# Association Between C-Reactive Protein, Uric Acid, Microalbuminuria and Insulin Resistance in Type 2 Diabetic Patients

## Tip 2 Diyabet Hastalarında C-Reaktif Protein, Ürik Asit, Mikroalbüminüri ve İnsulin Rezistansı Arasındaki İlişki

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**ABSTRACT Objective:** Microalbuminuria, hyperglycemia, insulin resistance, C-reactive protein and uric acid are thought to be associated with cardiovascular events. We planned to evaluate the relation of C-reactive protein and uric acid with microalbuminuria and insulin resistance in type 2 diabetic patients. **Material and Methods:** We recruited 114 type 2 diabetic patients. Seventy of them were without and 44 of them were with microalbuminuria. We compared various biochemical parameters including C-reactive protein and uric acid levels. Then we classified 114 patients according to having or not having insulin resistance. Fifty-two non-insulin resistant and 62 insulin resistant type 2 diabetic patients were grouped as without and with microalbuminuria. Afterwards we compared aforementioned parameters between the groups. **Results:** C- reactive protein and uric acid levels of type 2 diabetic patients having microalbuminuria were statistically higher than those patients without microalbuminuria (p:<0.001 both). Indirect insulin resistance index did not differ in two groups. After we grouped our type 2 diabetics according to their insulin resistance indices we found that C-reactive protein and uric acid levels were statistically higher in patients who had microalbuminuria than who did not have microalbuminuria in non-insulin resistant type 2 diabetics (p:<0.001 and p:<0.005 respectively). There was no significant difference in any of the parameters of insulin resistant type 2 diabetic patients without and with microalbuminuria including C-reactive protein and uric acid levels. **Conclusions:** These results suggests that high C-reactive protein and uric acid levels are associated with microalbuminuria in type 2 diabetic patients. We speculate that the relation of C-reactive protein and uric acid with microalbuminuria may be independent of insulin resistance in the beginning of diabetes.

**Key Words:** Type 2 diabetes mellitus; C-Recative protein; uric acid; albuminuria; insulin resistance

**ÖZET Amaç:** Mikroalbüminüri, hiperglisemi, insülin rezistansı, C-reaktif protein ve ürik asitin kardiyovasküler olaylar ile bağlantılı olduğu düşünülmektedir. Araştırmamızda tip 2 diyabetik hastalarda C-reaktif protein ve ürik asitin mikroalbüminüri ve insülin rezistansı ile ilişkisini değerlendirmeyi planladık. **Gereç ve Yöntemler:** Yüz on dört tip 2 diyabetik hastayı çalışmamıza dahil ettik. Hastalarımızı mikroalbüminüri varlığına göre iki gruba ayırdık. Yetmişinde mikroalbüminüri yokken, 44'ünde mikroalbüminüri mevcuttu. Bu iki grupta C-reaktif protein ve ürik asit de dahil olmak üzere tüm parametreleri kıyasladık. Daha sonra hastalarımızı insülin rezistansı varlığına göre sınıfladık. Elli iki hasta non-insülin rezistan iken 62'si insülin rezistan idi. Non-insülin rezistan ve insülin rezistan hastaları mikroalbüminüri varlığına göre tekrar gruplandırdıktan sonra tüm parametrelerde kıyaslamalarımızı tekrarladık. **Bulgular:** Mikroalbüminürisi olan tip 2 diyabetik hastaların C- reaktif protein ve ürik asit seviyeleri mikroalbüminürisi olmayanlara göre belirgin olarak yüksekti (her ikisi de p:<0,001). İndirekt insülin rezistans indeksi iki grupta farklılık göstermedi. Hastalarımızı insülin rezistansı varlığına göre gruplandırdığımızda non-insülin rezistan grupta C-reaktif protein ve ürik asit seviyelerinin mikroalbüminürili hastalarda belirgin olarak yüksek olduğunu bulduk. İnsülin rezistan olup mikroalbüminürisi olan ve olmayan gruplarda C-reaktif protein ve ürik asit de dahil olmak üzere hiçbir parametrede farklılık yoktu. **Sonuç:** Bu bulgular tip 2 diyabet hastalarında C-reaktif protein ve ürik asidin mikroalbüminüri ile ilişkili olduğunu düşündürdü. Ayrıca bulgularımızla uyumlu olarak C-reaktif protein ve ürik asit ile mikroalbüminüri ilişkisinin diyabetin başlangıç safhalarında insülin rezistansından bağımsız olabileceği spekülasyonunu yapmak istiyoruz.

