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Serum Klotho as a feasible diagnostic biomarker for metabolic syndrome in Iraqi adults aged over 50 years

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ABSTRACT

Background: Metabolic Syndrome (MetS) is a cluster of cardiometabolic risk factors primarily driven by insulin resistance, with a high prevalence in older adult populations.

Objectives: This study aimed to evaluate the diagnostic accuracy of serum Klotho Beta (KLB) and insulin as novel biomarkers for MetS in Iraqi adults over 50 years old.

Materials and methods: This case-control study included 60 MetS patients and 30 healthy controls, recruited from Iraqi hospitals. MetS was diagnosed using harmonized IDF/AHA/NCEP ATP III criteria. Serum Klotho Beta and insulin levels were measured by ELISA.

Results: Serum Klotho Beta levels were significantly lower in the MetS group (25.54±4.41 nmol/L) compared to controls (59.00±11.05 nmol/L, $p<0.001$). Klotho Beta was inversely correlated with HOMA-IR (r=-0.59, $p<0.001$), BMI, HbA1c, and triglycerides, and positively with HDL-C. ROC analysis showed an AUC of 0.997 for Klotho Beta (sensitivity 95%, specificity 100% at ≤35.248 nmol/L) and an AUC of 0.998 for insulin. Logistic regression confirmed Klotho Beta as a strong independent predictor of MetS (OR=1.85 per 1 nmol/L decrease).

Conclusion: Serum Klotho Beta and insulin are highly sensitive and specific biomarkers for MetS in older adults. Klotho Beta deficiency, coupled with hyperinsulinemia, reflects underlying insulin resistance and metabolic dysregulation, highlighting its potential for risk stratification and early diagnosis in high-risk populations.

Introduction

Metabolic syndrome (MetS) is a cluster of interrelated cardiovascular risk factors, including abdominal obesity, dyslipidemia, impaired glucose tolerance, and hypertension, and is driven largely by insulin resistance.[1,2] The global prevalence of MetS has surged owing to rising obesity rates and sedentary lifestyles, posing a significant public health challenge.[3] Diagnostically, MetS is defined by the harmonized criteria established by the International Diabetes Federation (IDF), American Heart Association (AHA), and other major organizations, requiring the presence of at least three of the following: elevated waist circumference (≥90 cm for men and ≥85 cm for women), fasting glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, reduced HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women), or blood pressure ≥130/85 mmHg.[4]

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While earlier definitions (e.g., WHO) emphasized insulin resistance as a prerequisite, modern frameworks, such as the NCEP ATP III criteria, prioritize clinical applicability, reflecting the multifactorial nature.[5]

Geographic and demographic disparities in the prevalence of MetS are conspicuous. Urbanized regions and ethnic groups such as Mexican Americans exhibit considerably higher rates, with prevalence in Middle Eastern and Gulf nations frequently exceeding 35-40% among adults.[6,7] Latin American countries, including Mexico, Chile, and Brazil, report prevalence estimates between 30% and 35% due to shifting dietary patterns towards ultra-processed foods and reduced physical activity.[8] The United States has a prevalence of approximately 34%.[9,10] Rates in South and Southeast Asia, including India, Malaysia, and Thailand, remain low (20-25%) but are rapidly escalating.[11] Europe has a prevalence range of 20-30%, with higher rates in Eastern Europe than in Western regions, reflecting variances in healthcare access and lifestyle. Historically, low-prevalence settings such as sub-Saharan Africa are witnessing increases linked to urbanization and the adoption of Westernized dietary habits.[9]

Given the substantial morbidity associated with MetS, early identification and intervention are paramount. Traditional diagnostic parameters, while valuable, may lack the sensitivity to detect subclinical diseases, particularly in at-risk older adults. As a result, the search for reliable biomarkers that reflect the underlying pathophysiology and predict disease progression has intensified.[12,13] Klotho Beta has emerged as a promising candidate in this context. KLB is a type I transmembrane protein that is structurally related to the anti-aging factor α-Klotho and functions as a crucial co-receptor for the endocrine fibroblast growth factors FGF19 and FGF21.[14] It is highly expressed in metabolic organs such as the liver, pancreas, and adipose tissue and is integral to the regulation of lipid and carbohydrate metabolism.[15] Insulin, a peptide hormone produced by the pancreas, is pivotal for glucose uptake and metabolic regulation.[16,17] Dysfunction, manifested by insulin resistance, is a core driver of MetS and its related complications.[18] Despite the recognition of MetS burden, especially among elderly individuals, there remains a gap in validated, sensitive biomarkers capable of stratifying risk and reflecting disease mechanisms.[19]

