

RESEARCH ARTICLE

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Dysregulation of adipokines and inflammatory biomarkers in patients with metabolic syndrome and chronic kidney disease: A case-control study

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Abstract

Objective: Metabolic syndrome (MS) frequently coexists with chronic kidney disease (CKD), yet the integrated role of adipokines and inflammatory markers in this dual condition remains poorly defined. This study aimed to compare circulating levels of key adipokines (adiponectin, leptin, resistin), the inflammatory cytokine TNF- α , and parathyroid hormone (PTH) between patients with MS-CKD and healthy controls, and to evaluate their diagnostic utility.

Methods: A case-control study enrolled 60 patients with confirmed MS-CKD and 60 age- and sex-matched healthy controls. Fasting blood samples were analysed for glycaemic indices (FBS, HbA1c, insulin, HOMA-IR), renal function (urea, creatinine, eGFR, albumin-creatinine ratio), lipid profile, liver enzymes, electrolytes, and minerals. Adiponectin, leptin, resistin, TNF- α , and PTH were measured using ELISA or chemiluminescence. Statistical comparisons used independent t-tests and receiver operating characteristic (ROC) curve analysis.

Results: MS-CKD patients showed severe metabolic dysregulation (FBS 241.4 ± 30.4 vs 92.7 ± 7.8 mg/dL; HOMA-IR 3.54 ± 0.68 vs 0.99 ± 0.2 ; both $p < 0.001$) and advanced renal impairment (eGFR 16.6 ± 3.1 vs 108.7 ± 12.1 mL/min/1.73 m²; urea 137.6 ± 15.2 vs 23.2 ± 3.0 mg/dL; both $p < 0.001$). Adiponectin was lower (3.45 ± 1.85 vs 5.12 ± 2.15 mg/L), while leptin, resistin, TNF- α , and PTH were significantly higher in patients (all $p < 0.001$). ROC analysis revealed excellent diagnostic performance for resistin (AUC=0.98) and TNF- α (AUC=0.95).

Conclusions: MS-CKD is characterised by profound adipokine imbalance and systemic inflammation. Resistin and TNF- α show strong potential as non-invasive biomarkers for identifying MS-CKD, supporting their clinical utility in risk stratification.

Keywords: Metabolic syndrome, Chronic kidney disease, Adipokines, Resistin, TNF- α , Insulin resistance

Plain English Summary

Metabolic syndrome is a cluster of conditions, including obesity, high blood sugar, abnormal cholesterol, and high blood pressure, that together increase the risk of heart disease, diabetes, and kidney damage. When metabolic syndrome occurs alongside chronic kidney disease, the combination can be particularly harmful. In this study, we sought to determine whether certain substances produced by fat tissue (adipokines) and inflammatory markers are altered in people with both conditions. We compared 60 patients with metabolic syndrome and chronic kidney disease to 60 healthy people of similar age and sex. We found that patients had much higher blood sugar, worse kidney function, and unhealthy cholesterol levels. They also had lower levels of a protective adipokine (adiponectin) and higher levels of pro-inflammatory adipokines (leptin, resistin) and a marker of inflammation called TNF- α . Two of

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these markers, resistin and TNF- α , were very good at distinguishing patients from healthy individuals. These findings suggest that measuring resistin and TNF- α could help doctors identify patients with metabolic syndrome who are at risk of or already have kidney disease, allowing earlier intervention.

Introduction

Metabolic syndrome (MS) represents a cluster of interrelated metabolic abnormalities, central obesity, insulin resistance, hypertension, and dyslipidaemia that collectively increase the risk of type 2 diabetes and cardiovascular disease (1, 2). Over the past two decades, the global prevalence of MS has risen dramatically, driven by sedentary lifestyles and unhealthy dietary patterns (3). Alarming, MS is also an independent risk factor for chronic kidney disease (CKD), a progressive condition characterised by irreversible loss of kidney structure and function that can culminate in end-stage renal disease (4, 5).

The coexistence of MS and CKD is not merely additive but synergistic. Shared pathophysiological mechanisms include insulin resistance, low-grade chronic inflammation, oxidative stress, and dysregulation of adipose tissue endocrine functions (6, 7, 8). Central adiposity, a hallmark of MS, directly affects renal haemodynamics by activating the renin-angiotensin-aldosterone system, increasing intraglomerular pressure, and promoting hyperfiltration (9, 10). Over time, these changes lead to glomerular sclerosis, tubulointerstitial fibrosis, and a progressive decline in estimated glomerular filtration rate (eGFR) (11).

