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The Survey of Relationship Between Resistance Index of Renal Artery and Albuminuria in Diabetic Patients Referring to Shahid Sayyad Shirazi Hospital, 2017 to 2018

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Introduction. The Resistance Index by doppler ultrasound has been characterized as a non-invasive diagnostic method that has been well predictive of the outcome of renal function in type 2 diabetic patients. This study aims to investigate the relationship between renal artery resistance index (RI) and albuminuria in diabetic patients.

Methods. This descriptive, analytical, cross-sectional study was conducted on diabetic patients referred to the clinic for ultrasonography. Patients were divided into two groups: macro albuminuria and microalbuminuria or normoalbuminuria and for all patients, ultrasonography was done using the same ultrasound machine and by the same operator. Doppler sonography of the renal arteries was performed and the results were recorded.

Results. 52.4% of the patients were female. The mean age of these patients was 50.25 ± 16.41. The mean RI in the study population was 66.0 ± 0.01. In this study, RI with albuminuria and HbA1c levels in diabetic patients were not significant. However, there was a significant relationship between RI and serum creatinine in diabetic patients, with increasing creatinine level, RI was also increased. Also, there was a significant relationship between RI and gender and this indicator had a direct relation with male gender but there was no correlation with female gender.

Conclusion. In the current study, the patient's albuminuria, type of treatment and HbA1c had no effect on the RI. The study also found that an increase in the RI index could be a significant predictor of renal dysfunction and increased creatinine.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder associated with increased blood glucose levels and metabolic disturbances. Today diabetes is one of the most important health and socio-economic problems in the world. Studies show that by 2025 more than 75% of the total population in developing countries will have diabetes.[1,2] One of the most important complications of diabetes is renal complication that goes through various stages. It is estimated that approximately 25% to 30% of patients with type 2 diabetes develop nephropathy. The incidence is similar in patients with type 1 and type 2 diabetes.[3,4] Although reports have not been the same among the studies, they indicate that the incidence of nephropathy in diabetic patients increases with a rapid increase in the incidence of type 2 diabetes.[5,6] In fact, diabetic nephropathy is almost the largest single cause of the terminal stages of renal failure in Western countries.[7,8] Diabetic Nephropathy

is responsible for 15% to 40% of the ESRD.[9] The outcome of diabetic nephropathy varies from patient to patient: some may progress to ESRD and some may return to normal.[10,11] It is estimated that diabetes is responsible for 30% to 40% of all ESRD in the United States.[12] Many studies have also shown that long-term hyperglycemia can cause chronic complications of diabetes, including nephropathy.[13] Diabetic nephropathy is characterized by micro-albuminuria (30 to 300 mg/d).[14]

Micro-albuminuria is the first diagnostic sign of kidney disease and is a promising factor for the early detection of advanced stages of nephropathy in diabetic patients. Duration of disease is one of the most important causes of diabetes mellitus, including nephropathy. The incidence of micro-albuminuria has also been reported in people who have been diagnosed with diabetes.[15]

In some studies, the prevalence of micro-albuminuria and proteinuria in diabetic patients with newly diagnosed diabetes was 12% and 9.1%, respectively. These patients are 2 times more likely to die of heart disease than other diabetic patients. However, early diagnosis can reduce renal lesions by one-fifth.[16]

Initial and early treatment of diabetes may delay the development of diabetic nephropathy and ESRD, and regular follow-up of patients is the key to success in treatment.[17] High blood pressure is also a major contributor to diabetic nephropathy.[12] Several studies have shown that treating high blood pressure with ACEi medications can delay kidney damage in a large number of patients.[18-20] In addition to the usual changes in diabetic nephropathy, glomerular sclerosis leads to atherosclerosis in the evaluation of renal biopsy lesions in type 2 diabetes.[21] Hemodynamic changes, including increased intra-glomerular pressure and increased renal vascular resistance (so-called ischemic nephropathy), lead to various stages of diabetic nephropathy.[22]

The importance of preventing diabetic nephropathy is indicated in many reports.[23,24]

Pulsatility Index (PI) and RI are significantly correlated with the effective renal plasma flow, renal vascular resistance, and filtration fraction in patients with chronic renal failure.[25] In patients with ESRD, it has been shown that PI above 1.55 or RI higher than 0.75 is correlated with a rapid decline in renal function evaluated by serum creatinine.[26] In patients with renal dysfunction, who had type 2 diabetes, PI and RI showed a significant increase compared to patients with non-diabetic renal disease.[27]

