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Research Article

The Relationship Between Spot Urinary Protein/Creatinine Ratio and HbA1C, Metabolic Parameters and Other Complications in Patients with Type 2 Diabetes

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Abstract

Objectives: The purpose of the study was relationship between spot urinary protein/creatinin ratio and HbA1c, metabolic parameters and other complications in patients with type 2 diabetes.

Methods: The retrospective study was carried out in type 2 diabetes patients followed up for at least 2 years; during March 2016. Biochemical parameters in the last 3 visits were recorded. BMI, waist circumference and physical examination findings were recorded at the time of last visit. Patients were divided into groups according to their spot urine protein/creatinine ratios.

Results: This study was consisted of 198 patients, 113 females and 85 males. The mean age was 60.6±10.68. The total outpatient clinic follow-up time was 13.02±7.2 years in the entire patient group. In 198 patients evaluated, the average of HbA1c(first, second, last) and spot urine protein/creatinine ratios(first, second, last). There was an increase in both groups but no correlation was found between these increases. When urine protein/creatinine ratios of the last control were examined, the relationship between these rates and age, urea, creatinine, GFR, total cholesterol, triglyceride, HDL, LDL, AST, ALT, CRP, HbA1c values were investigated. When the patients were compared according to their spot urine protein/creatinine ratios being <150 mg/g and >150 mg/g; metabolic syndrome was detected 2,351 times (OR) higher in second group.

Conclusion: We found positive correlation between microalbuminuria and spot urinary protein/creatinine ratios. We also found a relationship between metabolic syndrome, frequency of retinopathy and spot urine protein/creatinine ratios.

Keywords: HbA1c, Spot urinary protein/creatinine ratio, type 2 diabetes mellitus

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The frequency of diabetes has been increasing in recent years, and diabetes' complications have also increased. Being aware of the risk factors of diabetes, diagnose and manage the disease at an early stage will decrease mortality and morbidity due to diabetes and its complications. Chronic kidney failure is one of the most important complications of diabetes.[1] Microalbuminuria provides information about chronic kidney failure, as well as endothelial damage, and is an indicator of an increased risk of other complications. In the evaluation of diabetic nephropathy, spot urine protein/creatinine ratio and albümin/creatinine ratio seem to be more useful than 24-hour urine collection. Spot urine protein/creatinine ratio also more cost-effective in outpatient follow-ups.

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Methods

The protocol of this study was approved by the Institutional Review Board of the Health Sciences University of Haseki Training and Research Hospital. In the study, type 2 diabetes patients who visited Haseki Training and Research Hospital Diabetes Outpatient Clinic during March 2016 and had been followed up for at least 2 years were evaluated retrospectively. Biochemical parameters (glucose, urea, creatinine, total cholesterol, HDL, LDL, triglyceride, AST, ALT, CRP, spot urine microalbumin, spot urine protein/creatinine ratio, HbA1c) in the last 3 visits of follow-up patients were recorded. BMI, waist circumference and physical examination findings were recorded at the time of last visit. The presence of metabolic syndrome was evaluated according to ATP 3 criteria (fasting blood glucose >110 mg/dl or presence of diabetes, systolic blood pressure >130 mmHg, diastolic blood pressure >85 mmHg or receiving antihypertensive therapy, triglyceride level ≥150 mg/dl or HDL level <40 mg/dl in men, <50 mg/dl in women, waist circumference >94 cm in men, >80 cm in women). The patients' medical records were controlled to evaluate the ECG findings (ST segment changes, T wave inversion, pathological Q wave, left bundle branch block were evaluated as ischemic findings), retinopathy examination findings in the last 6 months, antidiabetic drugs, disease duration and family history. The target value for HbA1c was accepted as 7%. Patients were evaluated in 3 groups according to spot urine protein/creatinine ratios: those below 150 mg/g in the first group, 150-500 mg/gr in the second group, and more than 500 mg/gr in the third group. In addition, patients were examined in two separate groups as spot urine protein/creatinine ratio below 150 mg/g and above 150 mg/g. The average values of the three HbA1c levels and spot urine protein/creatinine ratios were also recorded.

