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Renal Resistive Index as An Indicator of Atherosclerotic Changes and Renal Damage in Hypertension and Its Role in Therapeutic Intervention

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ABSTRACT

Background: Renal resistive index (RRI) was suggested as an indicator of renal atherosclerotic changes in hypertensive patients with possible prognostic role in treatment.

Objectives: This study aimed to assess RRI in hypertensive subjects, its relation to other predictors of target organ damage and prognostic usefulness in management, specifically, with different antihypertensive drugs.

Patients and methods: The study included 100 newly diagnosed hypertensive adult subjects, who underwent abdominal ultrasound with Doppler to assess RRI, which was correlated with their clinical parameters including estimated glomerular filtration rate (eGFR) and other subclinical atherosclerosis markers as carotid intima-media thickness (IMT) and aortic knob width (AKW) calculated from chest radiograph. Another 50 non hypertensive subjects were assessed for their RRI as a control group. In addition, some of hypertensive patients were followed up one year after starting treatment was done and effects of different antihypertensive agents on their RRI were compared.

Results: The mean baseline RRI in hypertensive patients (0.71 ± 0.04) was significantly higher compared to control group (0.60 ± 0.02) and was positively significantly correlated with their clinical parameters (age, systolic, diastolic, pulse pressure and eGFR) and with their atherosclerotic parameters (IMT and AKW). In addition, ACE/ARBs treatment was associated with significant decrease of RRI compared to other drugs [beta blocker (BB) and calcium channel blocker (CCB)], indicating their more renal protective effect.

Conclusion: Assessment of RRI in patients with primary hypertension not only reflecting intrarenal perfusion changes, but it indicates systemic atherosclerotic changes, so it can be useful as prognostic parameter in addition to its possible therapeutic implications.

Keywords: Renal resistive index, Atherosclerosis, Hypertension.

INTRODUCTION

Hypertension is a major health problem in all countries, affecting approximately 1 billion individuals worldwide. In Egypt, prevalence of hypertension was estimated to be 26.3% among adult subjects and increases with age, to reach around 50% of Egyptians over 60 years. It is considered a major risk factor for occurrence of cardio-vascular events, in addition to subsequent renal and cerebro-vascular complications [(1, 2)].

Aortic knob width (AKW) represents a measurement of the aortic arch and upper part of the descending aorta assessed in X-ray of the chest. Many studies of hypertensive patients showed intimate relation between AKW and cardiovascular diseases [(3, 4)]. As AKW was found to be increased with age and atherosclerosis, so it was suggested to be a major predictor of organ damage occurring in hypertension [(5)].

Increase of intima-media thickness (IMT) of the carotid artery is the first structural change occurring in atherosclerosis and so it is considered as another marker of target organ damage, which usually develops slowly and gradually, in different velocity resulting in many problems [(6)].

On the other hand, the renal resistive index (RRI) assessed by Doppler ultrasound was used for years in assessment of many kidney diseases as chronic allograft rejection of the kidney [(3)], stenosis of the renal artery [(4,5)], detection of obstructive renal disease and progress of chronic kidney disorders [(6)]. It was also used as a prognostic indicator of outcome in critical patients [(7, 8)]. Renal RI was suggested to reflect atherosclerotic changes secondary to hypertension either on the reno-vascular or systemic circulation. So, it was proposed to be used as a parameter of renal injury in hypertensive patients that may be affected by different antihypertensive medications [(9, 10)].

Accordingly, this study aimed to evaluate the RRI changes in adult Egyptian hypertensive subjects with no other risk factors of renal vascular disease, its relation to other target organ damage predictors and its prognostic usefulness in the diagnosis and management of these patients, specifically, the impact of different therapeutic agents of hypertension on it.

PATIENTS AND METHODS

One hundred patients ≥35 years old, newly diagnosed with essential hypertension attending Outpatient Internal Medicine Clinic, Ain Shams University Hospital during the period from March to December 2020 were included in this study. Hypertension was considered when blood pressure

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measurement was ≥140/90 mmHg on three or more separate occasions. Another 50 Non hypertensive patients attending the Radiology Department for other minor trauma reasons were chosen as a control group.

