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CLINICAL STUDY

Comparison of insulin resistance in the various stages of chronic kidney disease and inflammation

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Abstract

Objective: In this study, we compared predialysis and dialysis patients with the controls in terms of insulin resistance and evaluated the association with inflammation that is a risk factor for cardiovascular disease. *Materials and methods*: A total of 134 non-diabetic patients with controls ($n = 33$), predialysis ($n = 29$) and dialysis patient group ($n = 72$) were included in the study. Fasting blood glucose, insulin, C-peptide, albumin, CRP (C-reactive protein) and homocysteine plasma levels were simultaneously analyzed in all the patients. HOMA-IR index was calculated to show existence of insulin resistance. *Results*: Mean insulin and HOMA-IR index values were found to be higher in the predialysis and dialysis patient groups than in the control group ($p = 0.019$, $p = 0.014$; respectively). When three groups were compared in terms of C-peptide levels; these values were found to be statistically significantly higher in the predialysis patients than in controls ($p = 0.017$) and in the dialysis group than in the predialysis patients and controls ($p = 0.0001$, $p = 0.0001$; respectively). CRP and homocysteine levels were found to be statistically higher ($p = 0.0001$, $p = 0.0001$; respectively), while albumin levels were significantly lower ($p = 0.0001$) in the dialysis patient group. *Conclusion*: In our study, we demonstrated that insulin resistance was higher in patients in the various stages of chronic kidney disease compared to healthy population. We found that insulin resistance, C-peptid and inflammation related cardiovascular risk factors increased.

Keywords

Chronic kidney disease, inflammation, insulin resistance

History

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Introduction

Primary components of metabolic syndrome include hyperinsulinemia, obesity, impaired glucose tolerance, hypertriglyceridemia, low HDL-cholesterol, hypertension and coronary artery disease. Insulin resistance is one of the most important components of metabolic syndrome.

Pituitary or hypothalamus is not involved in the regulation of insulin release and the main stimulant is blood-glucose concentration.[1] When insulin resistance develops, plasma level of insulin rises to much higher concentrations than normal values compared to blood glucose.[2] Basic mechanism in insulin resistance is decreased effect of insulin on the metabolic events and increased insulin for compensation of the metabolic condition. Eventually, normoglycemia was achieved, insulin levels rise by 1.5–2 fold than normal values.[1] It has been found that insulin resistance developed with decreased renal functions in every stage of chronic kidney disease. Development of insulin resistance has been multifactorial in chronic kidney disease and hemodialysis patients.[3] Many factors contribute to development of insulin resistance such as untreated anemia or delaying in the treatment, erythropoietin deficiency, uremic toxins, exercise intolerance, vitamin D deficiency and inflammation.[4,5] Besides metabolic problems, dialysis inadequacy also plays an important role in development of insulin resistance in dialysis patients.[6] Insulin resistance which develops in chronic kidney disease and dialysis patients leads to oxidative stress and inflammation; contributing to development of cardiovascular diseases.[7,8] Cardiovascular diseases are the most common cause of mortality in every stage of chronic kidney disease.[9] In this study, we analyzed insulin resistance in the patients groups having metabolically controlled nondiabetic and various stage chronic kidney disease and those receiving dialysis replacement therapy compared to the healthy controls and evaluated its correlation with the risk factors of inflammation related cardiovascular disease.

Materials and methods

A total of 134 patients were included in the study as the healthy controls, predialysis and dialysis patient groups aged 30–65 years. There were 33 healthy individuals in the control group and 29 patients in the predialysis group and 72 patients in the dialysis group.

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Patients having diabetes mellitus, malignancy, collagen tissue disease and active infection were excluded from the study. The condition of the patients groups having a similar gender distribution, arterial blood pressures under 140/90 mmHg, body mass index (BMI) <29.9 kg/m^2 and adequate dialysis in the dialysis patient group was provided. All patients in the dialysis group were measured urine output below 100–300 cc/day, therefore residual renal function was not evaluated.

