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Research Article

The Prevalence Of Insulin Resistance In Non-Diabetic And Diabetic Patients With Chronic Kidney Disease

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Abstract
Objectives: Chronic kidney disease (CKD) is characterized by kidney damage lasting longer than three months and reduced kidney function according to the measured glomerular filtration rate (eGFR). The two main causes of CKD are diabetes mellitus and hypertension; however, insulin resistance (IR) is identified as a possible risk factor in CKD patients that can lead to an independent predictor of cardiovascular death. The study describes the prevalence of insulin resistance in diabetic and non-diabetic patients with CKD
Materials and Methods: A cross-sectional study was conducted on 88 CKD individuals among them 44 diabetic and 44 non-diabetics recruited from SRIHER for the period of 6 months. The association between IR and HOMA-IR was assessed using ELISA and the biochemical parameters of FBS, RFT and HbA1c.
Statistical analysis: The statistical analysis was done using SPSS version 23.0. Group variables are compared and presented as mean±SD using one-way ANOVA analysis of variance. Pearson's correlation was done among groups and significant levels is ($p<0.05$*).
Results: It showed a significant difference in insulin resistance between diabetic and non-diabetic groups. In diabetic patients, HbA1c and FBS levels were found significant whereas in non-diabetic levels of creatinine and fasting insulin increased compared to diabetic. A correlation analysis on insulin shows a significant difference among diabetic and non-diabetic CKD ($p<0.00$**).
Conclusion: Study shows significant increase in IR in non-diabetic compared to diabetic group. It also showed a positive correlation between insulin, glucose, HOMA-IR, and creatinine. This indicates high risk of developing diabetes in nondiabetic CKD patients.

Key Words: Chronic kidney Disease (CKD), Diabetes Mellitus (DM), Insulin resistance (IR).

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Introduction:

Chronic kidney disease (CKD) is a condition that gradually damages the structure and function of the kidney over months or years due to various clinical factors. To diagnose CKD, it is necessary to identify structural kidney damage and prolonged impairment in renal function. [1] A patient is considered to have CKD when they exhibit a glomerular filtration rate (GFR) lower than 60 ml/min for three months, along with evidence of injury to the renal structure. [1]

CKD can be caused by various factors, including glomerular kidney disease, tubular and interstitial kidney disease, obstructive uropathy, diabetes, and hypertension. [1,2] However, patients with CKD experience metabolic abnormalities due to the kidneys' reduced ability to maintain normal homeostasis, resulting in decreased GFR and hormone synthesis.[3]

Diabetes mellitus (DM) is a metabolic disorder that causes increased blood glucose levels.[4] It occurs when the pancreas produces insufficient insulin or cells fail to uptake glucose, resulting in fluctuating glucose concentrations in the blood.[4] One of the most common reasons for developing CKD is diabetes, which is referred to as (diabetic kidney disease) DKD, as both albuminuria and eGFR are linked to mortality and the development of end-stage renal disease (ESRD). Screening guidelines recommend assessing both DKD and the most common cause of ESKD (end-stage kidney disease), as both conditions have a strong correlation with coronary artery disease (CAD).[5]

Insulin resistance (IR) is recognized as one of the non-traditional risk factors and as an independent predictor of cardiovascular mortality in patients with CKD. The most common and early alteration is apparent even at normal glomerular filtration rate (GFR) levels and in mild-to-moderate CKD stages.[6] It plays a significant role in the pathophysiology of metabolic diseases like type 2 diabetes and the clinical features of several illnesses, including breast cancer, rheumatoid arthritis, polycystic ovarian syndrome, non-alcoholic fatty liver disease, and coronary artery disease (CAD).[6] Insulin resistance (IR) has been recognized as the key factor in type 2 diabetes mellitus (T_2DM) prevalence.[5]

CKD patients have a normal or slightly raised fasting blood sugar level and a quick rise in blood sugar after consuming glucose.[7] Individuals may have hyperinsulinemia at the expense of developing hyperglycemia, indicating peripheral resistance to insulin in action.[8] In ESRD patients, peripheral tissues are the site of insulin resistance.[9, 10]As previous studies have reported altered insulin resistance in CKD patients, this study is designed to understand the prevalence of insulin resistance in non-diabetic and diabetic patients with chronic kidney disease.