Exclusion criteria: Patients with malignant hypertension or if it was secondary to reno-vascular or endocrinal diseases [(10–12)], other cardiovascular disease (as congenital, rheumatic, ischemic heart diseases or heart failure), renal artery stenosis [(13)], renal compromise (Estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m^2 or serum creatinine above 2.0 mg/dl), and other marked systemic diseases (as malignancy, diabetes, cirrhosis of the liver, obstructive pulmonary disease, or severe obesity). Moreover, we excluded patients with deviation of the trachea or mediastinum shift, and those who had aortic disease.

Ethical consent:
An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Clinical assessment:
Patient' history was taken and then physical assessment was done with measurement of both body weight and height. After few minutes of rest, measurement of blood pressure was done in the sitting position following standard methods. Then routine laboratory tests were done, using an auto-analyzer. eGFR was estimated by the Cockcroft-Gault Equation [(12)]. Follow up of the patients for one year after starting their treatment with one antihypertensive drug (with or without diuretics) was done.

Radiologic interventions:
All subjects underwent abdominal ultrasonography (US) for their kidneys after fasting for 6 hours whenever possible, using US with color Doppler machine and convex linear transducer (2.8–5 MHz). Scanning in supine then prone positions was done. At first, general assessment of the kidneys then Doppler examinations were performed. For accurate measurements, Doppler angle was standardized at < 30º, to give better Doppler curves and so good ratio of signal-to-noise.

Assessment of the main renal artery was done at first to exclude atherosclerosis before proceeding to our target area (inter-lobar and arcute arteries adjacent to medullary pyramids). Measurements of peak-systolic velocity (PSV) and end-diastolic velocity (EDV) were done from the inter-lobar renal arteries branches using proper angle and then mean RRI was automatically calculated from the equation (RRI = [PSV - EDV]/PSV), by the US machine. Measurement of inter-lobar arterial resistance was done in different 3 zones of each kidney (upper, middle and lower ones) and the RRI mean value was calculated from these 6 measurements for each patient. Follow up Doppler US for assessment of the RRI was done for the hypertensive patients for at least one year after starting their antihypertensive treatment (Figure 1).

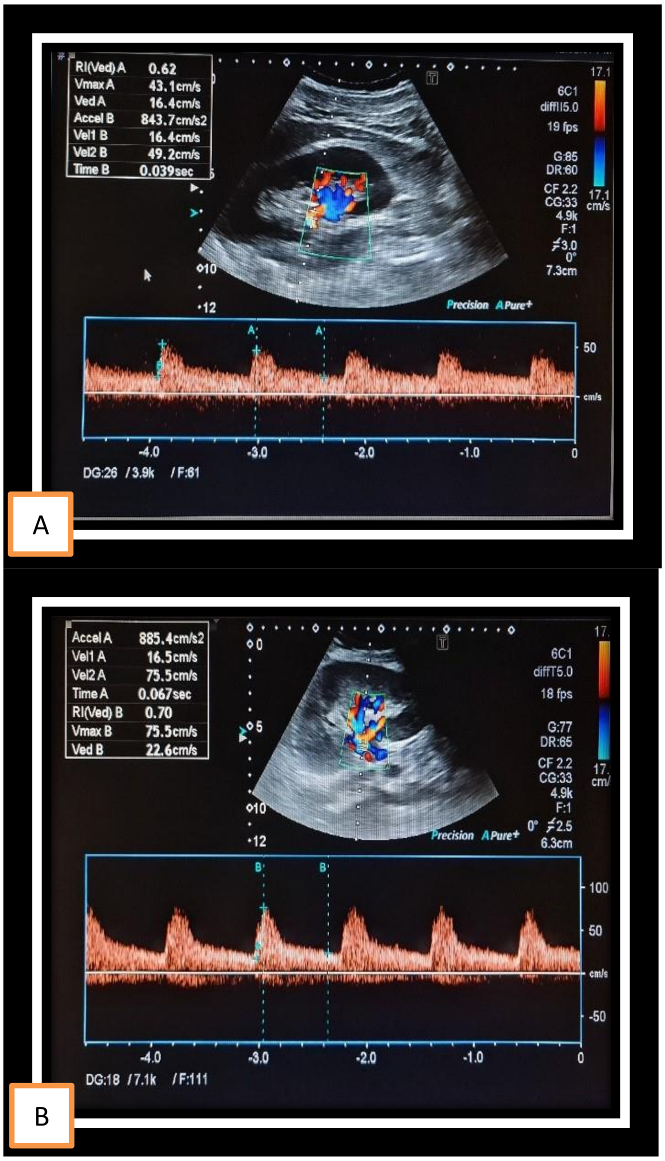

Figure (1): Renal RI during Doppler assessment of renal inter-lobar artery in hypertensive and normal controls. A, Renal RI in normotensive patient and B, Renal RI in hypertensive patient

For the assessment of AKW, the patients were exposed to a postero-anterior chest x-ray, which was assessed by radiologist, blinded to other data of the patients. A horizontal line from tracheal left lateral edge to aortic knob left lateral wall represented the AKW measurement (Figure 2).