In order to rule out the diagnosis of diabetes mellitus, $HbA1_c$ and fasting blood glucose values were studied and the patients with HbA1c <6% and fasting blood glucose <110 mg/dL were included. In order to evaluate insulin resistance; insulin and C-peptide were measured, while plasma levels of albumin, C-reactive protein (CRP) and homocysteine were analyzed in order to existence inflammation.

BMI values were calculated using the formula of (body weight)/(height)^2. Dry weight of the dialysis patient was considered in evaluation of the body weight.

In order to evaluate dialysis adequacy; Kt/V and URR values were calculated. $Kt/V = -In[(R-0.008 \times t) + (4-3.5 \times R)]\Delta BW/BW$ (R: ratio of postdialysis urea to predialysis urea, t: dialysis duration, BW: body weight) formula model was used for calculation of Kt/V. [URR = (postdialysis urea/predialysis urea)] formula was used for calculation of URR values. Kt/V>1.4 and URR>70% were considered as dialysis adequacy.

$HbA1_c$ was studied with Premier Hb9210-Primus ultra II device using HPLC (high performance liquid chromatography) method. Fasting blood glucose was studied with Abbott Architect device using standard methods.

Insulin was analyzed with Siemens Immulite 2000 device using enzyme-linked Chemiluminometric Immunoassay method, while C-peptide was studied with Siemens Immulite 2000 device using two-way Chemiluminometric Immunoassay method. HOMA-IR index was calculated using fasting blood glucose (mg/dL)×fasting insulin level (μU/mL)/405 formula.

Siemens Immulite 2000 device and two-way Chemiluminometric Immunoassay method were used to measure the plasma levels of homocysteine and CRP.

This study was approved by the Ethics Committee of Bakırköy Medical Hospital and conducted in accordance with the principles of the Declaration of Helsinki. All participants gave their written informed consent prior to participation in the study.

Statistical analysis

In this study, statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In evaluation of the data; one-way variance analysis was used in the descriptive statistical methods (mean, standard deviation) as well as inter-group comparisons, Tukey multiple comparison test in subgroup comparisons, independent t-test in comparison of two groups and Chi-square test in comparison of the qualitative data. ROC values were defined for the variables used in the separation of insulin resistance and sensitivity, specificity, positive cut-off point, negative cut-off point and LR+ values were calculated in order to define cut-off points. The results were evaluated in the significance level of $p < 0.05$ and confidence interval of 95%.

Results

Three groups were included in the study with healthy individuals who presented for control purpose to the nephrology polyclinic, predialysis patients who were under follow-up and dialysis patients with adequate dialysis provided who received dialysis replacement therapy for at least 6 months. No statistically significant different was found between the controls, predialysis and dialysis patient groups between mean age, gender and BMI values (Table 1).

Mean insulin and HOMA-IR index values were found to be higher in the predialysis and dialysis patient groups than in the control group ($p = 0.019$, $p = 0.014$; respectively) (Table 2). When three groups were compared in terms of C-peptide levels; these values were found to be statistically significantly higher in the predialysis patients than in controls ($p = 0.017$) and in the dialysis group than in the predialysis patients and controls ($p = 0.0001$, $p = 0.0001$; respectively) (Table 2). There were a significant positive correlation between C-peptide and insulin ($r = 0.601$, $p = 0.0001$), HOMA-IR ($r = 0.586$, $p = 0.0001$), CRP ($r = 0.395$, $p = 0.0001$) and homocysteine ($r = 0.271$, $p = 0.002$) (Table 2). CRP and homocysteine levels were found to be

Table 1. Demographic features and anthropometric values of the groups.

Values	Control group	Predialysis patient group	Dialysis patient group	p
Age	41.18 ± 10.97	47.79 ± 13.66	47.88 ± 17.59	0.101
Gender				
Male	12 (36.40%)	14 (48.30%)	37 (51.40%)	0.354
Female	21 (63.60%)	15 (51.70%)	35 (48.60%)	
Height	165.76 ± 7.55	166.24 ± 7.88	163.90 ± 8.60	0.336
Weight	62.61 ± 8.28	59.00 ± 11.46	61.56 ± 10.44	0.359
Body mass index	22.68 ± 1.43	21.34 ± 3.77	22.89 ± 3.31	0.07

Table 2. Comparison of insulin resistance and the risk factors for inflammation and cardiovascular disease between the groups.