This study specifically investigated the predictive utility of serum β-Klotho and insulin as direct indices of metabolic regulation and insulin resistance in Iraqi adults aged ≥ 50 years with MetS.

Materials and methods

Study design and participants

This case-control study was conducted from January 1st to April 30th, 2025. Participants were recruited from the outpatient clinics of several public hospitals in the Diyala Governorate, Iraq. The study comprised 90 adults aged over 50 years: 60 patients diagnosed with MetS and 30 age- and sex-matched healthy controls.

Inclusion and exclusion criteria

MetS was diagnosed according to the harmonized criteria, which mandates at least three of five components: 1) elevated waist circumference (≥90 cm in men, ≥85 cm in women), 2) elevated fasting blood glucose (≥100 mg/dL) or pharmacologic treatment for hyperglycemia, 3) hypertriglyceridemia (≥150 mg/dL) or lipid-lowering drug use, 4) low HDL-C (<40 mg/dL in men, <50 mg/dL in women), or 5) elevated blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg) or antihypertensive medication use.

Participants in the control group were confirmed to be free of MetS based on the same criteria. Exclusion criteria for both groups included a history of endocrine disorders (e.g., Cushing's syndrome, thyroid dysfunction), chronic organ failure (eGFR <60 mL/min/1.73 m^2; severe hepatic or pulmonary disease), cancer, rheumatoid arthritis, cerebrovascular disease, or current use of bone-modifying drugs (e.g., glucocorticoids, bisphosphonates, thiazolidinediones, SGLT-2 inhibitors, vitamin D/calcium supplements, estrogen).

Sample size justification

The sample size was determined as a convenience sample based on patient availability and logistical constraints during the study period, rather than by a formal a priori power calculation.

Biological sample collection

Fasting venous blood samples (5 mL) were collected from all participants in the morning (between 8:00 and 10:00 AM) after an overnight fast of 10-12 hours. Blood was drawn into two vacuum tubes: 1 mL in a K2EDTA tube and 4 mL in a serum separator gel tube. The serum tubes were allowed to clot for 30 minutes at room temperature before centrifugation at 3,000 rpm for 10 minutes. The resulting serum was aliquoted into cryovials and stored immediately at -20 °C until analysis. Hemolyzed samples were discarded. All samples were analyzed within one month of collection, undergoing a single freeze-thaw cycle.

Laboratory analysis

The MetS parameters, including fasting glucose and lipid profiles (total cholesterol, triglycerides, LDL, VLDL, and HDL), were assessed using an automated system. All measurements were performed as a single determination for each participant. Other biomarkers include liver enzymes (ALT) and (AST), uric acid, and glycated hemoglobin (HbA1c) using Cobas C111-Roche-Germany. Human Insulin was measured using a kit (Cat. No. E0010Hu, BT Laboratory, China) with a minimum detection limit of 0.11 mIU/L. The reported intra-assay CV was <8% and the inter-assay CV was <10%. Human Klotho Beta was measured using a

kit (Cat. No. E2782Hu, BT Laboratory, China) with a minimum detection limit of 0.29 nmol/L. The reported intra-assay CV was <6% and the inter-assay CV was <9%.

Statistical analysis

The data analysis was performed utilizing IBM SPSS Statistics software, Version 26 (IBM Corp., USA). Descriptive statistics for continuous measures are reported as means with their standard deviations. To compare these measures between the MetS and control cohorts, independent samples t-tests were employed. We evaluated the biomarker performance of serum klotho Beta, insulin, and HOMA-IR by constructing receiver operating characteristic (ROC) curves; the discriminatory power of each biomarker was quantified by the area under the curve (AUC). A p-value below 0.05 was established as the threshold for statistical significance.

