Study of association of insulin resistance in chronic kidney disease patients with and without diabetes

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Abstract
Introduction and Objectives: Chronic kidney disease is the pathophysiologic process with different etiologies, resulting in exorable attrition of nephrons and their function. The most frequent cause of CKD is diabetic nephropathy, caused by type 2 diabetes mellitus. Kidney disease worsens over time by transitioning through a defined sequence of stages. Thus it should be possible to detect CKD prior to kidney failure. Insulin levels, change with CKD as a result of reduced excretion, decreased degradation, or a defect in regulation. Insulin resistance is associated with CKD as an antecedent or as a consequence of CKD is not yet known. The prevalence of higher IR in CKD cases is due to the decrease in glomerular filtration rate and a disturbance in insulin metabolism. The presence of insulin resistance and hyperinsulinemia was observed in CKD patients both with and without diabetes. The aim is to evaluate their role in both diabetic and non diabetic CKD patients.

Materials and Methods: A case control study was done. Around 90 individuals were taken for the study and divided into 3 groups (healthy controls, CKD non diabetic patients and CKD diabetic patients). After taking informed consent blood samples were collected in individual’s fasting condition. Fasting plasma glucose, serum insulin measured and insulin resistance calculated by HOMA-IR. Multiple comparisons between different groups were done using ANOVA test.

Results: The present study showed that the mean±S.D of IR in controls was 1.7±1.5, in CKD without DM cases was 4.2±4.8 and in CKD with DM cases 11.1±11.8. Fasting Plasma Glucose, Fasting Insulin, IR were significantly increased (P<0.0001) in CKD with or without diabetes patients when compared to controls.

Interpretation and Conclusion: Insulin resistance was found to be associated with CKD in both diabetic and non diabetic patients. Increased insulin resistance causes more worsening of renal function. Thus, by introducing measures that can reduce insulin resistance like glycemic therapy and early detection of metabolic syndrome might delay the progression of renal dysfunction and cardiovascular mortality in chronic kidney disease cases.

Keywords: Chronic kidney disease (CKD), Insulin resistance (IR), Type 2 diabetes mellitus (T2DM), Homeostatic model assessment – insulin resistance (HOMA-IR).

Introduction
Chronic Kidney Disease (CKD) is a highly prevalent public health problem, with increasing incidence, high costs, and poor outcomes.¹ It is a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).² The burden of CKD is contributed abundantly by diabetes in developing countries. The early detection of diabetic nephropathy and targeting hyperglycemia may reduce the progression of renal disease.³ The mechanisms that lead to diabetic nephropathy, involve the effects of soluble factors (growth factors, angiotensin II, advanced glycation end products [AGEs] etc), hemodynamic alterations in the renal microcirculation and structural changes in the glomerulus like increased extracellular matrix, thickening of basement membrane, mesangial expansion, fibrosis.⁴

Even the nondiabetic adults with metabolic syndrome also had an increased risk for developing CKD.⁵ The changes like myointimal hyperplasia of interlobular and afferent arteriolar vessels, hyaline arteriolar sclerosis, wrinkling collapse of glomerular tuft and global glomerulosclerosis result from glomerular ischemia due to afferent arteriolar narrowing in response to increased afferent arteriolar flow secondary to hypertension.⁶

Insulin, a hormone produced by the pancreatic β-cells of the islets of Langerhans,⁷ Insulin resistance is caused by increased concentrations of insulin due to downregulation of insulin receptors and desensitization of postreceptor pathways.⁸ One of the multiple mechanisms that contribute to the increased vascular risk of CKD is the presence of insulin resistance.⁹ Decreased renal function is associated with the development of IR with impaired insulin-induced glucose utilization of peripheral target tissues.⁹ IR is shown to be associated with diminished renal function with and without diabetes.¹⁰ The greater the insulin resistance, the more is the worsening of renal function. Efforts taken to decrease insulin resistance would slow down the progression of renal disease and would also decrease cardiovascular mortality in chronic kidney disease cases.¹¹

Materials and Methods
A Case control study was performed with 90 subjects in the Department of Biochemistry, Osmania General Hospital,
Hyderabad, after approval from institutional ethics committee.

**Inclusion Criteria**
1. CKD patients with diabetes, in the age group 35–65 years.
2. CKD patients without diabetes, in the age group 35–65 years.
3. CKD patients with an etiology of nephrotoxic drugs in the age group 35–65 years and
4. Healthy Controls, In the Age Group 35–65 Years.

**Exclusion Criteria**
1. Patients with liver dysfunction,
2. Patients with anemia or any blood disorder
3. Patients with thyroid dysfunction.
4. Patients in younger age group (<30yrs).

**Grouping**
In the present study, 90 subjects were grouped as follows. Group 1: 30 healthy controls in the age group 35–65 years.

**Results**

The Mean± S.D of fasting plasma glucose was increased and statistically significant in CKD with and without DM cases when compared with controls. The Mean± S.D of fasting insulin and IR were increased and statistically significant in CKD with and without DM cases when compared with controls. In order to assess the significance of the differences observed in the mean values of different parameters observed in different groups studied, the data is subjected to ANOVA test. The significance of difference of mean values of different groups and within the groups is represented by p values and p value < 0.05 is considered as significant.

