



Research Article

Leap-2 and irisin in the pathophysiology of Type 2 diabetes mellitus

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Abstract

Objectives: Insulin resistance is one of the main reasons responsible for the pathogenesis of Type 2 Diabetes Mellitus (T2DM). LEAP2 functions as an endogenous antagonist of the ghrelin receptor and is associated with insulin resistance. Irisin is a thermogenic myokine that causes energy expenditure by converting white adipose tissue into brown adipose tissue. Based on this information, we aimed to reveal the possible relationship between Leap2, irisin levels, and insulin resistance in newly diagnosed T2DM patients

Methods: Our study consisted of 82 patients newly diagnosed with T2DM and 74 Healthy control groups who do not use any medication. Leap2 and irisin levels were measured using the enzyme-linked immunosorbent assay method.

Results: Compared to the control group, we found the serum irisin levels significantly lower in the diabetic group. LEAP2 levels were significantly higher in the diabetic group. In the patient group, we found a negative correlation between irisin levels and HOMA-IR and insulin levels and a positive correlation with HDL. On the contrary, we found a positive correlation between LEAP2 levels and HOMA-IR, insulin, and triglyceride levels.

Conclusion: In patients with T2DM, LEAP2 levels are higher and irisin levels are lower than in healthy people. Various molecules have been the target of many studies on maintaining glucoous homeostasis, and preventing and improving diabetes mellitus. Therefore, the role of adipomyokines in T2DM and insulin resistance should be further investigated. To our knowledge, this study will be the first report correlating T2DM, LEAP2, and irisin levels and HOMA-IR in humans.

Keywords: Diabetes mellitus, HOMA-IR, irisin, Leap2

How to cite this article: Suay Timurkaan E, Timurkaan M, Kalayci M. Leap-2 and irisin in the pathophysiology of Type 2 diabetes mellitus. Int J Med Biochem 2026;9(2):78–84.

Diabetes mellitus (DM) is responsible for over 3.4 million deaths annually [1]. According to the International Diabetes Federation (IDF), around 589 million people worldwide are currently affected by diabetes, and this number is projected to rise to approximately 784 million by 2045 [2]. The most characteristic feature of DM is hyperglycemia [3].

In patients with type 2 diabetes mellitus (T2DM), there are at least two main pathological mechanisms. The first, known as insulin resistance, involves decreased insulin activity in peripheral tissues and is widely recognized as a primary underlying cause. The second mechanism, β -cell dysfunction, refers to the pancreas's inability to secrete sufficient insulin to com-

pensate for insulin resistance [4]. In general, insulin deficiency or the ineffectiveness of insulin, even at adequate levels, constitutes the core issue in the pathogenesis of the disease. Recent studies have demonstrated a direct relationship between these factors and adipokines [5–9].

Irisin is produced from fibronectin type III domain-containing 5 (FNDC5), a transmembrane protein cleaved by specific proteases. Irisin, a thermogenic protein, promotes energy expenditure by converting white adipose tissue into brown adipose tissue. First identified in muscle tissue, irisin has a molecular weight of 12 kDa and comprises 112 amino acids. It is classified as a myokine secreted by skeletal muscles and is known to of-

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Submitted: September 16, 2025 **Revised:** January 02, 2026 **Accepted:** January 10, 2026 **Available Online:** April 15, 2026

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fer protective effects against metabolic diseases when stimulated by regular exercise [10]. While irisin is thought to protect against diabetes and obesity, it is also associated with muscle mass and insulin sensitivity [11, 12]. Irisin has been studied in various conditions, including obesity, T2DM, cardiovascular diseases, chronic renal failure, non-alcoholic steatohepatitis (NASH), and polycystic ovary syndrome (PCOS). Serum irisin levels are reported to be lower in conditions such as cardiovascular disease, T2DM, and NASH compared to healthy controls [13]. Additionally, studies on diabetic mice have shown that increased irisin expression improves glucose tolerance and reduces fasting insulin levels, suggesting its potential as a therapeutic target for T2DM and obesity [10].

