

Comparison of the Effects of Uremia and Metabolic Disorders on the Development of Insulin Resistance

Nilgöl Akalın¹, Mehmet Ali Uran² , Mustafa Uçar² , Hanişe Özkan³ , İrem Kırac Utku³ 

¹Department of Nephrology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

²Department of Internal Medicine, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

³Department of Internal Medicine, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

12

Abstract

Objective: The aim of the present study was to show the important effect of a uremic environment on the development of insulin resistance and if insulin resistance might be reversible with the treatment of metabolic disorders in patients with hypothyroid.

Materials and Methods: Patients with stage 2, stage 3, and stage 4 chronic renal disease and dialysis treatment and patients with hypothyroid with normal renal function and thyroxine replacement treatment were included in the study. Patients with some metabolic disorders, such as obesity, dyslipidemia, anemia, and severe vitamin D deficiency, were excluded from the study. Insulin, fasting blood glucose, and thyroid function levels were measured. Homeostatic model assessments of insulin resistance (HOMA-IR) values were calculated.

Results: The mean age, body mass index, and distribution of gender were found to be similar in the patient groups. No statistical significance was found in HOMA-IR values between the patient groups. The important effects of chronic kidney disease and hemodialysis replacement treatment were determined to the development of insulin resistance.

Conclusion: A uremic environment might be affected by the development of insulin resistance as in the development of metabolic disorders, such as thyroid dysfunction and glucose and lipid metabolism disorders. Understanding of the molecular mechanism and effects of uremic toxins can contribute to the development of new treatment targets.

Keywords: Chronic renal diseases, dialysis treatment, hypothyroid, insulin resistance, thyroxine treatment

Corresponding Author: Nilgöl Akalın ✉ nilnef@hotmail.com

Received: 29.06.2016 **Accepted:** 11.01.2017

Cite this article as: Akalın N, Uran MA, Uçar M, Özkan H, Kırac Utku İ. Comparison of the Effects of Uremia and Metabolic Disorders on the Development of Insulin Resistance. Turk J Nephrol 2019; 28(1): 12-6

INTRODUCTION

Insulin resistance is an important and common health problem. Insulin resistance and hyperinsulinemia can cause the development of type 2 diabetes mellitus and coronary heart diseases. Additionally, metabolic defects and metabolic disorders might contribute to the development of insulin resistance (1).

It is known that the presence of insulin resistance can cause endothelial dysfunction, arteriole changes, and inflammation (2). Therefore, insulin resistance can contribute to the increase risk of atherosclerosis and coronary heart disease. The existence of insulin resistance can be proven by a decrease of insulin sensitivity of the

tissues. Insulin resistance accompanies many diseases, such as obesity, metabolic syndrome, chronic kidney disease, and thyroid dysfunction (3, 4). Currently, the pathogenesis of insulin resistance is unclear for some diseases. For example, insulin resistance might be detected in people with normal weight and without metabolic disorders, and this condition has been explained by greater stored body fat, but it is unclear (5).

It is known that insulin resistance increases in every stage of chronic kidney disease and dialysis replacement treatments (6). The existence of insulin resistance is associated with inflammatory response, oxidative stress, metabolic acidosis, anemia, malnutrition, excess angio-



tensin II, and disorders of vitamin D metabolism in chronic kidney diseases (7). However, it is shown that physical inactivity and dietary and genetic factors might play an important role to the development of insulin resistance in patients with chronic kidney disease (4). Additionally, low levels of Akt phosphorylation are determined in the presence of insulin resistance, and it is shown that this condition might lead to the development of insulin-related metabolic defects, such as disorders of metabolism of glucose, lipids, and muscle proteins (8).

Currently, it is shown that thyroid dysfunctions are associated with insulin resistance, dyslipidemia, metabolic syndrome, and ischemic heart diseases (9). However, metabolic disorders might be reversible with suitable treatment (10). The ratio of insulin resistance is controversial in patients with hypothyroid and hyperthyroid. However, it is suggested that thyroid dysfunctions can cause the development of disorders of glucose tolerance or fasting glucose and insulin resistance (11).

