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Original Article

# Renal Artery Stenosis in Hypertensive Patients with or without Type 2 Diabetes: A Comparative Magnetic Resonance Angiography Study

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**Background:** Increased prevalence of various vascular diseases is common in type 2 diabetes mellitus. However, the increased prevalence of renal artery atheroma resulting in renal artery stenosis in patients with diabetes mellitus has not been fully assessed.

We used magnetic resonance angiography to assess the prevalence of renal artery stenosis in a group of patients with hypertension and type 2 diabetes mellitus and compared them with a group of hypertensive patients without diabetes.

**Methods:** One hundred and seventy-three individuals were recruited consecutively in this study. They were divided into two groups: 50 patients with known type 2 diabetes and coexistent hypertension in group A and 123 hypertensive patients without diabetes in group B. All the patients underwent magnetic resonance angiography of the renal arteries to assess the presence of renal artery stenosis.

**Results:** The prevalence of renal artery stenosis in groups A and B was 44% and 35.8%, respectively (*P*=0.402). However, there was a significant association between the age and renal artery stenosis (*P*=0.023).

**Conclusion:** Diabetes mellitus was not associated with the increased prevalence of renal artery stenosis in our study.

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**Keywords:** Hypertension • magnetic resonance angiography • renal artery stenosis • type 2 diabetes mellitus



## Introduction

Atherosclerotic disease accounts for most of the excess mortality in patients with diabetes mellitus. In the UK prospective diabetes study, fatal cardiovascular events were 70 times more common than deaths from microvascular complications.[1] The relation between glucose concentrations and macrovascular events is less powerful than for microvascular disease. Smoking, high blood pressure, proteinuria, and high cholesterol concentration are more important risk factors for atheromatous large vessel disease in patients with diabetes.[1]

Although prevalence of clinical atherosclerotic diseases such as coronary heart disease, peripheral vascular disease, and cerebrovascular disease is increased in patients with type 2 diabetes, the increased prevalence of renal artery atheroma resulting in renal artery stenosis has not been fully assessed.[2]

Renal artery stenosis is frequently an incidental finding during routine angiography for peripheral vascular disease, with a prevalence between 5% and 40%.[3–5] This finding is similar to the high prevalence of renal artery stenosis (5% to 20%) in patients who undergo routine coronary angiography.[6,7] Previous studies have shown that atherosclerotic renal artery stenosis is associated not only with hypertension, ischemic nephropathy, and cardiovascular disease,[8,9] but also with a

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considerably increased mortality.[10–12] The impact of renal artery stenosis as a risk factor for mortality was established mainly in patients who underwent a diagnostic evaluation for hypertension or renal failure or both. Evaluating data in patients who underwent diagnostic cardiac catheterization simultaneously with an aortography even showed that incidental renal artery stenosis can be an independent risk factor for mortality.[6,7]

On the other hand, the variable course of renal disease in type 2 diabetes mellitus may in part reflect the associated atherosclerotic nephropathy. The prevalence of renal artery stenosis in patients with hypertension and type 2 diabetes has yet to be established.[2] Having information about this prevalence may change the selection of specific antihypertensive drugs. Furthermore, renal artery stenosis is a potentially treatable cause of hypertension and progressive renal failure.

One of the reasons that the prevalence of renal artery stenosis has not yet been evaluated completely was the lack of noninvasive and valid screening procedures for this purpose. Moreover, screening for renal artery stenosis with intra-arterial angiography is expensive and has potential hazards. In addition to the potential for hemorrhage at the site of arterial puncture and the potential for arterial dissection, patients with diabetes are at significant risk for contrast nephropathy.[2] Magnetic resonance angiography (MRA) of the renal arteries, though expensive, is a noninvasive and sensitive technique for the diagnosis of renal artery stenosis.[13]

We therefore aimed to assess the prevalence of renal artery stenosis by using MRA in a group of patients with hypertension and type 2 diabetes, and compare this prevalence with that of hypertensive patients without diabetes.

## Materials and Methods

This study was conducted at Hypertension Clinic of Rasoul-e-Akram Hospital, affiliated to Iran University of Medical Sciences in Tehran, Iran, during 2006. One hundred and seventy-three individuals were recruited consecutively in this study. Regarding the type 2 diabetes and hypertension, they were divided into two groups: patients with known type 2 diabetes and coexistent hypertension in group A (case) and hypertensive patients without diabetes in group B (control).