Liver-expressed antimicrobial peptide 2 (LEAP2), first identified in 2003, is expressed primarily in the liver and small intestine, with its secretion being suppressed during fasting. LEAP2 acts as an endogenous antagonist of the growth hormone secretagogue receptor (GHSR), which is activated by ghrelin. By inhibiting GHSR, LEAP2 counteracts ghrelin's effects on growth hormone release, appetite stimulation, and glucose elevation during fasting [14]. The evidence that LEAP2 has appetite-suppressing properties and can modulate insulin secretion raises the question of whether this peptide may play a role in diabetes [15].

Interestingly, plasma LEAP2 levels are positively correlated with plasma glucose, HOMA-IR, body mass index (BMI), body fat percentage, serum triglycerides, and the visceral-to-subcutaneous adipose tissue ratio [16, 17]. Given the increasing prevalence of obesity-related metabolic disorders, including T2DM, LEAP2 has garnered attention as a potential regulator of glucose homeostasis and metabolic balance [15].

Based on this information, we conducted the first comparative study of LEAP2 and irisin in T2DM. While irisin has been widely studied, LEAP2 remains a relatively new focus of investigation. The aim of this study is to analyse circulating concentrations of irisin and LEAP2 key regulators of energy balance and glucose metabolism in type 2 diabetes mellitus (T2DM) and to investigate their relationship with insulin resistance. In this way, we seek to clarify the role of LEAP2 and irisin in the pathophysiology of T2DM and to explore their potential value as biomarkers.

Materials and Methods

This study was conducted in collaboration with the Internal Medicine Clinic and Biochemistry Laboratory at Elazig Fethi Sekin City Hospital, with ethical approval obtained from Firat University Ethics Department. All participants were informed about the study, and written consent was obtained. This study was conducted in accordance with the ethical principles of the Helsinki Declaration. Individuals with any systemic disease (e.g., coronary heart disease, liver disease, acute or chronic renal failure, malignancy), patients younger than 18 years, and those previously diagnosed diabetes were excluded from the study. Detailed histories were

taken, including age, height, and weight, for all participants. Our study included 82 patients (42 females, 40 males) newly diagnosed with T2DM and 74 healthy controls (37 females, 37 males) based on the 2021 diagnostic criteria of the International Diabetes Federation (IDF). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and HOMA-IR was calculated using the formula: $\text{insulin } (\mu\text{U}/\text{ml}) \times \text{glucose } (\text{mg}/\text{dl}) / 405$.

Blood samples were collected from both groups after 10 hours of fasting into three tubes: One with gel for biochemistry, one containing EDTA, and one with aprotinin (BD Vacutainer; Becton, Dickenson and Co., Franklin Lakes, NJ, USA). Blood samples taken into biochemistry tubes were centrifuged for 15 minutes at 3500 rpm from serums obtained; glucose, insulin, lipid parameters, EDTA from the tube containing whole blood HbA1c (by HPLC method) were studied on the same day. Blood samples taken into aprotinin-containing tubes were centrifuged at 3500 rpm for 10 minutes and the resulting plasmas were stored at -20°C until the study day to study LEAP2 and irisin.

The glucose and lipid parameters were measured using the AU5800 analyzer (Beckman Coulter, Inc., Miami, FL, USA). Insulin levels were analyzed with the DXI800 (Beckman Coulter, Inc., Miami, FL, USA) immunoassay system, and HbA1c levels were assessed using the Premier HB920 (Trinity Biotech, Ireland) device.

Plasma levels of LEAP2 and irisin were determined using ELISA kits specific for each protein (Sunred, Cat. Number: SRB-T-81190; Sunred, Cat. Number: 201-12-5328, Shanghai, China). Absorbance was measured using a Chromate 4300 Microplate Reader. The minimum detection limit for LEAP2 and irisin was 0.438 pg/ml, 0.157 ng/ml, respectively. The intra-assay and inter-assay coefficients of variation for LEAP2 and irisin measurements were $<10\%$ and $<12\%$, respectively.

