The Egyptian Journal of Radiology and Nuclear Medicine (2015) **46**, 1205–1213

Egyptian Society of Radiology and Nuclear Medicine

The Egyptian Journal of Radiology and Nuclear Medicine

www.elsevier.com/locate/ejrnm
www.sciencedirect.com

ORIGINAL ARTICLE

Relation between hyper-uricemia and renal resistivity index in non diabetic non hypertensive patients

Ahmed Mohamed Hussein [a,*], **Samer Malak Botros** [a,1], **Shereen A. Saleh** [b,2]

[a] *Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt*
[b] *Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt*

Received 27 April 2015; accepted 15 June 2015
Available online 3 July 2015

KEYWORDS

Hyper-uricemia;
Renal Doppler;
Renal artery resistive index

Abstract *Background:* Relationship between uric acid and renal artery resistive index (RRI) in hypertensive subjects was recently suggested.
Aim: The aim was to evaluate the effect of hyper-uricemia on RRI in adult Egyptian subjects with no other risk factors of renal vascular disease, and to assess the impact of therapeutic control of serum uric acid on the RRI.
Patients and methods: 50 adult hyper-uricemic subjects were included in this study, who underwent abdominal ultrasound with Doppler examination of the kidneys. The RI was automatically calculated by the US equipment. Intra-renal resistance was measured at inter-lobar arteries three times in different regions of each kidney (upper, middle, and lower zones) and the mean RI value was calculated. Each case had its pre and post 3 and 6 weeks treatment duplex measurement of RI together with uric acid measurement and correlation.
Results: Mean value of the baseline RI was 0.768 ± 0.01355 SD, and mean serum uric acid value was 10.86 ± 0.65 SD, with a positive significant correlation between both values. Mean value of the difference of the serum uric acid level and RRI prior to and 3 weeks after treatment was 2.68 ± 0.49, 0.04 ± 0.01 respectively, with positive significant correlation between the two values *p*-value: 0.001. Mean value of the difference of the serum uric acid level and RRI 3 and 6 weeks after treatment was 2.18 ± 0.5 and 0.06 ± 0.01 respectively, with significant positive correlation between the two values and *p*-value 0.00. Mean value of the total change of serum uric acid and RRI over the treatment period was: 2.38 ± 0.43 and 0.049 ± 0.01 with positive significant correlation between the two values and *p*-value: 0.00.

* Corresponding author. Tel.: +20 1115666504.
E-mail addresses: ahmed_hussein99@yaho.com (A.M. Hussein), samon24@yahoo.com (S.M. Botros), shereen_saleh2014@hotmail.com (S.A. Saleh).
[1] Tel.: +20 1223430633.
[2] Address: Ain Shams University, Internal Medicine Department, Unit 1, Egypt. Tel.: +20 01227834104.
Peer review under responsibility of Egyptian Society of Radiology and Nuclear Medicine.

http://dx.doi.org/10.1016/j.ejrnm.2015.06.011

Conclusion: Serum uric acid significantly correlates with RRI in the absence of other risk factors affecting renal vasculature. Improvement of serum uric acid is accompanied by the improvement in RRI.

1. Introduction

The resistive index of an artery is a hemodynamic measure considered to reflect its vascular impedance (1). Higher resistive index values consist in a manifestation of local arteriolopathy (2). Evaluation of vascular impedance at different sites of the renal parenchyma may suggest functional or structural changes within the kidneys and could provide useful diagnostic and prognostic information (3).

Indeed, the Doppler-derived renal resistive index (RRI) has been used in the assessment of chronic renal allograft rejection (4), detection and management of renal artery stenosis (5), evaluation of progression risk in chronic kidney disease (CKD) (6), and more recently as a predictor of renal and overall outcome in the critically ill patient (7).

Experimental data showed that uric acid stimulates proliferation, inflammation and oxidative stress in vascular smooth-muscle cells, induces endothelial dysfunction and activates the renin–angiotensin system (8).

Recent data demonstrated an independent relationship between uric acid and renal artery resistive index in hypertensive subjects, indicating that uric acid might be associated with microvascular damage and/or dysfunction in clinical settings (9).

However there were limitations in the literature in studying the effect of hyper-uricemia on renal artery resistive index in the absence of other risk factors of renal vascular disease e.g. diabetes and hypertension.

1.1. Aim of the study

This study was designed to evaluate the effect of hyperuricemia on RRI in adult Egyptian subjects with no other risk factors of renal vascular disease, and to assess the impact of therapeutic control of serum uric acid on the RRI.

2. Patients and methods

2.1. Patients

Our study comprised a total of 50 nonsmoking, non-diabetic, non-hypertensive, recently diagnosed hyperuricemic (serum uric acid > 7.0 mg/dL standard laboratory tests) otherwise healthy subjects attending the Internal Medicine outpatient clinics of private hospitals for annual checkup as requested by their companies.

All patients gave an informed consent before participating in the study.

