly decreased FPG, Insulin level, HOMA-IR, and irisin. However, there was no impact on the lipid profile or betatrophin.

**Table 1.** Comparison of the frequency of changes in metabolic syndrome indices before and after three months of nanocurcumin (80 mg) therapy in patients with metabolic syndrome (n=60)

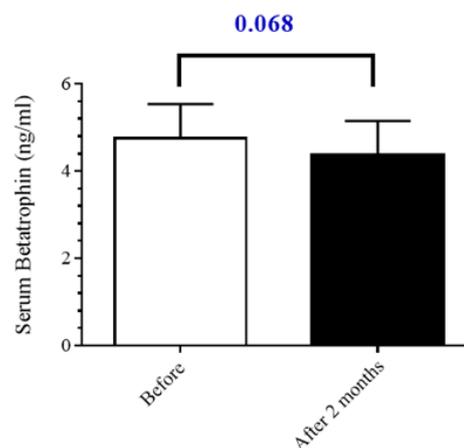
Variable	Before treatment	After treatment	<i>P</i> value
Waist	109.30 ± 7.77	105.11 ± 6.35	0.217
SBP (mm Hg)	118.33 ± 12.68	115.50 ± 10.03	0.341
DBP (mm Hg)	81.83 ± 7.36	78.66 ± 8.19	0.121
FPG (mg/dL)	105.91 ± 10.39	98.67 ± 12.01	0.016
Fasting insulin (μU/mL)	13.26 ± 1.05	12.63 ± 0.90	0.017
HOMA-IR	3.48 ± 0.55	3.08 ± 0.51	0.006
TG (mg/dL)	196.97 ± 17.15	176.30 ± 11.34	0.320
TC (mg/dL)	188.37 ± 30.54	190.06 ± 32.89	0.786
HDL-C (mg/dL)	36.83 ± 10.44	40.02 ± 8.95	0.150
LDL-C (mg/dL)	112.51 ± 23.78	108.23 ± 20.46	0.459

The results expressed as mean ± SD.

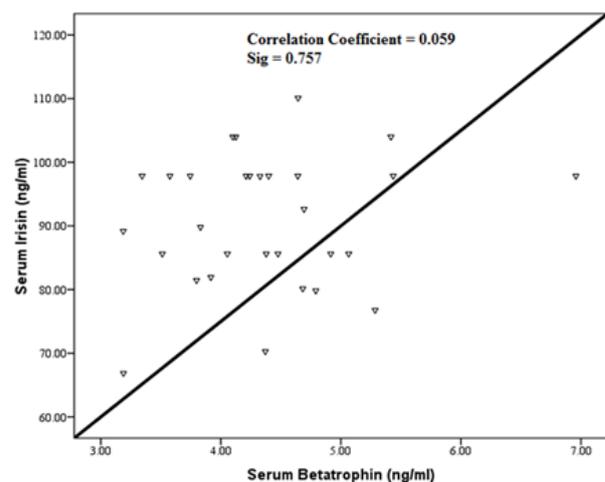
SD, Standard deviation; BMI, Body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglyceride.



**Figure 2.** Irisin levels before and after three months of nanocurcumin (80 mg) therapy in patients with metabolic syndrome (n=60). The results are expressed as mean ± SD. *P* values < 0.05 were considered statistically significant.



**Figure 3.** Betatrophin levels before and after three months of nanocurcumin (80 mg) therapy in patients with metabolic syndrome (n=60). The results are expressed as mean ± SD. *P* values < 0.05 were considered statistically significant.



**Figure 4.** Spearman correlation coefficient between irisin and betatrophin after three months of nanocurcumin (80 mg) therapy in patients with metabolic syndrome (n=60).

In the study of Shafabakhsh et al, individuals with diabetes receiving hemodialysis who consumed nanocurcumin for 12 weeks saw improvements in their lipid profiles (16).

According to the results of a meta-analysis conducted by Poolsup et al consumption of curcumin reduces FPG but has no effect on HOMA-IR in individuals with prediabetes and type 2 diabetes mellitus (17).

In a clinical trial investigation, Kocher et al demonstrated that participants with moderate hyperlipidemia who consumed 294 mg micellar curcumin daily for six weeks experienced no appreciable change in their blood glucose levels (18).