The patients were classified as having type 2 diabetes according to the conventional World Health Organization criteria.[14] Hypertension was defined if resting systolic blood pressure was ≥140 mmHg or resting diastolic blood pressure was ≥90 mmHg or both (in more than two occasions and when using the appropriate cuff size), or if the patients were currently receiving antihypertensive medications.

The age range of the included patients was 15 – 65 years. Older patients were excluded because renal artery stenosis is common in elderly individuals even in the absence of diabetes.[15,16] Patients with pacemakers, marked obesity (weight >120 kg), and claustrophobia were excluded from the study.

For all the included patients MRA of the renal arteries was done to assess the presence of renal artery stenosis.

### MRA of the renal arteries

MRA was carried out by using a 1.5 Tesla Intra scanner (Phillips, Philips Medical System, Eindhoven, Netherlands), and three-dimensional phase contrast MRA techniques were used. Phase contrast radiography relies on hemodynamic phase changes rather than on gadolinium. Repetition time was 33 ms, echo time was 7.5 ms, and the flip angle was 20°. The total scan time was 18 minutes. Images were reconstructed by using maximum intensity projection and were interpreted prospectively. Significant signal loss across the full width of the artery constituted a positive result. This has been shown to correspond to a stenosis demonstrated angiographically of >50%. All MRAs were performed in Radiology Department of Rasoul-e-Akram Hospital.

### Statistical analysis

The data were analyzed using SPSS software version 13 for Windows. In descriptive analysis, parameters such as frequency, mean, mode, and standard deviation (SD) were reported.

To test the difference between the frequencies of renal artery stenosis in the two groups of study, Chi- square test was used. Moreover, to compare parametric and nonparametric variable means in the two study groups, the independent *t*-test and Mann-Whitney test were used, respectively. One-way ANOVA and Kruskal-Wallis tests were also performed to compare parametric and non-parametric variable means among more than two groups, respectively. In addition, two-way ANOVA analysis was used to evaluate the confounding effect of diabetes on the association

between age and renal artery stenosis. Multivariate analysis was also performed to evaluate the confounding effect of age on the probable association between renal artery stenosis and diabetes.

A 5% probability of a type I error (two-tailed), and a power of 80% were considered in the analysis. All reported *P* values are two-tailed.

## Results

### Demographics

The mean age of the patients in group A was 61.52 (SD=13.23) years with the range between 20 to 81 years. Of them 28 (56%) were males and 22 (44%) were females. The mean systolic, diastolic, and mean arterial blood pressures of these patients were 161.60 (SD=25.50) mmHg, 89.40 (SD=8.96) mmHg, and 113.47 (SD=13.38) mmHg, respectively.

In group B, the mean age was 51.11 (SD=18.22) years, which ranged between 15 to 89 years. Of them 71 (57.7%) were males and 52 (42.3%) were females. The mean systolic, diastolic, and mean arterial blood pressures of these patients were 159.05 (SD=24.91) mmHg, 89.55 (SD=12.85) mmHg, and 112.72 (SD=15.72) mmHg, respectively.

The mean age of the patients in group A was significantly higher than that of group B ($P<0.001$, *t*-test). Whereas, there was not any significant difference in sex distribution between the two groups ($P=0.970$). Mann-Whitney test showed that the differences between systolic ($P=0.241$), diastolic ($P=0.509$), and mean arterial pressures ($P=0.249$) were not statistically significant in the two groups.

### MRA of renal arteries

In group A, 22 (44%) patients had renal artery stenosis detected by MRA. In group B, renal artery stenosis was detected in 44 (35.8%) patients. Chi-square test showed no significant difference ($P=0.402$).

On the other hand, the prevalence of type 2 diabetes in all hypertensive patients with positive MRA was 33.3% (22 patients out of 66), whereas, this prevalence was 26.2% (28 patients out of 107) among hypertensive patients with negative MRA.

Irrespective of the presence of diabetes, analysis of the data demonstrated that the mean age of the patients with hypertension and renal artery stenosis was significantly higher than the hypertensive patients with negative MRA [57.97 (SD=15.98) vs. 51.75 (SD=18.11) years, $P=0.023$]. More analysis with two-way ANOVA test showed that this significant difference was independent of the presence of type 2 diabetes ($P=0.044$). By contrast, considering the type 2 diabetes, these differences were not statistically significant within groups A [64.32 (SD=9.78) vs. 59.32 (SD=15.23) years, $P= 0.188$] and B [54.79 (SD=17.55) vs. 49.06 (SD=18.37) years, $P=0.095$]. Moreover, multivariate analysis showed that there was not any association between renal artery stenosis and diabetes even after fixing the confounding effect of age ($P=0.188$).