2.1.1. Exclusion criteria

Patients with hypertension (blood pressure ⩾ 140/90 mmHg), diabetes mellitus (FBS > 126 mg/dl, 2hPP > 200 mg/dl), Hyperlipidemia, smoking, renal vascular or parenchymatous diseases were excluded from the study.

All participants were subjected to the following:

1. Complete history taking and full physical examination including blood pressure measurement test to exclude the presence of hyper or hypo tension.
2. Laboratory testing including: serum uric acid, serum creatinine to exclude renal decompensation patients, fasting blood sugar and 2 h post prandial to exclude those with Diabetes Mellitus and lipid profile to exclude patients with dyslipidemia.
3. All patients underwent Baseline pretreatment bi-dimensional gray scale ultrasound and color duplex which were used to exclude patients with:

- Arterial reno-vascular kidney disease (renal artery stenosis manifested by decreased acceleration slope less than 3 meter per squared second and/or prolonged acceleration time more than 70 ms).
- Venous reno-vascular kidney disease (renal vein thrombosis).
- Renal stones.
- Hydronephrosis.
- Renal size abnormalities (too small being below 95 mm in length, too large being above 135 mm in length, or length discrepancy between both sides more than 2 cm).
- Any grade of unilateral or bilateral abnormally increased renal parenchymal echogenicity.

All these patients were excluded as all the previously mentioned conditions affect the renal resistivity index. Additionally patients with hemolytic anemias and hematological malignancies were excluded from the study.

All patients received xanthine oxidase inhibitor (Allopurinol 100–300 mg/day), and the renal resistivity index was measured before treatment and after treatment phases of 3 and 6 weeks of the treatment.

2.2. Methods figures from 1 to 4

Each case had his pre and post 3 and 6 weeks treatment duplex Doppler examination done by the same radiologist to avoid inter-observer variabilities. Doppler angle was standardized at 59°.

Patients underwent abdominal ultrasound with duplex Doppler examination of the kidneys. All subjects were examined after eight hours fasting. They underwent abdominal ultrasonography (US) using US equipment with color Doppler capability using convex linear (2.8–5 MHz) transducer (LOGIQ P6, General Electric Medical Systems, United States of America). The RI was automatically calculated by the US equipment. Intra-renal resistance was measured at inter-lobar arteries three times in different regions of each

kidney (upper, middle, and lower zones) and the mean value was calculated. Subsequently, a mean RI was calculated derived from 6 measurements for each patient.

3. Results

The study was conducted over 50 patients with hyper-uricemia.

Patient demographics: all 50 patients were males with a mean age of 37.5 years ± 4.61 years SD. The minimum, maximum and range of the age were 30, 45, and 15 respectively.

3.1. Analysis of patients' data prior to medical treatment

Each participant underwent ultrasound Doppler examination to calculate the renal arterial RI prior to the onset of medical treatment. A total of 6 readings were obtained for both the right and left renal arterial vasculature and a mean value was calculated for all readings of both kidneys for each patient.

The mean value of the RI of the renal arterial vasculature was 0.768 ± 0.01355 SD. The maximum, minimum and range values of the RI were 0.79, 0.75, and 0.04 respectively (Figs. 1 and 4).

The serum uric acid value was obtained for each participant prior to medical treatment. The mean serum uric acid value was 10.86 ± 0.65 SD. The minimum, maximum and range values were 10, 12, 2 and respectively.

3.1.1. Correlation between the serum uric acid and renal artery RI prior to treatment

No statistically significant relation was found between the participants' ages and the level of serum uric acid nor between their age and the mean value of the renal arterial RI using the one sample *T*-test, hence the null hypothesis could not be rejected (p-values = 0.311, and 0.214 respectively).

As regards the relation between the serum uric acid and renal arterial RI prior to the onset of therapy we were able to reject the null hypothesis using chi-squared test where the p-value = 0.001 (highly significant).

In addition there was a positive correlation between both values with a Pearson's correlation coefficient = 0.903 and *p-value 0.01* (Fig. 7 and Table 1).

3.2. Analysis of patients' data 3 weeks after onset of medical treatment

The difference between the level of the serum uric acid 3 weeks after and levels prior to medical treatment was calculated, with estimation of the mean difference for each participant. The same was done regarding the mean RI value for the same participant prior to and 3 weeks after onset of treatment (Figs. 2 and 5).

Comparing the mean values of the calculated means of the serum uric acid level differences prior to and after onset of treatment to the same calculated renal arterial RI values by using one sample *T* test, we were able to reject the null hypothesis as regards a possible relation between both variables, with a high significance (p-value = 0.001).

In addition correlation between both variables using bivariate correlation method showed positive correlation with a Pearson's correlation coefficient of 0.517, covariance value of 0.003 and *p-value 0.001* (Fig. 8 and Table 2).

