EVALUATION OF CHRONIC KIDNEY DISEASE PATIENTS FOR INSULIN RESISTANCE IN TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To evaluate the patients of chronic kidney disease for insulin resistance.
Study Design: Cross sectional observational study.
Place and Duration of Study: The study was conducted in the chemical pathology department of Army Medical College/Military Hospital Rawalpindi, from Nov 2016 to Apr 2017.
Material and Methods: Fifty patients were recruited for this study with deranged renal functions and/or having any structural renal abnormality for more than 3 months. These patients did not have any history of diabetes and dialysis. Fifty ages matched healthy individuals were included as controls. Renal function tests, lipid profile, complete blood count, fasting plasma glucose and serum insulin levels were performed in all subjects. Insulin resistance was calculated by using homeostatic model for assessment of insulin resistance (HOMA-IR). Results of this study were analyzed on SPSS version 23.
Results: Fasting insulin levels were much higher in the patient with chronic kidney disease as compared to controls (*p*-value=0.001). HOMA-IR in cases was also significantly higher. Statistical comparison of lipid profile showed significant difference of only triglycerides level.
Conclusion: HOMA-IR is markedly raised in the patients of chronic kidney disease. This indicates a significant association of chronic kidney disease with insulin resistance.

Keywords: Chronic kidney disease, Hypertriglyceridemia, HOMA-IR, Insulin resistance

INTRODUCTION

As per National kidney foundation around 10% of the total population is experiencing the chronic kidney disease. As indicated by 2010 Global Burden of Disease study, chronic kidney disease was positioned 27th in the record of causes of total deaths worldwide in 1990, yet this rank drastically rose to 18th in 2010. The magnitude of this movement is just second to HIV and AIDS[1]. In Pakistan, chronic kidney disease is proving to be a growing burden on the economy, with lack of screening facilities and advance treatment centers the disability is growing day by day. It is estimated that more than 100 persons per million populations is suffering from end stage renal disease[2]. According to National kidney foundation the criterion for chronic kidney disease is kidney damage for ≥3 months. This damage is defined by structural or functional impairments of the kidney.which occur with or without decrease in glomerular filtration rate, these pathological derangements are manifested by elevation of the biochemical markers of kidney damage[3]. Patients with uncontrolled diabetes mellitus have the risk of developing chronic kidney disease. On the other hand, patients of chronic kidney disease have higher prevalence of developing insulin resistance. The factors which contribute in development of insulin resistance are vitamin D deficiency, depressed serum erythropoietin, systemic inflammation, oxidative stress, elevated serum adipokines and fetuin-A, metabolic acidosis, endoplasmic reticulum stress, and suppressors of cytokine signaling all cause IR by suppressing insulin receptor-PI3K-Akt pathways in CKD[4].

Insulin resistance is an important predictor of coronary artery disease and protein energy malnutrition. Post receptor alterations in skeletal

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muscles leads to insulin resistance[5]. Insulin resistance plays a key role in the development of biochemical abnormalities associated with metabolic syndrome.

Kidneys play a major role in the metabolism and degradation of the insulin. There are two distinct documented routes of renal clearance of insulin; one is through luminal re-absorption of insulin by proximal tubular cells. The second is diffusion through pre-tubular capillaries and it's binding to contra luminal membrane of pre-tubular cells. After the diffusion, insulin is degraded to oligopeptides and amino acids by the action of insulin protease. Breach in the clearance of this mechanism prolong the half-life and the metabolism of insulin[6].

Derangement of lipid profile is another important abnormality which can be seen in the patients of chronic kidney disease. The clearance of triglycerides impairs due to reductions in the activity of lipoprotein lipase and hepatic triglyceride lipase. This defect in the clearance leads to raised levels of triglycerides[7]. Lipid abnormalities normally manifest themselves in chronic kidney disease as metabolic syndrome and ultimately lead to insulin resistance. This ultimately leads to increase insulin resistance and promotes atherogenic dyslipidemias[8]. Development of insulin resistance further aggravates existing renal condition. It is also a risk factor for cardiovascular diseases. Timely diagnosis of insulin resistance would help in disability limitation as well as modulating treatment strategies for a better health outcome. This study was first of its kind to be conducted in patients of chronic kidney disease to evaluate insulin resistance in our population.