Additionally, the presence of renal artery stenosis assessed by MRA was not statistically associated with sex ($P=0.817$). Regarding both diabetes and renal artery stenosis, the patients were divided into four groups. Their characteristics are listed and compared in Table 1. As shown, only the mean age of the patients with hypertension was significantly different between these four groups

**Table 1.** Characteristics of the patients in four different groups regarding both diabetes and renal artery stenosis.

| Variable | DM-, RAS- *n*=79 | DM-, RAS+ *n*=44 | DM+, RAS- *n*=28 | DM+, RAS+ *n*=22 | *P* value |
|---|---|---|---|---|---|
| **Age (year)** *Mean (SD)* | 49.06(18.37) | 54.80(17.55) | 59.32(15.23) | 64.32(9.79) | 0.001* |
| **Sex distribution** *No. (%)* | | | | | |
| Female | 32(40.5%) | 20(45.5%) | 15(53.6%) | 7(31.8%) | 0.439 |
| Male | 47(59.5%) | 24(54.5%) | 13(46.4%) | 15(68.2%) | |
| **Blood pressure indices (mm Hg)** | | | | | |
| *Mean (SD)* | | | | | |
| Systolic | 159.15(25.34) | 158.86(24.42) | 160.71(27.48) | 162.72(23.34) | 0.560 |
| Diastolic | 90.57(12.78) | 87.72(12.91) | 89.11(10.10) | 89.77(7.48) | 0.647 |
| Mean arterial | 113.43(16.00) | 111.44(15.31) | 112.98(14.53) | 114.09(12.08) | 0.533 |

*Statistical significant difference, RAS=renal artery stenosis, DM=diabetes mellitus.

(*P*=0.001). The highest and lowest mean ages were observed in patients with diabetes and hypertension who had positive MRA [64.31(SD=9.78) years] and hypertensive patients without diabetes and renal artery stenosis [49.06(SD=18.37) years], respectively.

## Discussion

It has been cleared that there is a close association between diabetes mellitus and cardiovascular disease. It has been estimated that the risk of cardiovascular disease is two to five times greater in patients with diabetes than in the normal population.[17] Renal arteries seem to be widely involved in the macrovascular disease caused by diabetes. However, the precise prevalence of renal artery stenosis in patients with type 2 diabetes and hypertension has not yet been established.

In this study, by using MRA to screen for renal artery stenosis in patients with type 2 diabetes and coexistent hypertension, the prevalence of renal artery stenosis was 44%; whereas, this prevalence in patients in group B was 36.1%, without statistical significance.

It seems that the way to detect renal artery stenosis may affect its prevalence. However, only a few previous studies have assessed the prevalence of this disease in patients with type 2 diabetes and coexistent hypertension specially by using MRA.

In a recent MRA study by Valabhji et al. to screen for renal artery stenosis in patients with type 2 diabetes and coexistent hypertension, a prevalence of 17% was demonstrated.[2] Although the mean age of the patients with hypertension and diabetes in both ours (61.5 years) and Valabhji et al's (64 years) study was similar, the prevalence of renal artery stenosis was dramatically higher in our patients.

In another study, using three-dimensional MRA, the authors concluded that MRA-detected renal artery stenosis was common (40%) in patients with type 2 diabetes with uncontrolled hypertension. And renal insufficiency and subcritical (<65%) renal artery stenosis was a significant risk factor for progressive renal failure.[18] In that study, the prevalence of renal artery stenosis was more similar to our study.

In an autopsy study on 5,194 consecutive cases, renal artery stenosis was found in 10.1% of the cases with both hypertension and diabetes compared with 6.1% in cases with hypertension alone.[19] The researchers concluded that the presence of noninsulin-dependent diabetes mellitus increased the risk of renal artery stenosis and the risk of bilateral stenosis was greater in diabetic patients. The clinical significance of stenosis found at autopsy, however, is unknown.[18]

In another study, 24 hypertensive, <70-year-old patients with type 2 diabetes were screened for renal artery stenosis by intravenous subtraction arteriography. Of them five (21%) had stenosis.[13] However, after functional tests in four of these five patients, including ratios of plasma renin activity (PRA) sampled from each renal vein, the authors concluded that the stenoses were not hemodynamically significant.

