SERUM MAGNESIUM AS AN INDEPENDENT PREDICTOR OF INSULIN RESISTANCE IN EARLY CHRONIC KIDNEY DISEASE

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Abstract

Objective: To evaluate serum magnesium levels in patients with early chronic kidney disease (CKD) and determine whether magnesium independently predicts insulin resistance. **Methods:** This analytical cross-sectional study was conducted at Jinnah Postgraduate Medical Centre (JPMC), Karachi, from January to August 2025. A total of 180 adults with CKD stages 1–3 were enrolled through consecutive sampling. Fasting blood samples were analyzed for serum magnesium, fasting glucose, insulin, creatinine, and HbA1c. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Intergroup comparisons were performed using one-way ANOVA, and associations were assessed using Pearson correlation and multivariate linear regression analysis. **Results:** Serum magnesium levels declined significantly with advancing CKD stage (2.12±0.21 mg/dL in stage 1, 1.98±0.19 in stage 2, and 1.82±0.17 in stage 3; $p<0.001$). In contrast, HOMA-IR increased progressively (2.1±0.8, 2.8±1.1, and 3.6±1.3, respectively; $p<0.001$). Serum magnesium showed a significant inverse correlation with HOMA-IR ($r = -0.52$, $p<0.001$) and fasting insulin ($r = -0.49$, $p<0.001$), and a positive correlation with eGFR ($r = 0.45$, $p<0.001$). After adjustment for age, BMI, HbA1c, and eGFR, serum magnesium remained an independent predictor of insulin resistance ($\beta = -0.38$, $p<0.001$). **Conclusion:** Lower serum magnesium levels are independently associated with increased insulin resistance in early CKD. Magnesium may serve as a useful metabolic marker and potential therapeutic target in this population.

Keywords: Serum Magnesium, Insulin Resistance, Chronic Kidney Disease, HOMA-IR.

INTRODUCTION

Chronic kidney disease (CKD) is a growing global health burden, affecting approximately 10–13% of the adult population worldwide[1]. Early CKD (stages 1–3) is frequently

asymptomatic yet metabolically active, and is associated with an increased risk of cardiovascular disease, insulin resistance, and progression to end-stage renal disease[2]. Among the metabolic derangements observed in CKD, disturbances in glucose metabolism and insulin signaling are particularly important, as they contribute to accelerated vascular damage and adverse renal outcomes[3].

Insulin resistance (IR) is defined as a diminished biological response to circulating insulin and is commonly assessed using surrogate markers such as the homeostasis model assessment of insulin resistance (HOMA-IR)[4]. Even in non-diabetic individuals, CKD has been associated with impaired insulin sensitivity, possibly due to chronic inflammation, oxidative stress, altered adipokine signaling, and uremic toxin accumulation[5]. Importantly, insulin resistance in CKD is not merely a metabolic abnormality but a predictor of cardiovascular morbidity and disease progression[6].

Magnesium is an essential intracellular cation involved in more than 300 enzymatic reactions, including those related to glucose metabolism, insulin receptor activity, and cellular energy production[7]. It plays a critical role in insulin-mediated glucose uptake by modulating tyrosine kinase activity at the insulin receptor level and influencing post-receptor signaling pathways[8]. Hypomagnesemia has been linked to impaired insulin secretion, reduced peripheral glucose utilization, and increased systemic inflammation[9].

Emerging evidence suggests that serum magnesium levels are frequently altered in patients with CKD. Although hypermagnesemia is more commonly associated with advanced renal failure, several studies have demonstrated that patients in early CKD stages may exhibit relative magnesium deficiency due to dietary restrictions, diuretic use, gastrointestinal losses, and altered renal handling[10]. Reduced magnesium levels in CKD have been associated with endothelial dysfunction, increased vascular calcification, and higher cardiovascular mortality[11].

The relationship between magnesium and insulin resistance has been extensively studied in diabetic and metabolic syndrome populations, where low magnesium concentrations have consistently been associated with higher HOMA-IR values and increased risk of type 2 diabetes mellitus[12]. However, data exploring this association specifically in early CKD remain limited. Since CKD itself predisposes individuals to metabolic dysregulation, evaluating magnesium as a potential independent determinant of insulin resistance in this population may provide important insights into disease mechanisms and risk stratification. Furthermore, magnesium deficiency may contribute to oxidative stress and low-grade inflammation both central mechanisms in CKD progression and insulin resistance development[13]. Chronic inflammation in CKD promotes cytokine-mediated interference with insulin signaling pathways, while oxidative stress impairs pancreatic β-cell function and peripheral glucose uptake[14]. Magnesium supplementation has been shown in some studies to improve insulin sensitivity and reduce inflammatory markers, suggesting a potentially modifiable therapeutic target[15]. Given the interplay between magnesium homeostasis, renal function, and metabolic regulation, it is plausible that serum magnesium levels may serve as an independent predictor of insulin resistance in early

CKD. Identifying such an association could have important clinical implications, including early metabolic risk detection and potential preventive strategies aimed at slowing CKD progression and reducing cardiovascular complications. Therefore, the present study was designed to evaluate serum magnesium levels across early CKD stages and to determine whether magnesium independently predicts insulin resistance after adjustment for demographic, anthropometric, and renal parameters.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted at the Nephrology and Medicine Departments of Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan, over a period of eight months from January 2025 to August 2025. Biochemical analyses were performed at the central diagnostic laboratory of JPMC. Written informed consent was obtained from all participants prior to enrollment. The study adhered to the principles outlined in the Declaration of Helsinki.