Statistical Analysis

All statistical data were analyzed using Statistical Package for Social Sciences (SPSS) version 17.0 software. In our study, the patients who were evaluated retrospectively were divided into 3 groups. Descriptive statistics (mean, std. deviation, median, minimum, maximum) were used for numerical variables, number of people and percentages were used for categorical variables. Student's T test was used in binary comparisons in numerical data with normal distribution. If the distribution is not normal, Mann-Whitney U was used in binary comparisons. More than two group comparisons of numerical variables were made with One Way Anova test when distribution was normal, and with Kruskal Wallis test if distribution was not normal. Subgroup analyzes were interpreted according to Tukey and Bonferroni correction in the parametric test. While evaluating categorical variables, chi-square test was used. The $p<0.05$ or 95% confidence interval were considered statistically significant.

Results

This study was consisted of 198 patients, 113 females and 85 males. The mean age was 60.6±10.68 (60.55±10.88 in men and 60.64±10.57 in women). The total outpatient clinic follow-up time was 13.02±7.2 years in the entire patient group (12.23±6.89 years in men and 13.62±7.09 in women). In 198 patients evaluated, the average of the first HbA1c values was 7.73±1.47 (5.7-13.5) mmol/mol, the average of the second HbA1c values was 7.89±1.48 (5.4-12.6) mmol/mol, the average of the last HbA1c values was 7.95±1.40 (5.5-12.6) mmol/mol and this increase in HbA1c values was statistically significant ($p<0.001$). Also in these patients, the mean of the first spot urine protein/creatinine ratios was 300.84±731.33 (6.5-8239.55) mg/g, the average of the second ratios was 334.36±828.45 (32.22-7302.82) mg/g, the average of the last ratios was 392.44±778.97 (11.61-5738.58) mg/g. When these data were evaluated, there was a statistically significant increase in spot urine protein/creatinine ratios during the follow-up of patients ($p<0.001$). However, although HbA1c levels and spot urine protein/creatinine ratios increased during follow-ups, no correlation was found between these increases ($p>0.05$). A positive correlation was found between spot urinary microalbumin values and protein/creatinine ratios in the last controls of the patients ($p<0.001$; $r=0.790$). When urine protein/creatinine ratios of the last control were examined, it was found as <150 mg/g in 105 patients, 150-500 mg/g in 59 patients and >500 mg/g in 34 patients. The relationship between these rates and age, urea, creatinine, GFR, total cholesterol, triglyceride, HDL, LDL, AST, ALT, CRP, HbA1c values were investigated. As a result, a statistically significant relationship was found with age, urea, creatinine, GFR, total cholesterol, triglyceride, LDL, CRP levels. No statistically significant relationship was detected between HDL, AST, ALT and HbA1c levels and urine test results (Table 1). When the average of the urinary protein/creatinine ratios of the patients which measured three times were evaluated, there were 116 patients in the first group with a protein/creatinine ratio of <150 mg/g, 26 patients in the second group with 150-500 mg/g and 26 patients in the third group with >500mg/g. Statistically significant difference was found in urea, creatinine, GFR, total cholesterol, triglyceride, LDL and CRP values among these three groups. However, there was no statistically significant difference in age, HDL, AST, ALT and HbA1c levels (Table 2). Considering the electrocardiograms of the patients, 47 patients had ischemic findings in total 23, 12 and 12 patients in the first, second and third groups, respectively. In these

Table 1. Distribution of groups according to last spot urine protein/creatinine ratios