Materials and Methods

The present study is a cross-sectional study taken up in the Department of Biochemistry and collaborated with the Department of Nephrology at Sri Ramachandra Medical College and Research Institute, Porur, Chennai during the period from May 2022 to April 2023. The study was conducted after obtaining ethical clearance from the Institutional Ethics Committee, Sri Ramachandra Medical College & Research Institute, (REF: CSP/22/SEP/116/490)**.** After obtaining the ethical clearance the Inclusion and exclusion criteria were applied to procure study participants and are characterized into two groups, group 1 consists of 44 patients with diabetic CKD, and Group 2 consists of 44 patients with non-diabetic CKD. Non-diabetic and diabetic CKD participants who are aged (>18) years, both male and female were included. In contrast, alcohol intake, pregnant women, anemia, and patients who are on medication that induces CKD were excluded from the study.

Blood sample collection and storage

The 5ml of the venous blood sample was collected from the participants. The samples were then allowed to clot and centrifuged at 2000-3000 RPM for 20 minutes. The serum thus obtained was separated and stored at -20℃. Then the following biochemical parameters were analyzed using various methods (Instrument and reagents at central laboratory SRIHER). Glucose, urea, and creatinine were measured using enzymatic methods, HbA1c was measured using the Chromatography (HPLC) method, and insulin was estimated using ELISA.

Insulin Resistance was calculated by(IR):

$$\text{HOMA IR} = \frac{\text{Fasting plasma insulin} \times \text{Fasting plasma glucose mg/dl}}{405}$$

Statistical analysis:

The data were consolidated and exported to an Excel sheet for statistical analysis. This Data were analyzed using the SPSS 23.0 version and expressed as mean ± standard deviation (SD). All statistical comparisons were performed using a one-way ANOVA analysis of variance between diabetic and nondiabetic CKD patients. Pearson's Correlation analysis was used to assess the insulin resistance between diabetic and nondiabetic CKD. The statistical significance was considered to be $p<0.05$*.

Results:

This study comprises 88 patients where the gender distribution of patients with CKD was 53 (60.2%) males

and 35 (39.8%) females, as shown in Table 1. The bar graph depicts the age group and distribution of gender in the study population, as shown in Figure 1.

Table 2 explains the relationship between the biochemical parameters in the non-diabetic CKD and diabetic CKD groups. The mean and standard deviation (SD) of the biochemical parameters of non-diabetic CKD and diabetic CKD patients were BUN (33.5±19.6), (34.0±18.3), Creatinine (5.56±3.77), (3.81±2.67), HbA1c (6.15±.55), (7.65±1.11), Glucose (92.0±20.8), (185.3±54.0), Insulin (43.14±29.9), (27.6±23.1), HOMAIR (9.86±7.45), (12.2±10.7), respectively. Here, all three groups were compared. HbA1c ($p<0.000$), glucose ($p<0.000$), insulin ($p<0.000$), and creatinine ($p<0.014$) showed statistically significant values, and the parameters BUN and HOMA-IR(Homeostasis Model Assessment of Insulin Resistance) showed no statistically significant value. However, Table 3 explains the correlation of insulin with other biochemical parameters among diabetic and nondiabetic CKD, which shows statistical significance in creatinine ($p<0.05$), glucose ($p<0.02$), and HOMA-IR ($p<0.01$), and parameters BUN and HbA1c show no statistical significance.