**Anahtar Kelimeler:** Tip 2 diabetes mellitus; C-reaktif protein; ürik asit; albüminüri; insülin direnci



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Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in most modern societies, with prevention and treatment and risk factors of the condition a focus of recent attention.[1] Clinical and laboratory evidence indicate that inflammation plays a crucial role in cardiovascular events. C-reactive protein (CRP) is both a marker and regulator of many inflammatory pathways. Several studies reported that increased CRP levels predicted increased risk of CVD.[2-7] It was also suggested that CRP may be associated with renal function loss and elevated urinary albumin excretion.[8-10]

The association of uric acid (UA) levels and risk for cardiovascular events is well established but whether this relationship is casual or not remains disputed.[11-13] UA was also found to be positively correlated with urinary albumin excretion.[14]

Microalbuminuria (MA) is considered the best non-invasive test for incipient nephropathy and a good predictor of progression to renal disease.[15] It is also found to be associated with increased cardiovascular mortality and morbidity in diabetic and non diabetics.[16-18] As increased urinary albumin excretion is supposed to be a cardiovascular risk factor, a strong relationship between microalbuminuria and the metabolic syndrome has been demonstrated.[19] Metabolic syndrome components such as elevated blood pressure, elevated triglycerides, low HDL cholesterol, abdominal obesity and impaired fasting glucose were found to be associated with microalbuminuria.[20]

Insulin resistance is a clinical condition characterized by a decrease in sensitivity and responsiveness to the metabolic actions of insulin, so that a given concentration of insulin produces a less-than-expected biological effect. Insulin resistance represents the earliest detectable abnormality in type 2 diabetes, and is one of the major underlying mechanisms of hypertension and cardiovascular diseases.[21,22] Lower glomerular filtration rate was found to be associated with insulin resistance.[23]

Bearing in mind the complex relationship between microalbuminuria, CRP, UA and insulin resistance, we planned to examine CRP and UA levels in type 2 diabetic patients with and without insulin resistance and with and without microalbuminuria.

## MATERIAL AND METHODS

### PATIENTS

In this cross-sectional study 114 Type 2 diabetic patients aged from 30-80 years, were recruited from the outpatient Clinic of Ankara Training and Research Hospital from February 2011 to October 2011. Type 2 diabetes mellitus (T2DM) was diagnosed according to the criteria of American Diabetes Association 2011. Fifty-two of them were without insulin resistance and 62 T2DM patients were with insulin resistance. The patients were also classified as having microalbuminuria (with 30-300 mg microalbumin in 24 hour urine) and without microalbuminuria (with <30 mg microalbumin in 24 hour urine). Among 52 non-insulin resistant patients, 26 of them dropped into microalbuminuria (-) group and another 26 of them dropped into microalbuminuria (+) group. Among 62 insulin resistant patients, 44 were without microalbuminuria and 18 were with microalbuminuria.

The patients did not show a history of diabetic ketoacidosis at the onset of diabetes and none were being treated with insulin at the time of recruitement. Patients using uric acid lowering agents, diuretics or alcholic beverages were excluded. Patients with acute illness, malignancy, chronic diseases, fever or urinary tract infection were likewise excluded. We also did not include patients who have chronic renal disease (glomerular filtration rate <60 mL/min), pregnancy and having other diseases which may interfere with serum CRP levels.

After detailed physical examination, we measured body weight and height of all the patients. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters ($kg/m^2$).

Blood was withdrawn after 12 hours of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting insulin (FI), serum total and HDL cholesterol

(HDL-C), triglyceride (TG), creatinine, CRP, uric acid levels. Another blood sample was taken for postprandial plasma glucose (PPPG) 2 h after breakfast.