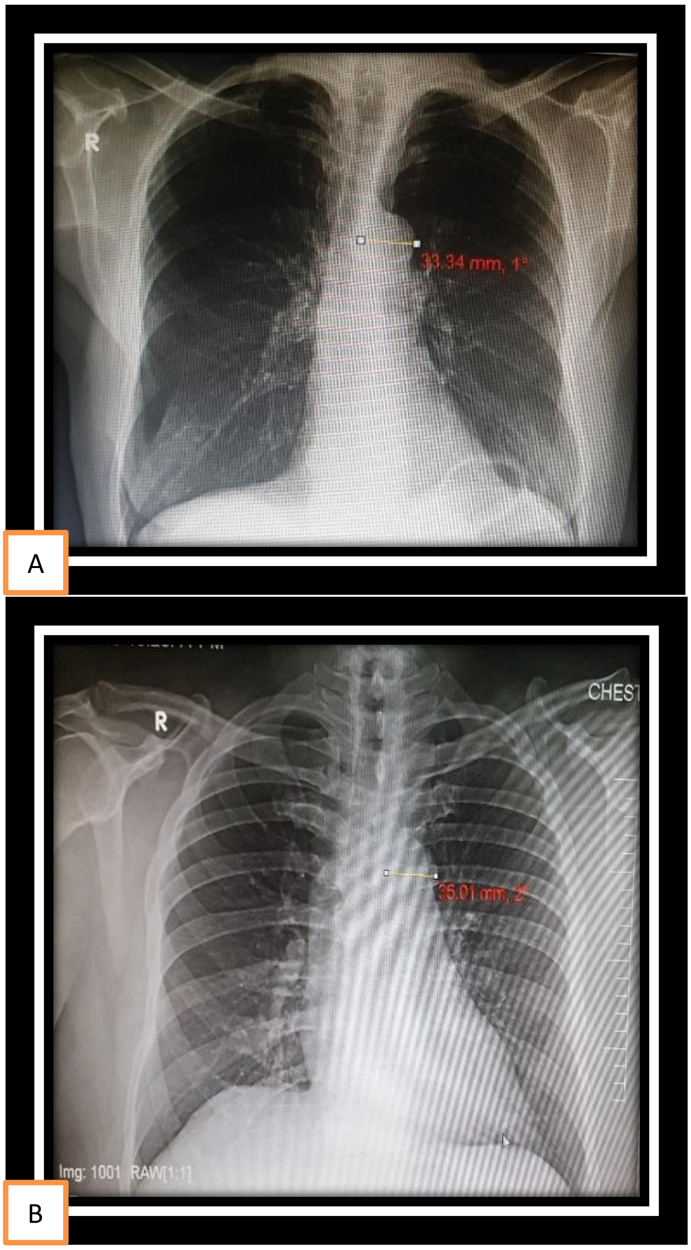

Figure (2): Aortic knob width (AKW) measurement method in chest radiography. A, AKW in normotensive patient and B, AKW in hypertensive patient.

For the intima-media thickness (IMT) assessment, examination of the common carotid artery (CCA) wall was done by B-mode ultrasonography, which is considered the best method for arterial wall structure evaluation. In the supine position, the probe was directed in the antero-lateral position of the extended patient's neck. On longitudinal 2D imaging, the near (media-adventitia) and far (lumen-intima) walls of the carotid artery were apparent as 2 bright echogenic lines separated by hypoechoic space. The carotid IMT was calculated from the distance between these 2 lines. Measurement was done on the distal 10 mm of the right and left common carotid arterial walls by electronic calipers after making zoom and freezing for the image, by recording 5 measurements on each side and taking the average of them for the IMT result, according to the Association for European Pediatric Cardiology [13] (Figure 3).