Results

The demographic and clinical characteristics of the study participants are summarized in Table 1. The groups were well-matched for age and sex. As expected, the MetS group exhibited significant alterations in classic metabolic parameters, including higher BMI, waist circumference, fasting glucose, HbA1c, insulin, HOMA-IR, and triglycerides, alongside lower HDL-cholesterol (all $p<0.001$). Crucially, the novel biomarker serum Klotho Beta was profoundly lower in the MetS group (25.54±4.41 nmol/L) compared to healthy controls (59.00±11.05 nmol/L; $p<0.001$).

Table 1. Demographic, clinical, and biochemical characteristics of the study participants.

Variable		Control group (N=30)	MetS Group (N=60)	*p* value
Demographics				
Age (years)		58.33±4.84	60.28±7.62	0.20
Gender (N, %)	Male	12 (40%)	21 (35 %)	0.34
	Female	18 (60%)	39 (65 %)	
Anthropometrics				
BMI (kg/m^2)		24.67±2.55	29.18±2.81	<0.001
Waist circumference (cm)		84.6±2.55	98.8±6.7	<0.001
Blood pressure (mmHg)				
Systolic		120.5±8.2	135.2±10.5	<0.001
Diastolic		78.9±5.6	88.1±7.3	<0.001
Glucose metabolism				
Fasting blood sugar (mg/dL)		80.90±11.03	124.23±44.11	<0.001
HbA1c (%)		5.22±0.52	7.68±2.15	<0.001
Insulin (mIU/L)		3.31±0.56	7.07±1.21	<0.001
HOMA-IR		0.63±0.14	2.16±0.82	<0.001
Lipid profile (mg/dL)				
Total cholesterol		172.07±32.37	171.15±41.11	0.92
Triglycerides		87.17±30.10	164.85±71.07	<0.001
HDL-cholesterol		51.13±7.84	40.37±9.72	<0.001
LDL-cholesterol		103.63±27.77	99.15±37.94	0.57
VLDL-cholesterol		17.37±5.90	33.00±14.54	<0.001
Other biomarkers				
Serum uric acid (mg/dL)		4.14±1.46	4.39±1.48	0.46
ALT (U/L)		20.43±5.68	20.60±6.15	0.90
AST (U/L)		21.53±6.19	19.37±6.74	0.14
Proposed biomarker				
Klotho Beta (nmol/L)		59.00±11.05	25.54±4.41	<0.001

Note: Data are presented as Mean±SD or counts, *p* values from independent samples t-tests (or Chi-square for gender). Statistically significant values ($p<0.05$).

Table 2 presents the association between serum Klotho Beta levels and the presence of individual components of metabolic syndrome, as defined by IDF criteria. The results demonstrate that Klotho Beta concentrations were significantly lower in participants with central obesity (24.8±5.1 nmol/L vs 31.5±12.1 nmol/L, $p<0.001$), hypertriglyceridemia (23.9±3.0 nmol/L vs 27.5±5.1 nmol/L, $p=0.0012$), low HDL-C (25.1±5.3 nmol/L vs 29.8±11.5 nmol/L, $p=0.002$), and impaired fasting glucose (24.6±3.5 nmol/L vs 27.5±5.2 nmol/L, $p=0.014$) compared to those without these components.

Table 2. Klotho Beta levels according to the presence of metabolic syndrome components (IDF criteria).

Metabolic syndrome component	Absent	Present	*p* value
Central obesity (waist circumference)	31.5±12.1 (N=12, 20%)	24.8±5.1 (N=48, 80%)	<0.001
Hypertriglyceridemia (≥150 mg/dL)	27.5±5.1 (N=25, 41.7%)	23.9±3.0 (N=35, 58.3%)	0.0012
Low HDL-C (<50 mg/dL F, <40 mg/dL M)	29.8±11.5 (N=13, 21.7%)	25.1±5.3 (N=47, 78.3%)	0.002
Impaired fasting glucose (≥100 mg/dL)	27.5±5.2 (N=20, 33%)	24.6±3.5 (N=40, 67%)	0.014

Note: Klotho Beta (nmol/L) is presented as Mean±SD.