The sample size was calculated using the formula for comparison of two means, as described by Charan and Biswas, with a confidence level of 95% and power of 80%. Based on previous literature indicating a moderate association between serum magnesium and insulin resistance, the minimum required sample size was estimated at 168 participants. To account for potential incomplete data, a total of 180 participants were recruited through non-probability consecutive sampling. Adult patients aged 25 to 65 years diagnosed with early-stage chronic kidney disease (CKD stages 1–3) according to KDIGO guidelines were included. CKD staging was based on estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI equation, with stage 1 defined as eGFR ≥90 mL/min/1.73m², stage 2 as 60–89 mL/min/1.73m², and stage 3 as 30–59 mL/min/1.73m². Only patients with stable renal function for at least three months were included. Individuals with CKD stages 4 and 5, acute kidney injury, type 1 diabetes mellitus, uncontrolled diabetes (HbA1c ≥7%), chronic liver disease, active infection, pregnancy, current magnesium supplementation, or medications significantly affecting magnesium levels were excluded.

Baseline demographic information, including age, gender, duration of CKD, and comorbid conditions, was recorded. Anthropometric measurements were obtained, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured using a calibrated sphygmomanometer after the participant had rested in a seated position for at least 10 minutes, and the average of two readings was recorded. After an overnight fast of 10–12 hours, venous blood samples were collected under aseptic conditions. Serum magnesium was measured using a colorimetric method. Fasting plasma glucose, fasting serum insulin, serum creatinine, and glycated hemoglobin (HbA1c) were also determined using standard laboratory techniques. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), calculated as fasting insulin (μIU/mL) multiplied by

fasting glucose (mg/dL) divided by 405. Serum creatinine values were used to calculate eGFR using the CKD-EPI equation.

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Normality of distribution was assessed using the Shapiro-Wilk test. Intergroup comparisons across CKD stages were performed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Pearson correlation analysis was used to assess the relationship between serum magnesium and metabolic parameters, including HOMA-IR, fasting insulin, BMI, serum creatinine, and eGFR. To determine whether serum magnesium independently predicted insulin resistance, multivariate linear regression analysis was performed after adjusting for potential confounders, including age, BMI, HbA1c, and eGFR. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 180 patients with early chronic kidney disease (CKD stages 1–3) were included. Serum magnesium levels declined progressively with advancing CKD stage (2.12±0.21 mg/dL in stage 1, 1.98±0.19 in stage 2, and 1.82±0.17 in stage 3; p<0.001). In contrast, insulin resistance increased significantly across stages, with HOMA-IR rising from 2.1±0.8 in stage 1 to 3.6±1.3 in stage 3 (p<0.001). Fasting insulin levels showed a similar upward trend (p<0.001).

Serum magnesium demonstrated a significant inverse correlation with HOMA-IR (r = −0.52, p<0.001) and fasting insulin (r = −0.49, p<0.001), while positively correlating with eGFR (r = 0.45, p<0.001). Multivariate regression analysis revealed that serum magnesium remained an independent predictor of insulin resistance after adjustment for age, BMI, HbA1c, and eGFR (β = −0.38, p<0.001). The model explained 42% of the variance in HOMA-IR.

These findings indicate that lower serum magnesium levels are significantly associated with worsening insulin resistance in early CKD.

Table 1: Baseline Characteristics Across CKD Stages

Variable	CKD Stage 1 (n=60)	CKD Stage 2 (n=62)	CKD Stage 3 (n=58)	p-value
Age (years)	44.6 ± 10.8	48.9 ± 11.2	51.7 ± 12.1	0.01*
Male, n (%)	30 (50%)	34 (54.8%)	31 (53.4%)	0.88
BMI (kg/m²)	26.1 ± 3.4	27.4 ± 3.7	28.2 ± 4.0	0.04*
SBP (mmHg)	124 ± 12	130 ± 14	136 ± 16	<0.001*
HbA1c (%)	5.6 ± 0.4	5.8 ± 0.5	6.0 ± 0.6	0.02*
eGFR (mL/min/1.73m²)	92.4 ± 8.1	71.3 ± 6.9	41.5 ± 7.8	<0.001*

*Values expressed as mean ± SD unless otherwise stated. *Statistically significant (p<0.05).*

Table 2: Comparison of Serum Magnesium and Insulin Resistance Markers

Parameter	CKD Stage 1	CKD Stage 2	CKD Stage 3	p-value
Serum Magnesium (mg/dL)	2.12 ± 0.21	1.98 ± 0.19	1.82 ± 0.17	<0.001*
Fasting Insulin (µIU/mL)	9.2 ± 3.1	12.6 ± 4.2	15.4 ± 5.0	<0.001*
Fasting Glucose (mg/dL)	94 ± 8	99 ± 10	104 ± 12	0.01*
HOMA-IR	2.1 ± 0.8	2.8 ± 1.1	3.6 ± 1.3	<0.001*

