

Insulin Resistance and Risk of Chronic Renal Impairment in Non and Diabetic Iraqi Adults

Dr. Mohammed Kamal Rasheed; F.I.C.M.S (Consultant Urologist), Assist Prof. Dr. Manal kamal Rasheed; Ph.D, Assist Lec. Rana Ali Hamdi

- *Al-Karama hospital.*

- *Clinical Biochemistry/ Department of biochemistry collage of medicine – university of Baghdad.*

- *Department of biochemistry/collage of Medicine/ University of Baghdad.*

Abstract

B **ackground:** Patients with chronic renal impairment (CRI) present a high prevalence of insulin resistance (IR). Chronic Renal Failure (CRF) is a syndrome of persistent renal impairment involving loss of glomeruli, tubular and nephron function. Dialysis may be used as a lineal treated to patients who have suddenly but temporarily, lost their kidney function (acute renal failure) or as a regular region for quite stable patients who have permanently lost their kidney function.

Central obesity, particularly visceral adiposity is considered to play a major role in causing insulin resistance and type 2 diabetes mellitus. Insulin resistance is characterized by a decrease in the insulin effect on glucose transport in muscle, adipose tissue and liver.

Aim of the study: The purpose of this study is to investigate the relationship between the level of serum Insulin and Homeostasis model Assessment (HOMA)-Insulin resistance levels to risk of chronic renal impairment (CRI)

Materials and methods:

This study include 50 patients (32 males and 18 females) who have chronic renal impairment disease with and without T2DM aged between (30-70) years, the mean age as (mean± SD) is (56.4± 10.7),(52.8±18.5) years who attended the hemodialysis (HD) at the artificial kidney in AL- Karama Hospital and 30 normal volunteers aged mach with (30-70 years)act as control. The mean age is (57±6) years .This study examined the relationship between fasting serum glucose ,insulin ,Homeostasis Model Assessment (HOMA) – Insulin resistance in CRI patients . Insulin was measured by (enzyme immunosorbant assay) .

Results: Mean systolic BP and body max index BMI values were significantly higher among persons with diabetes compared with their counters without diabetes and control. Diabetic participants had higher mean levels of serum glucose, serum insulin, HbA1c and HOMA-insulin resistance compared with non diabetic participants and control. Diabetic participants also had a higher prevalence of elevated serum creatinine, urea and cholesterol level with CRI compared with their counterparts without diabetes and control .

Conclusion: This study documents the presence of a strong, positive correlation between insulin resistance and chronic renal impairment among non diabetic patients .These data demonstrate that patients with chronic renal impairment have a high prevalence of IR, insulin levels .

Key words: chronic kidney disease, Insulin resistance & non-diabetes

Introduction

Patients who have chronic renal impairment (CRI) present a high prevalence of metabolic syndrome (MS)

and insulin resistance (IR) ⁽¹⁾, which are associated with a high risk for diabetes ⁽²⁾ and cardiovascular disease (CVD) ⁽³⁾ and high all-cause mortality ⁽⁴⁾. At the same time, cross-sectional and prospective ⁽⁵⁾

studies have demonstrated that metabolic syndrome MS is independently associated with an increased risk for CRI in adults without diabetes, and IR is already present in patients with mild degrees of renal dysfunction⁽⁶⁾. This supports a close relationship between CRI and metabolic syndrome MS/IR syndrome and can contribute to a high risk for CVD related to early stages of CRI⁽⁶⁾. Metabolic syndrome MS is a constellation of interrelated risk factors of metabolic origin that identifies individuals at a high, long-term risk for CVD and type 2 diabetes (T2D). The various MS definitions include the same core criteria of: obesity, IR, dyslipidemia and hypertension, The WHO, for instance, requires evidence of IR or DM to make a diagnosis of MS⁽⁷⁾

Insulin resistance: is the condition in which normal amounts of insulin are inadequate to keep blood glucose in a normal range. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake, whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often lead to metabolic syndrome and type 2 diabetes⁽⁸⁾ High levels of insulin cause several problems: One of them is high blood pressure⁽⁹⁾.

Several small clinical studies have noted insulin resistance in non diabetic patients with mild renal dysfunction⁽¹⁰⁾. However there are sparse data on the relation among insulin resistance, compensatory hyperinsulinemia, and risk of chronic renal impairment (CRI) in non diabetics⁽¹¹⁾.

We took advantage of the representative sample of Iraqi adults who participated in AL-Karama hospital to examine the relationship among glucose, Insulin, Insulin resistance index and the risk of CRI.

Materials and methods

The study design includes a wide range of age group. Blood samples were collected from 50 patients (32 males & 18 females) with (mean± SD) age of (56.4± 10.7) years with diabetic type 2, (52.8±18.5) years without diabetic type 2 aged between (30-70) years who have chronic renal impairment undergoing hemodialysis (HD) at the artificial kidney in AL-Karama hospital through the period from March to August 2012 and thirty healthy individual(10 female & 20 male) as a control group with a (mean± SD) age of (57.0±6.0) years.

