Journal of Turkish
Clinical Biochemistry

RESEARCH ARTICLE
DOI: 10.65717/jtcb.2026.26021

Circulating Irisin, Adropin, and Preptin as Biomarkers of Obesity and Obesity-Related Type 2 Diabetes Mellitus: A Multinomial Logistic Regression and Receiver Operating Characteristic Curve Analysis

Muzaffer Katar[1], Merve Çatak[2]

[1]Department of Medical Biochemistry, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Türkiye
[2]Department of Internal Medicine, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Türkiye

ABSTRACT

Objective: Obesity represents a significant global health concern characterized by substantial metabolic abnormalities and a heightened risk of developing type 2 diabetes mellitus (T2DM). Novel peptides including irisin, adropin, and preptin have been shown to play important roles in the regulation of energy homeostasis and glucose metabolism. However, their relative metabolic associations and combined diagnostic relevance in obesity and obesity-related T2DM remain incompletely understood.

Methods: This cross-sectional study included healthy controls, obese individuals, and obese patients with T2DM. Anthropometric measurements and serum levels of irisin, adropin, and preptin were assessed. Group comparisons, correlation analyses, and multinomial logistic regression models were performed to evaluate independent associations after adjustment for potential confounders. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic accuracy of individual biomarkers as well as a combined biomarker model.

Results: Circulating irisin and adropin levels were significantly lower, whereas preptin levels were significantly higher, in obese and obese+T2DM groups compared with controls. Multivariable-adjusted analyses demonstrated that lower irisin levels were independently associated with obesity and obesity-related T2DM, whereas higher preptin levels were independently associated with obesity-related T2DM. Individual biomarkers exhibited moderate discriminative ability in ROC analyses; however, the combined model incorporating irisin, adropin, and preptin consistently achieved higher area under the curve (AUC) values than individual parameters for both obesity and obesity-related T2DM.

Conclusion: Irisin, adropin, and preptin show differential associations with obesity and obesity-related T2DM. The combined assessment of these biomarkers provides improved discriminative performance compared with individual markers and may offer complementary insight into metabolic dysregulation associated with obesity and T2DM.

Keywords: Adropin, biomarkers, irisin, obesity, preptin, ROC analysis, type 2 diabetes mellitus

Corresponding author: Muzaffer Katar
✉ muzaffer.katar@gop.edu.tr
Received: May 22, 2026
Revision Requested: July 7, 2026
Last Revision Received: July 7, 2026
Accepted: July 27, 2026
Publication Date: August 25, 2026

Cite this article as: Katar M, Çatak M. Circulating irisin, adropin, and preptin as biomarkers of obesity and obesity-related type 2 diabetes mellitus: a multinomial logistic regression and receiver operating characteristic curve analysis. *J Turk Clin Biochem.* 2026;24(2):32-39.

INTRODUCTION

Obesity is a complex and chronic metabolic condition characterized by excessive accumulation of adipose tissue, resulting in substantial endocrine and metabolic alterations. These disturbances play a critical role in the development of type 2 diabetes mellitus (T2DM), cardiovascular diseases, and several other long-term health complications.[1]

Beyond its traditional role as an energy storage site, adipose tissue is now recognized as an active endocrine organ that secretes a wide variety of hormones, cytokines, and biologically active peptides

© 2026 by the authors.
Licensees Turkish Society of Clinical Biochemistry. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

involved in the regulation of lipid metabolism, glucose homeostasis, insulin responsiveness, and inflammatory pathways.[2]

Recently, increasing attention has focused on newly identified peptides, including irisin, adropin, and preptin, because of their potential roles in maintaining metabolic equilibrium and energy regulation. Irisin, predominantly secreted by skeletal muscle tissue, promotes the conversion of white adipose tissue into brown-like adipose tissue and enhances glucose uptake, thereby increasing overall energy consumption.[3] Adropin, encoded by the ENHO gene, has been implicated in the control of glucose and lipid metabolism and appears to contribute to metabolic adaptation according to nutritional conditions.[4] Preptin, a peptide released simultaneously with insulin from pancreatic β-cells, functions as a natural enhancer of glucose-mediated insulin secretion and supports glucose balance within the body.[5]

Despite accumulating evidence linking irisin, adropin, and preptin with obesity and T2DM, findings in the literature remain inconsistent, and the precise clinical relevance of these biomarkers has not yet been fully clarified. Accordingly, the current study was designed to investigate the associations between circulating irisin, adropin, and preptin concentrations and both obesity and obesity-associated T2DM, with a particular focus on determining their comparative contributions and potential combined diagnostic utility across distinct metabolic phenotypes.

METHODS

Study Design and Participants

This cross-sectional investigation was conducted at Tokat Gaziosmanpaşa University Hospital. Ethical clearance was obtained from the Institutional Ethics Committee (Approval No: 25-MOBAEK-292; Date: 02.09.2025). All procedures complied with the ethical standards outlined in the Declaration of Helsinki, and written informed consent was secured from each participant prior to inclusion in the study.

Eligible participants were adults aged between 18 and 50 years. The study cohort consisted of 180 individuals divided equally into 3 groups: individuals who are not obese without T2DM (n = 60), patients who are obese diagnosed with T2DM (n = 60), and healthy normal-weight controls (n = 60).

Sample Size Determination

Sample size estimation was performed using the G*Power software package version 3.1.2.4 (Heinrich Heine University, Düsseldorf, Germany). Based on an anticipated medium effect size (Cohen's f = 0.25), a significance level of 0.05, and a statistical power of 80%, at least 52 subjects were required in each study group. To strengthen statistical reliability and compensate for potential missing data, 60 participants were ultimately recruited per group.