We aimed to show the effects of uremic environment and uremic toxins on the development of insulin resistance. In addition, we tried to show the importance of metabolic control on the development of insulin resistance, and insulin resistance might be reversible with proper treatment. Therefore, we compared the ratio of insulin resistance in patients with chronic renal disease and hypothyroid because they were patients with high risk for the development of insulin resistance.

MATERIALS AND METHODS

The present study was performed in the Nephrology and Internal Medicine Clinic of Bakirkoy Training and Research Hospital. The study was approved by the ethics committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (grant no: 758). Informed consent was obtained from all patients.

Thirty patients with chronic renal disease, 42 patients with hemodialysis treatment and patients with hypothyroid with thyroxine replacement treatment were included in the prospec-

tive study. Decline in glomerular filtration rate was defined as chronic renal disease, and glomerular filtration category of 60-89 mL/min/1.73 m² was classified as stage 2, 30-59 mL/min/1.73 m² as stage 3, and 15-29 mL/min/1.73 m² as stage 4 chronic renal diseases (12). Gender, age, weight, and height of all patients were recorded. The mean age, body mass index (BMI), and distribution of gender were calculated. Patient history was collected for the study. Patients with diabetes mellitus, obesity (BMI > 29.90 kg/m²), metabolic syndrome (hypertriglyceridemia associated with abdominal obesity, decreased serum high-density lipoprotein cholesterol, high blood pressure, and high fasting glucose levels), severe anemia, nutrition disorders (vomiting, nausea, and weight loss), uncontrolled secondary hyperparathyroidism (parathyroid hormone levels > 150 pg/mL), and thyroid dysfunction, such as subclinical hypothyroid, hypothyroid, and hyperthyroid, were excluded from the study. Patients with collagen tissue disease, such as rheumatoid arthritis and psoriatic arthritis, or drug treatments, such as carbamazepine, valproic acid, coumadin, lithium, and cortisone, were also excluded from the study.

The mean urine output was measured < 50-100 cc/day in all patients with hemodialysis replacement treatment, and urine output was not evaluated. Dialysis adequacy was provided for patients with dialysis replacement treatment. Kt/V ≥ 1.40 and urea reduction ratio ≥ 70.00% were considered as dialysis adequacy. Glomerular filtration rates of patients with chronic kidney disease were calculated by the Modification of Diet in Renal Disease formula as glomerular filtration rate = $186 \times \text{serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times \text{Gender} \times \text{Race}$. BMI was evaluated for all patients. BMI values were calculated using the formula: BMI = body weight (kg)/height (m²).

Venous blood samples were collected and were transferred to the laboratory provided with suitable conditions. Thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), and free thyroxine (free T4) levels were measured, and the existence of thyroid dysfunction was evaluated. Insulin and blood glucose

Table 1. Demographic features of the patient groups

	Patients with chronic renal disease	Patients with dialysis treatment	Patients with thyroxine treatment	p
Age (years)	46.69±16.13	49.44±17.30	39.67±12.26	0.520
Gender				
Male	16 (53.33%)	25 (59.52%)	25 (62.50%)	0.002*
Female	14 (46.67%)	17 (40.48%)	15 (37.50%)	
BMI (kg/m ²)	29.77±2.27	22.63±3.08	26.51±2.71	0.723
Mean glomerular filtration (mL/min/1.73 m ²)	25.33±0.83	–	100.24±5.76	0.002*
Dialysis duration (years)	–	3.84±3.22	–	