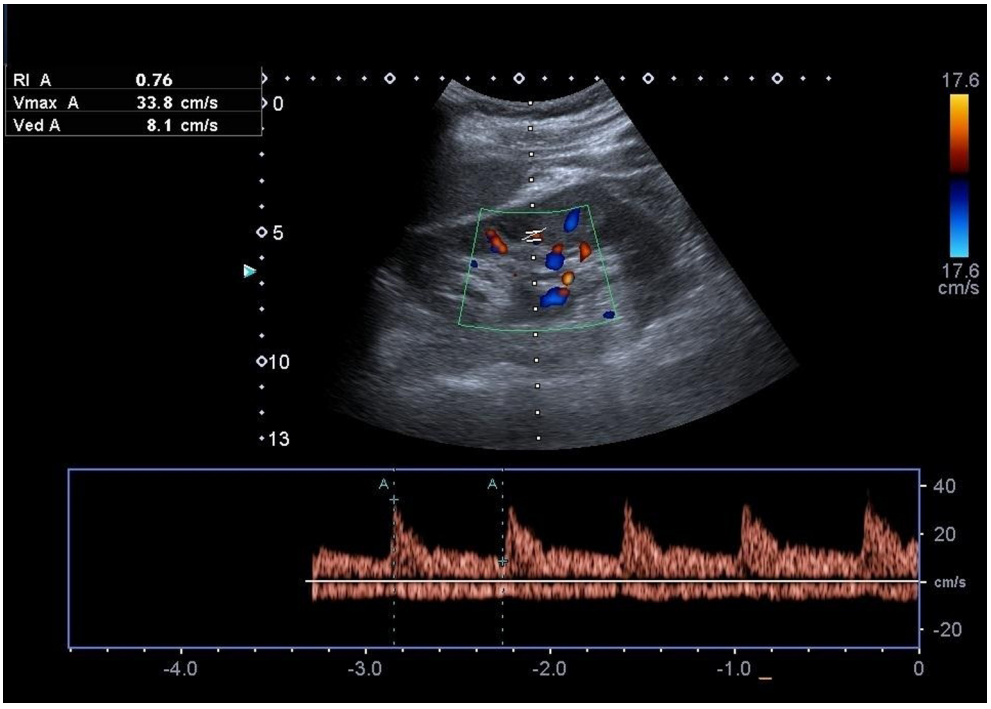

Fig. 1 Showing renal artery flow by spectral pulsed duplex with automated RRI calculation before initiation of treatment (S. uric acid = 10.3).

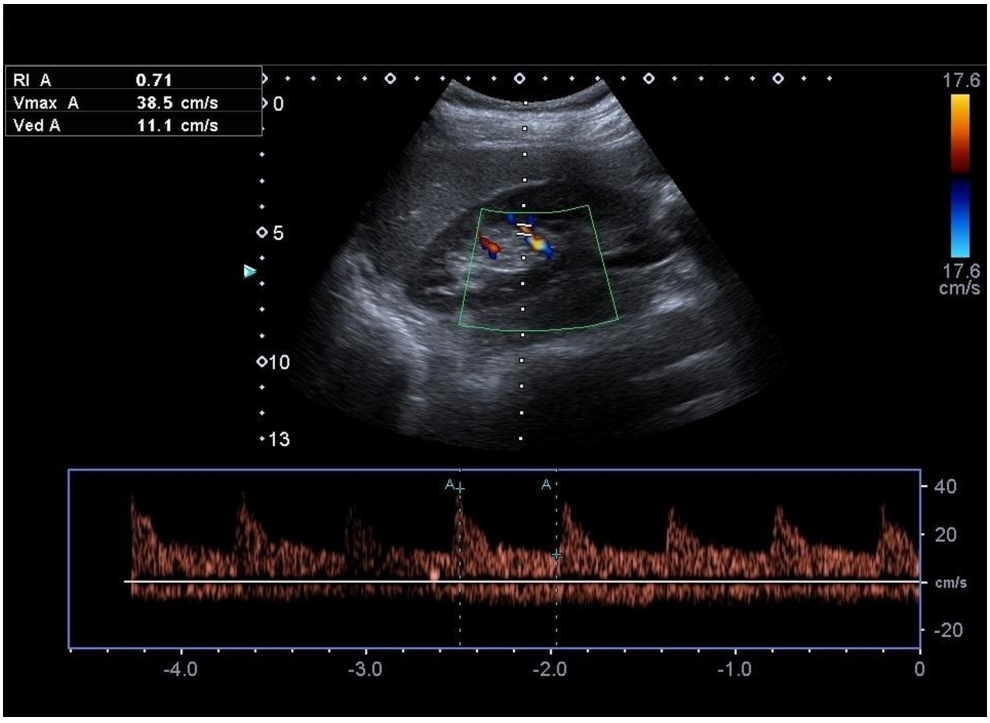

Fig. 2 Showing renal artery flow by spectral pulsed duplex with automated RRI calculation 3 weeks after treatment (S. uric acid = 7.9).