Analysis revealed that serum Klotho β levels were significantly inversely correlated with key indicators of metabolic dysregulation, including HOMA-IR (r=-0.59, $p<0.001$) as shown in Figure 1, triglycerides (r=-0.44, $p<0.001$), HbA1c (r=-0.41, $p<0.001$), BMI (r=-0.32, $p<0.01$), and WC (r=-0.28, $p=0.03$). In contrast, Klotho Beta showed a favorable positive correlation with HDL-C (r=0.38, $p<0.01$). We have also specified that Pearson correlation was used for this analysis.

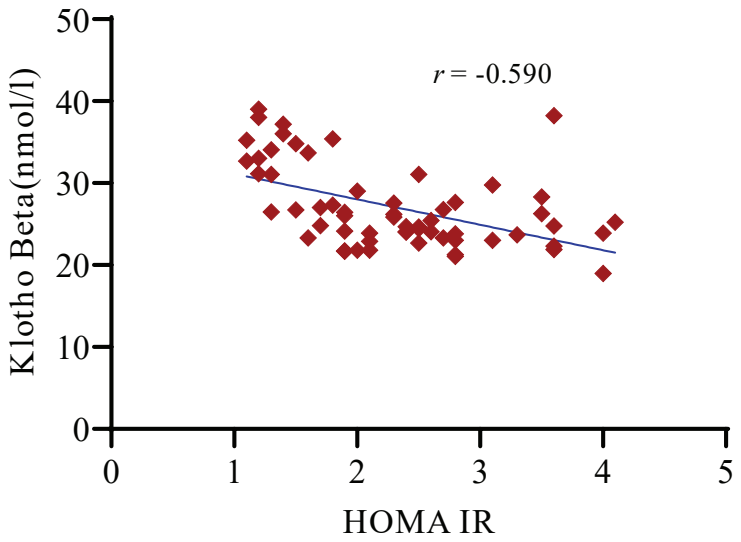

Figure 1. *Scatter plot illustrating the inverse correlation between serum Klotho Beta levels and HOMA-IR.*

The diagnostic performance of serum Klotho Beta and insulin for distinguishing individuals with MetS from healthy controls was evaluated using ROC curve analysis. Klotho Beta exhibited exceptional discriminatory ability, with an AUC of 0.997 (95% CI: 0.953-1.000), achieving a sensitivity of 95.00% and a specificity of 100% at an optimal cutoff value of ≤35.248 nmol/L as show in Figure 2. Similarly, insulin demonstrated near-perfect discrimination, with an AUC of 0.998 (95% CI: 0.955-1.000), a sensitivity of 96.67%, and a specificity of 100% at a cutoff value of >4.755 mIU/L.

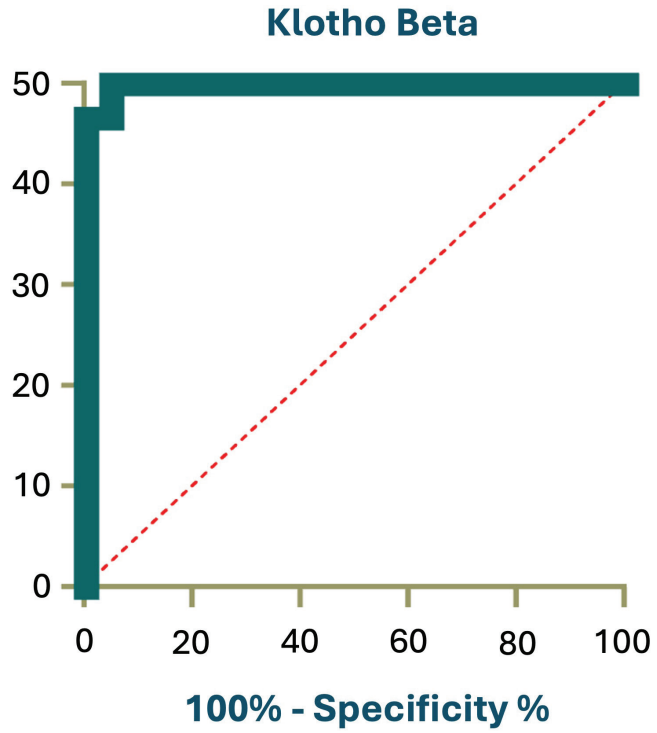

Figure 2. *Receiver operating characteristic (ROC) curve for Klotho Beta in classifying patients from controls.*