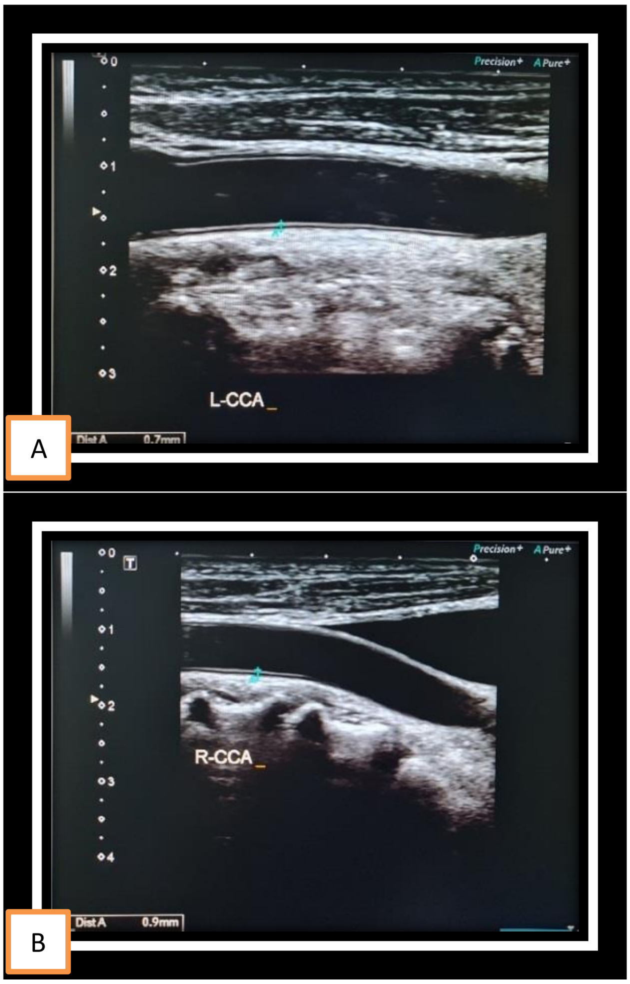

Figure (3): Intima-media thickness (IMT) definition – IMT is measured as the distance between lumen-intima and media-adventitia interfaces. (A) IMT in normotensive patient; (B) IMT in hypertensive patient.

Statistical analysis

The statistical program for social science (SPSS) version 20 was the one utilized in analysis of the results. The mean, standard deviation, minimum and maximum were calculated. For comparison of data, the student's t test was applied for quantitative data and Chi square test for qualitative ones. For correlation of data, Pearson test was performed. Level with P value ≤ 0.05 was considered significant.

RESULTS

The mean value of the baseline RRI in patients with hypertension was 0.71 ± 0.04, which was significantly higher compared to the control group (0.60 ± 0.02) (Table 1) and was positively significantly correlated with their clinical parameters (age, weight, BMI, systolic, diastolic, pulse pressure and eGFR) and at the same time correlated with their atherosclerotic parameters (AKW and IMT) (Table 2).

Both groups were comparable in the mean of their age, weight, height and BMI, while the hypertensive patients had significantly higher mean values of their blood pressure (systolic, diastolic and pulse pressure) in addition to estimated glomerular filtration rate in comparison with the control group as expected**.**

Regarding the mean values of the AKW and IMT, they were significantly increased in hypertensive patients (37.10 ± 0.96 and 0.75 ± 0.13 mm respectively) when compared to those of the control group (33.86 ± 1.34 and 0.59 ± 0.10 mm respectively) (P< 0.01). Moreover, a highly significant decrease in renal RI mean value was found on follow up of 60 patients (who were attended) after treatment for at least 1 year (0.71 ± 0.04 and 0.69 ± 0.04 before and after treatment respectively (P < 0.01). In addition, it was interesting that we found significant decrease of mean renal RI in patients group (22 patients) treated with angiotensin channel blockers or angiotensin receptor blockers (ACE/ARBs) (P < 0.01) after treatment, when compared to before treatment. Patients groups treated with other drugs namely, 20 patients with beta blockers (BB) and 18 patients with calcium channel blockers (CCB) showed non-significant change when pre-treatment was compared to post-treatment (P > 0.05) in both of them, which indicated more renal protective effect of (ACE/ARBs) than the other drugs (Table 3).

