Evaluation of C-peptide and insulin resistance in nondiabetic patients with chronic kidney disease

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Received 22 November 2018
Revised 07 January 2019
Accepted 12 January 2019
Published 11 June 2021

Journal of Current Medical Research and Practice
2021, 6:134–139

Introduction
Chronic kidney disease (CKD) is a pathophysiologic process with several etiologies, resulting in remarkable decrease in nephron number and function. Patients with CKD have reduced life span, and a considerable proportion of these individuals die owing to cardiovascular complications. In CKD, degradation of insulin in nonrenal tissues such as liver and muscle is impaired, and the half-life of insulin is prolonged, so a state of hyperinsulinemia with increased C-peptide levels occurs in patients with CKD.

Aim
To assess serum insulin and C-peptide along with homeostasis model assessment-insulin resistance (IR) in nondiabetic patients with CKD.

Patients and methods
The study included 70 nondiabetic patients with CKD and 20 controls. Fasting serum C-peptide and insulin were done by enzyme-linked immunosorbent assay technique, and IR was calculated using the homeostasis model assessment-IR formula.

Results
Fasting serum levels of insulin and C-peptide were statistically significantly higher in nondiabetic patients with CKD compared with control individuals. Patients with stage 4 CKD had a statistically significant increase in fasting insulin levels compared with stage 3 patients, whereas there was no statistically significant difference between stage 5 and stage 4 patients. Fasting C-peptide levels show no statistically significant difference between the different stages of patients with CKD. IR levels were statistically significantly higher in the patient group compared with the controls. Patients with stage 4 CKD had statistically significantly higher levels of IR compared with stage 3 patients. There was no statistically significant difference between patients with stage 4 and stage 5 CKD.

Conclusion
The study demonstrates an increase in the IR in nondiabetic patients with CKD.

Keywords:
chronic kidney disease, C-peptide, insulin resistance

J Curr Med Res Pract 6:134–139

2357-0121

Introduction

Chronic kidney disease (CKD) is a broad term describing any abnormality of kidney structure or function. It is often asymptomatic in the early stages and coexists with other chronic illnesses, such as diabetes and hypertension, cardiovascular disease, end-stage renal failure, anemia, insulin resistance (IR), and metabolic bone disease [1].

CKD was classified according to the glomerular filtration rate (GFR) to five stages

(1) Stage 1: normal GFR above 90 ml/min/1.73 m^2, with persistent microalbumin.
(2) Stage 2: GFR of 60–89 ml/min/1.73 m^2, with persistent microalbumin.
(3) Stage 3: GFR of 30–59 ml/min/1.73 m^2.
(4) Stage 4: GFR of 15–29 ml/min/1.73 m^2.
(5) Stage 5: GFR below 15 ml/min/1.73 m^2 or end-stage renal disease [2].

IR is the reduced sensitivity of target organs to the biologic effects of insulin. This means that a normal dose of insulin produces less than normal biological effect. Insulin is the main regulator of glucose homeostasis. The major functions of insulin include stimulation of glucose uptake by skeletal muscles, inhibition of hepatic gluconeogenesis, and inhibition of lipolysis in adipose tissues [3].

Distinct and separate from diabetes, the presence of IR and compensatory hyperinsulinemia is powerfully associated with the presence of CKD different stages [4]. In CKD, IR results from substandard uptake, metabolism, or storage of glucose in the target

tissues (muscles, liver, and adipose tissue) because of changes in insulin signaling at receptor or postreceptor level. The primary site for glucose disposal is the muscle, and IR in uremia depends on peripheral resistance to the action of insulin at postreceptor level [5].

Remarkably, several clinical consequences have been linked to IR. Indeed, IR may promote endothelial dysfunction and increased cardiovascular mortality. Although evidence is not conclusive, some data also suggest that IR is a strong factor responsible for CKD incidence and progression. Based on these lines of evidence, it is conceivable that IR represents a changeable risk factor and a potential therapeutic target to improve CKD outcomes [6].

In uremia, degradation of insulin in nonrenal target tissues such as liver and muscle is impaired, and the half-life of insulin is prolonged. It is hypothesized that accumulation of uremic toxins may inhibit insulin degradation particularly by the liver, although the liver is responsible for removal of ~ 50% of the insulin secreted into the portal circulation [7]. This results in a state of hyperinsulinemia with increased C-peptide levels in patients with CKD [8].