Obesity Criteria

Obesity status was assessed according to body mass index (BMI), calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Individuals with BMI values below 25 kg/m^2 were classified as normal weight and assigned to the control group, whereas participants with BMI values exceeding 30 kg/m^2 were categorized as obese.[1]

Diagnosis of Type 2 Diabetes Mellitus

The diagnosis of T2DM was established according to the American Diabetes Association (ADA) 2010 guidelines.[6] Diagnostic criteria included fasting plasma glucose levels ≥ 126 mg/dL, plasma glucose levels ≥ 200 mg/dL measured 2 hours after a 75-g oral glucose tolerance test, random plasma glucose ≥ 200 mg/dL accompanied by classic symptoms of hyperglycemia, or glycated hemoglobin (HbA1c) levels above 6.5%.

Exclusion Criteria

Participants were excluded if any of the following conditions were present: (i) current use of medications capable of influencing body weight or metabolic parameters, including systemic glucocorticoids; (ii) history or presence of hypertension, previously diagnosed diabetes mellitus, kidney disease, coronary artery disease, heart failure, or cerebrovascular disorders; (iii) age younger than 18 years or older than 50 years. For the T2DM group, antidiabetic treatment was not an exclusion criterion; detailed medication class and dose data were not available for covariate adjustment.

Blood Collection and Sample Handling

Following an overnight fasting period, venous blood specimens were obtained using serum separator gel tubes. All participants were sampled under the same fasting protocol; detailed dietary intake during the preceding days and physical activity during the 48 hours before sampling were not systematically recorded. Samples were centrifuged at 3500 rpm for 10 minutes at 4°C. Serum fractions were subsequently transferred into Eppendorf tubes containing aprotinin to minimize peptide degradation and preserved at −20°C until laboratory analyses were completed.

Anthropometric and Biochemical Measurements

Anthropometric measurements including body weight, height, and BMI were obtained from all participants.

Serum irisin levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cusabio, competitive sandwich ELISA method). Adropin concentrations were measured using an ENHO ELISA kit employing the sandwich ELISA technique, whereas preptin levels were analyzed using a Sunred double-antibody sandwich ELISA kit. Optical density readings were obtained at 450 nm with a microplate spectrophotometer, and concentrations were derived from standard calibration curves in accordance with the manufacturers' protocols.

Routine biochemical analyses including fasting glucose, insulin, HbA1c, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) were performed using Roche Cobas 8000 and Abbott Architect c16000 analyzers. Insulin resistance was calculated according to the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

Statistical Analysis

All statistical evaluations were carried out using IBM SPSS Statistics software version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation. Normality of data distribution was evaluated using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Duncan's multiple comparison post hoc test where appropriate. Statistical significance was accepted at a 2-tailed *P*-value below .05.

RESULTS

Baseline Characteristics of the Study Population

The demographic, clinical, and biochemical features of the study groups are summarized in Table 1.

Table 1. Baseline Clinical and Biochemical Characteristics of the Study Groups (N = 180)

Variables	Total	Group			*P*
		Normal	Obesity	T2DM	
Age (years)	35.64 ± 9.32	35.57 ± 10.04	36.75 ± 7.63	35.12 ± 9.49	.397
Weight (kg)	81.90 ± 19.49	59.07 ± 8.59 (a)	95.80 ± 13.46 (b)	90.83 ± 9.47 (c)	<.001
Height (cm)	162.19 ± 8.74	166.10 ± 9.29 (a)	159.80 ± 7.37 (b)	160.68 ± 8.21 (b)	<.001
BMI (kg/m^2)	31.44 ± 8.20	22.05 ± 2.81 (a)	37.63 ± 5.80 (b)	34.63 ± 4.83 (c)	<.001
Irisin (ng/mL)	14.29 ± 13.30	22.28 ± 18.20 (a)	10.31 ± 7.30 (b)	10.28 ± 7.41 (b)	<.001
Adropin (pg/mL)	284.02 ± 198.29	340.39 ± 229.90 (a)	265.86 ± 181.74 (ab)	251.38 ± 165.65 (b)	.047
Preptin (pg/mL)	423.53 ± 307.20	312.72 ± 283.27 (a)	448.92 ± 296.39 (b)	508.93 ± 312.51 (b)	.001
HbA1c (%)	6.09 ± 1.49	5.35 ± 0.37 (a)	5.29 ± 0.37 (b)	7.63 ± 1.69 (b)	.001
Glucose (mg/dL)	117.49 ± 51.60	83.86 ± 5.15 (a)	105.04 ± 19.90 (b)	163.58 ± 64.70 (c)	.001
Insulin (µIU/mL)	13.61 ± 8.13	9.05 ± 2.70 (a)	15.36 ± 7.31 (b)	16.41 ± 10.37 (b)	<.001
TG mg/dl	148.20 ± 67.89	131.90 ± 35.43 (a)	137.08 ± 41.94 (b)	175.62 ± 99.03 (b)	<.001
LDL mg/dl	117.31 ± 31.88	113.79 ± 28.43	119.82 ± 30.10	118.33 ± 36.72	.560
HOMA-IR	4.09 ± 3.39	1.87 ± 0.55 (a)	3.91 ± 1.83 (b)	6.48 ± 4.50 (c)	<.001
Sex	Female	46(76.70)	51(85.00)	41 (68.30)	.097
	Male	14(23.30)	9(15.00)	19 (31.70)	

(a-b): Shared letters within a row indicate no statistically significant difference.
Correlations were identified between BMI and circulating peptide levels in any group.
BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL, low-density lipoprotein; TG, triglycerides; T2DM, type 2 diabetes mellitus.