Table (1): Characteristics, biochemical and radiologic parameters of hypertensive patients and control group

Parameter	**Case group** n = 100 Mean ± SD	**Control group** n = 50 Mean ± SD	**Statistical Test**	**P (Significance)**
Age (Years)	55.4 ± 8.32 (40 – 68)	55.3 ± 8.69 (40 – 66)	t = 0.067	> 0.05 (NS)
Sex(n)				
Male	45	21	X^2 = 0.12	> 0.05 (NS)
Female	55	29		
Weight (Kg)	78.56 ± 14.73	75.06 ± 14.18	t = 1.407	> 0.05 (NS)
Height(cm)	166.55 ± 8.09	166.82 ± 7.83	t = 0.195	> 0.05 (NS)
BMI (kg/m2)	28.33 ± 5.07	26.93 ± 4.68	t = 1.679	> 0.05 (NS)
SBP (mmHg)	150 ± 7.21	128 ± 7.13	t = 17.748	< 0.01(HS)
DBP (mmHg)	98 ± 5.63	85 ± 3.68	t = 20.357	< 0.01(HS)
PP (mmHg)	69 ± 4.81	65 ± 3.41	t = 5.873	< 0.01(HS)
eGFR (mL/min/1.73 m^2)	84.21 ± 6.83	96.88 ± 11.27	t = 8.536	< 0.01(HS)
RRI	0.71 ± 0.04	0.60 ± 0.02	t = 22.454	< 0.01(HS)
AKW (mm)	37.10 ± 0.96	33.86 ± 1.34	t = 17.267	< 0.01(HS)
IMT (mm)	0.75± 0.13	0.59± 0.10	t = 8.329	< 0.01(HS)

BMI indicates body mass index, SBP indicates systolic blood pressure, DBP indicates diastolic blood pressure, PP indicates pulse pressure, eGFR indicates estimated glomerular filtration rate, AKW indicates aortic knob width, and IMT indicates intima-media thickness.

Table (2): Correlations of the demographic characteristics, biochemical and radiologic parameters with the renal resistive index (RI) of hypertensive patients

Parameter	**Renal Resistive index** r	**P (Significance)**
Age (Years)	0.406	< 0.01(HS)
Weight (Kg)	0.705	< 0.01(HS)
Height (cm)	0.054	> 0.05 (NS)
BMI (kg/m2)	0.879	< 0.01(HS)
SBP (mmHg)	0.620	< 0.01(HS)
DBP (mmHg)	0.543	< 0.01(HS)
PP (mmHg)	0571	< 0.01(HS)
eGFR (mL/min/1.73 m^2)	- 0.745	< 0.01(HS)
AKW (mm)	0.802	< 0.01 (HS)
IMT (mm)	0.847	< 0.01 (HS)

Table (3): Comparison of renal resistive index (RI) before and after treatment with different antihypertensive drug groups

Treatment group	No of patients	Renal Resistive index (mean ± SD)		Statistical test	P (Significance)
		Before treatment	After treatment		
BB group	20	0.70 ± 0.05	0.69 ± 0.04	t = 1.339	> 0.05 (NS)
CCB group	18	0.71 ± 0.04	0.70 ± 0.03	t = 1.713	> 0.05 (NS)
ACE/ARBs group	22	0.71 ± 0.04	0.67 ± 0.04	t = 13.586	< 0.01(HS)
Total	60	0.71 ± 0.04	0.69 ± 0.04	t = 6.222	< 0.01(HS)

BB indicates Beta blocker, CCB indicates Calcium Channel blocker, ACE indicates Angiotensin Channel blocker, and ARBs indicates Angiotensin receptor blockers.

DISCUSSION

Target organ damage detection is a major issue in evaluation and further treatment of patients with hypertension. As the kidney is one of these target organs, detection of renal indicators as increased albumin in urine or diminished GFR were suggested to be checked early in these cases as primary parameters for evaluation of their renal and further cardiovascular risks. Currently, renal resistive index was suggested as a noninvasive evaluation method for hypertensive renal and cardiovascular pathological changes [(1)].

In the present study, we have tried to evaluate the RRI changes in adult Egyptian hypertensive subjects with no other risk factors of renal vascular disease, its relation to other target organ damage predictors and its prognostic usefulness in the diagnosis and management of these patients.