A sample of 80 patients with and without type 2 diabetes mellitus who were 20 year and older were selected to take part in the morning visits at which fasting blood specimen were obtained. Persons without a fasting blood sample (n=30), and those with kidney failure according to national Kidney Foundation definition of an estimated GFR<15 ml/min per 1.73 m² (n=10) were excluded from the current analysis. We were able to utilize experience from 25 person with and 25 without diabetes for the main analyses.

All data were collected by administration of a standardized questionnaire during a hospital interview by conduct of a detailed physical examination with collection of the blood specimens Information on a wide variety of sociodemographic ,medical history, nutrition history, and family history questions, such as reported age , gender, years of duration of disease, history of smoking and hypertension, use of antihypertensive medication.

Blood pressure for any individual participant was calculated as the average of all available systolic and diastolic readings. Hypertension was defined as the presence of a mean systolic BP≥ 140mmHg and /or diastolic BP≥90 mmHg and /or use of antihypertensive medication. Body weight and height were measured according to a standard protocol,

and body mass index was calculated as an index for obesity.

A blood sample was collected after an overnight fast ≥ 8 hrs. Blood glucose level was measured with enzymatic oxidation⁽¹²⁾, serum insulin level by means of a ELISA⁽¹³⁾. Serum total cholesterol was measured enzymatically using a commercially available reagent mixture⁽¹⁴⁾, and creatinine was analyzed by the modified kinetic Jaffe reaction method⁽¹⁵⁾.

A homeostasis Model Assessment (HOMA) was used to evaluate insulin resistance⁽¹⁶⁾. The values for a patient can be calculated from the fasting concentrations of insulin and glucose using the following formula: fasting serum insulin ($\mu\text{u/ml}$) x fasting blood glucose (mmol/L)/22.5⁽¹⁶⁾.

Statistical analyses

Data are presented as mean \pm S.D. Differences between two groups were analyzed by the unpaired Student's *t*-test,

A *P* value of <0.05 was considered statistically significant. Simple correlation coefficients between HOMA and various parameters were calculated⁽¹⁷⁾.

Results

General characteristics of the study participants are presented by diabetic status in table 1 on average non-diabetic patients were about match age to diabetic patients. The percentages of females were lower in those without diabetes versus those diabetes and control. Mean systolic BP in diabetic patients with chronic renal impairment (135.1 mm Hg) significant higher than non diabetic patients with chronic renal impairment (120 mm Hg) and controls (120 mmHg). Body max index values were significantly higher among persons with diabetes (31.2 \pm 3.5) compared with their counters without diabetes (23.8 \pm 3.7) and control (25 \pm 2.3). Diabetic patients with chronic renal impairment had significant higher mean levels of serum glucose, serum insulin, HbA1c and HOMA-insulin resistance (8.5 \pm 2.9), (24.0 \pm 21.0), (7.8 \pm 1.83), (9.05 \pm 7.9) respectively as compared with non diabetic patients with chronic renal impairment (4.8 \pm 1.0), (13.3 \pm 12.19), (5.18 \pm 0.27), (3.2 \pm 3.4) and control (4.9 \pm 0.7), (7.5 \pm 4.7), (5.08 \pm 0.25), (1.6 \pm 1.1). Diabetic patients with chronic renal impairment also had a higher significant level of serum cholesterol (226.7 \pm 48.1) as compared with non diabetic patients with chronic renal impairment (208.6 \pm 36.8), and control (185.1 \pm 29.4).

Table 1: Characteristics of the patient study participants by diabetes status

Variable	Diabetes (n=25)	Non-diabetes n=25	Control n=30	P -value
Age (yr)	56.4 \pm 10.7	52.8 \pm 18.5	57 \pm 6	
female %	25	12	18	
Systolic Bp mmHg	135.1*	120	120	P<0.05
Hypertension%	2.8	0.9		
Body mass index (kg/m ²)	31.2 \pm 3.5*	23.8 \pm 3.7	25 \pm 2.3	P<0.05
Fasting blood glucose (mmol/l)	8.5 \pm 2.9*	4.8 \pm 1.0	4.9 \pm 0.7	P<0.05
Blood urea (mmol/L)	26.6 \pm 8.1	25.1 \pm 10.9	4.2 \pm 1.1*	P<0.05
Creatinine mmol/l	577.8 \pm 136.6	573.4 \pm 260.5	85 \pm 17.68*	P<0.05
HbA1c%	7.8 \pm 1.83*	5.18 \pm 0.27	5.08 \pm 0.25	P<0.05
Serum Insulin $\mu\text{u/ml}$	24.0 \pm 21.0*	13.3 \pm 12.19*	7.5 \pm 4.7*	P<0.05
HOMA-Insulin resistance	9.05 \pm 7.9*	3.2 \pm 3.4*	1.6 \pm 1.1*	P<0.05
Serum cholesterol mg/dl	226.7 \pm 48.1*	208.64 \pm 36.8*	185.1 \pm 9.4	P<0.05
Chronic kidney disease%	9.4	1.9	-	P<0.05

*Star indicate there is significant correlation $P < 0.05$.