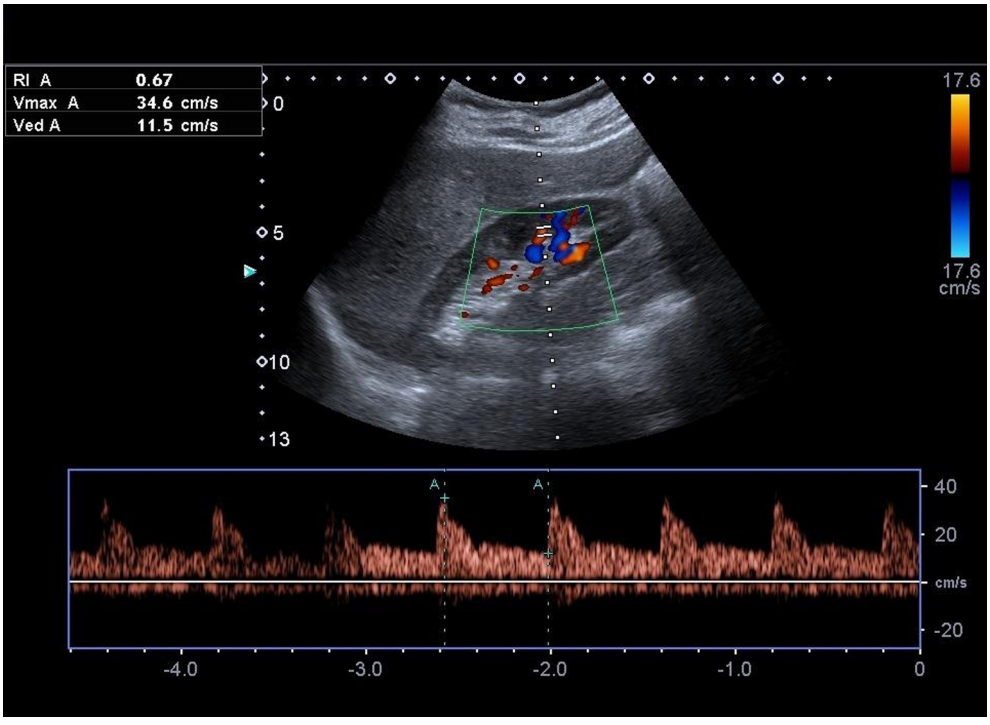

Fig. 3 Showing renal artery flow by spectral pulsed duplex with automated RRI calculation 6 weeks after treatment and achieving normal serum uric acid level (S. uric acid = 6).

3.3. Analysis of patients' data 6 weeks after onset of medical treatment

The difference between the level of the serum uric acid 3 and 6 weeks after onset of medical treatment was calculated, with estimation of the mean difference for each participant. The same was done regarding the mean RI value for the same 3 and 6 weeks after onset of treatment (Figs. 3 and 6).

Comparing the previously calculated serum uric acid and renal arterial RI differences using one sample *T* test, we were

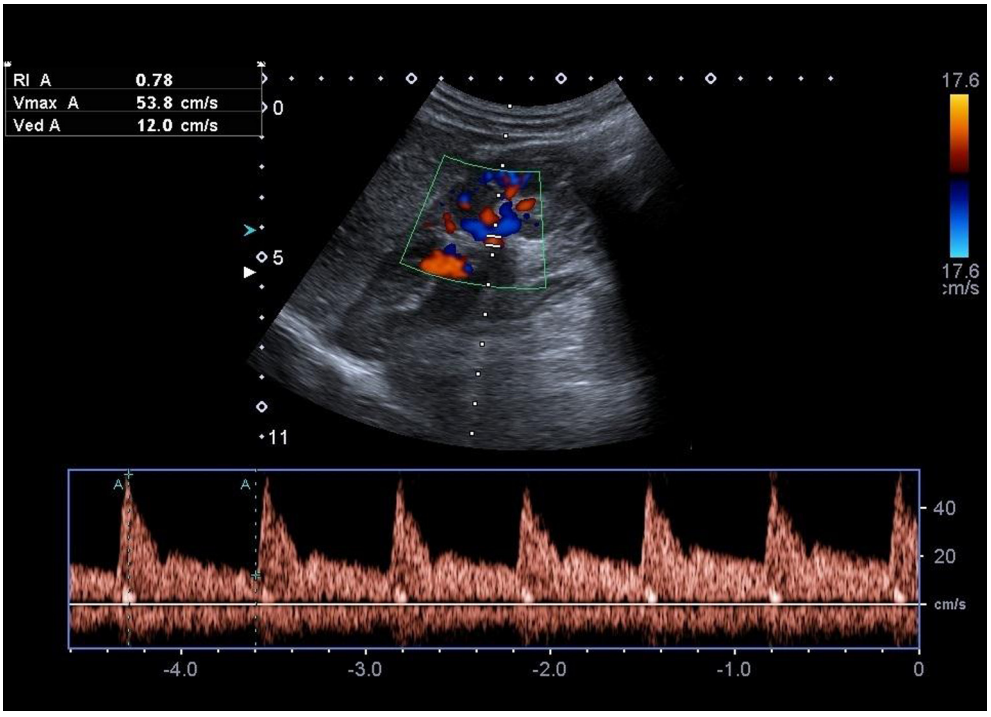

Fig. 4 Showing renal artery flow by spectral pulsed duplex with automated RRI calculation before initiation of treatment in another patient (S. uric acid = 11.5).