Figure-1: Depicts the age group and distribution of gender in the study population

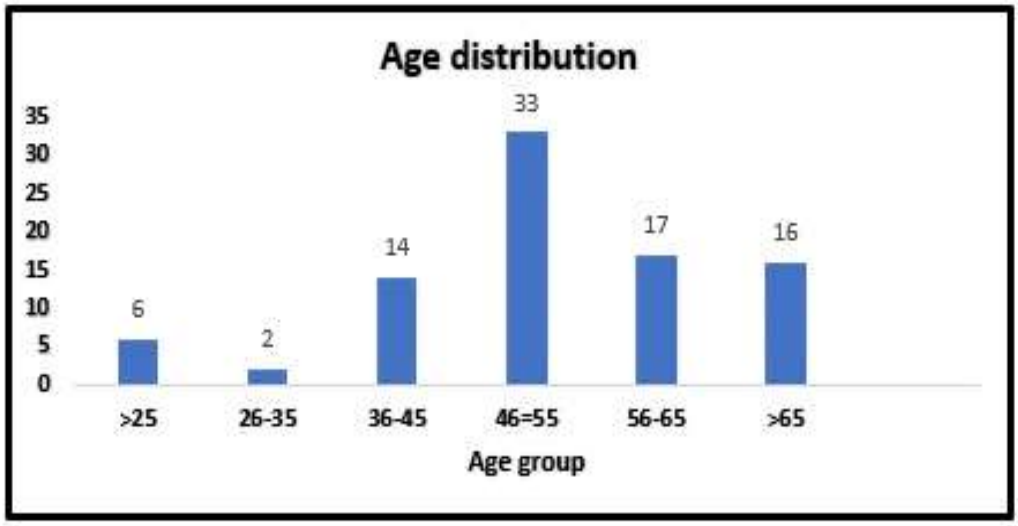

Table 1: Gender distribution of study participants among males and females:

Gender	Frequency	Percent (%)
Female	35	39.8
Male	53	60.2
Total	88	100.0

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	p-value
						Lower Bound	Upper Bound			
BUN	Nondiabetic	44	33.591	19.6544	2.9630	27.615	39.566	6.0	102.0	0.907
	diabetic	44	34.068	18.3371	2.7644	28.493	39.643	6.0	69.0	
	Total	88	33.830	18.8991	2.0147	29.825	37.834	6.0	102.0	
CREATININE	Nondiabetic	44	5.568	3.7771	.5694	4.420	6.717	1.3	15.5	0.014*
	diabetic	44	3.816	2.6734	.4030	3.003	4.629	1.5	12.7	
	Total	88	4.692	3.3705	.3593	3.978	5.406	1.3	15.5	
HbA1C	Nondiabetic	44	6.159	.5550	.0837	5.990	6.328	5.0	8.8	0.000**
	diabetic	44	7.652	1.1130	.1678	7.314	7.991	6.0	11.0	
	Total	88	6.906	1.1525	.1229	6.661	7.150	5.0	11.0	
GLUCOSE	Nondiabetic	44	92.023	20.8488	3.1431	85.684	98.361	42.0	168.0	0.000**
	diabetic	44	185.364	54.0788	8.1527	168.922	201.805	131.0	351.0	
	Total	88	138.693	62.1567	6.6259	125.523	151.863	42.0	351.0	
INSULIN	Nondiabetic	44	43.1468	29.91856	4.51039	34.0507	52.2429	5.91	88.67	0.000**
	diabetic	44	27.6584	23.15409	3.49061	20.6189	34.6979	.86	88.67	
	Total	88	35.4026	27.71377	2.95430	29.5306	41.2746	.86	88.67	
HOMAIR	Nondiabetic	44	9.8611	7.45754	1.12427	7.5938	12.1284	1.02	26.27	0.222
	diabetic	44	12.2895	10.76525	1.62292	9.0166	15.5625	.29	43.94	
	Total	88	11.0753	9.28754	.99005	9.1075	13.0432	.29	43.94	

Table 2: **Comparison of biochemical parameters between the 3 groups using the ANOVA test**

Note: In the above table, HbA1c (6.159±7.652) (<0.000**), Glucose (92.023±185.364) (<0.000**), Insulin (43.1468±27.6584) (<0.000**), and creatinine (5.568±3.816) (<0.014*) were compared between the 2 groups (non-diabetic CKD and diabetic CKD) and are statistically significant (p-values *≤0.05 and **≤0.001). (BUN) Blood Urea Nitrogen and (HOMA- IR) Homeostasis Model Assessment of Insulin Resistance.