The overall mean age of the participants was 35.64 ± 9.32 years, with no statistically significant age difference observed among the groups (*P* = .397). In contrast, anthropometric parameters showed marked differences between groups. Both body weight and BMI were significantly greater in the obesity and T2DM groups compared with the healthy control group (*P* < .001).

Circulating Peptide Levels

Significant intergroup differences were identified in circulating peptide levels. Serum irisin concentrations were substantially higher in healthy controls (22.28 ± 18.20 ng/mL) than in the obesity group (10.31 ± 7.30 ng/mL) and the T2DM group (10.28 ± 7.41 ng/mL) (*P* < .001). Adropin concentrations were highest among controls and demonstrated a gradual decline across the obesity and T2DM groups (*P* = .047). In contrast, preptin levels were significantly increased in both obesity and T2DM groups relative to controls (*P* = .001).

With respect to metabolic variables, HbA1c and fasting plasma glucose levels were markedly elevated in patients with T2DM (*P* = .001). Additionally, insulin concentrations and HOMA-IR values exhibited a progressive increase from the control group to the obesity and T2DM groups (*P* < .001).

Correlation Analyses

Correlation analyses revealed weak-to-moderate relationships between circulating peptide biomarkers and metabolic indicators (Table 2). Within the T2DM group, preptin levels showed a statistically significant inverse correlation with HOMA-IR values (*r* = −0.282, *P* = .029). No other significant correlations were identified between the evaluated biomarkers and metabolic parameters.

Multinomial Logistic Regression Analyses

Multinomial logistic regression models were constructed to determine the independent associations of irisin, adropin, and preptin with obesity and obesity-related T2DM (Tables 3 and 4).

In the multivariate analysis, BMI (OR = 3.001, *P* = .006) and HOMA-IR (OR = 4.409, *P* = .023) emerged as independent predictors of obesity. Likewise, among participants with T2DM, BMI (OR = 2.775, *P* = .011), and HOMA-IR (OR = 5.557, *P* = .008) remained independently associated with disease status.

After inclusion of circulating peptide variables in the regression model, higher irisin concentrations were independently associated with the control group (OR = 1.991, *P* < .001). Reduced adropin levels were linked to both obesity and T2DM, whereas elevated preptin concentrations were significantly associated with T2DM status (OR = 1.007, *P* = .001).

Receiver Operating Characteristic Analyses

The diagnostic performances of irisin, adropin, preptin, and the combined biomarker model are presented in Table 5 and Figures 1-2.

Table 2. Correlation Analyses Between Circulating Peptides and Metabolic Parameters

		Control			Obesity			T2DM		
		Adropin	Preptin	Irisin	Adropin	Preptin	Irisin	Adropin	Preptin	Irisin
	r	**0.005**	**−0.078**	**−0.088**	**0.027**	**0.038**	**0.021**	**0.118**	**0.077**	**0.129**
BMI (kg/m^2)	*P*	.970	.555	.502	.836	.774	.872	.369	.557	.326
HOMA-IR	r	−0.020	0.157	−0.044	−0.158	−0.142	0.106	−0.225	−0.282*	0.243
	P	.881	.230	.741	.227	.278	.418	.083	.029	.061

r, Pearson Correlation Coefficient.
BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; T2DM, type 2 diabetes mellitus.
* *P* value is significant at the .05 level.

Table 3. Multinomial Logistic Regression Analysis Identifying Clinical Predictors of Obesity and Obesity-Related Type 2 Diabetes Mellitus

		Univariate				Multivariate			
				95% Confidence Interval for Odds Ratio				95% Confidence Interval for Odds Ratio	
Group a		*P*	Odds Ratio	Lower Bound	Upper Bound	*P*	Odds ratio	Lower Bound	Upper Bound
Obesity	Age	.003	1.065	1.022	1.109	.752	1.026	0.873	1.208
	BMI	<.001	2.592	1.742	3.854	.006	3.001	1.36	6.623
	TG mg/dl	.568	1.002	0.995	1.009	.232	0.982	0.954	1.012
	LDL mg/dl	.298	1.006	0.995	1.018	.947	0.999	0.96	1.039
	HOMA_IR	<.001	4.35	2.447	7.731	.023	4.409	1.231	15.784
	[Gender = Female]	.249	1.725	0.682	4.36	.954	1.107	0.036	33.791
	[Gender = Male]b	—	—	—	—	—	—	—	—
T2DM	Age	.035	1.044	1.003	1.087	.937	0.993	0.844	1.169
	BMI	<.001	2.331	1.577	3.448	.011	2.775	1.259	6.115
	TG mg/dl	.002	1.011	1.004	1.018	.409	0.988	0.959	1.017
	LDL mg/dl	.43	1.005	0.993	1.016	.765	0.994	0.955	1.034
	HOMA_IR	<.001	5.686	3.166	10.21	.008	5.557	1.551	19.91
	[Gender = Female]	.308	0.657	0.293	1.474	.706	0.523	0.018	15.237
	[Gender = Male]b	—	—	—	—	—	—	—	—

BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL, low-density lipoprotein; TG, triglycerides; T2DM, type 2 diabetes mellitus.

Obesity vs. Control

Among the individual biomarkers, irisin demonstrated moderate discriminative performance (AUC = 0.719). Preptin showed modest diagnostic accuracy (AUC = 0.656), whereas adropin displayed limited discriminative capability (AUC = 0.529).

In contrast, the combined biomarker model markedly enhanced diagnostic performance, achieving an AUC of 0.879 (95% CI: 0.807-0.932), with a sensitivity of 95% and specificity of 81.7%.

Type 2 Diabetes Mellitus vs. Obesity

When distinguishing T2DM from obesity, the predictive performances of the individual biomarkers remained relatively weak, with AUC values ranging between 0.52 and 0.63. However, the combined biomarker model provided improved discrimination, yielding an AUC value of 0.759 ($P < .001$).