Table 1 Mean values of serum uric acid and RI of renal arterial vasculature in patients with hyper-uricemia prior to treatment.

	Mean value ± SD	Minimum	Maximum	Range	*p*-value	Pearson's correlation coefficient
Serum uric acid	10.86 ± 0.65184	10	12	2	0.01	0.903
Renal arterial RI	0.768 ± 0.01355	0.75	0.79	0.04		

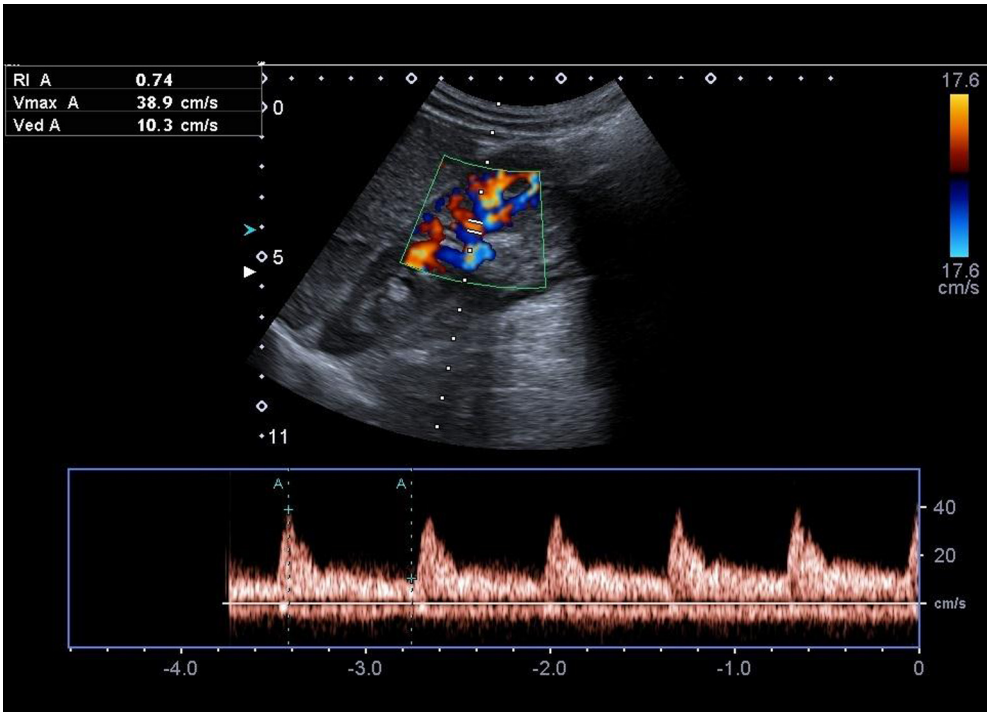

Fig. 5 Showing renal artery flow by spectral pulsed duplex with automated RRI calculation 3 weeks after treatment in another patient (S. uric acid = 9).

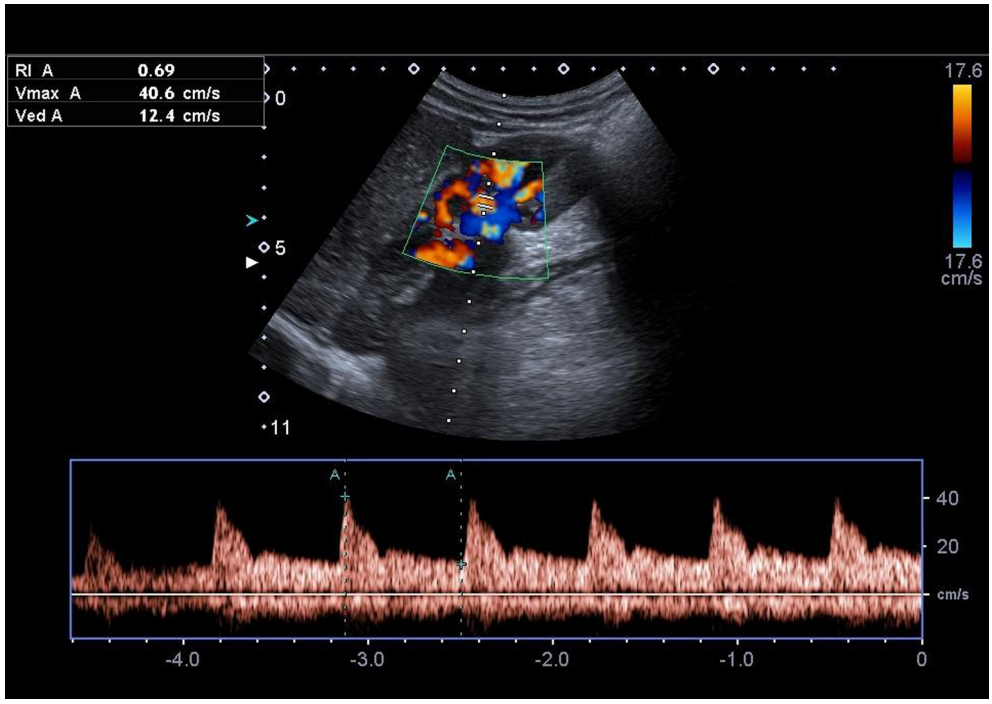

Fig. 6 Showing renal artery flow by spectral pulsed duplex with automated RRI calculation 6 weeks after treatment and achieving normal serum uric acid level (S. uric acid = 6.7).