Table 3: Correlation of insulin with other biochemical parameters by using Pearson Correlation analysis among Diabetic and non-diabetic CKD

		BUN	creatinine	HbA1c	Glucose	HOMA-IR
Insulin	Pearson correlation	00.12	.213*	0.163	.248*	.820**
	Sig(2-tailed)	0.91	0.047	0.129	0.02	0.001
	N	88	88	88	88	88

Note: ** Correlation is significant at 0.001 (2 -tailed). * Correlation is significant at 0.05 (2-tailed). In the above table Creatinine (.213*) (0.047*), Glucose (.248*) (0.02*) and HOMA-IR (.820**) (0.001**) compared the groups with insulin and showed a significant correlation. (BUN) Blood Urea Nitrogen and (HOMA- IR) Homeostasis Model Assessment of Insulin resistance.

Discussion:

The intersection of diabetes mellitus and kidney illness involves a complex relationship in modern medicine, with considerable consequences for public health, clinical practice, and biomedical research.[11] chronic kidney disease (CKD) is characterized by a gradual

decline in kidney function causing a significant cause of morbidity and mortality in the 21st century.[12]

The association between diabetes and kidney disease is reciprocal and complex, demonstrating a comprehensive network of relationships that includes pathophysiology, clinical treatment, and epidemiology.[13] This study assessed the serum creatinine, urea, fasting blood glucose, HbA1c, Insulin, and HOMAIR levels between non-diabetic CKD and diabetic CKD patients. A significant increase in glycaemic control of HbA1c was found in the non-diabetic CKD group with a mean value of (6.159) associated with an elevated risk of developing a prediabetic state. So, the prevalence of risk for non-diabetic CKD patients to develop diabetes is significantly high ($p<0.00$**).

Chen, J et al., indicate that glycosylated hemoglobin A, a marker of long-term glycaemic control, is linearly correlated with chronic kidney disease (CKD) risk in individuals without diabetes. An HbA1c level of 5.7% or above is linked to an increased risk of CKD.[14] According to criteria from the American Diabetes Association (ADA), an HbA1c level below 5.7% is considered normal, while a level beyond 5.7% to 6.4% is categorized as prediabetes (Chi-Chih Hung, et al.,). It has been shown that prediabetes, which is defined by an elevated HbA1c but not fasting plasma glucose, is associated with outcomes including death and cardiovascular disease. [15]

Similar to this, a study by Kumar M et al., found that individuals with diabetes had a higher chance of developing chronic kidney disease (CKD). However, other kidney diseases also contribute to the development of diabetes because the kidneys regulate blood glucose levels by filtering blood and selectively reabsorbing glucose when necessary. When kidney function deteriorates owing to chronic kidney disease (CKD), it can result in impaired glucose metabolism, which can accelerate the development of insulin resistance and, eventually, diabetes.[16]

The kidneys are essential for blood glucose regulation because they filter blood and selectively reabsorb glucose to maintain glucose homeostasis. On the other hand, CKD may cause disruptions to the diverse regulation of glucose management. Glycosuria is a medical condition characterized by the presence of glucose in the urine and caused by problems in renal glucose reabsorption. As a result of this event, blood glucose levels rise, bringing a person closer to diabetes. Individuals with chronic kidney disease (CKD) may have abnormal glucose metabolism, including decreased insulin sensitivity and poor glucose tolerance, which increases the risk of developing diabetes.[17]