**Table 1: The Mean ± SD of all the parameters in controls, in CKD patients without diabetes and in CKD patients with diabetes**

| Parameters  | Mean±S.D of controls | Mean±S.D of non diabetics with CKD | Mean±S.D of diabetics with CKD |
|-------------|----------------------|------------------------------------|-------------------------------|
| FPG         | 92.8±17.8            | 107.8±31.8                         | 191±61.6                      |
| Fasting Insulin | 7.7±6.0             | 15.8±15.6                          | 21.4±18.9                    |
| IR          | 1.7±1.5              | 4.2±4.8                            | 11.1±11.8                    |
| Urea        | 28±10                | 138.6±35.6                         | 128±50.7                     |
| Creatinine  | 0.9±0.4              | 8.6±3.2                            | 5.9±2.4                      |

**Table 2: Pearsons Correlation between parameters in control group**

| Parameters | FPG | S.insulin | IR |
|------------|-----|-----------|----|
| FPG        |     |           |    |
| S.insulin  |     |           |    |
| IR         |     |           |    |

**Blood Urea measured by** kinetic enzymatic method. Talke and Schubert, Tiffany et al.

**Serum Creatinine measured by** Modified Jaffes reaction

**Statistical Analysis**
The data was analyzed using graphpad prism software version 6.05. Descriptive results were expressed as mean and SD of various parameters in different groups. Multiple comparisons ANOVA was used to assess significance of difference of mean values of different parameters in between the groups. The significance of difference of mean values of different groups and within the groups is represented by p values and p value < 0.05 is considered as significant.
Table 3: Pearson's Correlation between parameters in CKD without T2DM cases

|                        | FPG       | S.Insulin | IR         |
|------------------------|-----------|-----------|------------|
| **FPG**                | Pearson's correlation | 0.049     | 0.185      |
|                        | p value   | 0.794     | 0.326      |
| **S.Insulin**          | Pearson's correlation | 0.049     | 0.967      |
|                        | p value   | 0.794     | 3.379e-018 |
| **IR**                 | Pearson's correlation | 0.185     | 0.967      |
|                        | p value   | 0.326     | 3.379e-018 |

Table 4: Pearson's Correlation between parameters in CKD with T2DM cases

|                        | FPG       | S.Insulin | IR         |
|------------------------|-----------|-----------|------------|
| **FPG**                | Pearson's correlation | 0.379     | 0.604      |
|                        | p value   | 0.038     | 0.001      |
| **S.Insulin**          | Pearson's correlation | 0.379     | 0.917      |
|                        | p value   | 0.0       | 1.021e-012 |
| **IR**                 | Pearson's correlation | 0.604     | 0.917      |
|                        | p value   | 4.063e-004| 1.021e-012 |

Discussion

Chronic kidney disease (CKD) is the persistent kidney damage with a reduction in the glomerular filtration rate (GFR). CKD is a worldwide threat to health especially for developing countries because of its expensive therapy which is life-long. To identify and treat the risk factors of CKD in the early stages would be the best approach to prevent and delay adverse outcome.

Diabetes Mellitus is a major risk factor for the initiation and progression of CKD. The metabolic dysregulation due to DM causes secondary pathophysiologic changes in multiple organ systems. Hence DM being the most common cause of end-stage renal disease. Insulin resistance, the decreased ability of insulin to act on target tissues, is an important feature of type 2 DM, usually caused due to genetic susceptibility and obesity.

Non diabetic kidney disease spectrum constitutes hypertension, chronic glomerular nephritis, chronic interstitial disease, ischaemic nephropathy, obstructive uropathy and miscellaneous. Nondiabetic adults with the metabolic syndrome also had an increased risk for developing CKD. IR is usually present in CKD patients in nondiabetic adults. The presence of hyperinsulinaemia
exert deleterious effects on vasculature even in the absence of hyperglycaemia.25

Insulin resistance (IR) is the failure of insulin to maintain glucose homeostasis and is believed to play a prominent role in the pathogenesis of the metabolic syndrome.26 IR causes progression of kidney disease by worsening renal hemodynamics, releasing inflammatory cytokine and renal endoplasmic reticulum stress. Renal ER stress is associated with proteinuria induced damage of the podocytes and alteration of nephrin N-glycosylation in podocytes.27 Kidney damage induced by IR includes glomerular hyperfiltration, endothelial dysfunction, increased vascular permeability, increased glomerular capillary pressure, mesangial hyperplasia, renal hypertrophy and increased endothelial cell proliferation.28 Thus the Prevention and treatment of insulin resistance may reduce the burden of CKD.

The present study was undertaken to identify the association of IR in CKD patients without diabetes and in CKD patients with diabetes. IR was increased significantly in CKD patients with and without diabetes when compared with controls (p value < 0.0001). These findings were in accordance with M. V. Chandrakanth et al. Jing Chen et al., identified a strong, positive, significant, relationship among insulin resistance, insulinlevel, and risk of CKD among nondiabetic participants.29

Conclusion

In this study we have observed that the decline of renal function is associated with the development of IR. We have found that there is a significant increase in IR in CKD patients both with and without T2DM when compared to controls. IR was increased more in CKD cases with diabetes when compared to the CKD cases without diabetes. To conclude, there is a universal presence of insulin resistance and increased insulin levels in patients with diabetic and non-diabetic chronic kidney disease. Increased insulin resistance predispose to worsening of renal function. Implementing measures towards decreasing insulin resistance would be beneficial in delaying the progression of renal disease and towards reduction of cardiovascular mortality in chronic kidney disease cases.

Conflict of Interest: None.

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