

INSULIN RESISTANCE IN CHRONIC KIDNEY DISEASE PATIENTS WITHOUT DIABETES

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Abstract

Background: Cardiovascular disease is the leading cause of morbidity and mortality in patients of Chronic Kidney Disease (CKD). According to recent studies, insulin resistance and compensatory hyperinsulinemia may have some important roles in cardio-renal complications of these patients. So, the aim of this study was to evaluate the insulin resistance status in nondiabetic CKD patients and whether it correlates with glomerular function. **Materials and methods:** This cross-sectional comparative study was carried out in the Department of Biochemistry, Chattogram Medical College from January to December, 2016. A total of 130 subjects of 30-60 years were included by nonprobability consecutive sampling. Of them, 80 were nondiabetic CKD patients of stages III-V and 50 were healthy controls. Fasting plasma glucose, creatinine and insulin concentrations were measured using automated analyzers. Insulin resistance index was determined by Homeostatic Model Assessment Insulin Resistance (HOMA-IR) whereas eGFR was calculated by MDRD formula. **Results:** The nondiabetic CKD patients had significantly higher mean fasting plasma insulin (18.08 mIU/L) compared to controls (9.43 mIU/L). They also showed significantly higher mean HOMA-IR values (4.37) relative to healthy individuals

(2.23). Overall, insulin resistance was 66% in nondiabetic CKD patients vs. 18% in controls. There was significant association of insulin resistance with CKD. But, HOMA-IR did not seem to correlate with CKD stages or eGFR.

Conclusion: In conclusion, this study revealed significant association between insulin resistance and nondiabetic CKD, even though substantial correlation between insulin resistance and glomerular filtration rate was absent.

Key words

Chronic Kidney Disease; eGFR; Insulin; Insulin resistance; HOMA-IR.

Introduction

Chronic Kidney Disease (CKD) is an important public-health problem with high prevalence, increasing incidence, and very high morbidity and mortality¹. Significant proportion of CKD patients die from cardiovascular diseases². Insulin Resistance (IR) the central component of metabolic syndrome, as well as compensatory hyperinsulinemia have drawn significant attention regarding this increased cardiovascular morbidity or mortality in CKD. This is largely due to the established role of insulin resistance in cardiovascular pathogenesis and particularly high prevalences of both insulin resistance and cardiovascular mortality in chronic kidney disease. According to some recent studies, insulin resistance is quite common in both diabetic and nondiabetic CKD, even when GFR is within normal range³⁻⁶. Besides, a growing body of evidence suggests that not only CKD aggravates insulin resistance but insulin resistance and the associated metabolic disorders also contribute to CKD and its cardiovascular problems⁷⁻¹¹. So, insulin resistance is supposed to be a novel target for prevention and management of CKD and its cardiovascular complications¹²⁻¹³. Yet, to the best of our knowledge, there had been no reference regarding insulin resistance in Bangladeshi CKD patients. So, aim of this study was to examine the insulin resistance in nondiabetic CKD patients and how it correlates with renal function.

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Materials and methods

This cross-sectional comparative study was carried out in the Department of Biochemistry and Department of Nephrology of Chattogram Medical College Hospital from January 2016 to December 2016. Permission of the study was taken from the concerned departments and authorities. 130 adults aged between 30 to 60 years fulfilling the enrollment criteria were included by nonprobability consecutive sampling. CKD was defined as either kidney damage or Glomerular Filtration Rate (GFR) < 60 mL/min/1.73 m² for three or more months. The subjects were divided into two groups (Group A & B). Group A was of 80 nondiabetic CKD patients of stages III-V, whereas 50 healthy controls made Group B.

GROUP A: Inclusion Criteria:

Nondiabetic CKD patients (Stages III to V) aged 30-60 years with eGFR < 60 ml/min/1.73m².

GROUP A: Exclusion Criteria:

Patients suffering from diabetes mellitus, acute kidney injury, nephrotic syndrome, end-stage liver disease or cancer, patients on drugs known to affect blood glucose or insulin resistance, dialysis patients, pregnant and lactating mothers.