In a further clinical study using angiography on 60 hypertensive patients with type 2 diabetes who consumed three or more antihypertensive agents, 13 (22%) had renal artery stenosis.[20]

Analysis of a retrospective study on consecutive renal arteriograms of hypertensive patients showed renal artery stenosis in 10 (36%) of 28 patients with diabetes and in 50 (48%) of 104 individuals without diabetes.[21] This study is one of the rare ones to compare the prevalence of renal artery stenosis in hypertensive patients with or without diabetes. Their sample size was smaller than ours. Moreover, our results showed that the prevalence of renal artery stenosis was higher in hypertensive patients with type 2 diabetes (44%) than those without diabetes (35.8%); although, this difference was not statistically significant (power=75%).

In another retrospective study on renal arteriograms, 44% of the 55 hypertensive patients with renal artery stenosis had diabetes.[22]

In a cohort of 589 hypertensive patients with diabetes, 99 (16.6%) had renal artery stenosis (at least 50% of one renal artery).[23] In another series of patients with both hypertension and type 2 diabetes, a prevalence of 16 – 17% was reported.[24]

In the study by Tanemoto et al. the combined prevalence of hemilateral and bilateral renal artery stenosis was 20.8% in 202 randomly selected patients with atherosclerotic risk factors.[25]

Atherosclerosis is a systemic disease, and atherosclerotic change occurs even in renal arteries without apparent stenotic lesions. Although such a change does not manifest as renal artery stenosis in its early stages, it is thought to progress without apparent clinical symptoms and will develop into stenosis in its later stages.[26] Therefore, it is anticipated that patients with more severe renal

artery stenosis, which often presented as bilateral stenosis, will tend to be older. In the present study, patients with renal artery stenosis were significantly older than those without stenosis. These results support the notion that atherosclerotic vascular disease progresses in the absence of proper treatment, and thus renal artery stenosis might be detected in its early stage.

Regarding the method of detecting renal artery stenosis, MRA is noninvasive and increasingly available, but it does not reliably predict clinical significance regarding the further deterioration of glomerular filtration rate with ACE inhibitor therapy.[2]

Several well-established clinical predictors of incidental renal artery stenosis are older age,[15,16,27-29] hypertension,[27,28,30,31] impaired renal function,[27,31] a history of coronary artery disease,[6,7,27,29] diabetes,[28,30,31] and a history of smoking.[28,30]

Similar to some previous studies,[15,16,27-29] we also showed that older age was an independent risk factor for the presence of renal artery stenosis, and the mean age of the patients with stenosis was significantly higher than those without stenosis. By contrast, Valabhji et al.[2] concluded that the presence of renal artery stenosis assessed by MRA was not statistically associated with sex, age, ethnicity, smoking status, duration of diabetes, family history, number of current antihypertensive agents prescribed, type of current antihyperglycemic therapy, retinopathy, nephropathy, peripheral neuropathy, systolic blood pressure, diastolic blood pressure, or waist-to-hip ratio.[2] we also showed that gender distribution, systolic, diastolic, and mean arterial blood pressures were not significantly different between hypertensive patients with or without stenosis.

A high prevalence of renal artery stenosis was found in males in a study by Courrèges et al.[24] In our study we did not find such association.

Renal artery stenosis can lead to deleterious pathophysiologic effects by excess production of angiotensin II,[32] which is a potent vasoconstrictor and has been implicated in the activation of cell proliferation systems.[33] In addition, high levels of angiotensin II are associated with left ventricular hypertrophy, endothelial dysfunction, and target organ damage.[34] This pathway could explain, at least partially, the increased mortality in symptomatic atherosclerotic renal artery stenosis.

Progressive stenosis has been reported in 51% of renal arteries five years after diagnosis: 3 – 16% of renal arteries became totally occluded and renal atrophy developed in 21% of patients with renal artery stenosis of >60%.[35] Expansion rate of the renal stenosis is directly associated with hypertension, supporting the clinical importance of blood pressure control.[36]

In conclusion, although the prevalence of renal artery stenosis was considerable in hypertensive patients with type 2 diabetes in our study, this prevalence was not significantly higher than that of nondiabetic group; even when the patients with diabetes were older than nondiabetic ones. In addition, it seems that patient's age is a more important factor for the presence of renal artery stenosis. However, further studies with higher sample sizes are required to understand the natural history and clinical significance of renal artery stenosis in hypertensive patients with type 2 diabetes. Basic studies and comparison of renal artery stenosis with other more frequent macrovascular involvements in type 2 diabetes may lead to increase the knowledge on the pathogenesis and pathophysiology of vascular disease in diabetes.

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