Original Research Article

THE RELATIONSHIP OF RENAL RESISTIVE INDEX AND CAROTID INTIMA MEDIA THICKNESS IN PATIENTS WITH DIABETIC MICROALBUMINURIA

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Abstract

Objectives: Diabetes is a chronic disease with increasing morbidity and mortality. Microalbuminuria is seen in diabetic patients due to nephropathy. Patients with microalbuminuria are at high risk for atherosclerosis. It is thought that comparing the carotid artery, which is most frequently affected by atherosclerosis, by measuring and comparing the renal resistive index, may be beneficial for early diagnosis and treatment of diabeticcomplications.
Methods: Our study included 108 patients with diabetic microalbuminuria. Carotid intima media thickness (CIMT) and renal resistive index (RRI) measured, who came to tertiary care hospital for a period of six months. We aimed to evaluate the patients with normal-abnormal RRI and normal-abnormal CIMT. The patients' diabetes age, weight, height, fasting blood sugar, HbA1c, and creatinine parameters were compared.
Results: We observed an increase in RRI in parallel with the increase in CIMT in diabetic microalbuminuric patients (p<0,001). There was also a positive correlation between the creatinine value and the RRI (p:0.021). The increase in creatinine was significantly associated with the increase in CIMT(p<0.001). However, we could not detect the similar correlation with body mass index (BMI) in terms of both RRI and CIMT.
Conclusion: RRI measurement can be performed together with CIMT measurement for early detection of atherosclerosis. Patients with microalbuminuria and prone to atherosclerosis that cannot be detected by measurement of CIMT can be detected by measurement of the RRI.

Keywords: microalbuminuria, atherosclerosis, Carotid intima media thickness (CIMT), renal resistive index (RRI)

Introduction

Diabetes mellitus (DM) is a disease with a rapidly increasing incidence in our country and in the world, with the increase in sedentary life and unhealthy diet. According to the International Diabetes Foundation (IDF) 7th diabetes atlas, 1 in 11 adults had diabetes in 2015 (415 million). 1 in 2 adults with diabetes (46.5%) is undiagnosed, meaning they do not know they have diabetes. 12% of global health expenditures are used for diabetes (US$673 billion). 1 in 7 births areaffected by gestational diabetes. Three-quarters of diabetes patients (75%) live in low-and middle-income countries. 542,000 children suffer from type 1 DM. Every 6s, 1 person dies due to DM [1, 2].
Chronic complications occur in the later stages of diabetes and cause serious problems. Diabetes-related chronic complications can be prevented or delayed with good diabetes control. Reducing risk factors and early diagnosis are important in preventing chronic complications. Microalbuminuria is an early chronic complication. In addition, microalbuminuria is an early predictor of cardiovascular complications which can cause myocardial infarction and ischemicStrokes[3].The common pathophysiological feature of diabetic microvascular complications is inadequate perfusion and function in the affected tissues, with progressive narrowing and eventual occlusion of the vascular lumen. Pathogenesis of diabetic nephropathy is a process that starts on a certain genetic basis and has various stages in diabetics who are prone to injury with increased glucose levels.
Cardiovascular diseases are the most important cause of morbidity and mortality in patients with diabetes. The risk of coronary artery disease in people with type 2 diabetes is 2-4 times higher than those without diabetes. 60-75% of these patients die due to macrovascular events. In patients with diabetes, atherosclerosis occurs at an earlier age, has multisegmental involvementand is more common [4].
Carotid arteries are the earliest affected vascular structures [5-8]. It is known that the renal resistive index (RRI) measured by renal color Doppler USG reflects renal vascular resistance [9]. As the vascular resistance increases, the renal blood flow decreases and the RRI increases. High RRI can be seen in many diseases and is affected by factors such as age, hypertension and diabetes, which are extrarenal factors rather than intrarenal factors [10]. As a result, the RRI is not useful in determining renal parenchymal damageand the renal resistive index has prognostic value in systemic diseases rather than renal abnormalities [11]. However, renal resistive index measurement in vasculopathies occurring in systemic diseases gives us information about the severity of the nephropathy. Hypertension, diabetes, obesity, age, etc. increase vascular resistance. Factors such as these affect the RRI and provide important information regarding atherosclerotic changes [12-14]. Since histopathological changes in the kidneys in diabetic nephropathy may cause an increase in renal vascular resistance, various stages of diabetic nephropathy can be determined by measuring the resistivity index of the intrarenal arteb6ies with renal Doppler USG in patients at different stages of diabetic nephropathy. Although there are studies in the literature showing that the RRI is associated with microalbuminuria, we could not find enough studies showing the relationship between the RRI and the CIMT. We aimed to investigate whether microalbuminuria, an early marker of atherosclerosis, is more associated with the CIMT or with the RRI.