Overall, these findings indicate that the combined evaluation of multiple metabolic peptides may provide greater diagnostic utility than the assessment of single biomarkers alone.

DISCUSSION

In the present study, anthropometric parameters together with circulating irisin, adropin, and preptin concentrations were investigated in healthy individuals, obese subjects, and obese patients with T2DM.

Table 4. Multinomial Logistic Regression Models Evaluating the Association of Circulating Irisin, Adropin, and Preptin with Obesity and Obesity-Related Type 2 Diabetes Mellitus

		Univariate				Multivariate			
				95% Confidence Interval for Odds Ratio				95% Confidence Interval for Odds Ratio	
		P	Odds Ratio	Lower Bound	Upper Bound	*P*	Odds ratio	Lower Bound	Upper Bound
Group a									
Control	Irisin (ng/mL)	<.001	1.084	1.040	1.129	<.001	1.991	1.482	2.675
	Adropin (pg/mL)	.070	1.002	1.000	1.003	<.001	0.979	0.969	0.99
	Preptin (pg/mL)	.008	0.998	0.996	0.999	.001	0.994	0.99	0.998
T2DM	Irisin (ng/mL)	.986	1.000	0.953	1.049	.578	0.929	0.716	1.205
	Adropin (pg/mL)	.660	1.000	0.998	1.002	.045	0.991	0.982	1.000
	Preptin (pg/mL)	.332	1.001	0.999	1.002	.001	1.007	1.003	1.012
Group b									
Control	Irisin (ng/mL)	<.001	1.084	1.040	1.130	<.001	2.143	1.579	2.909
	Adropin (pg/mL)	.027	1.002	1.000	1.004	.033	0.989	0.978	0.999
	Preptin (pg/mL)	.001	0.997	0.996	0.999	<.001	0.987	0.981	0.992
Obesity	Irisin (ng/mL)	.986	1.000	0.954	1.050	.578	1.077	0.830	1.397
	Adropin (pg/mL)	.660	1.000	0.998	1.002	.045	1.009	1.000	1.019
	Preptin (pg/mL)	.332	0.999	0.998	1.001	.001	0.993	0.988	0.997

T2DM, type 2 diabetes mellitus.

Table 5. Receiver Operating Characteristic Analysis of Individual and Combined Biomarkers for Obesity and Obesity-Related Type 2 Diabetes Mellitus

Comparement	Metrics	Irisin	Adropin	Preptin	Combined (Predicted Probability)
Obesity vs Control	Cutoff	≤7.36	≤128.77	>186.38	>0.584
	AUC [CI]	0.719 [0.627-0.799]	0.529 [0.431-0.621]	0.656 [0.562-0.743]	0.879 [0.807-0.932]
	Sens	0.63	0.037	0.963	0.95
	Spec	0.80	0.783	0.417	0.817
	PPV	0.739	0.133	0.598	0.838
	NPV	0.706	0.475	0.926	0.942
	P	<.001	.623	.003	<.001
T2DM vs Obesity	Cutoff	>6.16	>147.41	>344.28	>0.533
	AUC	0.56	0.524	0.627	0.759
	Sens	0.767	0.917	0.733	0.60
	Spec	0.467	0.267	0.583	0.85
	PPV	0.59	0.568	0.638	0.80
	NPV	0.667	0.762	0.686	0.68
	P	.262	.158	.115	<.001

ROC curve analysis was performed to evaluate the diagnostic performance of individual biomarkers and their combined predictive probability model. AUC values with 95% CI are presented. Sens, Spec, PPV, and NPV were calculated based on optimal cutoff values determined by the Youden index.
AUC, area under the curve; CI, confidence intervals; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics; Sens, sensitivity; Spec, specificity; T2DM, type 2 diabetes mellitus.

The findings demonstrate that these biomarkers exhibit distinct association profiles across different metabolic conditions, suggesting that they reflect separate dimensions of obesity-related metabolic impairment rather than functioning as uniform indicators of disease.

Although the control group demonstrated a slightly greater mean height, height was not included as a covariate in the primary analyses. Because height and body composition may influence skeletal-muscle mass and circulating irisin, this between-group difference should