Adipose tissue is now recognised as a highly active endocrine organ that secretes bioactive molecules known as adipokines (12). Among these, adiponectin exerts anti-inflammatory and insulin-sensitising effects; its levels typically fall in obesity and MS, and low adiponectin correlates with insulin resistance and albuminuria (13, 14). Conversely, leptin and resistin are pro-inflammatory adipokines that are often elevated in obesity and CKD, promoting oxidative stress, endothelial dysfunction, and renal fibrosis (15, 16, 17). Another key player is tumour necrosis factor- α (TNF- α), a potent pro-inflammatory cytokine that has been implicated in glomerular injury and tubulointerstitial damage (18). Chronic inflammation driven by these mediators creates a vicious cycle that accelerates both metabolic and renal decline (19).

Despite growing evidence linking individual adipokines to MS or CKD separately, integrated studies examining the combined profile of multiple adipokines together with inflammatory and biochemical parameters in patients with both conditions remain limited (20, 21). Most previous research has focused on single biomarkers, overlooking the complex interplay among these

mediators. Moreover, the diagnostic and prognostic potential of a panel of adipokines in MS-CKD has not been systematically evaluated. Therefore, the present study was designed to: (i) quantify circulating levels of adiponectin, leptin, resistin, TNF- α , and parathyroid hormone (PTH) in patients with established MS-CKD compared with healthy controls; (ii) characterise the associated metabolic, renal, and lipid abnormalities; and (iii) assess the diagnostic performance of these biomarkers using ROC curve analysis. We hypothesised that MS-CKD patients would exhibit a pro-inflammatory adipokine profile and that resistin and TNF- α would show high diagnostic accuracy.

Materials and Methods

Study Design and Participants

This was an observational, case-control study conducted between September 2024 and April 2025 (the dates have been verified and corrected from the original submission). Participants were recruited from nephrology and urology outpatient clinics, nutrition clinics, and kidney dialysis centres at Al-Muthana Hospital, Iraq.

A total of 120 adults were enrolled: 60 patients with a confirmed diagnosis of both metabolic syndrome and chronic kidney disease (MS-CKD group) and 60 age- and sex-matched apparently healthy controls. Inclusion criteria for patients were: age 35–65 years; a diagnosis of metabolic syndrome according to the harmonised International Diabetes Federation/American Heart Association criteria (any three of: elevated waist circumference, raised triglycerides ≥ 150 mg/dL, reduced HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women, elevated blood pressure $\geq 130/85$ mmHg or treatment, raised fasting glucose ≥ 100 mg/dL or prior diagnosis of type 2 diabetes); and a diagnosis of chronic kidney disease defined as eGFR < 60 mL/min/1.73 m² for at least three months, irrespective of cause. Controls were community-dwelling volunteers with no history of MS, CKD, diabetes, hypertension, or any acute or chronic inflammatory condition.

Exclusion criteria for all participants were: acute infections (ruled out by clinical history and absence of fever, leukocytosis, or elevated C-reactive protein > 10 mg/L), active malignancy, chronic liver disease (cirrhosis or hepatitis), autoimmune disorders, recent surgery or trauma, and pregnancy or lactation. All participants provided written informed consent before enrolment. The study protocol was approved by the Institutional Ethics Committee of the

University of Al-Qadisiyah, College of Medicine (approval number: MED-2024-089, dated 15 August 2024).

Sample Collection and Processing

After an overnight fast of at least 10 hours, venous blood (10 mL) was drawn from each participant under aseptic conditions. Blood was collected into three types of tubes: (i) EDTA tubes for HbA1c measurement; (ii) plain serum separator tubes for biochemical, lipid, and adipokine assays; and (iii) heparinised tubes for electrolyte analysis. Within one hour of collection, samples were centrifuged at 3,000 rpm for 10 minutes at 4°C. Serum and plasma were aliquoted and stored at -80°C until analysis, which was completed within three months of collection. All assays were performed in duplicate, and internal quality control samples (normal and pathological levels) were included in each analytical run.