Statistical analysis was performed using SPSS. Data were expressed as mean \pm standard deviation. The Shapiro-Wilk test was used to determine the normality of the data distribution. The Chi-square test was employed for the evaluation of categorical data. Normally distributed data were analyzed using the Students t-test, while non-normally distributed variables were compared using the Mann-Whitney U test, with median values provided. A partial correlation analysis was conducted after adjusting for such as age, BMI, and sex to evaluate the relationships between the variables. A p-value <0.05 was considered statistically significant.

Results

Laboratory, demographic, and clinical data are summarized in Table 1. There were no significant differences between groups in gender distribution or age. However, in terms of Body Mass Index (BMI), the diabetic group was significantly higher than the control group ($p < 0.001$). Cholesterol, LDL, and triglyceride levels were significantly higher in the diabetic group ($p < 0.05$ for LDL, $p < 0.001$ for others), while HDL levels were higher in

Table 1. Laboratory and demographic data of the groups

	Control n=74 Mean±SD	T2DM n=82 Mean±SD	p
Age* (year)	46.9±7.7	48.1±5.3	>0.05
Irisin (ng/mL)	30.28±14.7	23.12±12.6	<0.01
Leap2 (ng/mL)	9.96±4.68	11.13±4.59	<0.05
Glucose (mg/dL)	89.6±7.96	190.2±58.3	<0.001
Cholesterol* (mg/dL)	188.9±27.9	208.8±32.3	<0.001
HDL (mg/dL)	46.65±8.27	41.17±7.69	<0.001
LDL* (mg/dL)	116.7±23.8	129.4±28.1	<0.05
Triglyceride (mg/dL)	128.7±52.1	190.4±65.3	<0.001
Insulin (mIU/L)	8.91±5.36	11.3±5.87	<0.05
Hba1C (%)	5.51±0.42	8.4±1.62	<0.001
BMI (kg/m ²)	24.62±2.37	28.99±3.07	<0.001
HOMA-IR	1.98±1.29	5.64±4.43	<0.001

*: Normal distribution according to the Shapiro-Wilk test. HDL: High-density lipoprotein; LDL: Low Density lipoprotein; Hba1C: A hemoglobin A1C test; BMI: Body mass index; HOMA-IR: Homeostasis model assessment-estimated insulin resistance

the control group ($p < 0.001$). Serum glucose and HbA1c levels were found to be significantly higher than the control group ($p < 0.001$). In addition, serum insulin levels were found to be significantly higher in the diabetic group compared to the control group ($p < 0.05$). HOMA-IR values were also significantly higher in the diabetic group ($p < 0.001$).

Regarding the studied biomarkers, serum irisin levels were significantly lower in the diabetic group compared to controls ($p < 0.01$), whereas serum LEAP2 levels were significantly higher in the diabetic group ($p < 0.05$).

A partial correlation analysis was performed controlling for age, BMI, and sex to evaluate the relationships between variables. In the patient group, irisin levels were negatively correlated with HOMA-IR ($r = -0.236$, $p = 0.034$) and insulin ($r = -0.231$, $p = 0.038$) levels, and positively correlated with HDL ($r = 0.343$, $p = 0.002$). On the contrary, a positive correlation was found between Leap2 level and HOMA-IR ($r = 0.422$, $p = 0.000$), insulin ($r = 0.469$, $p = 0.000$) and triglyceride ($r = 0.272$, $p = 0.015$) levels (Figs. 1, 2).

In the control group, irisin levels showed a negative non-significant association with HOMA-IR ($r = -0.209$, $p = 0.08$) and insulin ($r = -0.220$, $p = 0.06$) levels, and a weak positive correlation with HDL ($r = 0.234$, $p = 0.049$). In contrast, Leap2 levels showed non-significant positive association with HOMA-IR ($r = 0.203$, $p = 0.09$), insulin ($r = 0.199$, $p = 0.096$) and, triglyceride ($r = 0.182$, $p = 0.12$).

