ORIGINAL PAPER

Longitudinal prospective observational type study about determinants of renal resistive index variations in chronic renal failure patients treated with conventional medical and dietetic therapy

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__Summary__ *Objective: This longitudinal prospective observational type study was conceived with the aim to examine the impact on renal resistive index (RRI) of the variables that we can manipulate with therapeutic and or dietetic interventions in a chronic kidney disease population in order to known which of these variables was statistically related to changes in RRI and therefore could become the object of the greatest therapeutic effort.*
Material and methods: This study was undertaken between May 2016 to May 2017 in the outpatient nephrology and urology clinic of San Donato Hospital in Arezzo. The study population (84 patients: 47 males and 37 females) was randomly selected among the chronic kidney patients (with various degrees of renal impairment) affected by hypertension and or diabetes mellitus. After a comprehensive medical examination these patients were submitted to determination of serum creatinine, glycated hemoglobin, 24-hour urinary albumin excretion and finally renal Doppler ultrasonography. Then the patients were submitted to a full therapeutic and dietetic intervention to ameliorate the renal impairment by a wide range of actions and after on average a one-year interval were submitted again to a new medical examination and a second determination of serum creatinine, glycated hemoglobin, 24-hour urinary albumin excretion and a new renal Doppler ultrasonography too.
Results: The comparison between basal and final data revealed a slight reduction in the mean of bilateral renal resistance indices (Delta RRI: -0.0182 ± 0.08), associated to a slight increase in the mean glomerular filtration rate (Delta GFR: 0.8738 ± 10.95 ml/min/1.73 m^2), a reduction in mean body weight (Delta weight: -1.9548 ± 5.26 Kg) and mean BMI (Delta BMI: -0.7643 ± 2.10 Kg/m^2) as well as a reduction in the mean systolic blood pressure (Delta systolic blood pressure: -8.8333 ± 25.19 mmHg). Statistical analysis showed statistically significant correlations (p < 0.05) between Delta RRI and Delta weight (p < 0.03), Delta BMI (p < 0.02) and Delta systolic blood pressure (p < 0.05).
Conclusion: Despite the many limitations the our study clearly identifies the targets (yet widely known) to act on to prevent kidney alterations related to RRI and provides further evidence, if any, of the utility of RRI as a key parameter in monitoring patients with chronic renal failure and as a valuable tool to drive the clinical efforts to contrast the kidney disease.

KEY WORDS: *Longitudinal prospective observational type study; Renal ultrasonography; Renal resistive index; Chronic kidney patients; Conventional medical and dietetic therapy.*

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INTRODUCTION

The *renal resistive index* (RRI) in segmental and interlobar arteries of the kidney is calculated on the basis of Pourcelot's equation as the ratio of the difference between the maximum *systolic velocity* (Vs) and the end-diastolic velocity (Vd) to the maximum systolic velocity: RI = (Vs-Vd)/Vs (1).
Normal RRI values in adults are in the range of 0.47-0.70 with a difference between two kidneys of < 5-8% (2).
RRI has shown to be related with glomerulosclerosis, arteriolosclerosis and tubulointerstitial lesions more than others morphologic parameters like renal length and cortex area (3).
Although RRI examinations do not recognize among different renal medical pathologies, patients with higher RRI (< 0.7) generally show more severe arteriolosclerosis than others with normal (< 0.65) or high normal RRI (0.65 ≤ RI < 0.7) so that in mild to moderate renal dysfunction RRI predicts CKD progression and poor outcome especially when RRI ≥ 0.7 (3-6).
Also in the patients affected by diabetic nephropathy (where RRI is higher in comparison with those affected by others kidney diseases with an equivalent GFR) in both < 60 and > 60 years old subjects and even in subjects on RAS inhibitors therapy or not, *Sugiura et al.* (7) proved that a RRI > 0.7 is an independent predictor of the risk of worsening renal function.
Renal resistive index is therefore tightly related to renal arteriolosclerosis (4) and represents an integrated index of arterial compliance, pulsatility and downstream microvascular impedance.
Moreover since RRI is markedly affected by renal (renal interstitial and venous pressure) and systemic (aortic stiffness, pulse pressure) determinants (8) RRI not only predicts renal prognosis (9), as already mentioned, but also gives information regarding general atherosclerotic damage.
Thus currently, RRI is accepted as a well-known marker of renal vascular and interstitial damage, corresponding to an increased total cardiovascular risk (10).
To this regard we can cite a study where RRI, measured at interlobar arteries, shown to be associated with the

severity and duration of essential hypertension (11) while in 426 patients with essential hypertension was also demonstrated that impairment of renal hemodynamics, as assessed by an increased RRI, was associated with an increased risk of cardiovascular and renal outcomes (12).

Moreover it is also known that RRI decreases with use of *renin angiotensin system* (RAS) inhibitors, due to the hemodynamic changes induced by these antihypertensive agents. (13)

Anyway there are some points that still need to be clarified and among these it is not known whether and how much dietetic and therapeutic interventions may affect RRI (10) except for the fact that RRI, as already mentioned, is known to decrease with use of RAS inhibitors (13) and that it is also known that intensive blood pressure lowering to the recommended values is associated with a significant improvement of intrarenal arterial functional properties and renal function (14).

Moreover longitudinal population studies are still needed to clarify whether Doppler changes in intrarenal arteries may be associated to an improvement in the cardiovascular and renal outcome in the hypertensive patients (15).