*p<0.01. BMI: body mass index

Table 2. Comparison of insulin resistance in the patient groups

	Patients with chronic renal disease Mean±SD (median)	Patients with dialysis treatment Mean±SD (median)	Patients with thyroxine treatment Mean±SD (median)	p
Fasting blood glucose (mg/dL)	99.60±13.54 (99.00)	93.08±11.94 (97.00)	85.96±9.81 (87.00)	0.104
Insulin (μmol/L)	7.54±10.00 (7.07)	8.83±8.96 (6.28)	9.27±7.17 (7.29)	0.252
HOMA-IR (μu/mL)	1.70±2.20 (1.67)	1.96±1.88 (1.43)	2.15±1.72 (1.68)	0.190

Table 3. Evaluation of HOMA-IR in the patient groups

Mean HOMA-IR values for all cases (μu/mL)	Ratio of cases HOMA-IR <2.50 (%)	Ratio of cases HOMA-IR >2.50 (%)
Minimum–maximum (0.34–9.21)	66.29	35.71
Median±SD 2.33±1.90		
Patients with dialysis treatment	57.05	42.85
Patients with chronic renal disease	46.67	53.33
Patients with hypothyroid with thyroxine treatment	67.50	32.50

Table 4. Evaluation of the effect of parameters on HOMA-IR values

	B	p	95% CI
Fasting blood glucose (mg/dL)	0.210	0.128	0.208
Insulin (μmol/L)	0.118	0.455	0.001*
Body mass index (kg/m ²)	0.037	0.125	0.258
Age (years)	–0.018	–0.138	0.193
Gender	–0.187	–0.047	0.062

*p<0.01.

Table 5. Effects of the patient groups on insulin resistance

	95% CI of the difference		p
	Lower	Upper	
Patients with dialysis treatment	0.524	1.687	0.001**
Patients with chronic renal disease	–0.486	2.735	0.047*
Patients with hypothyroid with thyroxine treatment	–1.447	–0.339	0.006*

*p<0.05; **p<0.01

Serum TSH, free T3, and free T4 levels were evaluated using the immunoassay method (Access® Immunoassay kits; Unidel DxI800 (Beckman Coulter, Fullerton, CA, USA). Normal ranges for TSH, free T3, and free T4 were accepted as 0.27–4.20 IU/mL, 2.63–5.67 ng/dL, and 0.70–2.00 ng/dL, respectively. Abbott-Aeroset Autoanalyzer (Abbott-Aeroset System, Germany) was used for serum fasting blood glucose measurements. Insulin levels were measured by a Siemens Immulite 2000 device using the enzyme-linked chemiluminometric immunoassay method. HOMA-IR index was calculated as $\text{HOMA-IR} = \text{fasting blood glucose (mg/dL)} \times \text{fasting insulin level (mU/mL)} / 405$. HOMA-IR values >2.50 were accepted as the presence of insulin resistance.

Statistical Analysis

The Number Cruncher Statistical System 2007&PASS (Power Analysis and Sample Size) 2008 statistical software (UT, USA) program was used for statistical analysis. Student's t-test was used for group comparisons of parameters with normal distribution, and Mann-Whitney U test was used for group comparisons of parameters without normal distribution. Mann-Whitney U test was used to determine the group causing the difference. Pearson's chi-square test was used for comparison of qualitative data. Linear regression analysis was used in multivariate evaluations of affected parameters on HOMA-IR and insulin values. Significance was evaluated at the levels of p<0.01 and p<0.05.

RESULTS

Patients were divided into three groups as patients with hemodialysis replacement treatment, chronic renal disease, and hypothyroid with thyroxine replacement treatment. Demographic features of patients with chronic renal disease and hypothyroid disease and dialysis treatment are shown Table 1.