There are many methods identified for the quantification of IR. Mathematically derived nonlinear equations are used to quantify IR and the functions of the beta-cell from basal (fasting) glucose and insulin (or C-peptide) levels [9]. The homeostasis model assessment (HOMA) model has become a commonly used clinical and epidemiological tool, and when used appropriately, it yields valuable accurate data. It is a model of the relationship of insulin and glucose dynamics that predicts fasting steady-state glucose and insulin concentrations for a large range of possible combinations of IR and β-cell function [10]. It was described by Matthews *et al.* [11], using the following formula:

$$\text{HOMA - IR}\left(\text{mmol / L} \times \text{mU / L}\right) = \text{fasting glucose}$$
$$\left(\text{mmol / L}\right) \times \text{fasting insulin}\left(\text{mU / L}\right) / 22.5$$

Therefore, whether the progression of CKD could be delayed by improving the outcome/course/prognosis of IR is valuable for more studies [12].

C-peptide is produced in equal amounts to insulin, so it can be used to evaluate endogenous insulin secretion, including in patients who are insulin treated [13]. Approximately 50% of C-peptide produced is cleared by the kidneys, the majority of which is degraded via peritubular uptake with ~ 5% of total C-peptide produced excreted unchanged in the urine. So, blood levels of C-peptide can be falsely elevated in renal impairment diseases [14].

Aim

The aim was to assess the serum insulin and C-peptide along with HOMA-IR in nondiabetic patients with CKD and to study the correlation of these parameters with the GFR.

Patients and methods

This was a case–control study. The study included 70 nondiabetic patients with CKD. Their age ranged from 18 to 78 years. Overall, 32 were females and 38 were males. The patients were recruited from the outpatient clinic of Internal Medicine Department of Assiut University Hospital. In addition, 20 healthy individuals were taken as controls, and their age ranged from 23 to 29 years; four of them are males and the rest are females. The study was approved by the Institutional Review Board, and informed consents were obtained from patients and control individuals.

Patients with the following conditions were excluded:

Diabetic patients or those who were on dialysis and patients with any other chronic or malignant disease.

Patients with the following conditions were included:

Nondiabetic patients with CKD who were not on dialysis.

Sample collection, storage, and handling

(1) Fasting blood samples:
Overall, 7 ml of venous blood after fasting for 16 h was collected under complete aseptic conditions and divided into the following:

(a) Two milliliters was collected into EDTA-containing tube for complete blood count and glycated hemoglobin (HbA1c).
(b) Five milliliters was collected in plain tube without anticoagulant; blood was allowed to clot for 15 min at 37°C, and serum was separated by centrifugation at 3000 rpm for 10 min. Serum was used for the assay of kidney function tests, fasting glucose, lipid profile, fasting insulin, and fasting C-peptide.

(2) Morning urinary samples were collected for measuring urinary albumin/creatinine ratio.

The following investigations are done for all subjects

(1) Complete blood count: it was done on CELL-DYN 3700-Abbott (Bellport, NY 11713 US).
(2) Kidney function (serum urea and creatinine) test: it was done on Dimension RL-MAX.
(3) HbA1c: it was done on COBAS INTEGRA 400 plus (Roche, Berlin, Germany).
(4) Fasting blood glucose: it was done on Dimension RL-MAX.
(5) Lipid profile: it was done on COBAS INTEGRA 400 plus.
(6) Urinary albumin/creatinine ratio: it was done on FUS-100/H-800 Automatic Urinalysis System (Dirui Industrial Co., Ltd. Chang Chun Jilin Sheng 130103 China).
(7) Estimated glomerular filtration rate (eGFR): GFR was calculated using the Modification of Diet in Renal Disease formula available online.
(8) Fasting serum insulin level: it was measured by enzyme-linked immunosorbent assay technique and read on Stat-Fax 303 plus (GMI, 6511 Bunker Lake Blvd, Ramsey, MN 55303, USA). The kit used was HUMAN INSULIN Enzyme Immunoassay Test Kit Catalog Number: 10801 (Chemux Bioscience, South San Francisco, California USA).
(9) Fasting serum C-peptide level: it was measured by enzyme-linked immunosorbent assay technique and read on Stat-Fax 303 plus. The kit used is C-PEPTIDE Cat. No.: CAN-C-P-4380 (Diagnostics Biochem Canada Inc., Ontario, Canada)
(10) Calculation of IR (for patients and control subjects): HOMA-IR was done using the following formula:

HOMA-IR = fasting serum insulin (μIU/ml)×fasting plasma glucose (mg/dl)/405.