But no significant difference level of serum creatinine and urea of diabetic patients with chronic renal impairment and (577.8± 136.6) (26.6±8.1) as compared with their counterparts without diabetic patients with chronic renal impairment (573.4±260.5), (26.6±8.1) ,but significant as compared with control (85±17.68), (4.2±1.1).

Absent of star indicate no significant correlation.

The mean value of main biochemical parameters in type 2 diabetes with chronic renal impairment as compared to controls, as shown in figure 1. highly significant level of all biochemical parameters as compared to controls.

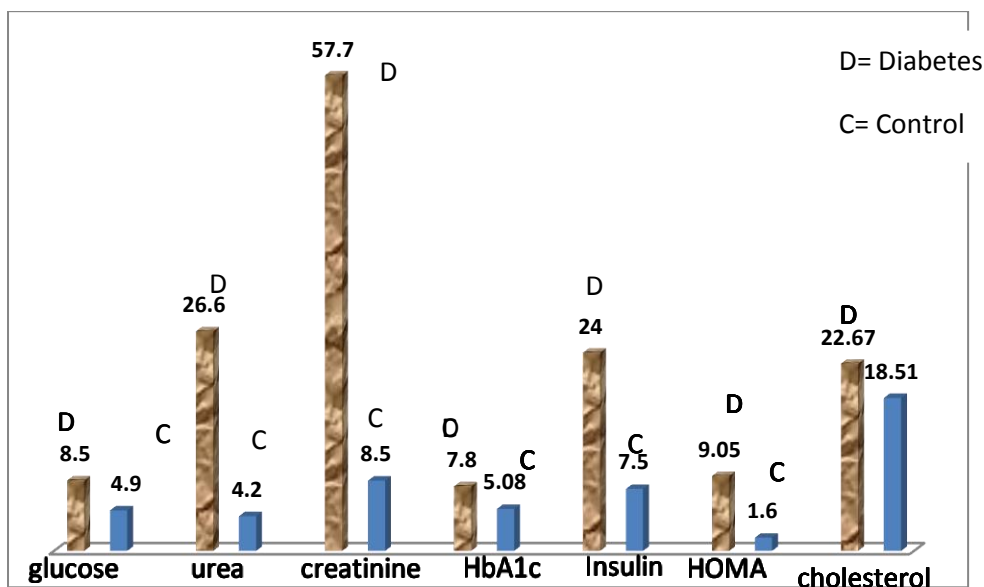


Figure 1: mean value of main biochemical parameters in type 2 diabetes patients chronic renal impairment and control .

The mean value of main biochemical parameters in non diabetes patients with chronic renal impairment as compared to controls , as shown in figure 2. no significant difference in levels of glucose , HbA1c . But significance elevation of urea ,creatinine , insulin , HOMA and cholesterol.

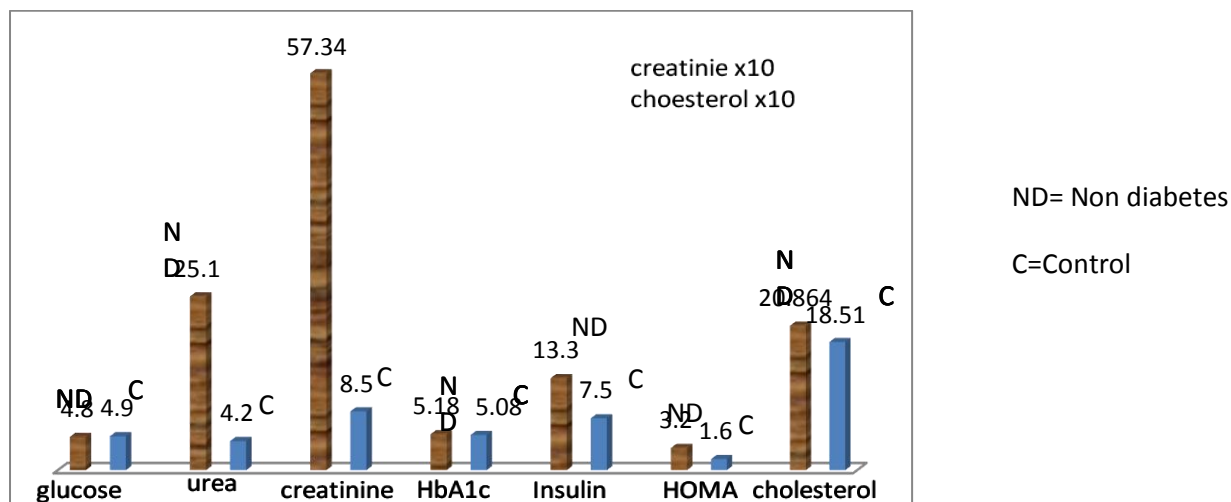


Figure 2: mean value of main biochemical parameters in non diabetes patients chronic renal impairment and control .