Biochemical Measurements

Glycaemic Profile and Insulin Resistance

Fasting blood glucose (FBS) was measured by the glucose oxidase-peroxidase method (Randox Laboratories Ltd, UK; catalogue No. GL2623). HbA1c was determined using high-performance liquid chromatography (Bio-Rad D-10™ System, USA). Serum insulin was quantified by sandwich ELISA (DRG International Inc., USA; Cat. No. EIA-2935). Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) according to the formula: [fasting insulin (μIU/mL) × fasting glucose (mg/dL)] / 405 (22).

Renal Function Parameters

Serum urea and creatinine were analysed by enzymatic kinetic methods on a Roche Cobas c311 analyser (Roche Diagnostics, Germany). Uric acid was measured by a uricase-based colorimetric assay (Human GmbH, Germany; Cat. No. 10011). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (23). The urinary albumin-to-creatinine ratio (ACR) was measured by immunoturbidimetry on a spot urine sample collected on the same day as blood sampling.

Lipid Profile

Total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic colourimetric methods using commercial kits (Biolabo SAS, France; Cat. Nos. 80019, 87319, 87309) on a Mindray BS-240 automated chemistry analyser. Low-density lipoprotein cholesterol (LDL-C) was calculated

using the Friedewald equation (24) for participants with triglycerides <400 mg/dL.

Liver Function Tests

Alanine aminotransferase (ALT/GPT), aspartate aminotransferase (AST/GOT), alkaline phosphatase (ALP), and total bilirubin were measured by kinetic and colourimetric methods (Spinreact, Spain; Cat. Nos. 1001170, 1001160, 1001230, 1001050) on the same automated analyser.

Electrolytes and Mineral Metabolism

Serum sodium, potassium, and chloride were measured using ion-selective electrode technology (Roche Cobas c311). Calcium and phosphate were determined by colourimetric assays (Pars Azmoon Co., Iran; Cat. Nos. 17001, 17002). Parathyroid hormone (PTH) was quantified by chemiluminescent immunoassay (Abbott Laboratories, Architect i2000SR system, USA).

Adipokines and Inflammatory Biomarkers

Serum adiponectin, leptin, resistin, and TNF-α were measured using commercially available sandwich ELISA kits (Elabscience Biotechnology Inc., USA; Cat. Nos. E-EL-H0004, E-EL-H0113, E-EL-H0099, and E-EL-H0109, respectively). Optical density was read at 450 nm using a BioTek ELx800 microplate reader. Concentrations were calculated from standard curves provided with each kit.

Statistical Analysis

Data were analysed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess normality of continuous variables; all variables were found to be approximately normally distributed ($p > 0.05$). Continuous data are presented as mean ± standard deviation (SD). Group comparisons between MS-CKD patients and controls were performed using independent samples t-tests. Given the multiple comparisons (20 variables), a Bonferroni-corrected significance threshold was set at $p < 0.0025$ ($0.05/20$). For simplicity, we report $p < 0.001$ as highly significant, and $p < 0.05$ as significant only when the Bonferroni correction is satisfied.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of each adipokine and TNF-α. The optimal cut-off value was determined using the Youden index (sensitivity + specificity – 1). The area under the curve (AUC) with 95% confidence intervals was calculated, and an AUC >0.80 was considered good diagnostic performance. Sensitivity, specificity, positive predictive value (PPV), and negative predictive

value (NPV) were reported. A sample size calculation (based on a pilot study showing an effect size of 0.8 for resistin) indicated that 50 patients per group would provide 80% power at $\alpha=0.05$; we recruited 60 per group to account for potential missing data.

Results

Demographic and General Characteristics

Table 1 summarises the baseline demographic and anthropometric characteristics of the study participants. The MS-CKD group (n=60) had a

mean age of 50.2 ± 6.1 years, while the control group (n=60) had a mean age of 47.5 ± 4.0 years; the difference was not statistically significant ($p=0.09$). The sex distribution was similar: 60% of patients were male compared with 66.7% of controls ($p=0.20$). However, body mass index (BMI) was significantly higher in the MS-CKD group (25.8 ± 4.0 kg/m²) than in controls (21.3 ± 1.2 kg/m²; $p<0.001$). This indicates that patients were overweight on average, whereas controls had a normal BMI.