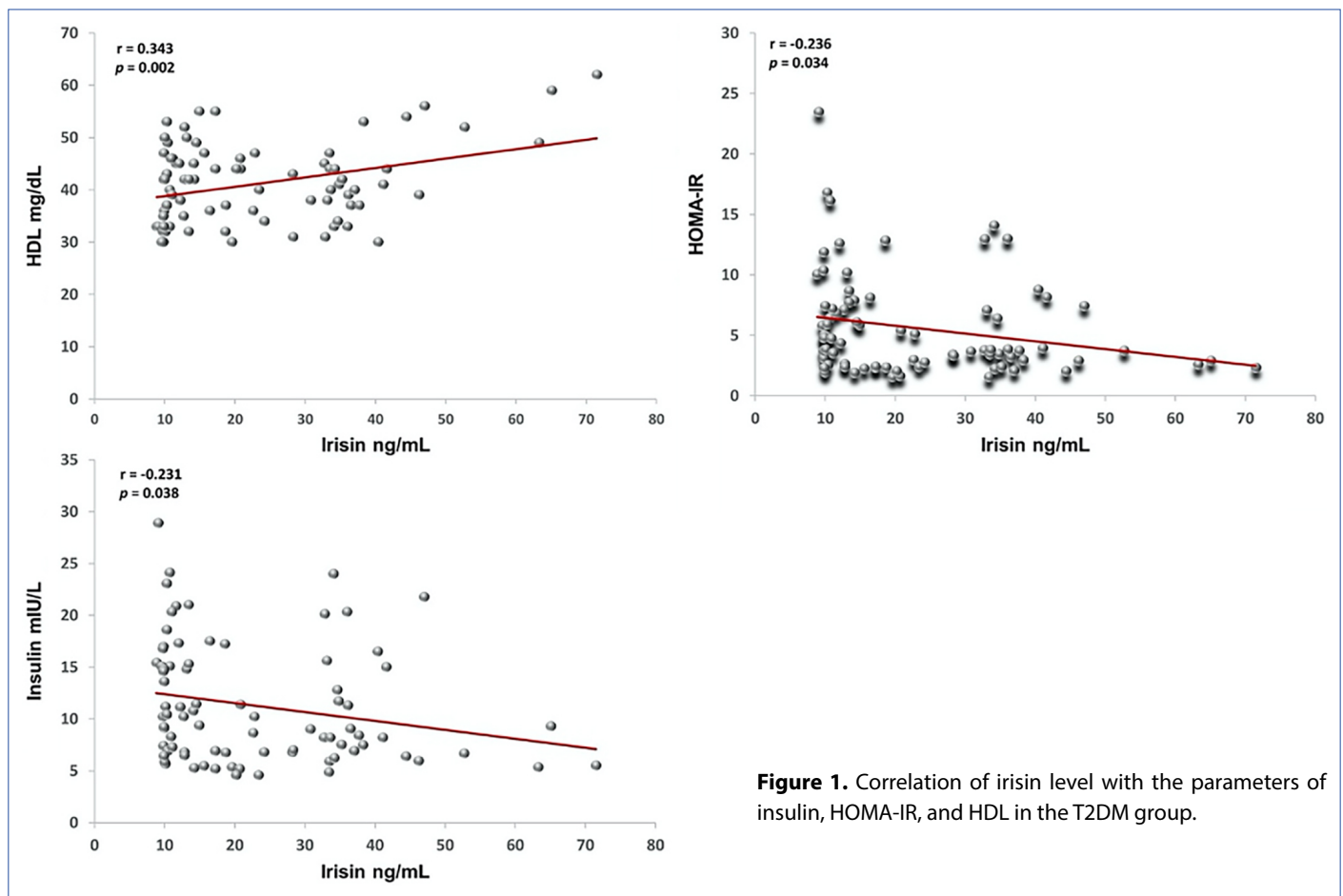
Discussion

The global prevalence of type 2 diabetes mellitus has reached epidemic proportions, currently affecting over 400 million individuals, with further increases anticipated in the coming decades [18]. These alarming projections highlight an urgent need for novel preventive and therapeutic strategies to combat the rising burden of T2DM worldwide [19]. Central to the