An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μunite /ml) x fasting plasma glucose (mmol/l) /22.5 formula as homeostasis model assessment-insulin resistance (HOMA-IR). Patients with HOMA-IR ≥ 2.7 were classified as insulin resistant. Creatinine clearance was calculated by the formula of urine creatinine x volume of the urine/serum creatinine x1440.

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 min rest in the semi-sitting position with a sphygmomanometer. Blood pressure (BP) was determined at least three times at the right upper arm, and the mean was used in the analysis. Korotkoff's first phase was accepted as systolic and fifth phase was accepted as diastolic pressure. Our patients were grouped according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and divided into stage 1 (BP <120/80 mm Hg), stage 2 (BP 120/80-139/89 mm Hg), stage 3 (BP 140/90- 159/99 mm Hg) and stage 4 (BP >160/100 mm Hg).

### LABORATORY METHODS

Plasma glucose, uric acid, total cholesterol, TG and HDL-C concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula ( LDL: Total cholesterol-HDL-TG/5). HbA1c was measured by turbidometric inhibition immunoassay in otoanalyser. FI was measured by TOSOH G7 HPLC system and high sensitivity C-reactive protein (CRP) by immunflowmetric tests with Beckman-Cutler device. Microalbuminuria was investigated in 24 h urine by turbidometric method.

### METHODS

We compared all the parameters in type 2 diabetics without and with microalbuminuria. Then we classified the patients as non-insulin resistant and insulin resistant and made the comparisons after grouping them with and without microalbuminuria.

This study was performed according to the Helsinki decleration 2008. The local ethics committee approved this study and all the subjects gave their written informed consent.

### STATISTICAL ANALYSIS

Calculations were performed using SPSS version 12. Student's test and Chi-square test were used to compare the groups. Data were presented as mean ± SD. A p value of $< 0.05$ was considered as statistically significant.

## RESULTS

We performed the study with 114 T2DM patients. All the demographic and laboratory findings of the patients were presented in Table 1.

Only CRP and UA of the pateints with microalbuminuria were higher than those of the patients without microalbuminuria (p:<0.001 both). HOMA-IR of both groups were indifferent.

After we groupped 114 patients according to their HOMA-IR, we found that 52 T2DM patients were non insulin resistants and 62 T2DM patients were insulin resistants. Then we classified our patients as they were having or not having microalbuminuria. All the demographic and laboratory findings of the T2DM patients without and with insulin resistance were presented in Table 2.

Among non-insulin resistant T2DM patients, those who have microalbuminuria displayed significantly high CRP and UA levels ( p:<0.001 and p:<0.005 respectively). Among insulin resistant T2DM patients with and without microalbuminuria, there were not any significant differences in terms of biochemical parameters including UA and CRP levels (Table 2).

## DISCUSSION

During the past decade, clinical researches have accumulated that elevated CRP levels are associated with a far higher incidence of adverse vascular events including myocardial infarction, stroke, un-

**TABLE 1:** Demographic and laboratory findings of type 2 diabetic patients with and without microalbuminuria.

| | MA (-) n: 70 | MA (+) n: 44 | P |
|---|---|---|---|
| Age (year) | 56.0 ± 8.3 | 56.5 ± 11.1 | NS |
| BMI (kg/m$^2$) | 29.1 ± 3.9 | 29.9 ± 5.6 | NS |
| BP (stage) | 2.0 ± 0.7 | 1.9 ± 0.5 | NS |
| FBG (mg/dL) | 150.2 ± 63.4 | 160.1 ± 61.0 | NS |
| PPBG (mg/dL) | 230.1 ± 103.7 | 235.7 ± 91.4 | NS |
| HbA1c (%) | 7.6 ± 1.8 | 8.2 ± 2.4 | NS |
| FI (μU/mL) | 8.9 ± 5.8 | 8.5 ± 4.9 | NS |
| HOMA-IR | 3.7 ± 2.5 | 3.9 ± 2.5 | NS |
| T.Chol. (mg/dL) | 196.8 ± 43.2 | 208.0 ± 43.1 | NS |
| LDL-C (mg/dL) | 119.1 ± 35.2 | 121.7 ± 32.3 | NS |
| HDL-C (mg/dL) | 44.8 ± 10.0 | 46.7 ± 8.7 | NS |
| TG (mg/dL) | 171.3 ± 100.9 | 195.2 ± 110.5 | NS |
| Cr. Cl. (mL/min) | 98.3 ± 29.6 | 89.9 ± 25.5 | NS |
| CRP (mg/dL) | 3.3 ± 2.5 | 5.6 ± 2.8 | <0.001 |
| UA (mg/dL) | 4.5 ± 1.1 | 5.3 ± 1.7 | <0.001 |