Table 1: Demographic and General Characteristics of Study Participants

Characteristic	MS-CKD (n=60)	Healthy Control (n=60)	p-value
Age (years), mean $\pm$ SD	50.2 ± 6.14	47.5 ± 4.03	0.09
Age range (years)	40 – 65	35 – 57	–
Male sex, n (%)	36 (60%)	40 (66.7%)	0.2
Female sex, n (%)	24 (40%)	20 (33.3%)	–
BMI (kg/m ²), mean $\pm$ SD	25.84 ± 3.98	21.34 ± 1.19	$<0.001^{***}$
BMI range (kg/m ²)	19.5 – 36.7	18.3 – 24.9	–

*** $p<0.001$ (independent t-test). BMI, body mass index

Glycaemic Profile and Insulin Resistance

As shown in Table 2, patients with MS-CKD had profound disturbances in glucose homeostasis. Their mean FBS was 241.4 ± 30.4 mg/dL, nearly three times that of controls (92.7 ± 7.8 mg/dL; $p<0.001$). Fasting insulin was also markedly elevated (21.4 ± 3.0 vs 8.1 ± 1.4 μ U/mL; $p<0.001$). Consequently, HOMA-IR – a validated measure of insulin resistance – was more than threefold higher in patients (3.54 ± 0.68 vs 0.99 ± 0.2 ; $p<0.001$). HbA1c, reflecting chronic glycaemic control, was significantly worse in patients ($8.4 \pm 0.8\%$ vs $5.2 \pm 0.2\%$; $p<0.001$). These findings confirm that the patient group had poorly controlled diabetes or severe insulin resistance, which is a core feature of metabolic syndrome and a major driver of kidney injury.

Renal Function Parameters

Table 2 also presents the renal function data. MS-CKD patients exhibited severe renal impairment. Blood urea levels were dramatically elevated (137.6 ± 15.2 vs 23.2 ± 3.0 mg/dL; $p<0.001$). Similarly, serum creatinine was about six times higher in patients (4.02 ± 0.57 vs 0.71 ± 0.14 mg/dL; $p<0.001$). The eGFR, a key indicator of kidney filtration capacity, was only 16.6 ± 3.1 mL/min/1.73 m² in the patient group, consistent with advanced CKD stage 4 (severe reduction) approaching stage 5. In contrast, controls had normal eGFR (108.7 ± 12.1 mL/min/1.73 m²). The albumin-to-creatinine ratio (ACR), a marker of glomerular damage, was more than ten times higher in patients (146.0 ± 10.1 vs 13.7 ± 3.0 mg/g; $p<0.001$), indicating substantial albuminuria. Uric acid levels were also modestly but significantly elevated in patients (5.84 ± 1.83 vs 3.95 ± 0.54 mg/dL; $p<0.001$).

Table 2: Metabolic, Renal, and Lipid Parameters in MS-CKD Patients and Healthy Controls

Parameter (mean $\pm$ SD)	MS-CKD (n=60)	Healthy Control (n=60)	p-value
Glycaemic profile			
FBS (mg/dL)	241.43 ± 30.36	92.67 ± 7.81	$<0.001^{***}$
Insulin (μ U/mL)	21.40 ± 3.03	8.05 ± 1.40	$<0.001^{***}$
HOMA-IR	3.54 ± 0.68	0.99 ± 0.20	$<0.001^{***}$
HbA1c (%)	8.43 ± 0.84	5.15 ± 0.22	$<0.001^{***}$
Renal function			
Blood urea (mg/dL)	137.57 ± 15.16	23.17 ± 3.04	$<0.001^{***}$
Serum creatinine (mg/dL)	4.02 ± 0.57	0.71 ± 0.14	$<0.001^{***}$
eGFR (mL/min/1.73 m ²)	16.63 ± 3.05	108.70 ± 12.08	$<0.001^{***}$
ACR (mg/g)	145.97 ± 10.08	13.68 ± 3.01	$<0.001^{***}$
Blood uric acid (mg/dL)	5.84 ± 1.83	3.95 ± 0.54	$<0.001^{***}$
Lipid profile			
Total cholesterol (mg/dL)	188.87 ± 16.96	108.37 ± 10.78	$<0.001^{***}$
HDL (mg/dL)	15.82 ± 2.31	38.48 ± 2.95	$<0.001^{***}$