	First group	Second group	Third group	p
Number of patient	105	59	34	
Age	59.17±9.51	60.47±11.81	65.24±11.03	0.015
Urea	34.93±12.47	38.23±19.66	48.56±27.55	0.001
Creatinine	0.79±0.26	0.85±0.34	1.15±0.6	<0.001
GFR	92.05±21.85	88.17±31.15	66.91±28.46	<0.001
Total cholesterol	184.94±30.51	190.88±44.38	214.06±53.31	0.001
Triglyceride	150.4±82.81	179.78±97.72	188.32±88.62	0.034
HDL	49.58±12.1	45.24±11.21	48.63±11.29	0.075
LDL	106.68±28.24	114.49±42.46	130.09±44.6	0.005
AST	24.2±12.07	25.08±13.46	23.15±8.52	0.75
ALT	26.98±26.48	23.66±14.81	22.09±15.73	0.437
CRP	4.38±4.18	10.05±20	7.33±8.95	0.019
HbA1c (last)	7.75±1.15	8.17±1.65	8.19±1.55	0.102

First group: urine protein/creatinine ratio <150 mg/g, second group: urine protein/creatinine ratio 150-500 mg/g, third group: urine protein/creatinine ratio> 500mg/g.

Table 2. Distribution of groups according to the average of the last three spot urine protein/creatinine ratios

	First group	Second group	Third group	p
Number of patient	116	56	26	
Age	59.26±9.42	61.66±12.32	64.31±11.47	0.063
Urea	34.21±11.85	39.58±19.53	39.58±19.53	<0.001
Creatinine	0.79±0.26	0.85±0.34	1.15±0.6	<0.001
GFR	92.25±21.18	84.25±33.04	66.27±30.16	<0.001
Total cholesterol	183.62±30.44	203.46±52.21	214.06±53.31	0.04
Triglyceride	152.39±81.21	203.46±52.21	184.19±93.47	0.045
HDL	49.22±12.25	46.14±10.37	47.51±12.53	0.267
LDL	105.17±28.89	125.54±46.83	121.12±36.42	0.002
AST	24.89±13.79	23.61±9.29	23.08±7.58	0.694
ALT	27.06± 26.1	23.3±13.65	20.65±14.02	0.308
CRP	4.54±4.28	10.61±20.77	6.59±5.56	0.01
HbA1c	7.71±1.1	8.09±1.5	7.94±1.24	0.161

First group: urine protein/creatinine ratio <150 mg/g, second group: urine protein/creatinine ratio 150-500 mg/g, third group: urine protein/creatinine ratio> 500mg/g.

groups, there were no ischemic findings in 93, 44, and 14 patients, respectively. There was a correlation between ischemic findings in electrocardiograms and spot urine protein/creatinine ratios, (p=0.015). In the first, second and third groups, a total of 76 patients, 33, 25 and 18 patients, respectively, had diabetic retinopathy. Diabetic retinopathy was not found in 83, 31 and 8 patients, respectively. There was a correlation between the diabetic retinopathy and spot urine protein/creatinine ratios, (p<0.001). When BMI average values are evaluated in patient groups; it was determined as 30.22±4.72 kg/m^2, 32.62±5.43 kg/m^2 and 32.39±5.39 kg/m^2, respectively, (p=0.038). These three groups were compared and no statistically significant difference was detected. Mean waist circumference of the patients in the groups were determined as 104.13±13.66 cm, 114.82±15.78 cm and 112.56±13.62 cm, respectively. When the groups were compared, it was determined that the statistically significant change was only between the first group and the second group, (p=0.001). Hypertension was present in 57 patients (49.1%) in the first group, 38 patients (67.9%) in the second group, and 23 patients (88.5%) in the third group, (p<0.001).

Metabolic syndrome was observed in 76 patients (65.5%) in the first group, 46 patients (82.1%) in the second group, and 21 patients (80.6%) in the third group. There was a correlation between spot urine protein/creatinine ratios and

frequency of metabolic syndrome, (p=0.027). When the patients were compared according to their spot urine protein/creatinine ratios being <150 mg/g and >150 mg/g; metabolic syndrome was detected in 76 (65.5%) of 116 patients in the first group and in 67 (81.7%) of 82 patients in the second group. According to these findings, it is observed that the presence of metabolic syndrome is 2.351 times (OR) higher in those with an average spot urine protein/creatinine ratios above 150 mg/g (p=0.012, 95% CI 1.193-4.632), (Fig. 1).