GROUP B: Inclusion Criteria:

Healthy individuals aged 30-60 years with eGFR 60 ml/min/1.73m², without proteinuria (Dip-stick test negative) and without any sign-symptoms of kidney disease.

GROUP B: Exclusion Criteria:

Subjects known or suspected to have any disease or pathology, on drugs that may affect blood glucose or insulin resistance (e.g metformin, corticosteroids etc.) pregnant and lactating mothers.

eGFR was calculated by MDRD formula. Insulin assay was carried out in ADVIA Centaur XP systems. Plasma glucose and creatinine were estimated in an automated analyzer (Siemens Dimension clinical chemistry system). Insulin resistance was calculated using the HOMA model [HOMA-IR = fasting insulin (mIU/L) \times fasting glucose (mmol/L) /22.5] higher values representing greater insulin resistance. Those with HOMA-IR value > 2.6 were categorized as insulin resistant. Normal value of fasting plasma insulin was up to 12 mIU/L and that of fasting plasma glucose was 3.9 to 6.1 mmol/L. All the data were processed and analyzed using computer-based statistical software. Confidence

level was fixed at 95% and p value < 0.05 was considered to be statistically significant. Different tests of statistical significance were done as appropriate.

Results

Table I: Distribution of fasting plasma insulin and HOMA-IR among the study groups, n = 130 (With ANOVA- test significance)

	Study Groups	n	Mean \pm SD	Range	Significance
Plasma Insulin (mIU/L)	Group A	80	18.08 10.72	3.80-49.04	p < 0.0001
	Group B	50	9.43 3.99	2.46-20.78	Highly Significant
HOMA-IR	Group A	80	4.37 2.50	0.84-11.01	p < 0.0001
	Group B	50	2.23 0.97	0.46-5.18	Highly Significant

Table shows that mean values of fasting plasma insulin and HOMA-IR were significantly higher in nondiabetic CKD patients compared to that in controls (Table I).

Table II: Distribution of fasting plasma insulin and HOMA-IR according to the stage of CKD, n = 80 (With ANOVA test significance)

	Study Groups	n	Mean \pm SD	Range	Significance
Plasma Insulin (mIU/L)	Stage III	12	14.82 7.82	7.35-27.21	p = 0.514666
	Stage IV	17	18.15 9.05	3.80-39.98	Not Significant
	Stage V	51	18.83 11.79	5.88-49.04	
HOMA-IR	Stage III	12	3.53 1.79	1.82-6.37	p = 0.376256
	Stage IV	17	4.22 2.07	0.84-9.67	Not Significant
	Stage V	51	4.63 2.76	1.16-11.01	

Table shows mean values of fasting plasma insulin and HOMA-IR in three different stages of CKD. The mean values tend to increase with CKD stage but the differences among them were not significant (Table II).

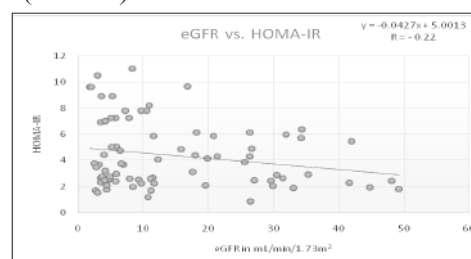


Fig 1: Negative correlation between eGFR and HOMA-IR in nondiabetic CKD patients

($r = -0.22$, $p > 0.05$, $n = 80$). Although eGFR was inversely correlated with HOMA-IR, the correlation was weak and statistically insignificant (Fig 1).

Table III: Association between nondiabetic CKD and insulin resistance, n = 130 (With χ^2 test of significance and odds ratio)

Study groups	Insulin resistance present	Insulin resistance absent	Total
Group A	53 (66.25%)	27 (33.75%)	80 (100.00%)
Group B	09 (18.00%)	41 (82.00%)	50 (100.00%)
Total	62 (47.69%)	68 (52.31%)	130 (100.00%)

χ^2 value = 28.71, $p < 0.0001$ (Highly significant)
Odds ratio = 8.94, $p < 0.0001$ (Highly significant)
significant association between nondiabetic CKD and insulin resistance (Table III).