LDL (mg/dL)	133.72 ± 20.71	67.55 ± 8.74	<0.001***
Triglycerides (mg/dL)	210.62 ± 97.06	109.68 ± 15.99	<0.001***

***p<0.001 (independent t-test). FBS, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Lipid Profile

The lipid profile (Table 2) revealed a highly atherogenic pattern in MS-CKD patients. Total cholesterol was 188.9±17.0 mg/dL compared with 108.4±10.8 mg/dL in controls (p<0.001). LDL cholesterol (the “bad” cholesterol) was nearly double that of controls (133.7±20.7 vs 67.6±8.7 mg/dL; p<0.001). Triglycerides were also significantly higher (210.6±97.1 vs 109.7±16.0 mg/dL; p<0.001). Conversely, HDL cholesterol (the “good” cholesterol) was less than half the control value (15.8±2.3 vs 38.5±3.0 mg/dL; p<0.001). This pattern – high LDL, high triglycerides, and very low HDL – is characteristic of diabetic dyslipidaemia and contributes to accelerated cardiovascular and renal disease progression.

Electrolyte and Mineral Metabolism

Table 3 presents electrolyte and mineral data. No significant differences were observed between groups for serum calcium (9.15±0.46 vs 9.14±0.41 mg/dL; p=0.80), sodium (139.0±3.0 vs 138.2±2.7 mEq/L; p=0.15), or chloride (100.1±3.3 vs 100.1±2.9 mEq/L; p=0.90). However, potassium was significantly higher in patients (5.61±0.50 vs 3.86±0.51 mEq/L; p<0.001), indicating mild hyperkalaemia likely due to reduced renal excretion. Phosphate was also elevated (4.19±1.52 vs 3.38±0.49 mg/dL; p<0.001), reflecting the hyperphosphataemia commonly seen in advanced CKD.

Table 3: Electrolyte and Mineral Metabolism in MS-CKD Patients and Controls

Parameter (mean ± SD)	MS-CKD (n=60)	Healthy Control (n=60)	p-value
Calcium (mg/dL)	9.15 ± 0.46	9.14 ± 0.41	0.8
Sodium (mEq/L)	138.98 ± 2.99	138.23 ± 2.70	0.15
Potassium (mEq/L)	5.61 ± 0.50	3.86 ± 0.51	<0.001***
Chloride (mEq/L)	100.07 ± 3.28	100.07 ± 2.85	0.9
Phosphate (mg/dL)	4.19 ± 1.52	3.38 ± 0.49	<0.001***

***p<0.001

Liver Function Tests

Liver function parameters are shown in Table 4. Both ALT (26.1±20.2 vs 15.5±3.8 U/L; p<0.001) and AST (26.6±15.9 vs 17.1±4.0 U/L; p<0.001) were significantly elevated in the patient group, suggesting non-alcoholic fatty liver disease (NAFLD) or mild hepatic steatosis – a common

comorbidity of metabolic syndrome. Alkaline phosphatase did not differ between groups (82.6±14.0 vs 81.7±10.2 U/L; p=0.69). Total bilirubin showed a small but statistically significant increase in patients (0.74±0.51 vs 0.60±0.12 mg/dL; p=0.032), though the clinical significance of this finding is uncertain.

Table 4: Liver Function Tests in MS-CKD Patients and Controls

Parameter (mean ± SD)	MS-CKD (n=60)	Healthy Control (n=60)	p-value
ALT (U/L)	26.07 ± 20.23	15.48 ± 3.81	<0.001***
AST (U/L)	26.58 ± 15.85	17.10 ± 3.97	<0.001***
ALP (U/L)	82.57 ± 13.95	81.67 ± 10.21	0.69
Total bilirubin (mg/dL)	0.74 ± 0.51	0.60 ± 0.12	0.032*

***p<0.001, *p<0.05 (after Bonferroni correction, this p=0.032 is not significant; threshold 0.0025).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase

Adipokines and Inflammatory Biomarkers

Table 5 and Figure 1 (conceptual bar chart) display the comparative levels of adiponectin, leptin, resistin, and TNF-α. Adiponectin, the protective adipokine, was significantly lower in MS-CKD patients (3.45±1.85 mg/L) than in controls (5.12±2.15 mg/L; p<0.001). In contrast, leptin – which promotes inflammation and sympathetic activation – was more than three times higher in patients (2.62±1.56 vs 0.78±0.54

ng/mL; p<0.001). Resistin, a pro-inflammatory adipokine linked to insulin resistance and endothelial dysfunction, was also markedly elevated (683.8±262.4 vs 308.5±149.8 ng/L; p<0.001). TNF-α, a central mediator of chronic inflammation, showed the most striking difference: patients had levels of 104.6±40.4 ng/L compared with 33.0±16.0 ng/L in controls (p<0.001). These data indicate a profound shift

towards a pro-inflammatory, pro-fibrotic adipokine milieu in MS-CKD.

Table 5: Adipokine and Inflammatory Biomarker Levels

Biomarker (mean $\pm$ SD)	MS-CKD (n=60)	Healthy Control (n=60)	p-value
Adiponectin (mg/L)	3.45 $\pm$ 1.85	5.12 $\pm$ 2.15	<0.001***
Leptin (ng/mL)	2.62 $\pm$ 1.56	0.78 $\pm$ 0.54	<0.001***
Resistin (ng/L)	683.8 $\pm$ 262.4	308.5 $\pm$ 149.8	<0.001***
TNF- α (ng/L)	104.6 $\pm$ 40.4	33.0 $\pm$ 16.04	<0.001***

***p<0.001. TNF- α , tumour necrosis factor-alpha

Parathyroid Hormone Levels

Table 6 shows that PTH was significantly elevated in the MS-CKD group (51.2 $\pm$ 47.4 pg/mL) compared with controls (24.9 $\pm$ 4.5 pg/mL; p<0.001). The wide range in patients (14.9–322.0

pg/mL) reflects the variability of secondary hyperparathyroidism in advanced CKD, a condition driven by phosphate retention, reduced calcitriol synthesis, and hypocalcaemia (though calcium was normal in this cohort).

Table 6: Parathyroid Hormone Levels

Parameter (mean $\pm$ SD)	MS-CKD (n=60)	Healthy Control (n=60)	p-value
PTH (pg/mL)	51.17 $\pm$ 47.39	24.90 $\pm$ 4.46	<0.001***

***p<0.001. PTH, parathyroid hormone

Diagnostic Performance of Biomarkers (ROC Analysis)

We performed ROC curve analysis to assess the ability of each biomarker to discriminate between MS-CKD patients and healthy controls. Table 7 summarises the results. Resistin showed excellent diagnostic performance, with an AUC of 0.98 (95% CI 0.82–0.94), sensitivity 83%, specificity 91%, PPV 91%, and NPV 83% at a cut-off >400 ng/L. TNF- α also performed very well (AUC 0.95, 95% CI 0.89–0.98), with

sensitivity 88%, specificity 85%, PPV 85%, and NPV 88% at a cut-off >50 ng/L. Leptin had good diagnostic accuracy (AUC 0.91, 95% CI 0.84–0.95), with sensitivity 90% and specificity 82% at a cut-off >1.1 ng/mL. Adiponectin had only fair performance (AUC 0.76, 95% CI 0.67–0.84), with low sensitivity (56%) but high specificity (96%). These findings suggest that resistin and TNF- α are the most promising non-invasive biomarkers for identifying patients with MS-CKD.

Table 7: ROC Curve Analysis for Diagnostic Performance

Biomarker	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	p-value*
Adiponectin (mg/L)	$\leq$ 2.8	56	96	94	69	0.76 (0.67–0.84)	<0.001
Leptin (ng/mL)	>1.1	90	82	84	88	0.91 (0.84–0.95)	<0.001
Resistin (ng/L)	>400	83	91	91	83	0.98 (0.82–0.94)	<0.001
TNF- α (ng/L)	>50	88	85	85	88	0.95 (0.89–0.98)	<0.001

*Test of null hypothesis: true AUC = 0.50. AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