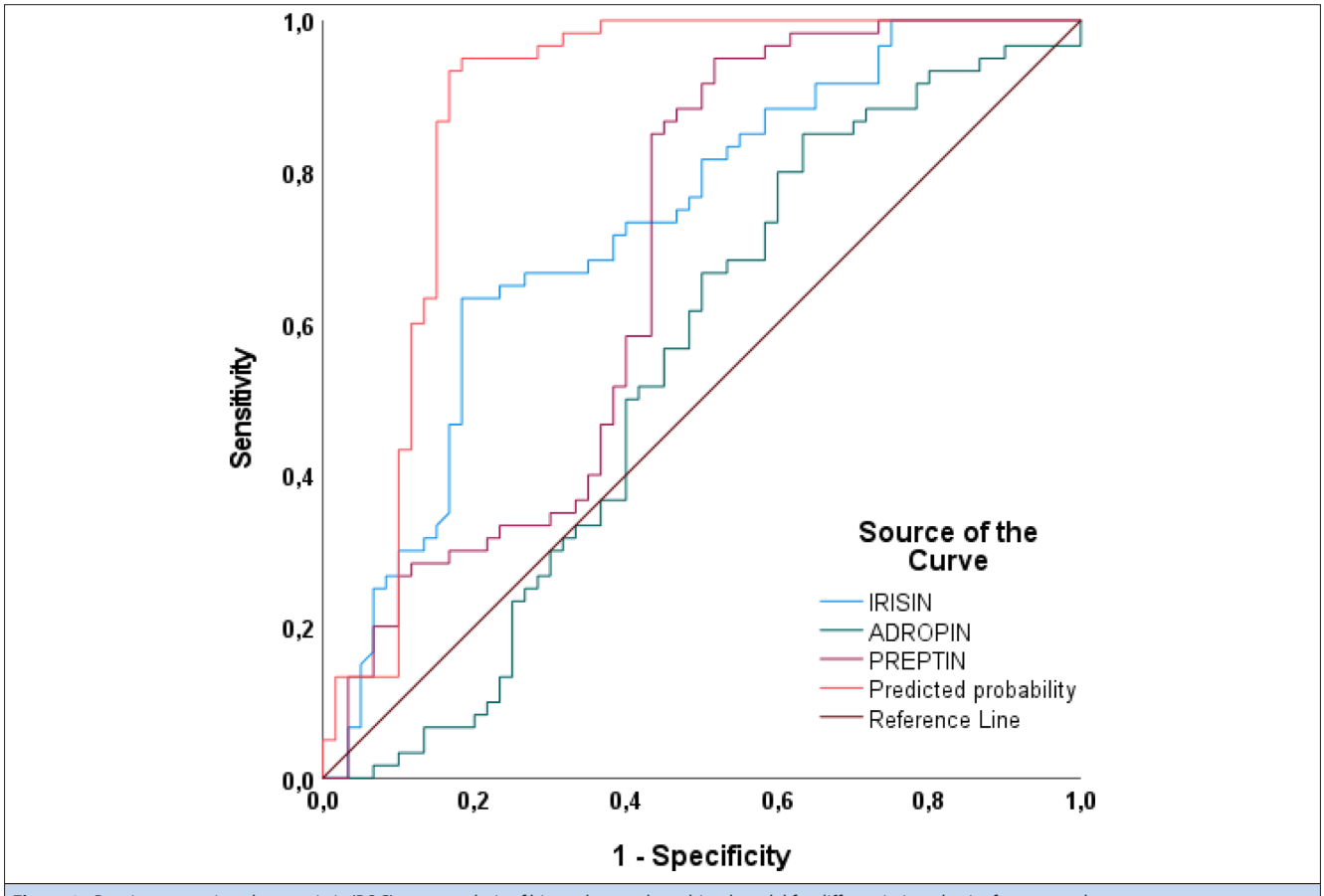

Figure 1. Receiver operating characteristic (ROC) curve analysis of biomarkers and combined model for differentiating obesity from control.

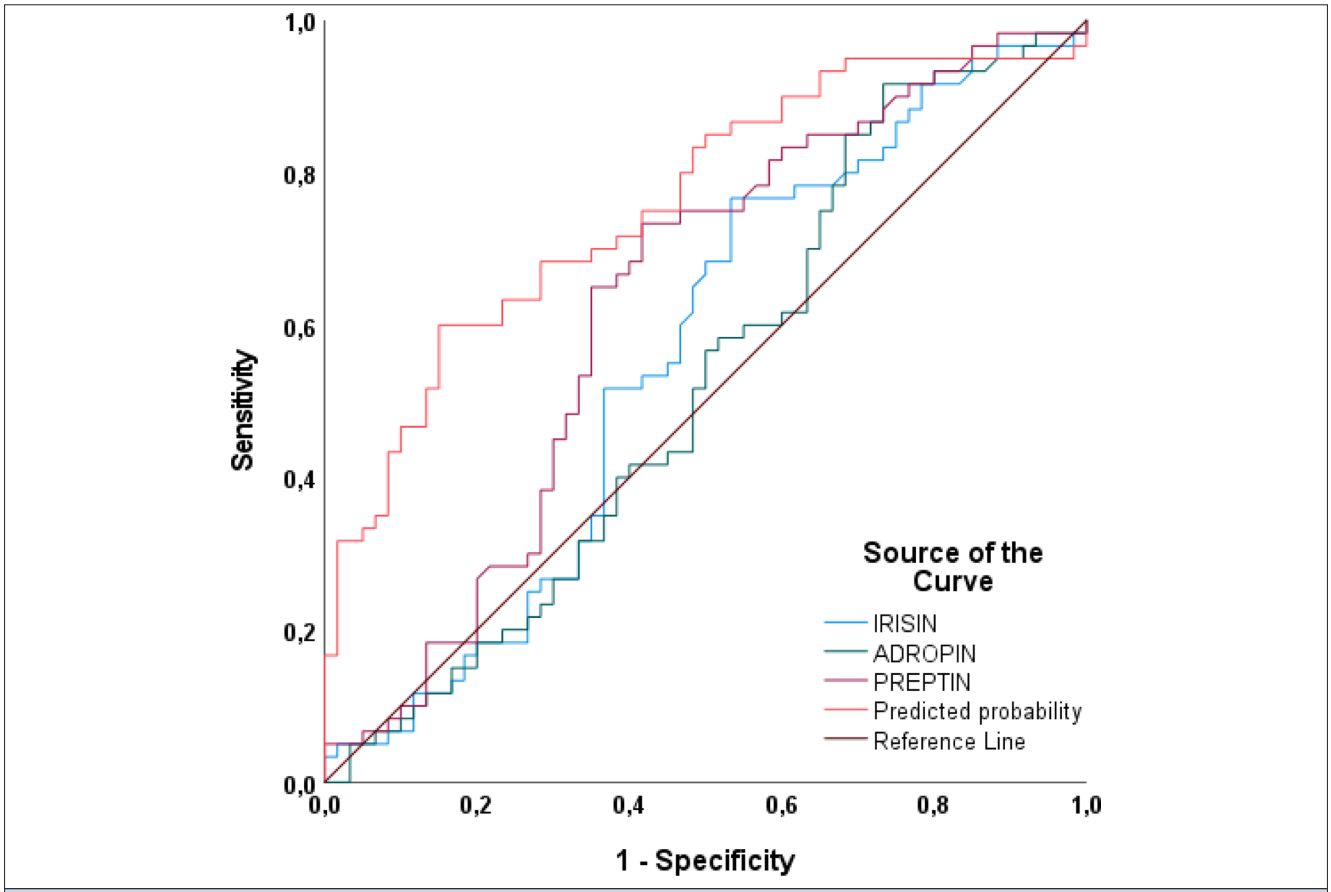

Figure 2. Receiver operating characteristic (ROC) curve analysis of biomarkers and combined model for differentiating type 2 diabetes mellitus (T2DM) from obesity.

be considered when interpreting the irisin findings. The observed associations therefore require confirmation in studies incorporating direct body-composition measures and covariate-adjusted analyses.