Variables	Control group	Predialysis patient group	Dialysis patient group	p
Insulin*	3.36 ± 2.14	7.54 ± 10	7.78 ± 8.05	0.019
C-peptide**	1.68 ± 0.56	4.04 ± 2.6	7.52 ± 4.22	0.0001
HOMA-IR***	0.73 ± 0.48	1.70 ± 2.19	1.78 ± 1.87	0.014
Albumin+	4.20 ± 0.3	3.88 ± 0.38	3.61 ± 0.47	0.0001
CRP++	0.18 ± 0.24	0.51 ± 0.46	1.10 ± 1.23	0.0001
Homocysteine+++	11.19 ± 5.02	23.74 ± 5.33	24.00 ± 12.32	0.0001

Notes: CRP, C- reactive protein.
C/PD: *0.048; **0.017; ***0.044;+0.007; ++0.344; +++0.0001.
C/D: *0.018; **0.0001; ***0.013; +0.0001; ++0.0001; +++0.0001.
PD/D: *0.989; **0.0001; ***0.978; +0.01; ++0.016; +++0.992.
C, control group; PD, predialysis patient group; D, dialysis patient group.
*Insulin, **C-peptide, ***HOMA-IR.
+Albumin, ++CRP, +++Homocysteine.
Evaluation of the control, predialysis and dialysis patient groups with Tukey multiple comparison test $p < 0.05$.

Table 3. Evaluation of the existence of insulin resistance in the control, predialysis and dialysis groups.

Existence of insulin resistance	Control group	Predialysis patient group	Dialysis patient group	
Insulin resistance (−)	100.00%	82.80%	80.60%	$p = 0.026$
Insulin resistance (+)	0.00%	17.20%	19.40%	

Table 4. Correlation of C-peptide and HOMA-IR with insulin resistance.

Variables	Insulin resistance (−)	Insulin resistance (+)	Cut-off point	Sensitivity	Specificity
C-peptide	5.60 ± 3.47	10.52 ± 4.43	>3.53	100	75.00%
HOMA-IR	0.95 ± 0.56	5.21 ± 2.06	>1.56	98.9	95.83%

statistically higher ($p = 0.0001$, $p = 0.0001$; respectively), while albumin levels were significantly lower ($p = 0.0001$) in the dialysis patient group (Table 2).

There were a statistically significant difference between the existences of insulin resistance in the control, predialysis and dialysis groups ($p = 0.026$) (Table 3). Risk for development of insulin resistance was found as 15 times higher in the predialysis and 16.6 times higher in the dialysis patients groups compared to the healthy controls (Table 3).

Risk for insulin resistance (+) in a patient with C-peptide value >3.53 was found to be 4 times higher than in a patient with C-peptid value <3.53 (Table 4). There were a significant positive correlation between C-peptide and insulin ($r = 0.601$, $p = 0.0001$), HOMA-IR ($r = 0.586$, $p = 0.0001$), CRP ($r = 0.395$, $p = 0.0001$) and homocysteine ($r = 0.271$, $p = 0.002$) (Table 4).

Risk for insulin resistance (+) in a patient with HOMA-IR value >1.56 was found to be 24 times higher than in a patient with HOMA-IR value <1.56 (Table 4).

Discussion

Insulin resistance is one of the most important of metabolic syndrome, causing an increase in the oxidative stress and release of many proinflammatory cytokines. Thus, it plays a role in development of atherosclerosis and increasing the risk for cardiovascular disease. Therefore, insulin resistance contributes to the development of cardiovascular diseases that are the most important cause of morbidity and mortality in chronic kidney disease and in patients receiving dialysis replacement therapy.[10,11]

It has been shown in uremic patients that, glucose uptake decreased in the extrahepatic tissues and insulin resistance essentially developed in the peripheral tissues.[3,12] In addition; many factors including age, BMI, hypertension and dyslipidemia have effects on the development of insulin resistance.