RI has been identified as a non-invasive diagnostic method that is well predictive of the outcome of renal function in type 2 diabetic patients (even when GFR is still normal).[28] Recently, it has been shown that increased renal arterial resistance predicts the process of kidney function in type 2 diabetes with microalbuminuria.[16] Both RI and PI may be used as a sensitive indicator for changes in the intra-renal vascular flow, although RI may have a smaller variance coefficient and it can be retrieved and used in comparison with PI.[29] Considering that studies in Iran to determine the relationship between RI index and renal function and protein excretion are very sparse and the available information is very limited, this study aims to investigating the relationship between renal artery RI and proteinuria and albuminuria in diabetic patients at Shahid Sayyad Shirazi Hospital implemented in 2017 to 2018.

MATERIALS AND METHODS

Methods

This descriptive/analytic/cross-sectional study was conducted in Shahid Sayyad Shirazi Hospital in Gorgan, Iran. This study was performed on patients referred to the department of radiology for ultrasonography in 2017 to 2018. First, the necessary authorization to start the project was obtained from the university. Then, patients were evaluated based on inclusion and exclusion criteria and were enrolled in the study. The purpose of the study was explained by the program's executor and written consent was obtained. Demographic and anthropometric information of the patients was recorded using the checklist and patient records. Patient information that was recorded in the patient's file was extracted and entered the checklist. These tests include Cr, HbA1c, proteinuria, albuminuria, Alb/Cr ratio, through blood tests, and 24-hour urine tests. The patient file was collected. Patients were divided into two groups: macro-albuminuria and without albuminuria or micro-albuminuria. Micro-albuminuria was defined as urinary albumin/Cr ratio 30 to 299 µg/mg and macro-albuminuria was defined as albumin/Cr ratio of equal or more than 300 µg/mg. For all patients

using the same ultrasound apparatus (Philips iu22) and by the same ultrasound operator, the Doppler ultrasound of inter-lobar renal arteries was performed and the results were recorded. Subsequently, the data obtained from two groups were compared and evaluated.

Data Analysis Method

The obtained data was entered into the SPSS version 21. The mean and frequency and percentage were used to describe the data. Regression, Pearson correlation coefficient, and ANOVA test were used to measure the relationship between variables. At the same time, the significance level was .05.

Inclusion Criteria

- Patient file completeness for blood and urine tests to measure creatinine, hemoglobin, and albuminuria
- Diagnosis of type 2 diabetes approved by an internist or endocrinologist
- GFR > 60 cc/min/ 1.73 m^2
- Control of hypertension (with diet or medication) to prevent kidney damage

Exclusion Criteria

- Lack of satisfaction to participate in the study
- Having kidney problems (other than diabetic nephropathy) due to the distortion of the results of diabetic nephropathy tests
- Pregnant patients
- Type 1 diabetes
- Lack of control of patient's blood pressure
- Single kidney
- Renal artery stenosis

RESULTS

In this study, data on 82 patients with diabetes was studied. The mean age of these patients was 50.25 ± 16.41. The youngest person was 17 years old and the oldest patient was 67 years old. Based on the Shapiro-Wilk-sen test, these patients had a normal distribution. 52.4% of the patients were female and 47.6% of them were male.

The descriptive findings of the research variables indicate that the mean and standard deviation of RI was 0.66 ± 0.01, mean and SD of proteinuria (more than 150 mg in daily urine) was 159.67 ± 32.46, mean and SD of the albuminuria variable was 155.34 ± 24.14. The mean and SD of other variables are listed in Table 1.

Pearson correlation coefficient was used to determine the relationship between renal RI and proteinuria in diabetic patients. The results showed that the correlation coefficient between RI and proteinuria in diabetic patients was -0.16, which was not significant (P > .05, Table 2).

To assess the relationship between RI and albuminuria in diabetic patients, Pearson correlation coefficient was used. In this study, more than 80% of patients were in the range of micro or normo-albuminuria. The results showed that the correlation between RI and albuminuria in diabetic patients was 0.75, which was not significant (P > .05, Table 3).

Pearson correlation coefficient was used to determine the relationship between RI and Cr level in diabetic patients. The results showed that the correlation coefficient between RI and Cr in diabetic patients was 0.37, which was significant (P < .05, Table 4).