From a biochemical perspective, circulating irisin concentrations were significantly higher in healthy controls and substantially reduced in obese participants and obese individuals with T2DM. These findings are consistent with previous evidence indicating that irisin, a myokine linked to exercise-mediated thermogenesis and enhanced insulin sensitivity, may represent a marker of favorable metabolic function rather than acting solely as a causal mediator.[7] Therefore, the lower irisin concentrations observed in obesity and T2DM may indicate impaired metabolic regulation. Previous investigations evaluating the effects of exercise on irisin levels have produced inconsistent findings, with some studies demonstrating increases following acute or chronic exercise interventions, whereas others reported no measurable change.[8] Such discrepancies may be explained by differences in exercise modality, intervention duration, baseline metabolic characteristics, and environmental factors.

Experimental studies have demonstrated that irisin promotes glucose uptake and stimulates browning of white adipose tissue, thereby increasing total energy expenditure.[9] Several clinical investigations have also identified inverse associations between circulating irisin concentrations and BMI.[10] However, a large cohort study involving approximately 3300 obese participants failed to detect significant differences in serum irisin levels compared with controls.[11] In addition, irisin has been proposed as a potential therapeutic target in insulin resistance and T2DM because of its effects on adipose tissue browning, skeletal muscle glucose uptake, hepatic glucose and lipid metabolism, and pancreatic β-cell preservation.[12] Experimental evidence further suggests that irisin enhances β-cell proliferation, stimulates insulin synthesis and secretion, and reduces glucotoxicity- and lipotoxicity-induced apoptosis, thereby contributing to improved glucose tolerance and reduced insulin resistance.[13] Animal studies have also shown that exogenous irisin administration may lower blood glucose concentrations and improve insulin responsiveness.[7]

Cross-sectional investigations evaluating irisin levels in different diabetic states have reported variable findings. Elevated irisin concentrations have been described in type 1 diabetes mellitus (T1DM), whereas lower levels have consistently been reported in patients with T2DM in several clinical studies and meta-analyses.[14,15] For example, Liu et al.[11] reported significantly reduced irisin concentrations in individuals with T2DM compared with non-diabetic controls, potentially reflecting impaired skeletal muscle function and diminished PGC-1α activity. Conversely, some reports have demonstrated reduced irisin levels in T1DM or elevated concentrations in T2DM, suggesting that irisin responses may vary according to metabolic context and compensatory mechanisms.[16]

Recent reviews have emphasized the central role of irisin in metabolic homeostasis, particularly regarding glucose regulation, insulin sensitivity, and adipose tissue browning, supporting its possible involvement in obesity-related metabolic disorders.[17]

Adropin concentrations in the current study were highest among healthy controls and lowest in obese participants with T2DM. Initially

identified by Kumar KG et al[4] adropin is recognized as a peptide involved in regulating glucose metabolism and systemic energy balance. Previous studies have demonstrated that circulating adropin concentrations are influenced by dietary macronutrient composition and overall energy intake.[18] Experimental work by Ganesh Kumar et al.[18] suggested that reduced adropin expression contributes to adiposity and dyslipidemia. Furthermore, several human studies have shown lower serum adropin levels in overweight and obese individuals, together with inverse correlations with BMI, indicating that adropin may function as an independent metabolic marker.[19]

Most clinical investigations have reported decreased adropin concentrations in T2DM together with inverse associations with insulin resistance measured by HOMA-IR.[2] Reduced adropin levels have also been documented in gestational diabetes mellitus, potentially reflecting impaired glucose tolerance.[20] Nevertheless, some experimental studies have demonstrated increased adropin expression in diabetic animal models, whereas a limited number of clinical studies in T2DM have also observed elevated circulating concentrations. These contradictory findings have been interpreted as possible compensatory responses to metabolic stress, endothelial dysfunction, or insulin resistance.[21] Emerging evidence additionally suggests that adropin may function as an endocrine regulator integrating cardiovascular, metabolic, and energy-related pathways.[22] In the present study, adropin displayed weaker and less consistent associations compared with irisin and preptin, supporting the hypothesis that its metabolic effects may be more context dependent.