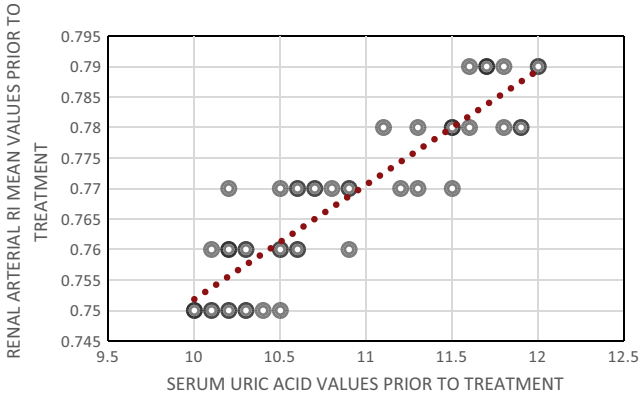

Fig. 7 Scatter plot depicting the values of the serum uric acid plotted against the mean value renal arterial RI in the participating patients prior to treatment.

able to reject the null hypothesis as regards a possible relation between both variables, with a high significance (p-value = 0.00).

In addition correlation between both variables using bivariate correlation method showed positive correlation with a Pearson's correlation coefficient of 0.544, covariance value of 0.004 and *p-value: 0.00* (Fig. 9 and Table 3).

Finally, the mean value of the difference of the serum uric acid levels measures prior to, 3, and 6 weeks after the onset of medical treatment was calculated. The same was done for the mean renal arterial RI for the same patients.

The values of the mean difference of the serum uric acid calculated in the previous step were compared to those of the difference in RI for the same participants using one sample T-test, and the null hypothesis could be rejected with high significance of the p-value (0.00).

Correlation using bivariate correlation method was done with confirmed positive correlation of both variables with Pearson's correlation coefficient = 0.903, covariance = 0.004 and *p-value: 0.00* (Fig. 10 and Table 4).

4. Discussion

The renal resistive index (RRI) is commonly used as an index of intra-renal arterial resistance (10). RI increases in various kidney diseases (11), and previous studies have shown the associations of RI with renal function and patient prognosis (12). Uric acid is the end product of human purine metabolism. Increased serum uric acid has been considered with different metabolic, cardiovascular, and renal disorders (13). Hyperuricemia is closely associated with chronic kidney disease (CKD), is a risk factor for renal insufficiency in general populations, and is a poor prognostic factor of renal function in patients who have nephropathy (14). Glomerular, tubulointerstitial, and vascular involvement (15) with eventual chronic renal disease has been reported in hyper-uricemia (16). Recognition of the different manifestations and complications of hyper-uricemia seems beneficial to prevent renal damage in the early phase (17). Effect of hyper-uricemia as a sole cause of increased renal resistive index with no other risk factors- has not been widely studied.

The current study shows significant correlation between baseline serum uric acid values and the RRI. This reflects the effect of hyper-uricemia -in the absence of any other risk factor of renal vascular affection such as hypertension, diabetes, hyperlipidemia and senile atherosclerosis-on RRI. This shows

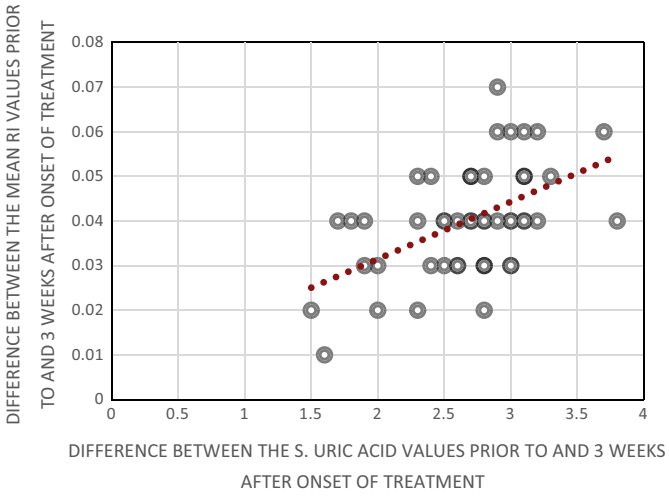

Fig. 8 Scatter plot depicting the mean differences of the serum uric acid prior to and 3 weeks after onset of treatment plotted against the RI differences for the same patients.

Table 2 Table representing the mean value of the difference of the serum uric acid level and renal arterial RI prior to and 3 weeks after treatment.