According to the study by Jazayeri-Tehrani et al, consuming 40 mg of nanocurcumin for three months, helped obese and overweight people with nonalcoholic fatty liver disease (NAFLD) significantly lower their FPG and HOMA-IR scores and improve their lipid profiles (19).

The study design, curcumin dosage, and length of the intervention are only a few examples of the variables that may have contributed to the conflicting and disparate results.

However, the lowering of insulin and hyperglycemia levels is the aspect that all of these studies have in common.

Curcumin reduces oxidative stress, which lowers hyperglycemia. Additionally, curcumin can increase insulin secretion and synthesis. Curcumin's positive impact on insulin resistance is achieved through liver glycolysis promotion and liver glyconeogenesis inhibition (16).

Our findings indicate that nanocurcumin significantly boosted irisin during a 12-week period. The expression of irisin in patients with metabolic syndrome and diabetes has been assessed in a number of investigations. They claim that research has indicated that irisin levels have fallen in diabetic people. On the other side, higher levels of this hormone's expression are linked to lower levels of insulin resistance, which in turn lowers blood sugar levels. The irisin antidiabetic actions are caused by an increase in the expression of the hexokinase-2 (HK2), peroxisome proliferator activated receptor alpha (PPARA) genes, and glucose transporter type 4 (GLUT4), as well as a decrease in the expression of the genes gluconeogenesis and glycogenolysis (20-22). Therefore, it may be deduced that drugs that can boost this hormone's expression could be used to treat metabolic syndrome and other related disorders.

The betatrophin protein, which was first discovered in 2012 in a diabetic animal model, has the capacity to promote the growth of pancreatic beta cells (8).

According to the study by Gao et al, a strong and positive correlation between the amount of betatrophin, triglycerides, and post-meal hyperglycemia was detected (23). After three months of therapy with nanocurcumin, however, there was no discernible connection between

betatrophin and any of the examined factors in our study.

The effects of microcurcumin on irisin and betatrophin have not been extensively studied.

In a study, Kheiripour et al found that 8 weeks of nanocurcumin consumption significantly reduced afamin levels in patients with metabolic syndrome (24).

Taking supplements containing curcumin can have anti-inflammatory and antioxidant effects, which are achieved by significantly lowering interleukin-6, high-sensitivity C-reactive protein, and malondialdehyde concentrations, according to a meta-analysis and systematic review of randomized controlled trials (25).

However, a meta-analysis found that participants with chronic inflammatory disease who consumed curcumin did not have a decrease in inflammatory cytokines (26). These differences could be the result of the study population's variations, the study's varied design, the disease and kind of curcumin used, the dietary supplements used, the caliber of the curcumin used, and the length of the intervention.

Small sample size was one of the study's shortcomings, and we also neglected to examine the impact of nanocurcumin on inflammatory markers and oxidative stress levels.

## Conclusion

According to our findings, adding nanocurcumin to the diets of patients with metabolic syndrome improved their FPG, insulin levels, HOMA-IR, and irisin levels. Perhaps it is possible to conclude that enhancing these markers has an impact on raising serum irisin levels. Therefore, additional studies are required to examine the outcomes of extended treatment durations and various nanocurcumin dosages.

## Limitations of the study

This study was a single-center study with a small sample size, and more studies with a big sample size are needed to confirm the results of this study. In addition, the short duration of the intervention was another limitation of the study.

## Acknowledgements

The present study was approved by the Medical Ethics Committee of the Hamadan University of Medical Sciences. We express our sense of gratitude to all participants of the study.

## Authors' contribution

HG did data validation and source preparation. SB participated in conceptualization, writing reviewing and editing of the article, project management and fundraising. NK contributed significantly to the methodology of the formal analysis, writing – preparing the original draft, project supervision. AR carried out the methodology of the research, MB had a significant contribution to the research. ZK performed data curation.

## Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Hamadan University of Medical Sciences approved this study (IIR.UMSHA.REC.1396.859). Written informed consent was taken from all participants before any intervention. The trial protocol was approved by the Iranian registry of clinical trial (Identifier: IRCT20120215009014N214; <https://www.irct.ir/trial/30187>). Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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