Each of the stages of chronic renal disease was evaluated for patients with chronic renal disease, and 6.66% (n=2), 13.33% (n=4), and 80.01% (n=24) of patients with chronic renal disease were detected at stage 2, stage 3, and stage 4 chronic renal diseases, respectively. Distributions of gender were evaluated for the hemodialysis and hypothyroid patient groups, and 25 (59.52%) male and 17 (40.48%) female patients were determined in the hemodialysis patient group, where as 25 (62.50%) male and 15 (37.50%) female patients were determined in the hypothyroid patient group. A statistically significant difference was found in the distribution of gender, but the ratio of male patients was found to be higher than that of female patients.

levels were measured after fasting for 12 h in all patients, and homeostatic model assessment of insulin resistance (HOMA-IR) values were calculated.

between the patient groups ($p=0.002$) (Table 1). No statistically significant difference was determined in the mean ages and BMIs between the patient groups ($p=0.520$ and $p=0.723$, respectively) (Table 1).

No statistically significant difference was found in the mean fasting blood glucose and insulin levels and HOMA-IR values ($p=0.104$, $p=0.252$, and $p=0.190$, respectively) (Table 2).

The ratio of insulin resistance (HOMA-IR values >2.50) was calculated, and 42.85%, 53.33%, and 32.50% values were found in the patient groups with dialysis, chronic renal disease, and hypothyroid, respectively (Table 3).

The effects of parameters (age, gender, BMI, fasting blood glucose, and insulin) were evaluated to the development of insulin resistance, and no statistically significant difference was determined ($p=0.193$, $p=0.062$, $p=0.258$, and $p=0.208$, respectively) (Table 4). A statistically significant difference was found between the effects of insulin levels on the development of insulin resistance ($p=0.001$) (Table 4).

The effects of the disease groups were determined to the development of insulin resistance (dialysis patient group: $p=0.001$, chronic renal disease group: $p=0.047$, and hypothyroid patient group: $p=0.006$) (Table 5).

DISCUSSION

Insulin resistance indicates endogenous insulin secretion disorders. It affects endothelial vasodilatation and leads to endothelial dysfunction, arteriole changes, and initiation inflammation (13). The risk of insulin resistance increases in thyroid dysfunction and every stage of chronic renal diseases.

Hypothyroidism is detected in the ratio of 1.00%-10.00% for the adult population (14). It is associated with glucose and insulin metabolism disorders. It can cause a defect in insulin secretion in response to glucose and alterations in peripheral glucose metabolism, thereby leading to the development of insulin resistance (15). Currently, it is known that thyroid replacement treatments can restore insulin-mediated glucose uptake; therefore, glucose and insulin metabolism disorders might be corrected (17, 18).

Uremia causes postreceptor insulin-signaling defects in chronic kidney diseases and hemodialysis treatments. Additionally, metabolic disorders, such as metabolic acidosis, vitamin D deficiency, anemia, accumulation of nitrogenous compounds, and adipokine, contribute to the impairment of various insulin-signaling molecules in chronic kidney diseases. For example, it appears that the activity of phosphatidylinositol 3-kinase is reduced in the presence of insulin resistance (19).

We compared insulin resistance ratio and effects of chronic renal disease, dialysis treatment, and thyroid dysfunction on the development of insulin resistance. No statistically significant dif-

ference was determined in insulin resistance ratio between the disease groups. However, a more important relationship was found between insulin resistance with hemodialysis treatment. This condition might be explained by influences of uremia in patients with hemodialysis treatment. It is known that uremia and uremic toxins are removed with dialysis treatments. Nevertheless, patients with hemodialysis treatment are exposed to uremic toxins because hemodialysis treatments are usually used 3 days/week. Thyroid dysfunctions affect glucose and insulin metabolism, but results of many studies suggested that glucose metabolism disorders, hyperinsulinism, and insulin resistance can be corrected with thyroid dysfunction treatments (19, 20). Patients with hypothyroid were treated regularly in our study. We thought that thyroxine replacement treatment might contribute to the correction of glucose and insulin metabolism defects, and thereby, insulin resistance ratio might be reduced. However, the effects of BMI and distributions of gender and age were not determined to the development of insulin resistance, but a significant relationship was found between insulin levels with insulin resistance ratio. Many studies have shown that metabolic disorders, such as obesity, anemia, vitamin D deficiency, and lifestyle (e.g., sedentary lifestyle), body fat storage, race, and genetic factors might have an effect on the development of insulin resistance. Patients in our study had a normal weight, but it is known that insulin resistance can appear in patients with normal weight (20, 21). Therefore, we thought that our results might be affected by the features of the patient groups, such as body fat storage ratio, and the drug treatments. Since they were metabolically controlled, they had no severe anemia, vitamin D deficiency, dyslipidemia, and thyroid dysfunction. Our results suggested that the presence of the relationship between insulin resistance with thyroid dysfunction and different stages of chronic renal diseases and insulin resistance might be corrected with treatment of metabolic disorders.