Correlation Analysis

We examined correlations among key metabolic, renal, and inflammatory parameters (detailed correlation matrix available as Supplementary Table S1). Strong positive correlations were observed between FBS and HOMA-IR (r=0.71, p<0.01), and between serum creatinine and urea (r=0.87, p<0.01), confirming the expected relationships. eGFR was strongly inversely correlated with both creatinine (r=-0.64, p<0.01) and urea (r=-0.67, p<0.01). Resistin correlated positively with triglycerides (r=0.48, p<0.01) and TNF- α (r=0.52, p<0.01). Leptin showed moderate positive correlations with BMI (r=0.44, p<0.01) and insulin (r=0.39, p<0.05). Adiponectin was positively correlated with eGFR (r=0.21, p<0.05) and inversely correlated with HOMA-IR (r=-0.28,

p<0.05), supporting its renoprotective and insulin-sensitising roles. These correlations underscore the interconnected nature of metabolic dysregulation, inflammation, and kidney dysfunction in MS-CKD.

Discussion

This case-control study provides a comprehensive analysis of adipokine and inflammatory profiles in patients with coexisting metabolic syndrome and chronic kidney disease. The key findings are threefold. First, patients with MS-CKD have profound metabolic, renal, and lipid disturbances consistent with advanced disease (eGFR $\sim$ 16.6 mL/min/1.73 m², i.e., stage 4 CKD). Second, they exhibit a striking adipokine imbalance: low adiponectin and high leptin,

resistin, and TNF- α , alongside elevated PTH. Third, resistin and TNF- α demonstrate excellent diagnostic accuracy, suggesting their potential as non-invasive biomarkers for identifying MS-CKD.

Metabolic and Renal Derangements in MS-CKD

The severe hyperglycaemia, hyperinsulinaemia, and elevated HOMA-IR observed in our patients are consistent with well-established evidence that insulin resistance is a central driver of both metabolic syndrome and CKD progression (6, 8). Chronic hyperglycaemia induces oxidative stress, advanced glycation end-products, and activation of the renin-angiotensin system, all of which contribute to glomerular injury and tubulointerstitial fibrosis (25). The very low eGFR and high ACR in our cohort confirm that these patients had not only metabolic syndrome but also advanced kidney damage, challenging the original description of “early” renal dysfunction. Indeed, our results align with previous reports that metabolic syndrome accelerates CKD progression from early stages to end-stage renal disease (4, 5).

The atherogenic lipid profile – high total cholesterol, LDL, and triglycerides, coupled with extremely low HDL – mirrors the dyslipidaemia of diabetic kidney disease. This pattern promotes renal lipotoxicity, where lipid accumulation in renal tubular cells triggers inflammation, apoptosis, and fibrosis (26). Recent studies from the Global South have similarly highlighted the burden of dyslipidaemia in patients with metabolic syndrome and CKD (27); for example, a report in *Global South Health Horizons* emphasised the need for aggressive lipid management in these high-risk populations.

Adipokine Dysregulation as a Link Between MS and CKD

Our finding of decreased adiponectin in MS-CKD is consistent with the known anti-inflammatory and insulin-sensitising actions of this adipokine. Low adiponectin levels have been associated with albuminuria and faster eGFR decline in patients with type 2 diabetes (13, 14). Conversely, elevated leptin in our patients may contribute to renal damage through several mechanisms: leptin promotes sympathetic nervous system overactivity, increases oxidative stress, and directly stimulates renal fibrosis via transforming growth factor-beta (TGF- β) pathways (15, 16).

Resistin, which showed the highest diagnostic accuracy (AUC=0.98), is a pro-inflammatory adipokine that correlates strongly with insulin resistance and endothelial dysfunction. In the context of CKD, resistin levels are elevated due to both increased production by adipose tissue and reduced renal clearance (17). Our ROC data

suggest that a resistin cut-off of >400 ng/L can identify MS-CKD patients with 83% sensitivity and 91% specificity, outperforming many conventional markers. This finding echoes a study from the *Babcock University Medical Journal* that identified resistin as a promising biomarker for early diabetic kidney disease (28). TNF- α , the prototypical inflammatory cytokine, was markedly elevated in our patients. TNF- α induces podocyte injury, disrupts the glomerular filtration barrier, and promotes tubulointerstitial inflammation (18). The high AUC (0.95) for TNF- α supports its role as a key mediator of the cardio-renal-metabolic axis and a potential therapeutic target.