The patients were divided into two groups as spot urine protein/creatinine ratios below 150 mg/g and above 150 mg/g and evaluated for diabetic retinopathy. Diabetic retinopathy was detected in 33 patients (28.4%) in the first group and 43 patients (52.4%) in the second group. Those with an average spot urine protein/creatinine ratios above 150 mg/g also had diabetic retinopathy 2.773 times (OR) more, (p: 0.001, 95%CI 1.534 – 5.013). The effect of regression model created from variables that differed from the endpoint in the univariant analysis (age, CRP and presence of metabolic syndrome) on the spot urine protein/creatinine values being above 150 mg/g was investigated. According to the Backward Stepwise method, CRP (p=0.007, OR 1.091) and the presence of metabolic syndrome (p=0.026, OR 2.275) were identified as the most effective risk factors, (Table 3).

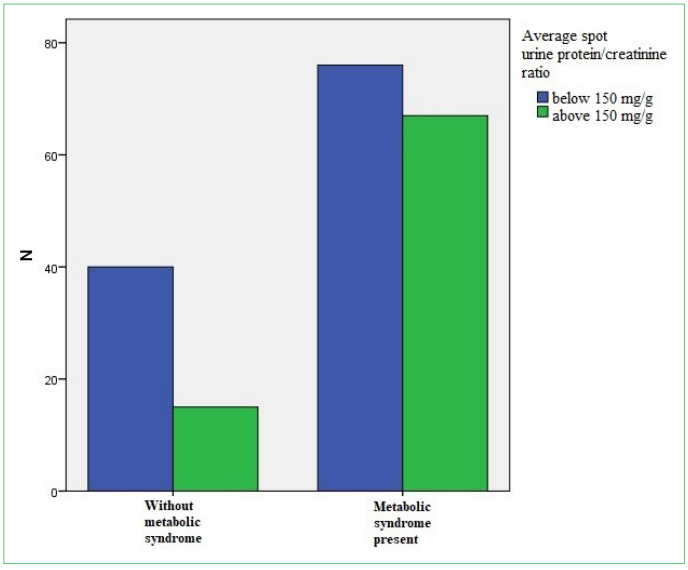

Figure 1. The relationship of average spot urine protein/creatinine ratio and metabolic syndrome.

The effect of similarly created regression model (age, CRP, triglyceride >150 mg/dl, HDL-cholesterol<40 mg/dl [in men] or <50 mg/dl [in women], waist circumference ≥94 cm [in men] or ≥88 cm [in women], presence of hypertension and LDL cholesterol levels), on the spot urine protein/creatinine ratios being above 150 mg/g were also investigated. According to the Backward Stepwise method, CRP (p=0.013, OR 1.085), presence of hypertension (p=0.036, OR 2.128) and LDL cholesterol (p=0.005, OR 1.014) were the most effective risk factors (Table 3).

Discussion

In our study, a positive correlation between microalbuminuria and spot urinary protein/creatinine ratios was found in diabetic patients followed up during 2 years. While the relationship between diabetes regulation and spot urine protein/creatinine ratios could not be determined, we found a relationship between metabolic syndrome and these ratios. We also found a relationship between the frequency of retinopathy and spot urine protein/creatinine ratios. Diabetes is a disease with chronic complications, its prevalence is gradually increasing, and it requires regular follow-up and treatment. Diabetic nephropathy is the most common cause of end-stage renal failure. Diabetic patients account for 39% of patients on dialysis treatment due to

Table 3. Multivariete analysis of factors affecting spot urine protein/creatinine ratio