	Mean ± SD	*p*-value	Pearson's correlation coefficient	Covariance
Mean value of the difference of the serum uric acid level prior to and 3 weeks after treatment	2.68 ± 0.49857	0.001	0.517	0.003
Mean value of the difference of the renal artery RI prior to and 3 weeks after treatment	0.0402 ± 0.01237			

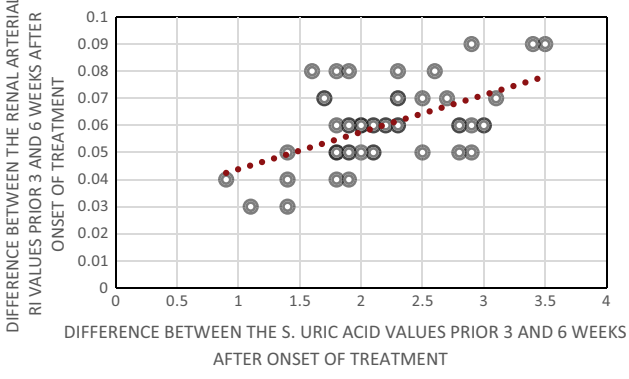

Fig. 9 Scatter plot depicting the mean differences of the serum uric acid 3 and 6 weeks after onset of treatment plotted against the RI differences for the same patients.

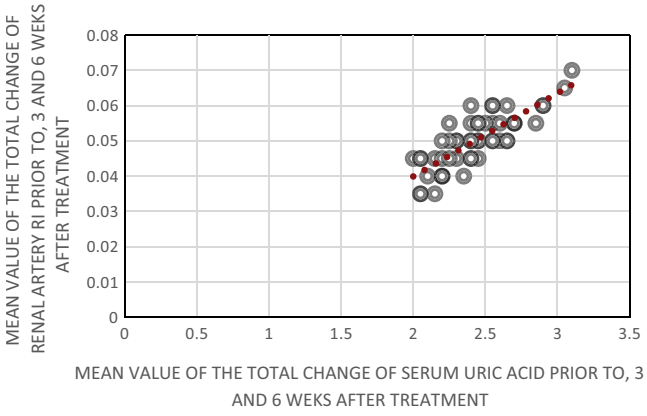

Fig. 10 Scatter plot depicting the mean differences of the serum uric acid prior to, 3 and 6 weeks after onset of treatment plotted against the RI differences for the same patients.

Table 3 Table representing the mean value of the difference of the serum uric acid level and renal arterial RI 3 and 6 weeks after treatment.

	Mean ± SD	*p*-value	Pearson correlation	Covariance
Mean value of the difference of the serum uric acid level 3 and 6 weeks after treatment	2.182 ± 0.56737	0.00	0.544	0.004
Mean value of the difference of the renal artery RI 3 and 6 weeks after treatment	0.06 ± 0.01429			

Table 4 Table representing the mean value of the difference of the serum uric acid level and renal arterial RI prior to, 3 and 6 weeks after treatment.

	Mean ± SD	*p*-value	Pearson correlation	Covariance
Mean value of the total change of serum uric acid prior to, 3 and 6 weeks after treatment	2.384 ± 0.43	0.00	0.903	0.004
Mean value of the total change of renal artery RI prior to, 3 and 6 weeks after treatment	0.0493 ± 0.01			

some similarity to the results of a study done by Berni et al., who found that hyperuricemics had significantly higher RRI than normouricemics but in hypertensive patients indicating that serum uric acid might be associated with microvascular damage and/or dysfunction in clinical settings (2). Hyperuricemia was found to result in the activation of renin–angiotensin system, down-regulation of nitric oxide, vascular muscle proliferation, afferent arteriolosclerosis, altered pressure natriuresis, endothelial dysfunction, and abnormal cellular sodium transport (18), all of these factors may explain the increase in RRI and its correlation with hyper-uricemia in the current study. These results are also similar to results of Messerli et al., who found that renal blood flow was lower and renal vascular and total peripheral resistances were increased in patients with high uric acid levels (19).

Different results were observed by Pontremoli et al., who found that the degree of RI correlated with age, blood pressure, target organ damage despite similar body mass index, uric acid, fasting blood glucose, lipid profile and duration of hypertension upon their patients (20).

This study also revealed significant correlation between serum uric acid and RRI after 3 and 6 weeks of medical treatment of hyper-uricemia using xanthine oxidase enzymes inhibitor (Allopurinol) (21), denoting significant positive impact of the management of hyper-uricemia on renal resistive index. Similar results were reached by Nickavar et al., who observed that proteinuria decreased significantly by uric acid lowering agents and antiproteinuric treatment in a patient with familial juvenile hyperuricemic nephropathy (17). Sezer et al., found that allopurinol treatment decreased cardiovascular risk factors and slowed the progression of renal disease pre-dialysis chronic kidney disease patients with hyper-uricemia (22). Allopurinol, by decreasing the serum UA levels, may serve as an agent to decrease glomerular hydrostatic pressure indirectly and thus help alleviate the renal damage. Kanbay et al. reported that the treatment of asymptomatic hyperuricemia improved renal function (23). Likewise, Siu et al. reported that the treatment of asymptomatic hyper-uricemia delayed disease progression (24).