MA: Microalbuminuria, BMI: Body Mass Index; BP: Blood Pressure; FBG: Fasting Blood Glucose; PPBG: Post Prandial Blood Glucose; HbA1c: Hemoglobin A1c; FI: Fasting Insulin; HOMA-IR: Homeostasis Model Assesment Index-Insulin Resistance; T.Chol: Total Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; TG: Triglyceride; Cr. Cl: Creatinine Clearance; CRP: C-Reactive Protein; UA: Uric Acid; Data were presented as mean±SD. NS: Nonsignificant.

stable angina and sudden coronary death.[2-7] Traditionally assumed to be produced only in the liver, it has recently been shown that CRP is also produced locally in atheromatous lesions.[24] Recent laboratory data have suggested that CRP may contribute to the progression of cardiovascular disease by reducing nitric oxide (NO) production, decreasing fibrinolytic capacity and increasing endotelin-1 production.[25-27]

Emerging data suggest that CRP may be a risk marker for renal function loss. High CRP levels were found to be closely related to elevated urinary albumin excretion in patients with and without diabetes.[28-32] Consistent with these findings we demonstrated that CRP levels of the diabetic patients were higher in the patients who had MA than the ones of the patients without MA as well as in non-insulin resistant patients with MA compared to the ones without MA.

Uric acid levels are associated with an increased risk of hypertension and cardiovascular events.[11-13]Hyperuricemia, occurs in many renal diseases.[33] The mechanisms underlying hyper-

**TABLE 2:** Demographic and laboratory findings of non-insulin resistant and insulin resistant type 2 diabetic patients with and without microalbuminuria

| | Non-Insulin Resistant T2DM | | | Insulin Resistant T2DM | | |
|---|---|---|---|---|---|---|
| | MA (-) n: 26 | MA (+) n: 26 | P | MA (-) n: 44 | MA (+) n: 18 | P |
| Age (year) | 56.1±8.2 | 56.5±11.2 | NS | 54.0±7.3 | 53.5±14.1 | NS |
| BMI (kg/m$^2$) | 29.2±4.0 | 29.9± 5.7 | NS | 29.4±2.9 | 29.1± 6.6 | NS |
| BP ( stage) | 2.2±0.6 | 1.8± 0.6 | NS | 2.6±0.7 | 1.7± 0.2 | NS |
| FBG (mg/dL) | 125.8±27.3 | 122.7±36.6 | NS | 170.4±70.0 | 199.6±68.1 | NS |
| PPBG (mg/dL) | 179.3± 62.6 | 184.9 ±58.6 | NS | 260.1± 111.7 | 284.5 ±99.2 | NS |
| HbA1c (%) | 6.9±1.7 | 7.5±2.1 | NS | 7.8±1.7 | 8.3±2.3 | NS |
| FI (μU/mL) | 2.0±0.01 | 2.0±0.02 | NS | 9.6± 4.7 | 11.9±6.4 | NS |
| HOMA-IR | 1.6± 0.6 | 1.7±0.6 | NS | 5.0± 2.3 | 5.3±2.9 | NS |
| T.Chol. (mg/dL) | 187.3±38.8 | 215.5± 37.8 | NS | 202.4±45.0 | 197.0± 48.8 | NS |
| LDL-C (mg/dL) | 109.8±27.7 | 128.8± 31.4 | NS | 124.5±38.2 | 111.4± 31.5 | NS |
| HDL-C (mg/dL) | 44.3±10.9 | 47.2±9.2 | NS | 45.1±9.5 | 46.1±8.0 | NS |
| TG (mg/dL) | 173.1± 67.9 | 196.7± 97.2 | NS | 182.1± 115.4 | 192.8± 130.2 | NS |
| Cr. Cl. (mL/min) | 92.3± 22.4 | 89.8± 16.7 | NS | 89.5± 24.3 | 98.3±17.3 | NS |
| CRP (mg/dL) | 2.8 ±1.9 | 6.3±2.9 | <0.001 | 3.6 ±2.8 | 4.3±2.2 | NS |
| UA (mg/dL) | 4.5 ±1.2 | 5.7±1.6 | <0.005 | 4.3 ±0.9 | 4.6±1.5 | NS |