In our patients with hypertension, the mean value of the baseline RRI (0.71 ± 0.04) was significantly higher compared to its value in the control group (0.60 ± 0.02). These findings are comparable to those of **Madubueze and Ugwa** [(14)] and **Viazzi *et al.*** [(15)]. However, **Yusuf *et al.***[(16)] reported results of 0.56 ± 0.04 on the right and 0.56 ± 0.04 on the left sides in normal individuals which were higher than our results. Also, **Galesic *et al.***[(17)] found a higher mean RRI in hypertensive European patients (0.66 ± 0.05) when compared to healthy normotensive individuals (0.60 ± 0.03). However, their mean RRI result in hypertensive patients was lower compared to Egyptian patients that may be related to genetic or environmental variations. According to **Madubueze and Ugwa** [(14)] "this increase in mean renal RI value is an early sign seen in adults with essential hypertension as a result of hypertension-induced myointimal hyperplasia of the renal arterioles". A normal cutoff value of RRI was considered as 0.7 by **Sevencan and Ozkan** [(1)] and some other studies and any subjects with higher values are prone to more prevalence of hypertensive end-organ damage and rapid occurrence of renal deterioration [(15, 18)].

In addition, we found significant positive correlations of RRI in our hypertensive patients with their clinical parameters (age, weight, and BMI), in addition to blood pressure (systolic, diastolic and pulse pressure) and reduced renal function diagnosed by eGFR. These results are supported by other studies [(19, 20)] that emphasize the suggestion that RRI could be used as an indicator of systemic vascular changes and increased cardiovascular risk [(11, 21)].

Regarding other target organ damage indicators, namely AKW and IMT, we found highly significant increase of both of them in hypertensive patients when compared to the control. In fact, this is supposed to be not expected in newly diagnosed cases, however, this may be explained by the fact that most of cases usually seek medical advice too late and does not convince to start antihypertensive drugs except when they have complications. **Erkan *et al.*** [(22)] recommended AKW and carotid IMT as predictors for sub-clinical atherosclerosis with a strong correlation between them. Moreover, the RRI in our hypertensive patients showed highly significant correlation with both AKW and carotid IMT parameters. **Sevencan and Ozkan** [(1)] observed a close relationship between AKW and RRI with an AKW value of ≥ 36 in hypertensive patients having high RRI (≥ 0.7). In addition, **Doi *et al.*** [(18)] found significant correlation between RRI and carotid IMT similar to our results and RRI was increasing in a significant manner with increasing target organ damage. Severity was assessed by the number of organs involved. These findings emphasize the importance of RRI as an early and non-invasive indicator of end-organ damage in hypertension, atherosclerosis and its sequels [(15, 23)].

On follow up of 60 of our patients for 1 year after treatment with different antihypertensive drugs, we found significant decrease in the mean of RRI after treatment compared to the level before starting treatment. **Doi *et al.*** [(18)] studied the prognostic role of RRI in primary hypertension patients and found that it predicted worse cardiovascular and renal outcomes, especially when associated with reduced GFR. So, it provides a useful diagnostic complement to renal function assessment in these patients. In addition, it was interesting in our study that we found significant decrease of RRI in patients group treated with angiotensin channel blockers or angiotensin receptor blockers (ACE/ARBs), when compared to patients groups treated with other drugs namely; beta blockers (BB) or calcium channel blockers (CCB). To our knowledge, only one study of **Leoncini *et al.*** [(24)] found significant decrease of RRI in few patients treated with

ACE inhibitor (lisinopril) compared to others treated with CCB (nifedipine), which indicated more renal protective effect of ACE/ARBs than other antihypertensive drugs. **Yamaguchi *et al.*[25],** by studying RRI in patients with chronic kidney disease (CKD), found negative association between RRI and use of rennin-angiotensin system inhibitors (RAS-I), and they concluded that "RAS-Is could contribute towards suppressing the elevation of RI in CKD patients and towards preventing the development of renal failure in CKD patients".

CONCLUSION

We recommend routine assessment of RRI as a screening tool in all primary hypertensive patients; as an increased RRI in these patients not only reflecting intrarenal perfusion changes, but it indicates systemic atherosclerotic changes. So, it can be useful prognostic parameter in addition to its possible therapeutic implications.

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