Several studies have explored the effects of physical activity on circulating adropin concentrations because of its proposed role in metabolic regulation. Aerobic exercise interventions have frequently been associated with increased serum adropin levels. For example, Zhang et al[23] demonstrated that a 12-week aerobic training program significantly increased serum adropin concentrations in obese adolescents independent of weight loss. Similarly, Fujie et al[24] observed increased adropin levels after an 8-week aerobic exercise intervention in middle-aged and older adults, accompanied by improvements in arterial stiffness and aerobic capacity. Another investigation reported that an 18-week aerobic exercise program elevated resting adropin levels in obese individuals, with changes inversely correlated with visceral adiposity.[25] However, Özbay et al[26] found no significant alteration in adropin concentrations following a 16-week exercise program in healthy young men. Experimental evidence further indicates that adropin expression increases during the fed state and decreases during fasting, reinforcing its potential role in metabolic adaptation.[18]

Preptin concentrations were significantly elevated in both obesity groups compared with controls. Preptin is a 34-amino acid peptide generated from pro-insulin like growth factor II (ProIGF-II) and released together with insulin from pancreatic β-cells.[5] It functions as a physiological enhancer of glucose-stimulated insulin secretion and therefore contributes to glucose homeostasis. Multiple studies have demonstrated elevated preptin concentrations in individuals with impaired glucose tolerance, T2DM, and gestational diabetes mellitus.[27] Increased circulating preptin levels, together with higher osteocalcin concentrations, have also been associated with obesity and increased adiposity.[28] Immunohistochemical investigations have shown colocalization of ProIGF-II and insulin within β-cell secretory granules, whereas synthetic preptin has been shown to augment insulin secretion from glucose-stimulated β-cells in a dose-dependent fashion. Serum preptin levels are consistently elevated in patients with T2DM, and some studies have also identified sex-related differences.[5] Elevated preptin concentrations may therefore reflect compensatory β-cell activation secondary to insulin resistance.[29] Beyond its metabolic effects, preptin has additionally been implicated in bone metabolism through promotion of anabolic bone formation without significantly affecting osteoclast activity.[30]

Importantly, multivariable regression analyses in the present study demonstrated that reduced irisin levels were independently associated with obesity and obesity-related T2DM, whereas elevated preptin concentrations remained independently associated with obesity-related T2DM after adjustment for major confounding variables. These findings suggest that irisin and preptin may provide complementary information regarding different aspects of metabolic dysfunction, including skeletal muscle endocrine signaling and pancreatic β-cell activity.

Another notable finding was that individual biomarkers demonstrated only limited diagnostic performance, whereas the combined biomarker model incorporating irisin, adropin, and preptin substantially improved discrimination for both obesity and obesity-associated T2DM. This observation highlights the multifactorial nature of metabolic disorders and indicates that single biomarkers may not adequately capture the complexity of underlying pathophysiological mechanisms. Instead, combined biomarker panels representing multiple metabolic pathways may provide a more comprehensive characterization of metabolic status.

The integrated pattern of biomarker alterations observed in this study may reflect interactions among skeletal muscle, adipose tissue, and pancreatic β-cells in the maintenance of metabolic homeostasis. Irisin, predominantly secreted by skeletal muscle, promotes browning of white adipose tissue and enhances energy expenditure. Adropin appears to regulate lipid metabolism and systemic energy balance, whereas preptin, co-secreted with insulin from pancreatic β-cells, may indicate compensatory β-cell responses to insulin resistance. Consequently, combined assessment of these peptides may provide insight into multiple components of metabolic regulation, including muscle-derived endocrine signaling, adipose tissue adaptation, and pancreatic β-cell function.

From a clinical perspective, identification of circulating biomarkers associated with obesity-related metabolic dysfunction may improve risk stratification and facilitate earlier recognition of metabolic deterioration. Although HbA1c and traditional metabolic parameters remain essential for diabetes diagnosis, emerging biomarkers such as irisin, adropin, and preptin may offer additional information regarding the underlying biological mechanisms. In particular, multi-biomarker strategies may help identify individuals at elevated risk for progression from obesity to overt diabetes mellitus.

Third, potentially important confounding variables, including dietary habits, habitual and recent physical activity, and inflammatory markers, were not comprehensively assessed. Medication use was screened through the exclusion criteria; however, detailed medication classes and doses among participants with T2DM were not available for formal adjustment. These factors may have influenced circulating peptide concentrations and should be standardized and recorded prospectively in future studies.

Collectively, these findings support the emerging concept that irisin, adropin, and preptin participate in an integrated endocrine network regulating insulin sensitivity, metabolic adaptation, and energy homeostasis.

CONCLUSION

The present study demonstrates that circulating irisin, adropin, and preptin concentrations are differentially associated with obesity and obesity-related T2DM. Reduced irisin levels together with elevated preptin concentrations appear to indicate an unfavorable metabolic profile, whereas adropin exhibits weaker and more variable associations. Importantly, combined evaluation of these biomarkers improved discrimination of metabolic phenotypes, suggesting that a multi-biomarker strategy may provide a more comprehensive assessment of obesity-associated metabolic dysregulation. Further longitudinal and mechanistic investigations are warranted to clarify causal relationships and determine the potential clinical utility of these biomarkers.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Tokat Gaziosmanpaşa University (Approval No.: 25-MOBAEK-292; Date: 02.09.2025).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceptualization – M.K.; Data curation – M.K.; Formal analysis – M.K.; Funding acquisition – M.K.; Investigation – M.K., M.Ç.; Methodology – M.K., M.Ç.; Project administration – M.K., M.Ç.; Resources – M.K., M.Ç.; Software – M.K., M.Ç.; Supervision – M.K., M.Ç; Validation – M.K., M.Ç.; Visualization – M.K., M.Ç.; Writing – original draft – M.K., M.Ç.; Writing – Review & Editing – M.K., M.Ç.