MA: Microalbuminuria; BMI: Body Mass Index; BP: Blood Pressure, FBG: Fasting Blood Glucose; PPBG: Post Prandial Blood Glucose HbA1c: Hemoglobin A1c; FI: Fasting insulin; HOMA-IR: Homeostasis Model Assesment Index-Insulin Resistance; T.Chol: Total Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol, TG: Triglyceride, Cr. Cl: Creatinine Clearance, CRP: C-Reactive Protein; UA: Uric Acid; Data were presented as mean±SD. NS: Nonsignificant.

uricemia as a result of reduced renal clearance of uric acid may involve a reduced glumerular filtration rate or dysfunctional handling of filtered uric acid by proximal tubules.[34] Furthermore, elevated serum uric acid itself may increase the risk for development of renal disease in both the general population and patients with diabetes.[14,35-38] In our study we also demonstrated the relation of UA with MA in T2DM patients by finding higher UA levels in microalbuminuric diabetic patients than non-microalbuminuric ones. Also, in diabetic patients without insulin resistance UA levels of microalbuminuric patients were higher than those of the patients without MA.

So far magnitude of insulin resistance and both CRP[39,40] and UA[41,42] concentrations were found to be significantly related. In concordance with these studies and keeping in mind the relation of MA with CRP and UA we thought that we would find higher CRP and UA levels in microalbuminuric patients compared to non-microalbuminuric ones especially in insulin resistant diabetics. However, it is interesting that we could only show this positive correlation of CRP and UA with microalbuminuria in non-insulin resistant T2DM patients, instead of insulin resistant patients. It is very easy to say that the reason of this finding may be the limited number of our groups. Instead we want to speculate that the relation of CRP and UA with MA may be independent of insulin resistance, at least when diabetes is not yet serious. Considering the inclusion criteria, we had chosen diabetics who were not complicated with other comorbidities, who did not have the history of diabetic ketoasidosis or who were not having insulin treatment. Their glomerular filtration rate were above 60 mL/min and they had not severe hypertension. Also their HbA1c levels were not very high.

Some methodological issues have to be addressed. First we included diabetic patients with hypertension. All these patients were being treated with one or more antihypertensive drugs, including angiotensin II receptor blockers, angiotensin converting enzyme inhibitors and calcium channel antagonists, before enrollment. All these drug classes have been reported to improve insulin resistance. In addition our patients were diagnosed as dyslipidemic. All these patients were being treated with statins. In this regard these drugs have been reported to decrease the levels of CRP. Therefore, it may be said that these medications might have affected beneficially our results, although CRP levels of every group were high. Also as to antidiabetic medications, a considerable number of our patients were being treated with glitazones, insulin sensitizing drugs reported to reduce CRP. Second, our study was a cross-sectional one, performed in a single center, so it can not be generalized in Turkish population. Additionaly, enlargement of sizes of the groups are needed.

Despite the aforementioned limitations of our study, in conclusion, CRP and UA levels are related to microalbuminuria in type 2 diabetic patients. We also speculate that this relationship did not depend on insulin resistance, probably at the beginning of type 2 diabetes.

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