Method

Study design, population and parameters the study was conducted by retrospectively examining the files of diabetic patients with microalbuminuria who came to tertiary care centre.

Consent was obtained from all participants of the study.

For our study, the files of 1684 diabetic patients who applied to our hospital between for a period of 6 months were scanned. However, 108 patients with microalbuminuria who had CIMT and RRI measured for various indications were included in the study.

Demographic characteristics, physical examination, biochemical values and ultrasonographic measurements of patients with microalbuminuria and CIMT and RRI were measured for various indications. Care was taken to ensure that the patients did not have obvious chronic kidney failure, acute kidney failure, active infection, febrile illness, pregnancy, and breastfeeding that would affect albuminuria. Patients with creatinine values above normal for their gender andage were excluded from the study.

Height, weight, creatinine, age, gender, HbA1c, fasting blood glucose, RRI, CIMT, diabetes age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and microalbumin content in 24-hour urine were recorded from the files of the patients by retrospectively scanning. Body mass index (BMI) was calculated with the formula weight (kg)/height^2(meter).

The results of the venous blood samples given by the patients after at least 8 h of fasting were evaluated. Serum glucose, creatinine values were measured with Beckman Coulter Synchron LX 20 using commercially available kits. The percentage of HbA1c was analyzed using high performance lipid chromatography. Microalbumin measurements in 24-hour urine were measured by spectrophotometric method using Roche COBAS INTEGRA 800 device. In CMT and RRI measurements, the results may vary depending on the patient's position, the mode of measurement, cardiac cycle, and age. In order to overcome such problems, care was taken to achieve the same standardization in all patients in the measurements [15,16]. Sonographic evaluation was performed by same radiologist with the patients lying in the supine position. LOGIQ P6 and TOSHIBA APLIO 500 devices were used for the examination. Linear probes were used for CIMT measurement and convex probes were used for RRI measurement. CIMT measurement was performed manually on the BMODEimage by obtaining an image from the carotid in the transverse position. Measurements with a CIMT >0.8 mm were considered abnormal. RRI measurement was calculated automatically in Doppler US mode after obtaining an image at the appropriate angle from the renal artery, since the necessary software was available in the ultrasound 32 device. Patients with a RRI measurement ≥0.7 were considered abnormal.

Statistical analysis

IBM SPSS Statistics Version 20.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and numerical measurements as mean and standard deviation (median and minimum-maximum where appropriate). Chi-square test statistic was used to compare categorical measurements between normal-abnormal groups (CIMT or RRI). Whether numerical measurements provided the assumption of normal distribution was tested with the Shapiro Wilk test. In the comparison of numerical measurements between normal-abnormal groups (CIMT or RRI), T test was used in Independent groups if assumptions were met, and Mann Whitney U test was used if assumptions were not met. One-way analysis of variance was used to compare CIMT

and RRI values between DM age groups. Paired subgroup comparisons were made according to Tamhane test for thecases found significant here. Pearson Correlation coefficient and related p value were obtained to examine the interaction between CIMT and RRI measurements and other numerical measurements. Statistical significance level was taken as 0.05 in all tests.
SPSS reference: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. CIMT: Carotid intima media thickness RRI: Renal resistive index