The shapes of the association between serum HOMA- insulin resistance and serum insulin versus BMI in type 2 diabetes chronic renal impairment were highly significant correlation between HOMA and BMI $r=0.7, p<0.05$ as shown in figure 3 , and significant correlation between insulin and BMI $r=0.4, p<0.05$ as shown in figure 4.

The association between serum HOMA-insulin resistance and serum insulin versus fasting serum glucose in type 2 diabetes

chronic renal impairment were significant correlation between HOMA and fasting serum glucose $r=0.4, p<0.05$ as shown in figure 5 and non significant correlation between serum insulin and fasting serum glucose $r=0.1, p>0.05$. as shown in figure 6.

Highly significant positive correlation between serum HOMA-insulin resistance and serum insulin in diabetic chronic renal impairment patients $r=0.9, p<0.05$ as shown in figure 7.

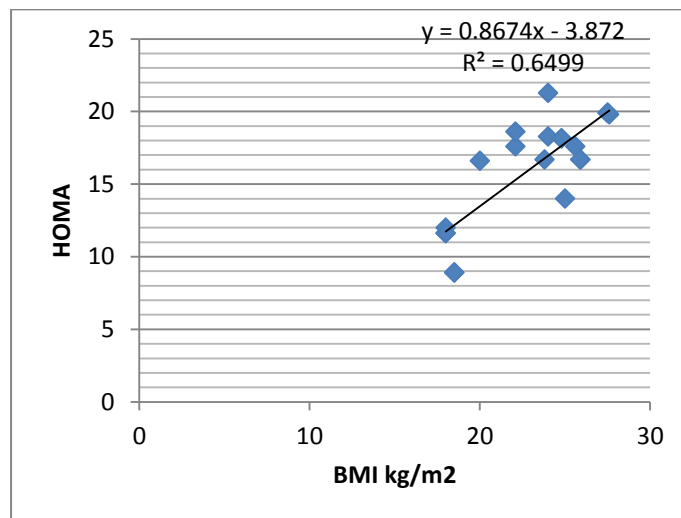


Figure 3 :Correlation between insulin homeostasis HOMA and BMI in diabetes patients

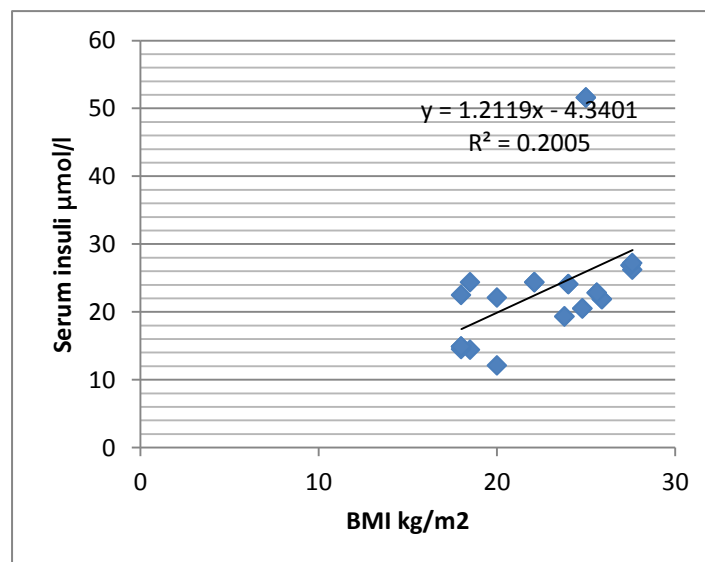


Figure 4:Correlation between Serum insulin and BMI in diabetes patients

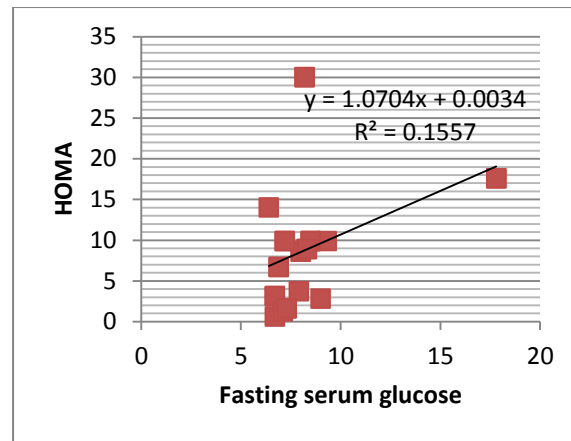


Figure 5:Correlation between insulin resistance HOMA and fasting glucose in diabetes patients

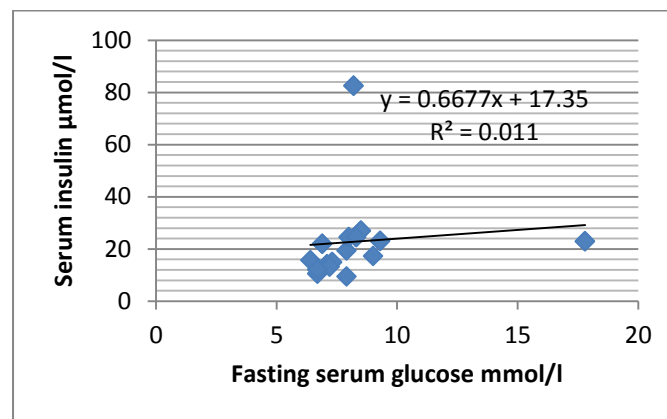


Figure 6: Correlation between Serum insulin and fasting glucose in diabetes patients