Secondary Hyperparathyroidism in Advanced CKD

The elevated PTH levels observed in our patients (mean 51.2 pg/mL) are consistent with secondary hyperparathyroidism, a near-universal complication of advanced CKD (stage 4–5). Phosphate retention, reduced renal 1-alpha-hydroxylase activity, and consequent calcitriol deficiency drive parathyroid gland hyperplasia and PTH hypersecretion (29). Although serum calcium was normal in our cohort, this is typical in early secondary hyperparathyroidism due to compensatory PTH-mediated calcium mobilisation. The wide range of PTH levels (15–322 pg/mL) reflects the heterogeneity of bone-mineral disorders in MS-CKD.

Diagnostic Implications and Comparison with Existing Literature

Our ROC analysis demonstrates that resistin and TNF- α have excellent discriminatory power, outperforming leptin and adiponectin. These findings extend previous work by showing that a panel of inflammatory biomarkers may be more useful than single markers in risk stratification. However, it is important to note that our study was cross-sectional; we cannot infer causality or claim that these biomarkers predict future progression. The high AUC values indicate good case-control discrimination, but prospective studies are needed to validate their prognostic value.

Several limitations of our study warrant consideration. First, the cross-sectional design precludes any assessment of temporal relationships or causality. Second, the single-centre nature and relatively modest sample size (60 per group) limit generalisability. Third, we did not adjust for multiple comparisons in all analyses, although we applied a Bonferroni correction post hoc; the very low p-values (<0.001) for most comparisons make it unlikely that these findings are spurious. Fourth, the

patient group had advanced CKD (stage 4), so our results may not apply to early-stage disease. Fifth, we did not measure all potential confounders, such as medication use (e.g., statins, ACE inhibitors, SGLT2 inhibitors), which could influence adipokine levels. Sixth, the lack of a validation cohort means that the reported cut-off values need external validation.

Future Directions

Longitudinal studies are urgently needed to determine whether elevated resistin and TNF- α predict incident CKD in patients with metabolic syndrome, or whether they decline with effective treatment (e.g., lifestyle modification, metformin, GLP-1 agonists, or SGLT2 inhibitors). Additionally, interventional trials targeting inflammation – such as anti-TNF- α biologics or resistin antagonists – could clarify causality and open new therapeutic avenues. Finally, cost-effectiveness analyses would help establish whether routine measurement of these biomarkers is feasible in low- and middle-income countries, where the burden of MS-CKD is rising fastest.

Conclusion

This study demonstrates that patients with coexisting metabolic syndrome and chronic kidney disease have severe metabolic dysregulation, advanced renal impairment, and a highly pro-inflammatory adipokine profile characterised by low adiponectin and elevated leptin, resistin, TNF- α , and PTH. Among the studied biomarkers, resistin and TNF- α show excellent diagnostic performance, suggesting their potential as non-invasive screening tools for MS-CKD. However, due to the cross-sectional design and advanced disease stage of our cohort, these findings should be considered hypothesis-generating rather than clinically definitive. Future prospective studies are required to validate the prognostic value of these biomarkers and to explore whether targeting inflammation or adipokine dysregulation improves renal outcomes in patients with metabolic syndrome.

List of Abbreviations

ACR: Albumin to creatinine ratio
ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
AUC: Area under the curve
BMI: Body mass index
CI: Confidence interval
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate
ELISA: Enzyme-linked immunosorbent assay
FBS: Fasting blood glucose

HbA1c: Glycated haemoglobin
HDL: High-density lipoprotein
HOMA IR: Homeostatic model assessment of insulin resistance
LDL: Low-density lipoprotein
MS: Metabolic syndrome
NPV: Negative predictive value
PPV: Positive predictive value
PTH: Parathyroid hormone
ROC: Receiver operating characteristic
SD: Standard deviation
TNF α : Tumour necrosis factor alpha

Declarations

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Ethics Committee of the University of Al-Qadisiyah, College of Medicine (approval number: MED-2024-089, dated 15 August 2024). All procedures followed the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Consent for Publication

All authors gave consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

MLB worked on the conceptualisation, methodology, investigation, formal analysis, writing the original draft and visualisation. AAG worked on the conceptualisation, methodology, supervision, validation, writing the review & editing and project administration.

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