Statistical analysis

All statistical analyses were performed using Statistical Package for the social sciences, version 18 (SPSS v18 software; SPSS Inc., Chicago, Illinois, USA). Categorical variables were described by number and percent, where continuous variables were described by mean and SD. χ^2 test was used to compare between categorical variables, whereas we compared between continuous variables by unpaired *t* test. Pearson correlation coefficient was used to assess the association between continuous variables. A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

In the present study, we examined a random sample of 70 nondiabetic patients with CKD. Their age ranged from 18 to 78 years, with mean ± SD of 34.47 ± 10.63 years. Overall, 37 of them are males and 33 of them are females. Moreover, 20 healthy control individuals were included. Their age ranged from 23 to 29 years, with mean ± SD 26.05 ± 1.57 years. Overall, four of them are males and 16 of them are females (Table 1).

Regarding the complete blood picture, there was a statistically significant increase in white blood cell count in patients compared with control individuals, with *P* value 0.023. Moreover, there was a statistically highly significant decrease in hemoglobin level in patients compared with control individuals, with *P* value less than 0.002. There was no statistically significant difference in platelet count between patients and control groups, with *P* value of 0.730 (Table 2).

Regarding the levels of urea, creatinine, albumin/creatinine ratio, and eGFR, there was a statistically highly significant increase in urea, creatinine, and albumin/creatinine ratio in patients compared with controls, whereas there was a statistically significant decrease in eGFR in patients compared with control individuals, with *P* value less than 0.001 (Table 3).

Concerning the lipid profile, there was a statistically highly significant increase in triglyceride levels in patients compared with control individuals, with *P* value of 0.002, whereas there was no statistically significant difference between patients and control

Table 1 Demographic data of patients and controls

	Patients [*n* (%)] *n*=70)	Control [*n* (%)] *n*=20)	*P*
Sex			
Male	37 (52.8)	4 (20)	0.01*
Female	33 (47.2)	16 (80)	
Age			
Mean±SD	34.47±10.63	26.05±1.57	
Range	18-78	23-29	

*Significant

Table 2 Comparison between patients and control groups regarding complete blood picture

	Patients	Control	*P*
WBC (×10^9/l)			
Mean±SD	7.8±2.3	6.5±1.8	0.023*
Range	4-14	4-10	
Hb (g/dl)			
Mean±SD	11.3±1.3	12.9±0.7	0.002**
Range	8.8-13.2	12-14.2	
PLT (×10^9/l)			
Mean±SD	293.2±66	244.9±56.5	0.730
Range	150-400	165-380	

Hb, hemoglobin; PLT, platelet; WBC, white blood cell, **Highly significant

individuals regarding low-density lipoprotein (LDL), cholesterol, and high-density lipoprotein (HDL) levels, with *P* value of 0.18, 0.26, and 0.062, respectively (Table 4).

Concerning the fasting blood glucose and HbA1c levels, there was no statistically significant difference between patients and control individuals regarding fasting blood glucose and HbA1c, with *P* value of 0.75 and 0.78, respectively (Table 5).

Concerning fasting serum C-peptide, fasting serum insulin, and IR, there was a statistically significant increase in the three parameters in the patient group compared with the control group, with *P* value of 0.001 (Table 6).

Patients were divided into three groups according to the previously mentioned classification regarding the eGFR and the microalbuminuria.

Regarding fasting serum insulin, there was a statistically significant increase in the fasting insulin levels in stage 3, stage 4, and stage 5 patients with CKD compared with the control group, with *P* value less than 0.001, 0.001, and 0.02, respectively. There is a statistically significant increase in the fasting insulin level in patients with stage 3 CKD compared with those with stage 4, with *P* value 0.02. There is no statistically significant difference in the fasting insulin levels between patients with stage 4 and stage 5 CKD, with *P* value 0.689 (Table 7).

Regarding C-peptide, there was a highly significant increase in the C-peptide levels in patients with stage 3, stage 4, and stage 5 CKD compared with the control group, with *P* value less than 0.001. There was no statistically significant difference between C-peptide levels on comparing patients with stage 3 CKD with those with stage 4 or stage 5 CKD or on comparing patients with stage 4 CKD with those with stage 5 CKD, with *P* value 0.91, 0.99, and 0.93, respectively (Table 8).