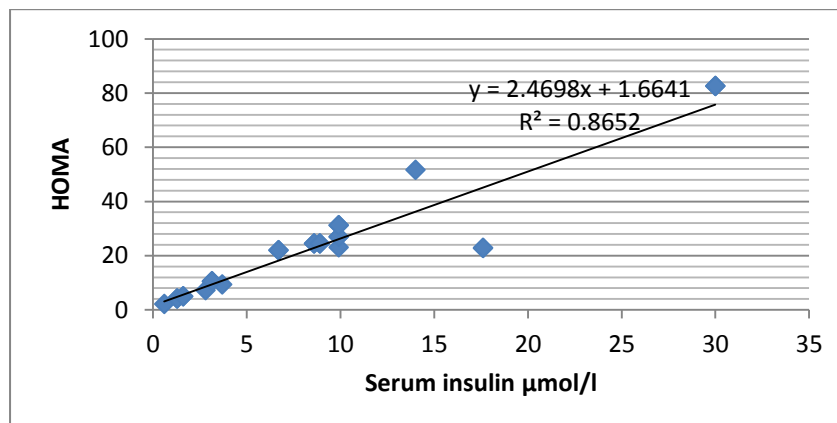


Figure7:Correlation between Serum insulin and HOMA-IR in diabetes chronic renal impairment patients

The shapes of the association between serum HOMA- insulin resistance and serum insulin versus BMI in non diabetes chronic renal impairment were significant between HOMA and BMI $r=0.4, p<0.05$, and highly significant between insulin

and BMI $r=0.7, p<0.05$.as shown in figures 8,9.

The association between serum HOMA- insulin resistance and serum insulin versus fasting serum glucose in non diabetes chronic renal impairment were highly

significant correlation between HOMA and fasting serum glucose $r=0.6$, $p<0.05$ and significant correlation between serum insulin and fasting serum glucose $r=0.5$, $p<0.05$ as shown in figure 10,11.

Highly significant positive correlation between serum HOMA-insulin resistance and serum insulin in non diabetic CRI patients $r=0.9$, $p<0.05$ as shown in figure 12.

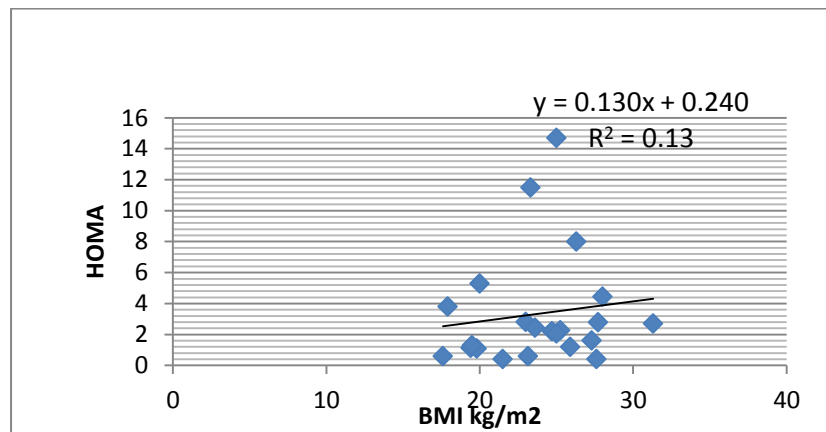


Figure 8: Correlation between insulin resistance HOMA and BMI in non diabetes patients CRI