In our study, three groups were provided to be similar in terms of age, BMI, gender distribution and controlled arterial blood pressures. Likewise, several studies, we found that mean insulin values and HOMA-IR indexes were significantly higher in the predialysis and dialysis patient groups compared to the controls.

Today, several studies report that insulin resistance increased in dialysis patients, but dialysis replacement therapies have positive effect on the insulin resistance.[13] In a study by Kobayashi et al.[13] with patients having peritoneal dialysis, besides metabolic problems dialysis adequacy also was shown to have important effects on the insulin resistance. Satirapoj et al.[14] studied predialysis insulin resistance in patients with end stage renal disease and then analyzed the insulin resistance again in the same patient groups after five weeks of hemodialysis and peritoneal dialysis therapies and demonstrated that insulin resistance decreased following the treatment of dialysis. In this study, no significant difference was found between the predialysis and dialysis groups. In addition to the similar age, gender, BMI and metabolic control of the patients, we believe this result could be attributed to the dialysis groups receiving treatment at least for 6 months and to the positive effect of dialysis adequacies.

Many proinflammatory cytokines such as CRP and interleukin-6 are released in the insulin resistance. Inflammation takes an important place in the onset of atherosclerosis and coronary disease. CRP is an independent factor in detecting cardiovascular diseases.[15] In this study, CRP levels were found to be higher in the dialysis group compared to the controls and predialysis patient groups. As it has been shown in many studies, these higher values of CRP in dialysis patients could be attributed to several factors including malnutrition, decreased exercise capacity and increased risk for calcification and atherosclerosis.[16,17] In our study, low albumin levels due to low protein diet with nutrition in dialysis patients might also contribute to the higher levels of CRP. Moderately high level of homocysteine is an independent risk factor for inflammation-related atherosclerosis and cardiovascular diseases in general population.[18] Homocysteine levels are higher in kidney disease compared to general population and have been shown to be correlated with early mortality.[19] In kidney disease, homocysteine levels can increase inflammation, malnutrition, hypoalbuminemia besides due to decreased renal excretion.[20] Furthermore, studies found a correlation between insulin levels, insulin resistance and homocysteine levels. Soonthornpun et al.[21] demonstrated that homocysteine levels altered with hyperinsulinemia and concluded that insulin resistance could affect homocysteine metabolism, and hyperhomocysteinemia could be resulted from insulin resistance.

In this study, homocysteine levels were higher in the predialysis and dialysis patients than in the controls. This result might be caused by impaired renal excretion of homocysteine in predialysis and dialysis patients and increased insulin resistance, and the risk for cardiovascular disease compared to the control group. Homocysteine levels were found similar and insulin resistance was not significantly different in predialysis and dialysis patients, while this result might be attributed to dialysis patients receiving more intense B6 and B12 therapies and to the dialysis adequacies.

Recent studies report that serum levels of C-peptide were more important than serum insulin levels in establishment of new-onset diabetes mellitus and, C-peptide levels could be studied in order to define the risk for diabetes.[22,23]

It has been shown that, besides insulin resistance and diagnosis of diabetes, high C-peptide levels lead to the onset of muscle proliferation and are correlated with atherosclerosis in these patients in the early period.[23,24] In this study; we found a positive correlation between C-peptide levels and insulin, HOMA-IR index as well as between CRP and homocysteine levels. Higher C-peptide levels in the dialysis groups compared to the controls and predialysis patient group might be attributed to atherosclerosis was more common due to longer-duration chronic kidney disease and increased insulin resistance in these patients.

In this study, increase in the insulin resistance with progression of chronic kidney disease besides in the patients were significantly higher levels of serum C-peptide and were significant positive correlation between levels of serum C-peptid with inflammation related cardiovascular. We think, measurement levels of serum C-peptide in the various stages of chronic kidney disease might be attributed predict to inflammation and risk of cardiovascular diseases.

Conclusion

Increase in the insulin resistance with progression of chronic kidney disease is known to be effective on the increase in morbidity and mortality by negatively affecting the risk factors for cardiovascular disease. We believe that, determination of the importance of C-peptide in early detecting the insulin resistance and risk factors for cardiovascular disease would lead to use of new therapeutic agents in the treatment.

Declaration of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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