Results

Half of the patients were female. The mean parametric values, demographic characteristics and physical examination findings of the patients included in the research population are shown in Table 1.
A positive correlation was found between CIMT and RRI. (r = 0,385 p<0,001) (Table 2).
In addition, the correlation between the CIMT and the demographic characteristics, biochemical values and blood pressure values of the patients were also examined. The evaluation is shown inTable 3 and Table 4.
CIMT was significantly increased in those with low BMI (p:0,022). CIMT increases significantly with age (p<0,001). CIMT was found to be statistically significantly higher in patients with high creatinine level (p<0.001) (Table 3).
The RRI value was found to be statistically significantly higher in patients with abnormal CIMT (p:0.044). In addition, the rate of patients with abnormal RRI value (35%) in patients with abnormalCIMT was found to be higher than those with normal CIMT (18%). The results are given in Table 5. The relationship between RRI and some parameters evaluated together is shown in Table 6. While the mean systolic blood pressure of patients with normal RRI was 125 mmHg,the mean of patients with abnormal RRI was found to be 130 mmHg (p:0.180). The diastolic blood pressure of patients with normal RRI value was measured as 78 mmHg, the diastolic blood pressure of patients with abnormal RRI was found to be 83 mmHg, and the p value was significant (p:0.043). In patients with abnormal RRI, age was statistically significantly higher (50.8 vs 61.5, p<0.001) and weight was lower (p:0.02). CIMT was found to be statistically significantly higher in patients with abnormal RRI (p:0.011).
The age of DM was divided into 0-5 years, 6-10 years, 11 years and above in order to facilitate statistical analysis. A statistically significant correlation was found between DM year groups and RRI values (p:0.005). According to the results of the pairwise comparison, the RRI value was found to be lower in cases with DM age between 0 and 5 years compared to the groups with DM years 6-10 years or 11 years and above.

Table 1: Mean Parametric Values

Measurements	Mean Values
24-hour microalbuminuria (mg/day)	252,41+/-531,91 81,5 (30-3301)
Fasting blood glucose (mg/dl)	233,99 +/- 98,8
Creatinine (mg/dl)	0,73 +/- 0
HbA1C (%)	10, 29 +/- 2
Carotid intima-media thickness (mm)	0,81+/-0,23
Renal resistive index	0,67+/-0,04
Age (Years)	53,65+/-12,29

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Height (cm)	164,63+/-9,16
Weight (kg)	84,16+/-15,6
BMI (kg/m2)	31,17+/-5,83
DM Years	9,31+/-7,78
SBP (mm/Hg)	126,54+/-16,83
DBP (mm/Hg)	79,75+/-10,36

Mean measurements are given as average +/-standard deviation. BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure. DM: Diabetes mellitus.

Table 2: Comparison of CIMT and Normal-Abnormal Values of RRI

Measurements	**Patients (%)**
Carotid intima-media thickness	
Normal (≤0,8mm)	60 (%56)
Abnormal	48 (%44)
Renal resistive index	
Normal (<0,7)	80 (%74)
Abnormal	28(%26)

Table 3: Correlations Between Carotid Intima Media Thickness and Other Measurements

Measurements	**Correlation Coefficient**	**p**
24-hour microalbuminuria(mg/day)	0,052	0,052
DM years	0,162	0,095
SBP (mm/Hg)	0,210	0,029
DBP (mm/Hg)	0,132	0,173
Fasting blood glucose (mg/dl)	0,074	0,445
Creatinine (mg/dl)	0,398	<0,001
HbA1C (%)	0,090	0,353
Age	0,462	<0,001
Height (cm)	0,137	0,156
Weight (kg)	_0,101	0,299
BMI (kg/m2)	_0,175	0,069

BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure. DM: Diabetes mellitus.

Table 4: Relationship Between Carotid Intima Media Thickness and Some Demographic and Laboratory Data

Measurements	**Carotid intima media thickness**		**p**
	Normal	**Abnormal**	
	Mean+/-standarddeviation	**Mean+/-standarddeviation**	
DM years	8,45+/-7,88	10,4 +/- 7,58	0,198
SBP (mm/Hg)	126,17+/-13,29	127+/-20,56	0,809
DBP (mm/Hg)	80,08+/-8,85	79,33+/-12,07	0,710
Fasting blood glucose(mg/dl)	229,05+/-95,04	240,17+/-104	0,564
Creatinine (mg/dl)	0,67+/-0,17	0,81+/-0,19	<0,001

HbA1C (%)	9,98+/-2,35	10,68+/-3,06	0,183

DBP: Diastolic blood pressure, SBP: Systolic blood pressure. DM: Diabetes mellitus.