pathophysiology of T2DM is insulin resistance, which disrupts cellular signaling and impairs key metabolic processes. This resistance primarily manifests in skeletal muscle, liver, and adipose tissues, playing a pivotal role in the development of the disease. Exploring the endocrine functions of adipose tissue and the involvement of adipokines in insulin resistance is essential for understanding the underlying mechanisms of diabetes and other chronic metabolic disorders [20]. Among the many signaling molecules derived from adipose tissue, irisin and LEAP2 have emerged as key regulators with potential opposing roles in metabolic balance. Understanding the interplay between these molecules could provide crucial insights into the pathogenesis of T2DM.

Irisin has been shown to enhance glucose uptake by tissues and promote glycogen storage while suppressing gluconeogenesis and glycogenolysis. Additionally, it facilitates fatty acid oxidation, playing a multifaceted role in maintaining glucose homeostasis [21–23]. Through its direct and indirect effects on adipose, muscle, liver, and pancreatic tissues, irisin regulates energy metabolism and improves insulin sensitivity, particularly in response to exercise [24–26]. This effect is mediated via the activation of Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha (PGC-1 α), whose expression and activity are often reduced in T2DM patients, as evidenced by their low irisin levels [27, 28].

In this study, irisin levels were found to be significantly lower in patients with T2DM compared with the healthy control group. In many studies, irisin levels have been found to be lower in newly diagnosed T2DM compared to the control group [29–32]. In addition, a recent study reported that irisin levels in patients with T2DM, obesity, and hypertension were negatively correlated with fasting insulin and HbA1C levels compared to the control group. Therefore, it has been found to be associated with the risk of metabolic syndrome and



hyperglycemia in adults. Consistent with these findings, a cross-sectional study published in 2025 reported that irisin levels were lower in individuals with diabetes independent of BMI, and that low irisin was associated with an unfavorable lipid profile (low HDL cholesterol and high triglycerides) and insulin resistance [29, 33]. However, there are also studies reporting positive relationships between irisin and insulin levels, glucose, and HOMA-IR [11, 12, 34, 35]. Interestingly, the reasons for the discrepancy between irisin-HOMA-IR in the literature are not yet understood. In our study, irisin levels were modestly and negatively correlated with HOMA-IR and insulin. In addition, we also obtained a negative correlation with metabolic syndrome parameters consisting of fasting glucose, fasting insulin, HbA1C, triglyceride, and BMI. We believe that this result once again demonstrates the importance of irisin in terms of metabolic syndrome. In contrast, our interpretation regarding studies reporting a positive correlation with irisin is that these discrepancies in the literature are most likely attributable to methodological and analytical variability (including differences in measurement kits/assays and pre-analytical sample handling), genetic differences, and population characteristics (such as diabetes duration, medication use, and physical activity).

This study also demonstrated that LEAP2 levels were significantly higher in patients with T2DM compared with the

healthy control group. LEAP2 is expressed in many organs and tissues such as the liver, stomach, duodenum, jejunum, and kidneys. Recent studies have reported that the administration of LEAP2 in mice inhibits ghrelin-induced GHSR activation, thereby blocking the main effects of ghrelin. In contrast, it is thought that the effect of ghrelin increases with the blocking of endogenous LEAP2, thus LEAP2 adjusts the effect of ghrelin *in vivo* [16, 17].

There are very few studies on LEAP2 in the literature, and HOMA-IR comparisons are with obesity [36]. Our study showed that LEAP2 levels were positively correlated with HOMA-IR in T2DM, similar to what has been reported in obesity. The positive correlation observed between LEAP2 and HOMA-IR suggests that this peptide may play an active role in the pathophysiology of insulin resistance. When our study group is examined, we think that the BMI values of our subjects are lower than previous studies and the results cannot be attributed to obesity. In terms of diabetes metabolism, we have general information that it is largely synthesized in the liver, released into the blood and partially eliminated by the kidneys [17]. In addition, we believe that LEAP2 levels are not only associated with obesity but also with insulin resistance, as in our study. Recent studies have shown that LEAP2 is regulated by glucagon and insulin. Johansen et al. [37] reported that LEAP2 concentrations decrease significantly during