5. Conclusion

There is significant correlation between serum uric acid and renal resistive index. Management of hyper-uricemia results in lowering of serum uric acid which correlates significantly with the decrease in RRI.

Conflict of interest

The authors declare that there are no conflict of interest.

References

(1) Staub D, Meyerhans A, Bundi B, Schmid HP, Frauchiger B. Prediction of cardiovascular morbidity and mortality: comparison of the internal carotid artery resistive index with the common carotid artery intima-media thickness. Stroke 2006;37:800–5.

(2) Berni A, Boddi M, Fattori EB, Cecioni I, Berardino S, Montuschi F, et al. Serum uric acid levels and renal damage in hyperuricemic hypertensive patients treated with renin–angiotensin system blockers. Am J Hypertens 2010;23:675–80.

(3) Viazzi Francesca, Leoncini Giovanna, Derchi Lorenzo E, Pontremoli Roberto. Ultrasound Doppler renal resistive index: a useful tool for the management of the hypertensive patient. J Hypertens 2014;32:149–53.

(4) Radermacher J, Mengel M, Ellis S, Stuht S, Hiss M, Schwarz A, et al. The renal arterial resistance index and renal allograft survival. N Engl J Med 2003;349:115–24.

(5) Crutchley TA, Pearce JD, Craven TE, Stafford JM, Edwards MS, Hansen KJ. Clinical utility of the resistive index in atherosclerotic renovascular disease. J Vasc Surg 2009;49:148–55.

(6) Radermacher J, Ellis S, Haller H. Renal resistance index and progression of renal disease. Hypertension 2002;39:699–703.

(7) Le Dorze M, Bouglé A, Deruddre S, Duranteau J. Renal Doppler ultrasound: a new tool to assess renal perfusion in critical illness. Shock 2012;37:360–5.

(8) Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183–90.

(9) Viazzi F, Leoncini G, Ratto E, Falqui V, Parodi A, Conti N, et al. Mild hyperuricemia and subclinical renal damage in untreated primary hypertension. Am J Hypertens 2007;20:1276–82.

(10) Hanamura K, Tojo A, Kinugasa S, Asaba K, and Fujita T. The resistive index is a marker of renal function, pathology, prognosis, and responsiveness to steroid therapy in chronic kidney disease patients. Int. J. Nephrol. 2012. Article ID 139565, 9 pages http://dx.doi.org/10.1155/2012/139565.

(11) Hamano K, Nitta A, Ohtake T, Kobayashi S. Associations of renal vascular resistance with albuminuria and other microangiopathy in type 2 diabetic patients. Diabetes Care 2008;31:1853–7.

(12) Sugiura T, Wada A. Resistive index predicts renal prognosis in chronic kidney disease: results of a 4-year follow-up. Clin Experiment Nephrol 2011;2011(15):114–20.

(13) Preitner F, Bonny O, Laverrière A, Rotman S, Firsov D, Da Costa A, et al. Glut9 is a major regulator of urate homeostasis and its genetic inactivation induces hyperuricosuria and urate nephropathy. Proc Natl Acad Sci 2009;106:15501–6.

(14) Ohno I. Relationship between hyperuricemia and chronic kidney disease. Nucleosides, Nucleotides Nucleic Acids 2011;30(12):1039–44.

(15) Bellinghieri G, Santoro D, Savica V. Pharmacological treatment of acute and chronic hyperuricemia in kidney diseased patients. Contrib Nephrol 2005;147:149–60.

(16) Nakagawa T, Mazzali M, Kang DH, Sánchez-Lozada LG, Herrera-Acosta J, Johnson RJ. Uric acid: a uremic toxin? Blood Purif 2006;24:67–70.
(17) Nickavar A. Prevention of renal damage by treating hyper-uricemia. Int J Prev Med 2013;4:1318–20.
(18) Feig DI, Kang DH, Nakagawa T, Mazzali M, Johnson RJ. Uric acid and hypertension. Curr Hypertens 2006;8:111–5.
(19) Messerli H, Frohlich D, Dreslinski R, Suarez H, Aristimuno G. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Int Med 1980;93(6):817–21.
(20) Pontremoli R, Viazzi F, Martinoli C, Ravera M, Nicolella C, Berruti V, et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. Nephrol Dial Transplant 1999;14:360–5.
(21) Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51–9.
(22) Sezer S, Karakan S, Atesagaoglu B, Acar F. Allopurinol reduces cardiovascular risks and improves renal function in pre-dialysis chronic kidney disease patients with hyperuricemia. Saudi J Kid Dis Trans 2014;25:316–20.
(23) Kanbay M, Ozkara A, Selcoki Y, et al. Effect of treatment of hiperuricemia with allopurinl on blood pressure, creatinine clearance, and proteinuria in patients with normal renal function. Int Urol Nephrol 2007;39:1227–33.
(24) Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51–9.