	OR	95% CI		p
		Lower	Upper	
Age	1.030	0.999	1.062	0.059
CRP	1.091	1.024	1.163	0.007
Metabolic syndrom (present)	2.275	1.101	4.703	0.026
Age	1.031	0.996	1.067	0.080
CRP	1.085	1.018	1.157	0.013
Triglyceride >150 mg/dl	1.727	0.869	3.432	0.119
HDL-kolesterol <40 mg/dl (in men) or <50 mg/dl (in women)	1.159	0.590	2.278	0.668
Waist circumference ≥94 cm (in men) or ≥ 88 cm (in women)	1.046	0.537	2.038	0.894
Presence of hypertension	2.128	1.050	4.312	0.036
LDL cholesterol	1.014	1.004	1.023	0.005

chronic kidney failure. For diabetic nephropathy follow-up, it is recommended to examine albumin and protein levels in 24-hour urine samples. However, this measurement was replaced by the easier spot urine albumin/creatinine ratio or the more cost-effective spot urine protein/creatinine ratio as also recommended by Xin et al. in patients with GFR> 10 ml/min.[2] In our study, we grouped the patients according to spot urine protein/creatinine ratios at the intervals recommended in KDIGO 2012 and investigated the factors affecting these values in diabetic patients. In a study conducted in Thailand, Krairittichai U et al. suggested that the main factors affecting diabetic nephropathy are HbA1c and uncontrolled hypertension.[3] In our study, no relation was found between HbA1c spot urine protein/creatinine ratios in the follow-up of the patients. In our study group, the frequency of metabolic syndrome was 72.2% and the prevalence was higher than the general population. The relationship between the presence of metabolic syndrome and the categorized average spot urine protein/creatinine ratios (<150 mg/g, 150-500 mg/g and ≥500 mg/g) was statistically significant [116 (65.5%), 56 (82.1%) and 26 (80.8%), respectively], (p=0.027). The relationships between the number of metabolic syndrome parameters and the categorized average of spot urine protein/creatinine ratios, the presence of hypertension and the categorized average of the spot urine protein/creatinine ratios were statistically significant. (p=0.001 and p=<0.001, respectively). Relationships between metabolic syndrome parameters such as triglyceride, waist circumference and hypertension and the categorized mean spot urine protein/creatinine ratios were statistically significant, (p=0.034, p=0.001 and p<0.001, respectively). No statistically significant difference was found with HDL cholesterol levels, (p=0.267). When we examined the LDL levels, we found a statistically significant difference especially between the groups with spot urine protein/creatinine ratios <150 mg/g and 150-500 mg/g. In their study, Rossi et al. suggested that there is a relationship between microalbuminuria and the severity of diabetes, smoking and metabolic syndrome parameters such as high blood pressure, low HDL level, abdominal obesity, and they suggested to detect microalbuminuria and correct modifiable factors quickly.[4] According to the study of Zhang et al., the presence of diabetic nephropathy was associated with age, gender, blood pressure, and triglyceride, LDL, uric acid levels.[5] In another study by Chang YH et al., high or normal HDL levels were found to be protective against albuminuria.[6] In a study conducted by Hanai K et al. in Japan, abdominal obesity was shown to be an independent risk factor for albuminuria.[7] Laville M suggested that obesity will cause nephropathy or worsen nephropathy, regardless of whether hypertension and diabetes are present.[8] In their study, Khedr A et al. found that high BMI values were not a risk factor for chronic kidney disease independent of diabetes or hypertension.[9] We found a relationship between BMI and spot urine protein/creatinine values; but when the groups were compared, no significant difference was found. When we evaluate waist circumference measurements to assess abdominal obesity, statistically significant difference was found between groups with spot urine protein/creatinine ratios <150 mg/g and 150-500 mg/g. With this difference, it was seen that waist circumference measurements, hence abdominal obesity, are good messengers for microalbuminuria or proteinuria. Chuengsamarn S et al. suggested in their study that there is a relationship between hsCRP levels and diabetic vascular complications and nephropathy.[10] In a study conducted by Zambrano-Galvan G et al., a relationship independent of primary risk factors was observed between hsCRP levels and spot urine albumin/creatinine ratios.[11] Del Canizo Gomez FJ et al. found a relationship between urinary albumin excretion and hsCRP values, presence of hypertension in patients with Type 2 diabetes.[12] In our study, we found a relationship between CRP levels and spot urine protein/creatinine ratios. We found this relationship between the group with a spot urine protein/creatinine ratio of <150 mg/g and the group with a spot urine protein/creatinine ratio of 150-500 mg/g. Then, in our regression analysis, we found that high CRP level is an independent risk factor. The detection of a difference between these groups suggests that the increase in CRP level is a precursor to microalbuminuric proteinuria. It can also be thought that inflammation is an effective factor in the development and progression of diabetic nephropathy. In their study, Preciado - Puga MC et al. found that microalbuminuria levels increased in patients with Type 2 diabetes who had a high inflammatory response (especially TNF alpha) during 1 year follow-up.[13] Varma V et al. observed that high hsCRP levels increased the development of diabetic nephropathy.[14] In the study conducted by Chen YH et al., it was observed that microalbuminuria and retinopathy were frequently seen together and retinopathy also progressed in patients with advanced microalbuminuria.[15] In our study, we also found a relationship between diabetic retinopathy and spot urine protein/creatinine ratios. Retinopathy is 2,773 times (OR) higher in those with an average spot urine protein/creatinine ratio above 150 mg/g (p=0.001, 95% CI 1.534 - 5.013). Retinopathy and nephropathy are findings of microangiopathy in diabetes. Increased coexistence seems to be normal due to similar mechanisms involved in pathogenesis. Although diabetes regulation is important in pathogenesis, we could not find a relationship between diabetes regulation and spot urine protein/creatinine ratio due to the long duration