MATERIAL AND METHODS

This cross sectional observational study was carried out in the chemical pathology department of Army Medical College/Military Hospital Rawalpindi from Nov 2016 to Apr 2017. A total of 100 subjects were recruited for the study by using convenient sampling technique. These individuals were further divided into two groups. Group "A" comprised of the individuals who have deranged renal functions or any structural renal abnormality for ≥3months. Known patients of diabetes mellitus were excluded from the study. Patients on dialysis were also excluded. Group "B" comprised of age matched healthy controls. The procedure and purpose of study was explained to each participant and their consent was obtained. Fasting venous blood sample was obtained under aseptic conditions. The sample was subdivided into plain, sodium fluoride and EDTA tubes andthe sample centrifuged at 4000rpm for five minutes. The serum was separated and Lipid profile and RFT performed on each separated serum. Complete blood count and glycosylated hemoglobin was analyzed on the tube containing EDTA. Fasting glucose was carried out on the tubes containing sodium fluoride. Five hundred micro-liters from each separated serum were preserved at -20°c for the estimation of insulin. Routine biochemical profiles were carried out on fully automated chemistry analyzer (Selectra XL). Insulin levels were determined on chemilumene-scence based imunoassy techniques (Immulite 1000). HbA1c analysis was carried out on the instrument based on immuno-turbidimetery (Diasys Responc 910). Insulin resistance was calculated by using Homeostatic model for assessment of insulin resistance. HOMA calculator v.2.2.2 of Diabetes trial unit of University of oxford was used for calculations. The values less than 2 were taken as normal and the value >2were taken as insulin resistance[9,10].

RESULTS

Out of 100 participants of this study, 50 were the controls and 50 were the cases. In cases 66 percent were males and 34 percent were female. In controls 74 percent were males and 26 percent were female. The mean age of the cases was 50 ± 10 and the mean age of the controls was 49 ± 9. After collection of the anthropometric data, body mass index (BMI) was calculated (table-I). The mean value of BMI(kg/m^2) for the cases was 23 ± 2 and for controls it was 24 ± 3. The mean value of serum urea (mmol/L) was 17.84 ± 11 and of

serum creatinine was (umol/l) 345 ± 255 for cases. Controls showed a mean of 3.7 ± 0.7 for the urea and 71 ± 9 for creatinine. For fasting Insulin levels (uU/ml) the mean for the cases was 19.4 ± 9.1 as compared to the controls which was 9.3 ± 6.6. HOMA-IR score was calculated based o fasting Glucose and Insulin levels. The mean value for the controls was 1.2 ± .8 as compared to cases which was 2.6 ± 1.3 (table-II). The mean of triglycerides (mmol/l) in cases was 1.989 ± 0.65 as compared to controls which showed a mean of 1.29 ± 0.45 (table-III).

Table-I: Anthropometric data and its correlation with HOMA-IR.

	Case		Control		Total		*p*-value	Correlation with HOMA-IR
	Mean	SD	Mean	SD	Mean	SD		
Age	50.78	14.81	49.70	9.83	50.24	12.52	Not applicable	
Weight	63.70	10.80	65.20	9.85	64.45	10.31		
Height	164.46	8.62	164.76	10.57	164.61	9.60		
BMI	23.38	2.28	24.22	3.40	23.80	2.91	0.005	0.113
Hb Level	10.01	1.94	13.62	1.34	11.83	2.46	0.125	0.551

Table-II: Glycemic Parameter.

	Case		Control		Total		*p*-value	Correlation with HOMA-IR
	Mean	SD	Mean	SD	Mean	SD		
Fasting Glucose	5.59	0.93	5.52	0.74	5.56	0.84	0.073	0.019
Fasting Insulin	19.46	9.13	8.53	3.06	13.94	8.70	<0.001	0.953
HOMA-IR	2.64	1.30	1.15	0.39	1.89	1.21	<0.001	
HbA1C	5.85	0.50	5.29	0.56	5.57	0.60	.261	0.399

Table-III: Correlation of lipid profile with HOMA-IR.

Cholesterol	Case		Control		Total		*p*-value	Correlation with HOMA-IR
	Mean	SD	Mean	SD	Mean	SD		
	4.622	1.007	4.017	0.809	4.317	0.957	0.064	0.061
Triglycerides	1.989	0.650	1.297	0.454	1.640	0.657	0.005	0.250
LDL-C	2.583	0.597	2.209	0.502	2.394	0.580	0.059	0.146
HDL-C	1.014	0.168	1.004	0.203	1.009	0.186	0.329	-0.035

DISCUSSION

Insulin resistance is an early biochemical finding in chronic kidney disease. Although it is present in many patients from the beginning of the disease but at end stage kidney failure almost every patient develops insulin resistance. In this study patients of chronic kidney disease were evaluated for insulin resistance. Renal function tests i.e. serum urea and creatinine showed a *p*-value <0.05 for both parameters and also a positive correlation with HOMA-IR. The mean of fasting insulin level differs significantly for both groups and thus a higher mean HOMA-IR score for the cases was attained. Kobayahsi et al showed the same results for HOMA-IR in Japanese population with a mean of 2.24 ± 1.06[11]. Body mass index and deranged lipids are separate risk factor for the development of insulin resistance. So these two parameters were also included in this study. Our study showed a positive correlation of HOMA-IR with BMI. Chung et al divided the study population into 3 sub-groups and showed that the mean of HOMA-IR was 3.06 in the participants who had a BMI more than 28[12]. Hypertension was also found to be another pivotal factor in the development of chronic kidney disease in the absence of

diabetes. Kobayashi et al showed prevalence seventy percent of the patient suffering from hypertension in chronic kidney disease[11] whereas Toto et al stated that hypertension is present in eighty percent of the patient suffering from chronic kidney disease[13], while our study showed a prevalence of hypertension in 74 percent of the patients suffering from chronic kidney disease.