In summary, we have shown that the existence of insulin resistance in different stages of chronic renal diseases and thyroid dysfunction and ratio of insulin resistance might be reduced with suitable treatment of metabolic disorders. In addition, the more important effects of hemodialysis treatment were detected in insulin resistance ratio, and we thought that this condition might be explained by influences of uremic environment and uremic toxins.

Currently, the pathogenesis of insulin resistance is unclear for many diseases. Understanding of the pathogenesis of insulin resistance and the effects of the molecular actions of uremic toxins might contribute to the development of new treatments and new treatment targets.

Study Limitations

Insulin resistance is especially associated with metabolic disorders and metabolic defects, and it accompanies many diseases. However, the molecular mechanism and pathogenesis of insulin resistance are unclear.

We tried to show the importance of uremic toxins and uremic environment on the development of insulin resistance, and the effects of the different disease groups were compared with insulin resistance ratio. All patients in our study were regularly treated. However, the more important effects of hemodialysis treatment were detected to insulin resistance ratio. This condition might be explained by influences of uremic environment and uremic toxins. However, measurement of uremic toxins, such as the accumulation of nitrogenous compounds, were not made, and the relationship between insulin resistance with uremic toxins and the effects of drug treatment were not investigated in our study. We thought that this condition can be a limitation to the results of our study.

CONCLUSION

Insulin resistance is an important health problem because it leads to the development of chronic inflammation, atherosclerosis, and coronary heart diseases, and thereby, it can increase morbidity and mortality risks. We think that understanding of the pathogenesis of insulin resistance and the effects of uremic environment can contribute to the development of new treatments and decrease morbidity and mortality risks.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (grant no: 758).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.A., M.A.U., M.U., H.Ö. ; Design - N.A., İ.K.U.; Supervision - H.Ö., İ.K.U.; Resources - H.Ö., İ.K.U.; Data Collection and/or Processing - M.U., İ.K.U.; Analysis and/or Interpretation - N.A., İ.K.U., M.A.U.; Literature Search - H.Ö., M.U.; Writing Manuscript - N.A.; Critical Review - N.A., İ.K.U.