of diabetes and high average age of our patients. Trevisan R stated that microalbuminuria is a marker for endothelial dysfunction and is a risk factor not only for chronic kidney disease but also for cardiovascular diseases. In the same study, it was proposed to prevent microalbuminuria with successful treatment of diabetes and blockade of the renin angiotensin system in patients with both Type 1 and Type 2 diabetes.[16] In their study, Kim JJ et al. found that the prevalence of coronary artery disease increased in patients with asymptomatic microalbuminuria.[17] Savarese G et al. also found that myocardial infarction and stroke frequency decreased with effective treatment of albuminuria in diabetic or hypertensive patients.[18] In our study, we found that spot urine protein/creatinine ratios were high in patients with a history of ischemic heart disease or in patients with electrocardiograms in favor of ischemia. Along with the increase in the spot urine protein/creatinine ratio, the higher total cholesterol and LDL levels and the more frequent hypertension explain the increase in the risk of ischemic heart disease. Disadvantages in the follow-up of a disease that requires long-term follow-up, such as diabetes, are: the fact that the patient has drugs other than diabetes, the factors such as smoking, diet and exercise habits are not questioned, only the electronic data of the last 2 years are available. In patients with diabetic metabolic syndrome, the spot urine protein/creatinine ratio, which is the indicator of diabetic nephropathy, increases as the age, number of metabolic syndrome parameters, CRP value as an indicator of inflammation increase. Spot urine protein/creatinine ratio seems to be advantageous in evaluating diabetes complications since it is cheap, fast and easy to apply in the outpatient follow-up. In these patients, it is sufficient to check it once a year.

Conclusion

In the study, we found positive correlation between microalbuminuria and spot urinary protein/creatinine ratios. We also found a relationship between metabolic syndrome, frequency of retinopathy and spot urine protein/creatinine ratios.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Committee (Approval number: 407).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.S., E.H., H.E.A.; Design – S.S., E.H., H.E.A.; Supervision – S.S., E.H., H.E.A.; Materials – S.S., E.H., H.E.A.; Data collection &/or processing – S.S., E.H., H.E.A.; Analysis and/or interpretation – S.S., E.H., H.E.A.; Literature search – S.S., E.H., H.E.A.; Writing – S.S., E.H.; Critical review – S.S., E.H., H.E.A.

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