Regarding IR, there was a statistically significant increase in the IR in patients with stage 3 CKD compared with patients with stage 4 CKD, with *P* value 0.024. There is no statistically significant difference in the IR between patients with stage 5 CKD and patients with stage 3 and stage 4 CKD, with *P* value of 0.14 and 0.875, respectively (Table 9).

Correlations

There is a significant positive correlation between creatinine level and the IR, with *P* value equals 0.007, and there is a highly significant negative relation between eGFR and the IR, with *P* value equals 0.001 (Table 10).

Table 3 Comparison between patients and control groups regarding kidney function and estimated glomerular filtration rate

	Patients	Control	*P*
Urea (mmol/l)			
Mean±SD	18.6±4.4	4.7±0.9	<0.001**
Range	12-34	3-6.5	
Creatinine (μmol/l)			
Mean±SD	279.5±74	70±10.7	<0.001**
Range	171-498	55-91	
eGFR (ml/min/1.73 m^2)			
Mean±SD	23.5±6.8	106.2±16.5	<0.001**
Range	9.1-44.8	80-147	
Urinary albumin/creatinine ratio (mg/g)			
Mean±SD	83.85±81.35	10.95±4.7	<0.001**
Range	30-300	4-23	

eGFR, estimated glomerular filtration rate.

Table 4 Comparison between patients and control groups regarding lipid profile

	Patients	Control	*P*
Cholesterol (mg/dl)			
Mean±SD	165.6±20.3	141.7±23.3	0.26
Range	123-230	90-175	
Triglycerides (mg/dl)			
Mean±SD	106.7±31.4	78.7±16	0.002**
Range	60-200	55-110	
HDL (mg/dl)			
Mean±SD	41.2±5.5	43.5±5.8	0.062
Range	35-54	37-62	
LDL (mg/dl)			
Mean±SD	90.6±17.8	82.9±21.2	0.18
Range	33.6-126	42-120	

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 5 Comparison between patients and control groups regarding fasting glucose and glycated hemoglobin levels

	Patients	Control	*P*
Fasting glucose (mg/dl)			
Mean±SD	90.4±8.77	86.6±8.5	0.75
Range	71-108	70.2-100	
HBA1c %			
Mean±SD	5.28±0.34	5.1±0.33	0.78
Range	4.5-5.8	4.6-5.8	

HbA1c, glycated hemoglobin.

Table 6 Comparison between patient and control groups regarding fasting C-peptide, fasting insulin, and insulin resistance

	Patients	Control	*P*
Fasting C-peptide (ng/ml)			
Mean±SD	9.3±3.6	1.3±0.4	<0.001**
Range	1.3-19.3	0.4-2	
Fasting insulin (μIU/ml)			
Mean±SD	23.2±18.8	6.7±1.2	<0.001**
Range	3.6-92.7	4.7-8.8	
Insulin resistance			
Mean±SD	5.1±4.1	1.4±0.29	<0.001**
Range	0.84- 23.8	0.81-1.93	

Table 7 Comparison between patients and control subjects regarding fasting insulin levels according to the stage of the chronic kidney disease

Fasting insulin	Group I (control) (*n*=20)	Group II (stage 3 CKD) (*n*=10)	Group III (stage 4 CKD) (*n*=53)	Group IV (stage 5 CKD) (*n*=7)
Mean±SD	6.73±1.26	34.47±3.1	21±15.34	23.7±11.5
Range	4.7-8.8	5.4-92.7	3.6-65.4	11.1-41.3
*P*1		<0.001**	0.001**	0.02*
*P*2			0.02*	0.185
*P*3				0.689

CKD, chronic kidney disease.

Table 8 Comparison between patients and control subjects regarding fasting C-peptide according to the stage of the chronic kidney disease

Fasting C-peptide	Group I (control) (*n*=20)	Group II (stage 3 CKD) (*n*=10)	Group III (stage 4 CKD) (*n*=53)	Group IV (stage 5 CKD) (*n*=7)
Mean±SD	1.31±0.4	9.42±4	9.3±3.59	9.4±4
Range	0.4-2	1.3-16.2	3.5-19.3	2.1-13.6
*P*1		<0.001**	<0.001**	<0.001**
*P*2			0.91	0.99
*P*3				0.93

CKD, chronic kidney disease.