A binary logistic regression model (Table 3) was constructed to distinguish patients with MetS from controls based on key variables: Klotho Beta, BMI, HbA1c, gender, and age. The analysis identified a significant inverse relationship between serum Klotho Beta and MetS, where each 1 nmol/L decrement corresponded to an 85% increase in the odds of having MetS (OR=1.85, 95% CI: 1.52-2.25, $p<0.001$). Positive associations were also observed for BMI (OR=1.62, 95% CI: 1.28-2.05, $p<0.001$) and HbA1c (OR=8.45, 95% CI: 3.92-18.20, $p<0.001$). The model further indicated that being male was a protective factor (OR=0.24, 95% CI: 0.07-0.79, $p=0.019$), but age did not contribute significantly to predicting MetS status ($p=0.610$). Both the Hosmer-Lemeshow test ($p=0.451$) and a Nagelkerke R^2 value of 0.89 confirmed the model robust fit and explanatory power.

Table 3. Binary logistic regression for predicting patient status (patients vs controls).

Predictor	**Odds Ratio** (OR)	**95% CI for OR**	***p* value**
Klotho Beta (per 1 nmol/L decrease)	1.85	1.52-2.25	<0.001
BMI (per 1 kg/m^2 increase)	1.62	1.28-2.05	<0.001
HbA1c (per 1% increase)	8.45	3.92-18.20	<0.001
Gender (male vs female)	0.24	0.07-0.79	0.019
Age (per 1 year increase)	1.02	0.94-1.11	0.610

Note: Hosmer-Lemeshow test at $p=0.451$ indicates a good model fit). Nagelkerke $R^2=0.89$.

Discussion

The present study provides strong evidence supporting the utility of serum klotho Beta and insulin as highly sensitive and specific biomarkers for diagnosing MetS in Iraqi adults over 50 years of age. A key finding was the exceptional diagnostic performance of both biomarkers: Klotho Beta achieved an AUC of 0.997 with 95% sensitivity and 100% specificity, while insulin demonstrated near-perfect discrimination with an AUC of 0.998, 96.67% sensitivity, and 100% specificity.

Patients with MetS exhibited significantly lower serum Klotho Beta concentrations than healthy controls, a finding consistent with previous research suggesting its role as a protective factor in metabolic homeostasis.[20,21] The observed reduction may indicate compromised anti-aging and metabolic regulatory pathways, as Klotho deficiency has been implicated in impaired insulin signaling, diminished antioxidant capacity, and increased inflammation all pivotal mechanisms in metabolic dysfunction.[20,21] This substantial difference in Klotho Beta levels between groups supports its clinical relevance for risk stratification in aging populations.[20,22] The pronounced reduction suggests accelerated metabolic aging and a loss of protective mechanisms against oxidative damage and metabolic stress. Klotho Beta deficiency may contribute to insulin resistance by impairing insulin signaling pathways, reducing antioxidant capacity, and enhancing inflammatory responses.[23,24] This finding suggests that strategies aimed at restoring Klotho Beta function could represent a novel therapeutic target for addressing the underlying pathophysiology of metabolic dysfunction, aligning with the work of Wang *et al.*[25] and others who propose that reduced KLB function disrupts FGF21-mediated metabolic regulation.[26]

Parallel to the alterations in the FGF21-KLB pathway, our study confirmed the central role of insulin resistance in MetS, as evidenced by significantly elevated insulin levels and HOMA-IR values in the patient group. Hyperinsulinemia is initially a compensatory response to maintain euglycemia in the face of developing insulin resistance. However, chronic hyperinsulinemia itself contributes to the worsening of insulin resistance by promoting the downregulation of insulin receptors and impairing post-receptor signaling pathways.[27,28] This creates a vicious cycle that perpetuates metabolic dysfunction. The strong correlation between insulin and HOMA-IR in our study reinforces their utility as reliable measures of insulin resistance.[29,30] The elevated HOMA-IR values observed in our patients are consistent with established thresholds for increased risk of type 2 diabetes and cardiovascular complications, confirming a significant impairment in insulin-mediated glucose uptake and metabolism.[31]