Table 5: Relationship Between Carotid Intima Media Thickness and Renal Resistive Index

Measurements	**Carotid intima media thickness**		**p**
	Normal	**Abnormal**	
	Mean+/-standart deviation	**Mean+/-standartdeviation**	
Renal resistiveindex (RRI)	0,66+/-0,04	0,68+/-0,03	<0,001
Normal RRI	49 (82%)	31 (65%)	0,044
Abnormal RRI	11 (18%)	17 (35%)	

Table 6: Correlations Between Renal Resistive Index and Other Measurements

Measurements	**Correlation Coefficient**	**P**
24-hour microalbuminuria	_0,022	0,819
DM years	0,253	0,008
SBP	0,057	0,558
DBP	0,114	0,239
Fasting blood glucose	0,064	0,509
Creatinine	0,222	0,021
HbA1C	0,027	0,785
Age	0,441	<0,001
Height	<0,001	1000
Weight	-0,133	0,171
BMI	-0,143	0,140

BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolicblood pressure. DM: Diabetes mellitus.

Discussion

Previous studies have shown that diabetic microalbuminuria is a strong indicator of the onset of atherosclerosis and that the carotid artery is one of the first vascular structures to be affected [17]. However, recently, studies have been published showing that there may be a strong link between atherosclerosis and RRI. In our study, we investigated which of these two regions has a more sensitive relationship with microalbuminuria.
As a result of our study, the RRI was found to be significantly higher in diabetic patients with microalbuminuria and increased CIMT compared to those with normal CIMT. When the data were examined, it was seen that the carotid intima media measurement was more sensitive in terms of reflecting the severity of microalbuminuria. However, when analyzed individually on a patient basis, we found that the RRI measurement may be more valuable in terms of detecting patients with normal CIMT despite having microalbuminuria.
In other words, in terms of evaluating vasculopathy, the measurement of the RRI made us think that it could be a valuable method in terms of detecting false negative measurements that could not be detected by evaluating the CIMT. In this respect, measurement of RRI can be considered as a complementary and supportive test to measurement of carotid intima

media. When previous studies were examined, we did not find any studies that matched our study exactly, so we made comparisons with similar studies in some aspects. In the study of Leena Mykkanen*et al.*with 991 non-diabetic microalbuminuria and 450 diabetic microalbuminuria patients, a relationship was observed between the severity of microalbuminuria and atherosclerosis and CIMT from the earliest stages [18]. Unlike in our study, no correlation was found between CIMT and microalbuminuria. In our study, the number of patients with very high albuminuria was limited. In addition, in previous studies on this subject, comparisons were made with diabetic or healthy control groups without microalbuminuria. In our study, the fact that we did not create a control group from cases without microalbuminuria causes a limitation. In a study by Roberto Pontremoli*et al.*, which included 211 patients, similar to our study, but excluding microalbuminuria, a significantrelationship was found between RRI and age, CIMT, and diastolic blood pressure [19].

In our study, creatinine levels increased statistically significantly as the RRI and CIMT increased, in linewith the literature. This supports the knowledge that cardiovascular diseases, which are the major cause of mortality, increase in patients with chronic renal failure [20].

When the cases are examined in terms of diabetes years; When diabetes was examined in 3 periods as 0-5 years, 6-10 years, 11 years and above, it was observed that CIMT was affected earlier and at a higher rate than the RRI. We could not find any study on this aspect in the literature.

We found a positive correlation was found between CIMT and systolic blood pressure, consistent with the literature. In a study of 7983 patients by Michael L. Bots et al., CIMT increased in relation to hypertension [21]. In our study, we separately examined the relationshipbetween systolic and diastolic blood pressures and both RRI and CIMT. The increase in RRI was mostly associated with increased diastolic blood pressure, while CIMT was associated with increased systolic blood pressure. CIMT increased with increasing age of the patients. In the study of MarkisJuonala*et al.* in 2265 patients aged between 24 and 39 years, CIMT increased significantly with increasing age. Again, similar to our study, no correlation was found between gender and CIMT [22]. The retrospective nature of our study and the limited number ofpatients brought along several limitations. In addition, the presence of only diabetic patients and the absence of a non-diabetic control group is another shortcoming of the study.

Conclusion

The relationship between CIMT and/or RRI in the early diagnosis of atherosclerosis has been demonstrated in a limited number of previous studies. However, we could not find a study in the literature comparing the change of these two regions in terms of atherosclerosis and the relationship between microalbuminuria. We found a significant correlation between CIMT and RRI in diabetic patients. However, the correlation of both regions with microalbuminuria could not be demonstrated. In patients with diabetes mellitus, an increase in RRI was observed with an increase in CIMT. Measurement of RRI together with CIMT where atherosclerosis is seen earliest will be useful in demonstrating atherosclerosis.

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