Table 9 Comparison between patients and control individuals regarding insulin resistance considering the stage of the kidney disease

Insulin resistance	Group I (control) (*n*=20)	Group II (stage 3 CKD) (*n*=10)	Group III (stage 4 CKD) (*n*=53)	Group IV (stage 5 CKD) (*n*=7)
Mean±SD	1.42±0.29	7.58±7.3	4.7±3.37	4.9±2.1
Range	0.81-1.93	1.34-23.81	0.84-14.61	2.51-7.5
*P*1		<0.001**	0.001*0	0.028*0
*P*2			0.024*0	0.140
*P*3				0.875

CKD, chronic kidney disease.

Discussion

Glucose intolerance is a widespread sign in patients and animals affected by renal impairment [15]. Numerous studies reveal that peripheral IR and/or impaired insulin secretion are the main factors for diminished carbohydrate metabolism [16]. As IR in CKD is associated with diabetes, renal disease could also lead to a deterioration of insulin sensitivity [17]. IR is common among patients with kidney disease; it may occur in even very early stage of CKD. It exists in both patients with CKD with and without diabetes, apart from of the etiology of kidney disease, and it worsens as kidney functions decline [18].

In the current study, it was found that IR calculated by the HOMA-IR model is higher in patient group than that in control individuals. The results of Rodríguez-Carmona *et al.*[19] were consistent with our study results regarding C-peptide, fasting insulin levels, and IR, which were higher in patients than healthy persons. Kim *et al.*[20] also calculated the HOMA-IR in nondiabetic patients with CKD and proved that it is higher in the patient group than the healthy group, which is also in agreement with our current study.

Our study revealed that there is a statistically significant increase in the IR in patients with stage 3 CKD compared with patients with stage 4 CKD, whereas there is no statistically significant difference between patients with stage 5 CKD, patients with stage 3 CKD, and patients with stage 4 CKD. The study by Satirapoj *et al.*[21] revealed that there was no statistically significant difference in HOMA-IR levels between CKD groups.

In our study, there is no statistically highly significant increase in triglyceride and HDL in patients compared with control individuals, whereas there is no statistically significant difference between LDL and cholesterol levels in patients and control individuals. Paul and Kurien[22] conducted a study about the lipid profile in nondiabetic patients with CKD and revealed that patients had higher triglyceride levels with lower HDL levels than control individuals, and there was no statistically significant difference between patients and control individuals regarding LDL and cholesterol levels. Tauqeer *et al.*[23] found that levels of cholesterol, triglyceride, and LDL were higher in patient group, with HDL levels lower than normal individuals. The possible explanation of the different pattern of dyslipidemia may be different effect of exercise, dietary habits, or current hormonal problems. There are several important factors

Table 10 Correlation between insulin resistance and creatinine and estimated glomerular filtration rate (Pearson correlation)

Item	Insulin resistance	
	r	*P*
Creatinine*	0.282	0.007**
eGFR**	−0.351	0.001**

eGFR, estimated glomerular filtration rate. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

that can alter lipid metabolism and influence the nature of lipid abnormalities observed in patients with CKD. These include stage and severity of kidney disease, presence and degree of proteinuria, and features unique to each modality of renal replacement therapy [24].

In the current study, we found that there is a statistically significant decrease in hemoglobin level in the patient group compared with the control individuals. Chutia *et al.*[25] also found the presence of lower hemoglobin level in patients with CKD compared with control individuals and stated that those results can be owing to the secondary hyperparathyroidism associated with the CKD. There is also an evidence of restoration of the hematocrit after parathyroidectomy in uremic patients owing to restoration of bone marrow space after operation [26]. The severity of CKD is an important risk factor for the development of anemia in this group of patients. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) cohort have consistently revealed that the risk for anemia increases as CKD stage advances, with a prevalence of 73% at stage 3, 87% at stage 4, and more than 93% at stage 5 [27]. This is owing to the massive renal parenchymal loss that is present in advancing CKD as the principal cause of decreased red blood cell production. The shrinking, scarred kidney results in a decreasing number of type I dendritic cells, which are responsible for the production of erythropoietin, being the main stimulus for red blood cell production in the bone marrow, referred to as erythropoiesis [28].

Conclusion

We have found an increase in serum insulin, C-peptide, and IR in nondiabetic patients with CKD.

The levels of serum insulin, C-peptide, and IR have shown a strong negative correlation with serum creatinine and eGFR, which points to the existence of relationship between IR and CKD.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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