In other words, increased creatinine has a direct relationship with increased renal resistance.

Table 1. Descriptive Findings for People with Diabetes

Variable	Mean ± SD
Creatinine	0.90 ± 0.42
Proteinuria	159.70 ± 32.46
HbA1c	7.97 ± 0.96
Albuminuria	155.34 ± 24.13
Right Renal Artery Resistance	0.65 ± 0.13
Left Renal Artery Resistance	0.67 ± 0.12
Total Renal Artery Resistance	0.66 ± 0.01

Table 2. Pearson Correlation Test Results of the RI with the Degree of Proteinuria

Variable	Non-standard Coefficient	Correlation Coefficient	Statistical t-test	*P*
Proteinuria	0.00	-0.11	-1.01	> .05

Table 3. Pearson correlation Test Results of RI Index with Albuminuria

Variable	Non-standard coefficient	Correlation Coefficient	Statistical t-test	*P*
Albuminuria	0.00	-0.08	-0.67	> .05

Table 4. Pearson Correlation Test Results of RI Index with Creatinine Level

Variable	Non-standard Coefficient	Correlation Coefficient	Statistical t-test	*P*
Creatinine	0.02	0.37	3.51	< .05

Pearson correlation coefficient was used to determine the relationship between RI and HbA1c levels in diabetic patients. The results showed that the correlation coefficient between the RI and HbA1c in diabetic patients was -0.18, which was not significant (P > .05, Table 5).

Regression analysis and ANOVA analysis were used to determine the relationship between RI and albuminuria and proteinuria in diabetic patients.

The results of Table 6 show that the correlation coefficient was 0.133 and the F-value was 3,143 which was significant (P < .05). Therefore, the research hypothesis that "there is a significant relationship between RI and albuminuria and proteinuria in diabetic patients, was confirmed but the results of Table 7 show a correlation coefficient of 0.059 and F-value of 1.197 (P > .05). In other words, there was no correlation between RI and albuminuria and proteinuria with female gender. Therefore, it can be interpreted that the RI in men has a direct correlation with albuminuria, but there was no significant relationship in female.

To evaluate the association between RI and albuminuria in diabetic patients, Pearson correlation coefficient was used. The results of Table 8 showed that the correlation coefficient between the RI and albuminuria in diabetic patients was not significant with respect to treatment type (P < .05). It can be concluded that the type of treatment for diabetic patients (oral, insulin therapy, combination therapy) will not affect the rate of RI.

DISCUSSION

Diabetic Nephropathy is one of the vascular complications in diabetic patients. Functional and structural functional disorders may occur a few years after the onset of the disease. In recent decades, doppler sonography has been presented in a simple way for the hemodynamic examination of the kidneys. The RI in doppler sonography reflects intra-arterial resistance. The mechanism of increasing RI is unknown at the same time as decreasing glomerular kidney function in diabetic patients. In advanced nephropathy tubular atrophy, glomerular sclerosis, and increased interstitial fibrosis are main pathologic changes. Glomerular

Table 5. Pearson Correlation test Results of the RI Index with HbA1c

Variable	Non-standard Coefficient	Correlation Coefficient	Statistical t-test	*P*
HbA1c	0.67	-0.12	43.03	> .05

Table 6. The Regression Model Between Renal Resistance Index and Albuminuria in Diabetic Patients in Terms of Gender (Male Sex)

Variables	R Multiple Correlation	R2 Coefficient of Determination	Adjusted Coefficient of Determination	F Statistics	*P*
Albuminuria	0.37	0.13	0.09	3.14	> .05

Table 7. The Regression Model Between Renal Resistance Index and Albuminuria in Diabetic Patients by Gender (Female Sex)

Variables	R Multiple Correlation	R2 Coefficient of Determination	Adjusted Coefficient of Determination	F Statistics	*P*
Albuminuria	0.24	0.06	0.01	1.20	> .05

Table 8. The Results of the Correlation Test Between Renal Resistance Index and Albuminuria in Diabetic Patients According to the Type of Treatment Received in Diabetic Patients