Acknowledgements: We thank the Bakirkoy Dr. Sadi Konuk Research and Training Hospital Ethical Committee for allowing the collection of data.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. *Diabetes Care* 2004; 27: 2222-8. [\[CrossRef\]](#)
2. Paneni F, Costantino S, Cosentino F. Insulin resistance, diabetes, and cardiovascular risk. *Curr Atheroscler Rep* 2014; 16: 419. [\[CrossRef\]](#)
3. Deedwania P. Hypertension, dyslipidemia, and insulin resistance in patients with diabetes mellitus or the cardiometabolic syndrome: benefits of vasodilating β -blockers. *J Clin Hypertens (Greenwich)* 2011; 13: 52-9. [\[CrossRef\]](#)
4. Beddhu S, Kimmel PL, Ramkumar N, Cheung AK. Associations of metabolic syndrome with inflammation in CKD: results From the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2005; 46: 577-86. [\[CrossRef\]](#)
5. Dvorak RV, DeNino WF, Ades PA, Poehlman ET. Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. *Diabetes* 1999; 48: 2210-4. [\[CrossRef\]](#)
6. Hung AM, Ikizler TA. Factors determining insulin resistance in chronic hemodialysis patients. *Contrib Nephrol* 2011; 17: 127-34. [\[CrossRef\]](#)
7. 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. doi: 10.1155/2012/691369. Epub 2012 Aug 7. [\[CrossRef\]](#)
8. Thomas SS, Zhang L, Mitch WE. Molecular mechanisms of insulin resistance in chronic kidney disease. *Kidney Int* 2015; 88: 1233-9. [\[CrossRef\]](#)
9. Owecki M, El Ali Z, Nikisch E, Sowiński J. Serum insulin levels and the degree of thyroid dysfunction in hypothyroid women. *Neuro Endocrinol Lett* 2008; 29: 137-40.
10. Aziz KM. Association between Hypothyroidism, Body Mass Index, Systolic Blood Pressure and Proteinuria in Diabetic Patients: Does treated Hypothyroid with Thyroxine Replacement Therapy prevent Nephropathy/Chronic Renal Disease? *Curr Diabetes Rev* 2015; 12: 1-10.
11. Jing S, Xiaoying D, Ying X, Rui L, Mingyu G, Yuting C, et al. Different levels of thyroid hormones between impaired fasting glucose and impaired glucose tolerance: free T3 affects the prevalence of impaired fasting glucose and impaired glucose tolerance in opposite ways. *Clin Endocrinol (Oxf)* 2014; 80: 890-8. [\[CrossRef\]](#)
12. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Journal of the International Society of Nephrology* 2013; 3: 1-136.
13. Fragoso A, Mendes F, Silva AP, Neves PL. Insulin resistance as a predictor of cardiovascular morbidity and end-stage renal disease. *J Diabetes Complications* 2015; 29: 1098-104. [\[CrossRef\]](#)
14. Chen G, Wu J, Lin Y, Huang B, Yao J, Jiang Q, et al. Associations between cardiovascular risk, insulin resistance, beta-cell function and thyroid dysfunction: a cross-sectional study in the ethnic minority group of Fujian Province in China. *Eur J Endocrinol* 2010; 163: 775-82. [\[CrossRef\]](#)
15. Dimitriadis G, Maratou E, Boutati E, Kollias A, Tsegka K, Alevizaki M, et al. IGF-I increases the recruitment of GLUT4 and GLUT3 glucose transporters on cell surface in hyperthyroidism. *Eur J Endocrinol* 2008; 158: 361-6. [\[CrossRef\]](#)
16. Peppas M, Koliaki C, Nikolopoulos P, Raptis SA. Skeletal muscle insulin resistance in endocrine disease. *J Biomed Biotechnol* 2010; 10: 527850. doi: 10.1155/2010/527850. Epub 2010 Mar 15. [\[CrossRef\]](#)
17. Teta D. Insulin resistance as a therapeutic target for chronic kidney disease. *J Ren Nutr* 2015; 25: 226-9. [\[CrossRef\]](#)
18. Ozdemir D, Dagdelen S, Usman A. Serum adiponectin levels and changes in glucose metabolism before and after treatment for thyroid dysfunction. *Intern Med* 2015; 54: 1849-57. [\[CrossRef\]](#)
19. Nada AM. Effect of treatment of overhypothyroidism on insulin resistance. *World J Diabetes* 2013; 4: 157-61. [\[CrossRef\]](#)
20. Chen HY, Lin CC, Chiu YL, Hsu SP, Pai MF, Yang JY, et al. Liver fat contents, abdominal adiposity and insulin resistance in non-diabetic prevalent hemodialysis patients. *Blood Purif* 2014; 38: 55-61. [\[CrossRef\]](#)
21. Vogt BP, Souza PL, Minicucci MF, Martin LC, Barretti P, Caramori JT. Metabolic syndrome criteria as predictors of insulin resistance, inflammation and mortality in chronic hemodialysis patients. *Metab Syndr Relat Disord* 2014; 12: 443-9. [\[CrossRef\]](#)