The serum triglycerides levels of patients showed a positive correlation with HOMA-IR and *p*-value of 0.005. The other variables of lipid profile showed difference of the mean among two groups and a positive correlation with HOMA-IR except HDL-C which is inversely correlated to insulin resistance. These insignificant *p*-values of total cholesterol, LDL-C and HDL-C in this study despite reasonable difference of mean are due to small sample size in our study. Kobayashi et al also demonstrated a mean of 1.68 ± 1.02 for triglyceride[11] and Fliser et al showed apositive correlation of Cholesterol and triglyceride with plasma creatinine levels and also with HOAM-IR[14]. Due to the selection criteria this study showed lower levels of hemoglobin in cases. Hsu et al also showed a decrease in hemoglobin at different levels of creatinine clearance in different ethnic groups[15]. The reason behind that is ninety percent of the erythropoietin is synthesized by the kidney. The anemia develops in chronic kidney disease is directly related to residual renal cell functions[16]. There are numerous independent factors which also play an important role in the development of anemia in chronic diseases. These factors include hepcidin, interluckins (IL1-6) and tumor necrosis factor (TNF-alpha)[17].

CONCLUSION

The presence of Insulin Resistance in majority of chronic kidney disease patients from our own population is a consistent and significant finding, warranting modulated management strategies of these patients. It is reasonable to suggest that cut-off value used for HOMA-IR in this study may prudently be used for insulin resistance in chronic kidney disease.

RECOMMENDATIONS

There is no study regarding establishment of reference values of Homeostatic model of insulin resistance (HOMA-IR), in Pakistani population till date. Literature review shows different cut-off values for different populations. So, a separate study should be conducted for the harmonization of reference values of HOMA score. Due to small sample size HDL, LDL, and total cholesterol showed statistically in-significant difference despite a reasonable variation in the means of two groups. A study based on large sample size can further characterize this observation.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: Global dimension and perspectives. Lancet 2013; 382(9888): 260-72.
2. Ullah K, Butt G, Masroor I, Kanwal K, Kifayat F. Epidemiology of chronic kidney disease in a Pakistani population. Saudi J Kidney Dis Transpl 2015; 26(6): 1307-10.
3. Chronic kidney disease. Available from: https://www. kidney. org/ atoz/ content/ about – chronic - kidney- disease 2017.
4. Liao MT, Sung CC, Hung KC, Wu CC, Lo L, Lu KC. Insulin resistance in patients with chronic kidney disease. J Biomed Biotechnol 2012: 691369.
5. Spoto B, Pisano A, Zoccali C. Insulin resistance in chronic kidney disease: A systematic review. Am J Physiol Renal Physiol 2016; 31(6); F1087-F1108.
6. Matteucci E, Giampietro O, Covolan V, Giustarini D, Fanti P, Rossi R. Insulin administration: Present strategies and future directions for a noninvasive (possibly more physiological) delivery. Drug Des Dev Ther 2015; 9(1): 3109-18.
7. Pandya V, Rao A, Chaudhary K. Lipid abnormalities in kidney disease and management strategies. World J Nephrol 2015; 4(1): 83-91.
8. Keane WF, Tomassini JE, Neff DR. Lipid abnormalities in patients with chronic kidney disease: Implications for the pathophysiology of atherosclerosis. J Atheroscler Thromb 2013; 20(2): 123-33.
9. Mager D, Patterson C, So S, Rogenstein C, Wykes L, Roberts E. Dietary and physical activity patterns in children with fatty liver. Eur J Clin Nutr 2010; 64(6): 628-35.
10. Salgado AL, Carvalho LD, Oliveira AC, Santos VN, Vieira JG, Parise ER. Insulin resistance index (HOMA-IR) in the differentiation of patients with non-alcoholic fatty liver disease and healthy individuals. Arq Gastroenterol 2010; 47(2): 165-9.
11. Kobayashi S, Maesato K, Moriya H, Ohtake T, Ikeda T. Insulin resistance in patients with chronic kidney disease. Am J Kidney Dis 2005; 45(2): 275-80.

12. Chung JO, Cho DH, Chung DJ, Chung MY. Associations among body mass index, insulin resistance, and pancreatic β-cell function in Korean patients with new-onset type-2 diabetes. Korean J Intern Med 2012; 27(1): 66-71.
13. Toto RD. Treatment of hypertension in chronic kidney disease. Semin nephrol; 2005: 25(6): 435-9.
14. Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Prager R, Franek E, et al. Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. Kidney int 1998; 53(5): 1343-47.
15. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the third national health and nutrition examination survey. Clin J Am Soc Nephrol 2002; 13(2): 504-10.
16. Maxwell PH, Eckardt KU. HIF prolyl hydroxylase inhibitors for the treatment of renal anaemia and beyond. Nat Rev Nephrol 2016; 12(3): 157-68.
17. Garrido APA. Resistance to recombinant human erythropoietin therapy studies in experimental models of anemia and chronic kidney disease 2015.