*One-way ANOVA applied. *Statistically significant ($p < 0.05$).*

Table 3: Correlation of Serum Magnesium with Metabolic and Renal Parameters

Variable	Pearson r	p-value
HOMA-IR	−0.52	<0.001*
Fasting Insulin	−0.49	<0.001*
BMI	−0.31	0.002*
eGFR	+0.45	<0.001*
Serum Creatinine	−0.38	<0.001*

*Pearson correlation analysis. *Statistically significant ($p < 0.05$).*

Table 4: Multivariate Linear Regression Analysis for Predictors of HOMA-IR

Variable	β Coefficient	95% CI	p-value
Serum Magnesium	−0.38	−0.52 to −0.24	<0.001*
Age	0.12	0.01 to 0.23	0.04*
BMI	0.29	0.17 to 0.41	<0.001*
HbA1c	0.21	0.08 to 0.34	0.002*
eGFR	−0.15	−0.28 to −0.03	0.01*

*Model R^2 = 0.42; Adjusted R^2 = 0.39. *Statistically significant ($p < 0.05$).*

DISCUSSION

The present study demonstrates a significant inverse association between serum magnesium levels and insulin resistance in patients with early chronic kidney disease (CKD). Serum magnesium declined progressively across CKD stages 1 to 3, while HOMA-IR values increased significantly, indicating worsening insulin resistance with declining renal function. Importantly, multivariate regression analysis confirmed that serum magnesium remained an independent predictor of insulin resistance after adjustment for age, BMI, HbA1c, and eGFR. These findings highlight a potential metabolic link between magnesium homeostasis and early CKD progression.

Insulin resistance is increasingly recognized as a common metabolic abnormality in CKD, even in non-diabetic individuals[3–5]. Reduced renal function is associated with chronic inflammation, oxidative stress, and altered insulin receptor signaling, all of which impair glucose utilization[5]. Our finding of progressively increasing HOMA-IR across CKD stages is consistent with previous studies demonstrating a graded relationship between declining eGFR and worsening insulin sensitivity[2,6]. This supports the concept that metabolic dysregulation begins early in renal disease and may contribute to cardiovascular risk and

CKD progression. Magnesium plays a crucial role in glucose metabolism through its involvement in insulin receptor phosphorylation and post-receptor signaling pathways[7],[8]. Hypomagnesemia has been shown to impair insulin-mediated glucose uptake and pancreatic β-cell function[9]. In the present study, the observed inverse correlation between serum magnesium and HOMA-IR (r = −0.52, p<0.001) aligns with earlier findings in metabolic and diabetic populations[12]. However, evidence specifically in early CKD remains limited, making our findings particularly relevant.

The progressive decline in serum magnesium across CKD stages observed in this study is biologically plausible. Although advanced renal failure is typically associated with hypermagnesemia, early CKD may be characterized by relative magnesium deficiency due to dietary restrictions, increased urinary losses, and use of loop or thiazide diuretics[10]. Moreover, reduced magnesium levels have been associated with endothelial dysfunction, vascular calcification, and increased cardiovascular mortality in CKD patients[11]. Thus, magnesium imbalance may represent both a marker and a mediator of adverse metabolic outcomes.

Chronic inflammation and oxidative stress are central mechanisms linking CKD and insulin resistance[13],[14]. Magnesium deficiency has been shown to enhance inflammatory cytokine production and oxidative damage, further impairing insulin signaling pathways[13]. Experimental evidence suggests that magnesium supplementation may improve insulin sensitivity and reduce systemic inflammation[15]. Additionally, recent studies have demonstrated t

hat lower serum magnesium concentrations are independently associated with higher risk of incident type 2 diabetes and metabolic syndrome[16]. In CKD populations, low magnesium has also been linked to increased mortality and faster disease progression[17].

Our multivariate analysis demonstrated that serum magnesium independently predicted HOMA-IR after adjustment for confounding factors, including BMI and glycemic status. This suggests that magnesium deficiency may directly influence insulin sensitivity rather than merely reflecting metabolic comorbidity. Similar independent associations have been reported in population-based cohorts and CKD-specific studies[18].

The findings of this study carry important clinical implications. Early identification of hypomagnesemia in CKD patients may help identify individuals at higher metabolic risk. Given that magnesium is a modifiable factor, dietary optimization or supplementation could represent a simple adjunctive strategy to improve insulin sensitivity and potentially slow CKD progression. However, prospective longitudinal studies are required to confirm causality and evaluate the therapeutic impact of magnesium correction.

In conclusion, the present study provides evidence that lower serum magnesium levels are independently associated with insulin resistance in early CKD. These findings underscore the importance of metabolic assessment in CKD and suggest that magnesium may serve as both a biomarker and potential therapeutic target in this population.

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