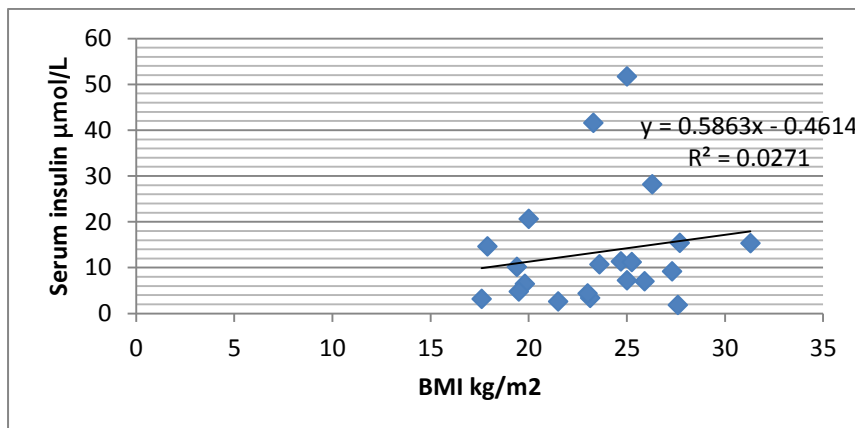


Figure 9: Correlation between Serum insulin and BMI in non diabetes patients CRI

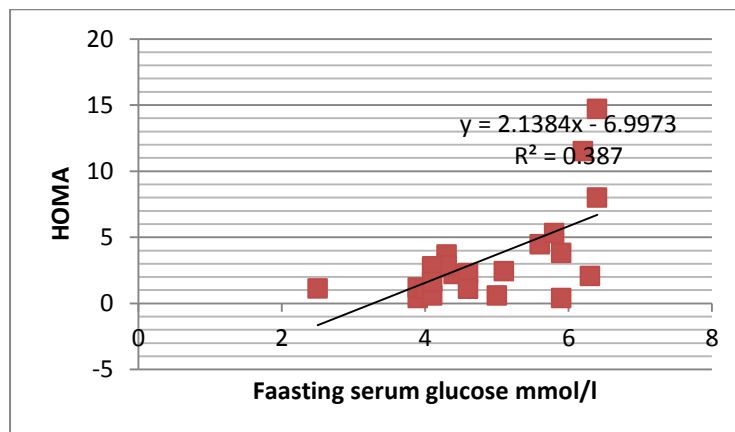


Figure 10: Correlation between insulin resistance HOMA and fasting serum glucose in non diabetes patients CRI patients

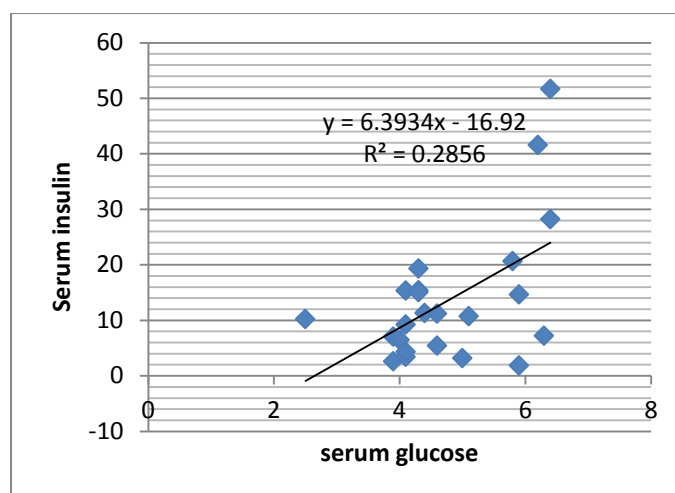


Figure 11: Correlation between Serum insulin and fasting glucose in non diabetes patients **CRI**.

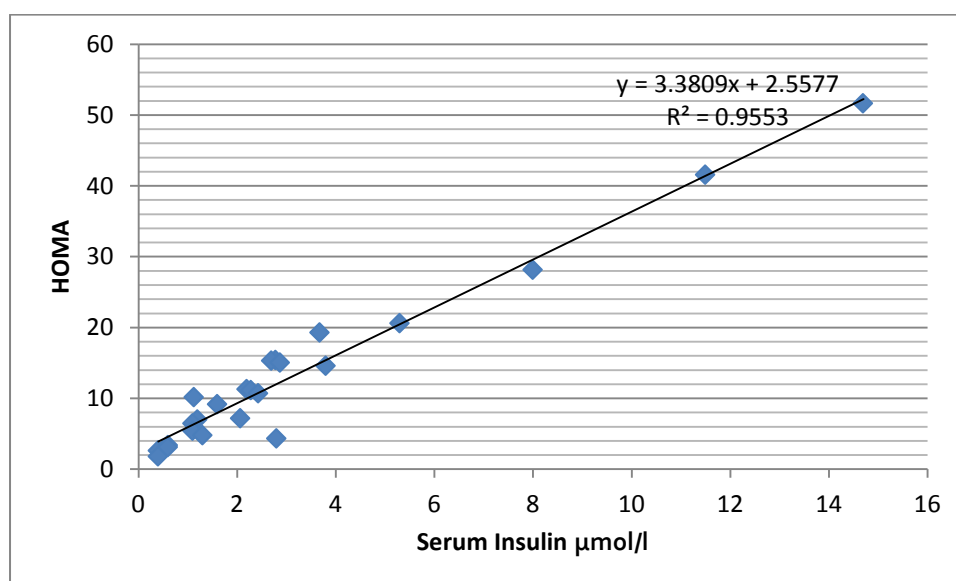


Figure 12: Correlation between Homeostasis HOMA and insulin level in non diabetic chronic renal impairment.

Discussion

The present study identified a strong positive significant correlation between insulin resistance, insulin level, fasting glucose and obesity with risk of chronic kidney disease in non-diabetes patients. This relationship was independent of age, gender, and other potential risk factors for chronic renal impairment (CRI), such as Bp, total cholesterol.