Type of Treatment	Non-standard Coefficient	Correlation Coefficient	Statistics t-test	*P*
Oral Medication	0.00	-0.15	-0.91	> .05
Insulin	0.00	-0.14	0.66	> .05
Oral + Insulin	0.00	-0.05	-0.18	> .05

sclerosis leads to increased blood flow. On the other hand, an increase in interstitial fibrosis can be a reason for increasing RI. The RI of inter-lobar arteries seems to be a reliable indicator of intra-renal pathologic changes.[30,31]

In this study, we investigated the relationship between RI and proteinuria and albuminuria in diabetic patients. In this study, 82 patients with diabetes were enrolled for renal artery doppler ultrasonography. The mean age of the patients was 50.52 ± 16.41 and the percentage of diabetic women was 52.5%. In this study, with a higher frequency of female, the RI in male population was more related to proteinuria and albuminuria. About one third of patients were between the ages of 63 to 74. It seems that due to higher prevalence of diabetes mellitus in the male population, it can be justified. On the other hand, men account for a higher percentage of dialyzed and transplanted patients due to diabetes, which is why they are likely to be relatively small in the group of outpatient diabetic patients.[32] It may be concluded that men diabetes is at a lower level in terms of health care and disease tracking than women.[38,39] In a study by Fallah *et al.* 81 diabetic patients with an average age of 85.5 ± 10.64 years were enrolled and nearly 70% of them were male.[29] In the Hamano *et al.* study, the mean age of patients was 66.1 ± 2.10, which was male in most cases.[28] In the study of Abdul Hamid *et al.* The highest percentage of patients in the three groups (without albuminuria, micro-albuminuria, and macro-albuminuria) were female and their mean age was between 51 to 55 years.[31] The differences in the frequency of age and gender of patients Could be due to differences in the statistical society of studies.

In this study, the mean renal artery resistance index was 0.66 ± 0.01 and there was no significant difference between the RI and proteinuria and albuminuria in diabetic patients. In a study done in 2007, two groups of patients Based on RI higher than 0.7 and less than 0.7. After a 6-month survey, it was found that 50% of patients with higher RI had a significant reduction in renal function.[33] On the other hand, in the study of Nakamori *et al.* both RI and PI were correlated with urinary protein excretion and RI was an important indicator in the evaluation of renal function.[34] In another study, RI with renal function, pathologic changes in long-term renal tubules, systemic vascular disease and albuminuria[35] showed that the RI of patients with macro-albuminuria (greater than 300 mg/dL) is more than micro-albuminuria or normo-albuminuria. In this study, more than 80% of patients were within the range of micro-albuminuria and normo-albuminuria. It may be possible that the index of RI did not show significant significance due to the low albumin excretion or its normalization in patients. In the study of Masulli,[36] there was no significant correlation between RI with albuminuria. Narooeinejad study[42] showed no significant correlation between RI and proteinuria index. In this regard, due to contradictory results reported, other causes for example the wrong technique for collecting 24-hour urine should be kept in mind and more studies with larger sample size that seem to be mandatory.

In the present study, a significant relationship was found between the RI and serum creatinine in diabetic patients, with an increase in creatinine level, the RI also increased. In the Milovanceva and Soldo study, there was a correlation between RI and serum creatinine, which was consistent with the results of ours.[34] In the study of Ohta *et al.* the RI was 0.7 ± 0.09 and the mean creatinine clearance was 70.1 ± 38.9, and a significant relationship was found between these two ratios, accordingly patients with RI greater than 0.7 had higher creatinine levels.[31] According to the results of these studies, it can be estimated that RI represents a high level of correlation with the serum creatinine level and can be used as a predictor in patients with advanced clinical diabetic nephropathy.

At last in our study, the correlation between RI, HbA1c and the type of treatment received in diabetic patients was investigated. No significant correlation was found between them. In Hamano Milovanceva's study and Abdul Hamid's study, there was no correlation between renal artery resistance index and HbA1c levels in diabetic patients; which is consistent with our results.[28,37,38]

CONCLUSION

In this study, the renal artery index was not associated with the amount of albuminuria or protein excretion in diabetic patients, which could be due to the small sample size. Similarly, the type of treatment received in patients could not affect the RI. On the other hand, there was a significant correlation between serum creatinine levels and

male gender with RI, which could indicate an increase in the resistance of the in vivo vessels in parallel with renal dysfunction in male patients and could be used as an important indicator in the evaluation of the prognosis of renal function.

LIMITATIONS

Small sample size was our limitation and further studies with larger sample size seem to be mandatory in order to confirm these relations.

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