This compensatory hyperinsulinemia has broader metabolic consequences, including enhanced lipogenesis, reduced lipolysis, and promotion of weight gain, creating a vicious cycle that perpetuates and worsens insulin resistance over time.[32] The HOMA-IR values in the patient group approached the threshold typically used to define insulin resistance (≥2.5), confirming a significant impairment in insulin-mediated glucose uptake and metabolism in peripheral tissues.[33] The higher variability in patients suggests varying degrees of insulin resistance severity, which is associated with an increased risk of T2DM progression, cardiovascular disease, and MetS.[34,35]

These biomarker alterations occur within the broader context of insulin resistance, the core pathophysiological mechanism of MetS, as reflected by the significant differences in HbA1c and fasting blood glucose between groups.[36,37] Focusing on an older cohort is clinically relevant, as MetS in this population often manifests with more severe complications and higher cardiovascular risk. The high diagnostic accuracy of these biomarkers in individuals over 50 points to their potential utility in targeted screening initiatives for this high-risk demographic, where early diagnosis is essential for implementing interventions to prevent adverse outcomes.[38,39]

The high diagnostic accuracy of both Klotho Beta and insulin in our study underscores their clinical relevance for risk stratification and early-stage screening of MetS in older adults.[12] Traditional diagnostic criteria for MetS identify individuals who already have a cluster of metabolic abnormalities. In contrast, Klotho Beta and insulin are biomarkers that reflect the underlying pathophysiology of the disease. A low Klotho Beta level may indicate a state of FGF21 resistance and a predisposition to metabolic dysfunction, while elevated insulin is a direct measure of insulin resistance. Therefore, these markers could potentially identify individuals at high risk for developing MetS even before they meet the full diagnostic criteria.[12] This would allow for earlier intervention with lifestyle modifications or pharmacological therapies to prevent or delay the onset of overt disease and its associated cardiovascular complications. Furthermore, monitoring these biomarkers could provide a more dynamic assessment of an individual's metabolic health and their response to treatment.

Limitations

The main strengths of this study are its exacting statistical methodology and the remarkable diagnostic results produced by both biomarkers. Strong proof of its clinical value is provided by ROC analysis combined with reliable AUC computations. The focus on persons over 50 targets a high-risk demographic where early diagnosis is especially beneficial, and the age-matched methodology reduces confounding by age-related metabolic changes. These large effect sizes are consistent with findings from prior research, which lends further support to the robustness of our results despite the modest sample size. Nevertheless, future multicenter studies with larger, more diverse populations and formal power calculations are warranted

to confirm these findings and enhance generalizability. Additional limitations include the study's single-center, cross-sectional design, which precludes causal inferences and may limit the external validity of our conclusions to other populations.

Conclusion

This study demonstrates that serum Beta-Klotho and insulin serve as highly sensitive and specific biomarkers for metabolic syndrome in older Iraqi adults. The exceptional diagnostic accuracy achieved supports the clinical utility of these markers for early diagnosis and risk stratification in aging populations. These findings contribute to the growing evidence base supporting Klotho-related pathways as key regulators of metabolic health and potential therapeutic targets for age-related metabolic dysfunction.

Ethical approval

An agreement to conduct this study was signed before sample collection began. The Tikrit University College of Medicine collaborated in this study. This study was approved by the research committee (No. 25/11/2024) in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available because of participant privacy and confidentiality concerns but are available from the corresponding author upon reasonable request.

Conflict of interests

The authors declare no competing interests, financial or otherwise.

CRedit authorship contribution statement

Haitham Ibrahim Azrak: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, visualization, project administration, funding acquisition, writing: original draft, review and edit; **Entedhar Rifaat Sarhat**: supervision, project administration, conceptualization, validation, writing: review and editing.

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