Certain limitations should be considered in the interpretation in these findings. First, the cross sectional study design the ability to draw inferences regarding causality among insulin resistance, hyperinsulinemia, and CRI. For instance, these findings do not allow one to determine whether insulin resistance and concomitant hyperinsulinemia contribute to the initiation or progression of CRI, whether impaired renal function contributes to the development of insulin

resistance, or whether insulin resistance is merely a marker for other causes of CRI.

Second, although the liver is the major site for insulin degradation, the kidney plays an essential role in the clearance and degradation of circulating insulin⁽¹⁸⁾. In addition, experiments in laboratory human subjects have indicated that the kidney plays an important role in glucose metabolism⁽¹⁹⁾. Human studies indicate that acute renal failure results in a reduction in the systemic removal of insulin⁽²⁰⁾. Therefore the elevated level of serum insulin observed in our study in CRI patients may be a consequence of a decline in renal function.

There is a positive correlation between BMI of diabetes patients and insulin resistance as shown in figure (3), this means the increase in BMI was a cause for insulin resistances and this will lead to hyperinsulinemia and an increase in HOMA value according to the HOMA equation. That the same is in non-diabetic patients CRI.

In addition, this data indicates that both serum insulin, HOMA and serum glucose levels are increased in patients with CRI, which suggests the presence of insulin resistance among these patients. A reduced clearance of insulin in acute renal failure patients has been associated with a decrease in levels of blood glucose⁽²¹⁾.

Furthermore, using a more precise method for measurement of insulin resistance (minimal model technique), insulin resistance has been documented in non-diabetic CRI patients⁽²²⁾. In these studies, plasma insulin levels were highly correlated with measured insulin resistance⁽²²⁾ as shown in figure (7,11).

Finally, serum creatinine levels and calculated GFR were used to identify and classify kidney disease in our study. Although insulin or creatinine clearance techniques may provide more sensitive estimates of renal function, serum creatinine has been used widely in large epidemiologic studies and in clinical

practice for estimation of renal function. As such, the findings from our study are applicable to clinical and public health practice settings.

Several prospective cohort studies have documented that diabetes is associated with an increased risk of diabetic and non-diabetic ESRD⁽²³⁾. Clinical trials have also demonstrated that intensive glycemic control slows the progression of diabetic nephropathy in both type 1 and type 2 diabetic patients⁽²⁴⁾. In this study, a HbA1c level greater than or equal to 5.7% was associated with an elevated risk of CRI. These findings support the theory that intensive blood glucose control in diabetics as well as a reduction of blood glucose level in persons with an impaired fasting glucose may be important strategies for primary prevention of CRI and slowing the progression of CRI.

There are sparse data on the relationship between insulin resistance and CRI in non-diabetic patients.

There are small clinical studies that suggest insulin resistance might be present in kidney disease patients without diabetes⁽²⁴⁾. Vareesangthip et al⁽²¹⁾ found that insulin sensitivity was significantly lower and fasting plasma insulin was significantly higher in 15 adult polycystic kidney disease patients compared with 20 age and sex matched subjects with normal renal function. Fliser et al⁽⁶⁾ examined 29 patients with adult polycystic kidney disease in different stages of renal failure, insulin sensitivity was significantly lower and plasma insulin concentration was significantly higher in the kidney disease patients compared with their matched controls.

Several epidemiologic studies have reported a positive relationship between insulin resistance and risk of microalbuminuria in non-diabetic patients^(25,26). In the insulin resistance atherosclerosis study, Mykkanen et al, examined the relationship of insulin sensitivity estimated by a frequently

sampled intravenous glucose tolerance test and the minimal model and fasting plasma insulin concentration, to microalbuminuria in study 982 non diabetic patients aged 40 to 69 yr. They reported that decreased levels of insulin sensitivity were related to an increased prevalence of microalbuminuria⁽²⁵⁾.

Fujikawa et al⁽²⁶⁾ conducted a 6 yr. prospective study to examine the relationship between insulin resistance and risk of microalbuminuria in 116 non diabetic Japanese Americans living in Hawaii. Their study indicated that fasting insulin levels and HOMA insulin resistance were significantly higher in participants developed microalbuminuria during follow-up compared with those who did not. They concluded that insulin resistance appeared earlier than the appearance of microalbuminuria⁽²⁶⁾.

This finding of a positive and significant association among insulin resistance, hyperinsulinemia, and kidney disease in non diabetic patients have both clinical and public health implications. First, they suggest that it may be beneficial to detect and treat insulin resistance and concomitant hyperinsulinemia in non diabetic patients with CRI.

Second, they suggest that a more aggressive approach to reducing insulin resistance in individual patients and in population would substantially lower the risk of CKD. Many lifestyle modification measures, such as a reduction in dietary fat intake and an increase in physical activity, have been demonstrated to reduce insulin resistance.

In conclusion, This study documents the presence of a strong, positive, independent, and dose response relationship between insulin resistance and CRI among non diabetic patients. These findings combined with knowledge from previous studies suggest that the insulin resistance and concomitant hyperinsulinemia are presented in CRI patients without clinical diabetes. Detection and treatment of

insulin resistance should be considered even in non diabetic patients with CRI.