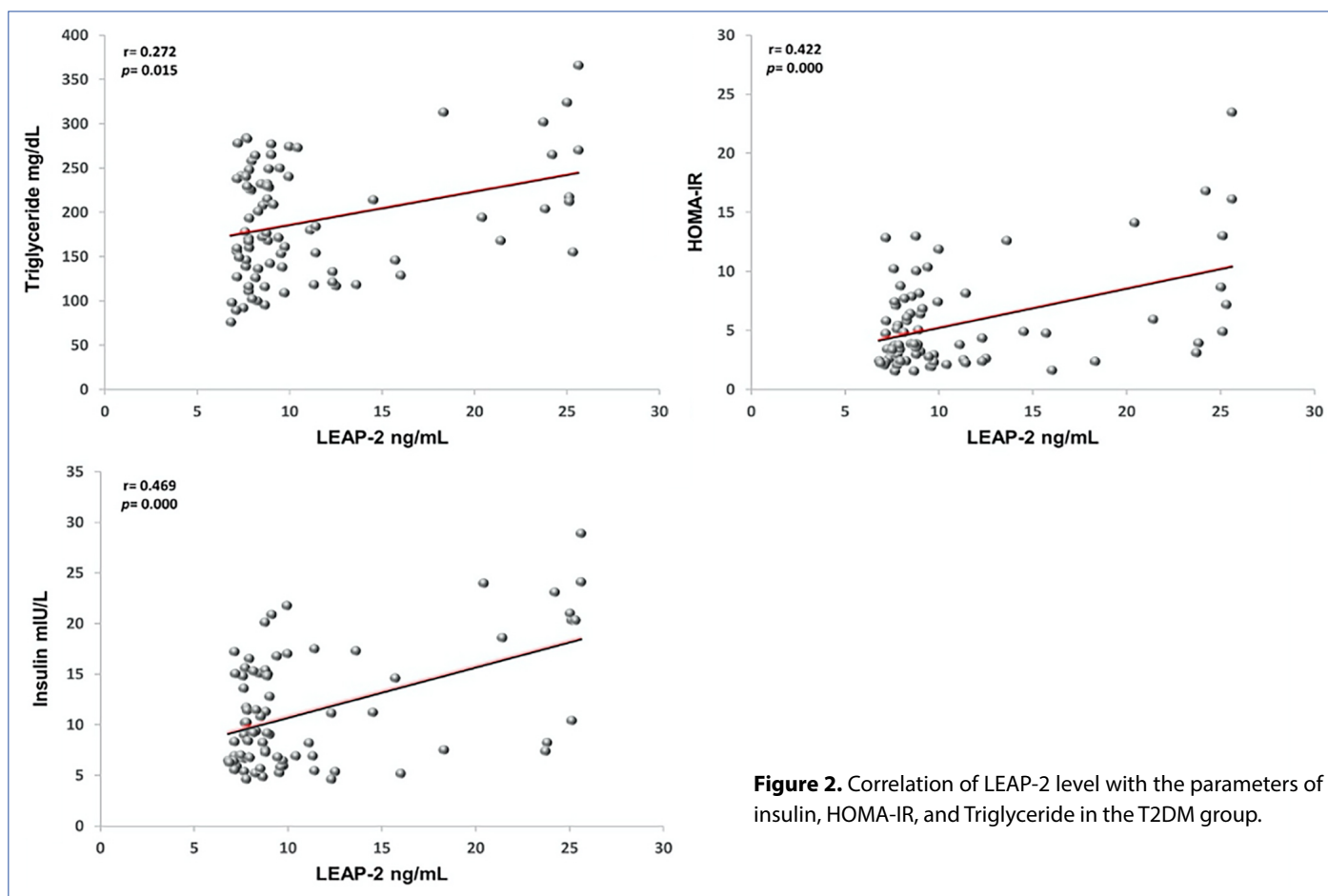


Figure 2. Correlation of LEAP-2 level with the parameters of insulin, HOMA-IR, and Triglyceride in the T2DM group.

glucagon infusion. This finding is relevant for understanding the hormonal control of energy homeostasis in T2DM.