Acknowledgments: Authors would like to thank Shilan Rashad Ali for her contributions in locating patients and collecting samples for this study.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

REFERENCES

1. Organization WHO. *Obes: Prev Manag Glob Epidemic*. 2000.
2. Zang H, Jiang F, Cheng X, Xu H, Hu X. Serum adropin levels are decreased in Chinese type 2 diabetic patients and negatively correlated with body mass index. *Endocr J*. 2018;65(7):685-691. [CrossRef]
3. Zhang Y, Li R, Meng Y, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes*. 2014;63(2):514-525. [CrossRef]
4. Kumar KG, Trevaskis JL, Lam DD, et al. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. *Cell Metab*. 2008;8(6):468-481. [CrossRef]
5. Buchanan CM, Phillips AR, Cooper GJ. Preptin derived from proinsulin-like growth factor II (proIGF-II) is secreted from pancreatic islet β-cells and enhances insulin secretion. *Biochem J*. 2001;360(2):431-439. [CrossRef]
6. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010;33(suppl 1):S62-S69. [CrossRef]
7. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481(7382):463-468. [CrossRef]
8. Pekkala S, Wiklund PK, Hulmi JJ, et al. Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health? *J Physiol*. 2013;591(21):5393-5400. [CrossRef]
9. Moreno-Navarrete JM, Ortega F, Serrano M, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J Clin Endocrinol Metab*. 2013;98(4):E769-E778. [CrossRef]
10. Hou N, Han F, Sun X. The relationship between circulating irisin levels and endothelial function in lean and obese subjects. *Clin Endocrinol*. 2015;83(3):339-343. [CrossRef]
11. Liu J-J, Wong MD, Toy WC, et al. Lower circulating irisin is associated with type 2 diabetes mellitus. *J Diabetes Its Complications*. 2013;27(4):365-369. [CrossRef]
12. Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. *Diabetes/Metab Res Rev*. 2016;32(1):51-59. [CrossRef]
13. Ates I, Arikan MF, Erdogan K, et al. Factors associated with increased irisin levels in the type 1 diabetes mellitus. *Endocr Regul*. 2017;51(1):1-7. [CrossRef]
14. Du XL, Jiang WX, Lv ZT. Lower circulating irisin level in patients with diabetes mellitus: a systematic review and meta-analysis. *Horm Metab Res*. 2016;48(10):644-652. [CrossRef]
15. Assyov Y, Gateva A, Tsakova A, Kamenov Z. Irisin in the glucose continuum. *Exp Clin Endocrinol Diabetes*. 2016;124(1):22-27. [CrossRef]
16. García-Fontana B, Reyes-García R, Morales-Santana S, et al. Relationship between myostatin and irisin in type 2 diabetes mellitus: a compensatory mechanism to an unfavourable metabolic state? *Endocrine*. 2016;52(1):54-62. [CrossRef]
17. Perakakis N, Triantafyllou GA, Fernández-Real JM, et al. Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol*. 2017;13(6):324-337. [CrossRef]
18. Ganesh Kumar K, Zhang J, Gao S, et al. Adropin deficiency is associated with increased adiposity and insulin resistance. *Obesity (Silver Spring)*. 2012;20(7):1394-1402. [CrossRef]
19. Chen R-M, Yuan X, Ouyang Q, et al. Adropin and glucagon-like peptide-2 are associated with glucose metabolism in obese children. *World J Pediatr*. 2019;15(6):565-571. [CrossRef]
20. Yildirim B, Celik O, Aydin S. Adropin: a key component and potential gatekeeper of metabolic disturbances in policystic ovarian syndrome. *Clin Exp Obstet Gynecol*. 2014;41(3):310-312. [CrossRef]
21. Palizban A-A, Yazdani A-H, Jahanbani-Ardakani H. Role of rs7903146 polymorphism and adropin serum level in patients with diabetes mellitus; a case–control study from Isfahan, Iran. *Arch Physiol Biochem*. 2022;128(2):378-381. [CrossRef]
22. Butler AA, Tam CS, Stanhope KL, et al. Low circulating adropin concentrations with obesity and aging correlate with risk factors for metabolic disease and increase after gastric bypass surgery in humans. *J Clin Endocrinol Metab*. 2012;97(10):3783-3791. [CrossRef]
23. Zhang H, Jiang L, Yang Y-J, et al. Aerobic exercise improves endothelial function and serum adropin levels in obese adolescents independent of body weight loss. *Sci Rep*. 2017;7(1):17717. [CrossRef]
24. Fujie S, Hasegawa N, Sato K, et al. Aerobic exercise training-induced changes in serum adropin level are associated with reduced arterial stiffness in middle-aged and older adults. *Am J Physiol, Heart Circ Physiol*. 2015;309(10):H1642-H1647. [CrossRef]
25. Fujie S, Hasegawa N, Kurihara T, Sanada K, Hamaoka T, Iemitsu M. Association between aerobic exercise training effects of serum adropin level, arterial stiffness, and adiposity in obese elderly adults. *Appl Physiol Nutr Metab*. 2017;42(1):8-14. [CrossRef]
26. Ozbay S, Ulupınar S, Şebin E, Altınkaynak K. Acute and chronic effects of aerobic exercise on serum irisin, adropin, and cholesterol levels in the winter season: indoor training versus outdoor training. *Chin J Physiol*. 2020;63(1):21-26. [CrossRef]
27. Dogan FB, Cicek D, Aydin S, et al. Serum preptin and amylin values in psoriasis vulgaris and Behçet's patients. *J Clin Lab Anal*. 2016;30(2):165-168. [CrossRef]
28. El-Eshmawy M, Abdel Aal I. Relationships between preptin and osteocalcin in obese, overweight, and normal weight adults. *Appl Physiol Nutr Metab*. 2015;40(3):218-222. [CrossRef]
29. Yang G, Li L, Chen W, Liu H, Boden G, Li K. Circulating preptin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. *Ann Med*. 2009;41(1):52-56. [CrossRef]
30. Höög A, Hu W, Abdel-Halim SM, Falkmer S, Qing L, Grimelius L. Ultrastructural localization of insulin-like growth factor-2 (IGF-2) to the secretory granules of insulin cells: a study in normal and diabetic (GK) rats. *Ultrastruct Pathol*. 1997;21(5):457-466. [CrossRef]