Prevention and treatment of insulin resistance in community might substantially reduce the societal burden of CRI.

References

1. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 140:167–175 (2004).
2. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM: The metabolic syndrome as predictor of type 2 diabetes. *Diabetes Care* 26: 3153–3159 (2003).
3. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS: Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation* 109: 42–46 (2004).
4. Srinivasan Beddhu, Sagar U. Nigwekar, Xilulian Ma, et al: Associations of resting heart rate with insulin resistance, cardiovascular events and mortality in chronic kidney disease: *Nephrol Dial Transplant*. August; 24(8): 2482–2488 (2009).
5. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 16: 2134–2140 (2005).
6. Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Franek E, Ritz E: Insulin resistance and hyperinsulinaemia are present already in patients with incipient renal disease. *Kidney Int* 53: 1243–1247 (1998).
7. Day C, Metabolic syndrome or what you will definition & epidemiology: *Diabetes Vasc Dis Res*, 4:32-8 (2007).
8. Aida A. Korish, Maha M. Arafah, Catechin: Combined with vitamins C and E ameliorates insulin resistance (IR) and atherosclerotic changes in aged rats with chronic renal failure (CRF) *Archives of Gerontology and Geriatrics* 46 25–39 (2008).
9. Reusch JE. "Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol*. 6;40:1609-1614 (2002).
10. Hjelmessaeth J, Hartmann A: Insulin resistance in patients with adult polycystic kidney disease. *Nephrol Dialysis Transplant* 14:2521-2522(1999).
11. Paul A. Sobotka, 1,2,7 Felix Mahfoud, 3 Markus P. Schlaich, 4 Uta C. Hoppe, 5 Michael

- Böhm, S and Henry Krum: Sympatho-renal axis in chronic disease, *Clin Res Cardiol*. December; 100(12): 1049–1057 (2011).
12. Pagana, K.D. & Pagana, T.J.: *Mosby's Manual of Diagnostic and Laboratory Tests*, 3rd ed. 8, (2006).
 13. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. "Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J". *Clin. Endocrinol. Metab.* ; 85: 2402-2410(2000).
 14. Richmond W, Preparation and Properties of a Cholesterol Oxidase from *Nocardia* sp. and Its Application to the Enzymatic Assay of Total Cholesterol in Serum. *Clinical Chemistry*; 19: 1350-1356:(1973)
 15. Henry, R.J.: *Clinical Chemistry, Principles and techniques*, second edition Harper and Row,;525. (1974).
 16. Matthews DR, Hosker JP, Rudenski AS, Naylor S, Homeostasis model assessment: Insulin resistance and β -cell function from fasting plasma glucose and insulin concentration. In *man.*: *Diabetologia* 28:412-419, (1985).
 17. Daniel WW.: *Biostatistics: Basic concepts & methodology for the Health sciences*. 9th Edition, John Wiley & Sons Inc. : 170–400, (2010)
 18. Craig S. Stump, Physical Activity in the Prevention of Chronic Kidney Disease, *Cardiorenal Med.* August; 1(3): 164–173 (2011).
 19. K. Štefík, A. Spustová, A. Krivosíková, A. Oksal, V. Gazdíková, V. Féelesová, D. Žuríková: Insulin Resistance and Vitamin D Deficiency in Patients With Chronic Kidney Disease Stage 2-3, *Physiol. Res.* 60: 149-155, (2011).
 20. William G Petchey, Ingrid J Hickman, Emma Duncan, Johannes B Prins, et al : The role of 25-hydroxy vitamin D deficiency in promoting insulin resistance and inflammation in patients with Chronic Kidney Disease: a randomised controlled trial, *BMC Nephrol.* 10: 41(2009).
 21. Vareesangthip K, Tong P, Wilkinson R, Thouras TH: Insulin resistance in adult polycystic kidney disease. *Kidney Int* 52:503-508,(1997).
 22. Francisco Caraveca, Isis Cerezo, Rosa Macías Elena García : Insulin resistance in chronic kidney disease: its clinical characteristics and prognostic significance: *Nefrología*; 30(6): 661-668(2010)
 23. Brancati FL, Whelton PK, Randall BL, Neaton JD: Risk of end-stage renal disease in diabetes Mellitus: L Prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. *JAMA* 278:2069-2074 (1997).
 24. UK Prospective Diabetes study Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications and risk of complications in patients with type 2 diabetes. *Lancet* 352:837-853(1998).
 25. Hjelmšaeth J, Hartmann A: Insulin resistance in patients with adult polycystic kidney disease. *Nephrol Dialysis Transplant* 14: 2521-2522 (1999).
 26. Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM: Microalbuminuria is associated with insulin resistance in nondiabetic subjects: The insulin resistance atherosclerosis study. *Diabetes* 47: 793-800 (1998) [Abstract]
 27. Fujikawa R, Okubo M, Egusa G, Kohno N: Insulin resistance precedes the appearance of albuminuria in non-diabetic subjects: 6 years follow-up study. *Diabetes Res Clin Pract* 53: 99-106, (2001) [CrossRef] [Medline].