Similarly, the correlation of Insulin between serum creatinine, urea, fasting blood glucose, HbA1c, and HOMAIR was analyzed between non-diabetic and diabetic CKD. There was a positive correlation found in creatinine (.213*+0.047), glucose (.248*±0.02), and HOMA-IR (.820**±0.001). To support this study, Hong Xu and Juan J. Carrero et al., stated that reduced insulin sensitivity is the primary cause of insulin resistance (IR) in people with chronic kidney disease (CKD) and end-stage renal disease (ESRD). This is most likely the result of a post-receptor deficit in peripheral skeletal muscle. [15, 18]

Insulin resistance is prevalent among individuals with renal illness and may manifest in the initial phases of chronic kidney disease. It affects both CKD patients with and without diabetes, independent of the underlying etiology of renal disease, and worsens as kidney function falls. Typically, 30–80% of the insulin in circulation is eliminated by the kidney. Maintaining healthy kidney function is essential in regulating blood sugar levels. Insulin resistance (IR) and reduced insulin-triggered glucose consumption in peripheral target tissues may be associated with impaired kidney function. According to earlier studies, insulin resistance (IR) in end-stage renal disease (ESRD) might result in variable degrees of pancreatic β-cell activity, which can induce glucose intolerance.[19]

Patients with and without diabetes were compared for insulin resistance in this study. In comparison with insulin, HOMA-IR was favorably and statistically significantly related to both diabetic and non-diabetic CKD. It was found to be strongly correlated with HOMA-IR in both US and Indian populations ($p<0.001$**), according to studies by Gwang Seok Kim al., Chen et al., and Srivastava et al. [20]

According to research by Xu H, Carrero JJ and Kumar M, et al., insulin signaling may deteriorate, particularly in conditions involving serious renal disease. This may result in the emergence of insulin resistance, a feature characteristic of type 2 diabetes. When renal function is compromised, other factors that may affect the insulin signaling pathways include obesity, a sedentary lifestyle, poor diet, smoking, adipokine deregulation and accumulation, mitochondrial acidosis, oxidative stress, chronic inflammation, vitamin D deficiency, anemia, uremic toxicity, and coexisting conditions like hypertension and hyperlipidemia. [21, 22]

Also, creatinine was compared with insulin between diabetic and non-diabetic CKD patients and was statistically significant ($p<0.05$*). Thomas SS, Liping Zhang, et al., state that even in cases when serum creatinine is relatively elevated, insulin resistance is frequently observed in CKD patients. In patients with chronic kidney disease (CKD), insulin resistance may exacerbate renal function and raise the risk of cardiovascular problems.[22]

Conclusion:

In the non-diabetic and diabetic CKD patients in our investigation, there was a marked rise in insulin resistance, which correlated favorably with glucose, HOMA-IR, and creatinine. HbA1c was linked to an increased risk of diabetes in individuals with chronic kidney disease (CKD) who were not diabetics, suggesting that there is a high prevalence of risk for these patients to become diabetics.

Limitation of study:

Only 88 individuals were included in this study; future research will examine a larger sample size and explore the various phases of CKD in detail. The study did not consider the impact of other drugs or diets. It is possible

to assess the development of risk of cardiovascular problems by including eGFR and lipid profiles.

Authors' Contributions:
AM wrote the manuscript, collected samples, and performed tests; AMK was involved in the planning of the research topic, and literature guidance and helped in the selection of patients; SV helped in the review of data analysis, statistics, and editing of the manuscript; SS was involved in patient handling and data collection, SR helped in sample collection and lab performance. All authors have read and approved the manuscript.

Consent to Participate:
Informed consent was obtained from all the participants.

Ethics Approval:
The study was approved by the Institutional Research Ethics Committee (IEC approval letter no: CSP/22/SEP/116/490). Sri Ramachandra Medical College & Research Institute, Chennai. The study was performed by the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Conflicts of Interest:
All the authors reported no conflict of interest.

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