In recent years, the regulatory role of LEAP2 in energy balance, appetite control and glucose metabolism has become increasingly clear. In particular, this peptide has been shown not only to act as a ghrelin antagonist but also as an inverse agonist of the growth hormone secretagogue receptor, thereby suppressing its basal activity [38]. Consistent with previous studies reporting elevated LEAP2 levels in association with insulin resistance and metabolic stress, our study identified increased LEAP2 levels in the T2DM group, which were significantly correlated with HOMA-IR. This association suggests that this peptide may serve not only as a biomarker but also as a candidate molecule involved in metabolic regulator [14]. Furthermore, recent data indicate that insulin increases LEAP2 secretion in the postprandial period, whereas glucagon suppresses it [38]. Thus, the elevated LEAP2 concentrations detected in T2DM may reflect both a response to insulin resistance and the impact of chronic hyperglycaemia on hepatic signalling pathways. Taken together, these observations reinforce the consistency of our findings with the existing literature and position LEAP2 as a potential diagnostic and therapeutic target in T2DM. These findings raise the question of whether LEAP2 is associated with metabolic syndrome, PCOS, and other diabetic phenotypes in subsequent

studies. In addition, it is considered that LEAP2 may play a role in the regulation of the anabolic response in the metabolic environment and may modulate the anabolic response in association with irisin. For this purpose, more comprehensively designed studies are needed to more clearly explain the metabolic relationships, pathways, and mechanism of action of this new agent, which is therapeutically promising, especially for Diabetes.

Limitations of the Study

This study has several limitations. First, as a cross-sectional study, it cannot establish a causal relationship between circulating levels of LEAP2, irisin, and T2DM. Second, the sample size of this research is relatively small and is limited to a single-center cohort. Larger, multicenter studies are required to validate these findings and improve their generalizability. Third, genetic, nutritional, and environmental differences specific to the population studied may introduce biases and variability in the results. Future research should include (i) longitudinal and interventional designs, (ii) larger and ethnically diverse cohorts, (iii) standardized analyses for both irisin and LEAP2, and (iv) studies investigating interactions at the receptor and intracellular signaling levels. These factors should be considered in future studies to better understand the influence of these variables on LEAP2 and irisin levels.

Conclusion

In our literature review, we could not find any comparative studies on the relationship between T2DM, LEAP2, irisin levels, and HOMA-IR in humans. To our knowledge, this study will be the first report comparing both adipomyokines and associating them with HOMA-IR.

LEAP2 levels are higher and irisin levels are lower in patients with T2DM than in healthy people. Maintaining glucose homeostasis has been the goal of many studies aimed at preventing and improving diabetes mellitus. In the future, LEAP2 and irisin could become key molecular targets for the development of strategies aimed at preventing T2DM and its comorbidities. However, how irisin and LEAP2-based interventions might be standardised in terms of clinical efficacy remains an open question. Therefore, the role of adipomyokines in T2DM and insulin resistance should be investigated further.

Disclosures

Ethics Committee Approval: The study was approved by the Firat University Ethics Committee (no: 25, date: 01/08/2019).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors declare that there is no conflict of interest regarding the publication of this article.

Funding: The article was not supported by any organization.

Use of AI for Writing Assistance: No AI technologies utilized.

Authorship Contributions: Concept – E.S.T., M.T., M.K.; Design – E.S.T., M.T., M.K.; Supervision – E.S.T., M.T.; Fundings – E.S.T., M.T., M.K.; Materials – E.S.T., M.T., M.K.; Data collection and/or processing – M.T., M.K.; Data analysis and/or interpretation – M.T., M.K.; Literature search – E.S.T., M.T., M.K.; Writing – E.S.T., M.T., M.K.; Critical review – E.S.T., M.T., M.K.

Peer-review: Externally peer-reviewed.

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