Discussion

In the present study, the nondiabetic CKD patients had significantly higher mean fasting plasma insulin (18.08 mIU/L) than controls (9.43 mIU/L) $p < 0.0001$. They also presented significantly higher mean HOMA-IR values (4.37) relative to that of healthy individuals (2.23) $p < 0.0001$. Here, insulin resistance was 66% in nondiabetic CKD patients vs. 18% in controls. χ^2 test and odds ratio proved strong association between insulin resistance and nondiabetic CKD. These results are in line with those of previous studies¹⁴⁻¹⁶. Similar studies also confirmed hyperinsulinemia and insulin resistance to be highly prevalent in both diabetic and nondiabetic CKD patients. Even the earliest stage of renal dysfunction was found to be associated with insulin resistance³⁻⁶.

In this study, no significant differences of mean fasting plasma insulin and HOMA-IR were observed amongst different stages of nondiabetic CKD. For the same reason, fasting plasma insulin and HOMA-IR did not seem to correlate with eGFR. While this may be due to smaller sample size or single estimation of HOMA-IR, other investigators also concluded similar observations^{4, 5, 14}. Thus, how or whether the severity of CKD affects hyperinsulinemia and insulin resistance remains to be explained.

Studies recognized a number of CKD specific factors to be involved in the pathogenesis of insulin resistance in chronic kidney disease. Some of them include- anemia, dyslipidemia, metabolic acidosis, uremic toxins, post translational protein modification, malnutrition, vitamin D deficiency, excess of parathyroid hormone, oxidative stress and proinflammatory cytokines¹⁷⁻¹⁹. Insulin resistance is also known to play a significant role in the progressive deterioration of renal function through

mechanisms such as activation of sympathetic nervous system, sodium retention, decreased Na^+ K^+ -ATPase activity, endoplasmic reticulum stress and changes in endothelial and podocyte function^{9, 10}. Thus, a reciprocal relationship is believed to exist between IR and CKD.

As observed in this study, insulin resistance in CKD is often associated with hyperinsulinemia. Initially this is due to a compensatory response. But as renal function declines decreased catabolism and excretion of insulin also contribute to hyperinsulinemia. Despite this increased level of circulating insulin, reduced sensitivity of target organs contributes to poor biological action of the hormone³⁻⁵.

Limitation

The present study had certain limitations. The purposive method of sampling and relatively small sample size can be mentioned as examples. Besides, cross-sectional study is observational and causality cannot be inferred. Finally, the gold standard for quantifying insulin resistance is hyperinsulinemic euglycemic clamp. Nevertheless, Homeostatic Model Assessment Insulin Resistance (HOMA-IR) is also a reliable indicator of insulin resistance.

Conclusion

In summary, the study found significantly higher mean fasting plasma insulin levels and HOMA-IR values in nondiabetic CKD patients when compared to healthy individuals. The occurrence of insulin resistance was also fairly high among the cases. Although HOMA-IR did not seem to correlate with CKD stages or GFR, significant association between insulin resistance and nondiabetic CKD was observed.

Recommendation

The high rate of insulin resistance and hyperinsulinemia in nondiabetic CKD patients as observed in this study cannot be overlooked since insulin resistance is a potentially modifiable risk factor and had been closely associated with CKD and CVD. Hence, further studies are needed in this area to improve our understanding because early detection and treatment of insulin resistance in CKD patients and in population at large might be a reasonable way to lower the risk of development and progression of CKD and its complications.

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Contribution of authors

SD-Conception, design, acquisition of data, manuscript writing and final approval.

PB-Analysis and interpretation of data, manuscript writing, critical revision and final approval.

AMMDA-Interpretation of data, critical revision and final approval.

PK-Analysis of data, critical revision and final approval.

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Disclosure

All the authors declared no competing interest.

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