So with the aim to examine the impact on RRI of the variables that we can manipulate with therapeutic and or dietetic interventions in a chronic kidney disease population we concept this pivotal longitudinal prospective study in order to known which of these variables was statistically related to changes in RRI and therefore it could become the subject of the greatest therapeutic effort.

MATERIALS AND METHODS

This study was undertaken between May 2016 to May 2017 in the outpatient nephrology and urology clinic of *San Donato Hospital in Arezzo*.

The study population was randomly selected among the chronic kidney patients (with various degrees of renal impairment) and affected by hypertension and or diabetes mellitus with exclusion of those with obstructive uropathy, acute or chronic glomerulonephritis, tubulointerstitial renal diseases, renal artery stenosis and malignant disease.

The same population was already treated by a variety of drugs including RAS inhibitors too.

So we enrolled 84 patients (47 males and 37 females, with an average age of 74.5 ± 11 years) almost all with hypertension (except only four) and affected by diabetes mellitus with a rate of 54%.

The average glomerular filtration rate (GFR) (calculated by the CKD EPI equation) (16), was 43 ± 18 ml/min/1.73 m^2 (Table 1).

After the evaluation of medical history and physical examination, comprehensive of the recording of weight and height, a measure of blood pressure was taken with a mercury sphygmomanometer applied around each patient's non-dominant arm after the patient had rested for 15 minutes in a sitting position and with his/her arm placed at the level of the heart. Two consecutives blood pressure recordings, taken at 5 minute interval, were averaged to provide clinic systolic and diastolic blood pressure values.

Table 1.
Baseline characteristics of the population enrolled.

Parameter	Average	Standard deviation
Age (years)	74.5	11
Weight (kg)	77.0	13.1
Body mass index (kg/m^2)	29.0	4.1
Glomerular filtration rate (ml/min/1.73 m^2)	43	18
24-hour urinary albumin excretion (gr/24)	0.4	0.9
Glycated haemoglobin (%)	6.3	0.9
Renal resistive index (as bilateral mean of renal resistive index)	0.7	0.0
Systolic blood pressure (mmHg)	128.7	18.3
Diastolic blood pressure (mmHg)	78.7	11.5
Mean arterial pressure (mmHg)	95.4	11.1

Then these patients were submitted to determination of serum creatinine, glycated hemoglobin, 24-hour urinary albumin excretion and finally renal Doppler ultrasonography.

All examinations were carried out by the same nephrologist experienced in ultrasound examination using the same ultrasound device that was a Logiq S7 (*GE Medical Systems Italy S.P.A. Milan, Italy*) sonographic system equipped with 3 to 5 Mhz transducers.

Doppler signals were obtained from the interlobar arteries from the upper, middle and lower third of both kidneys and resistive index was calculated as the average of 6 measurements (3 from each of the 2 kidneys) taken for each patient.

The Doppler angle was chosen as close to 0° as possible and special care was taken not to compress the kidney and not to have the patient performing Valsalva maneuver because both of them can increase the renal resistive index value.

We recorded also the diameters in the longitudinal axis of each kidney and finally the cortical thickness of each kidney, measured in the portion closer to the upper pole and the lower pole of the same kidney.

Then the patients were submitted to a full therapeutic and dietetic intervention to ameliorate the renal impairment by a wide range of actions such as removal of nephrotoxic drugs (eg. metformine, hydroclorothiazide diuretics, etc.), improvement of blood pressure and proteinuria by a strengthened therapy and/or by introducing, in relation to blood pressure control and the entity of proteinuria, new antihypertensive medications among which RAS inhibitors and/or non-dihydropyridine calcium channel blockers (17) (considering not all the population or even most of it was treated by RAS inhibitors). Furthermore it was ameliorated the control of the diabetes by new drugs or higher doses of pre-existing drugs. Eventually, when it was indicated, it was introduced an hypoproteic, hyposodic and hypoglicemic as well as hypocaloric diet (18, 19).

After on average a one-year interval the same patients were submitted again to physical examination comprehensive of the recording of weight and clinic blood pressure measurement performed with the same modalities above mentioned.

Then these patients were also submitted to a second deter-

mination of serum creatinine, glycated hemoglobin, 24-hour urinary albumin excretion and eventually to a new renal Doppler ultrasonography carried out by the above mentioned nephrologist experienced in ultrasound investigation and by using the same ultrasound device.

Statistics

The bivariate linear Pearson correlation analysis was applied to variable changes, by evaluating the coefficients r and r-squared. A statistical significance of 95% was considered to assess the association between variables.

RESULTS

The comparison between basal and final control (that we named Delta as the variation of a variable between basal and final control) revealed a slight reduction in the mean value of bilateral renal resistive index (Delta RRI: -0.0182 ± 0.08), associated with a slight increase in the mean glomerular filtration (Delta GFR: 0.8738 ± 10.95 ml/min/1.73 m^2), a reduction in mean body weight (Delta weight: -1.9548 ± 5.26 Kg) and in mean BMI (Delta BMI: -0.7643 ± 2.10 Kg/m^2) as well as a reduction in the mean systolic blood pressure (Delta systolic blood pressure: -8.8333 ± 25.19 mmHg), mean diastolic blood pressure (Delta diastolic blood pressure: -5.0000 ± 15.76 mmHg) and mean arterial pressure (Delta mean arterial pressure: -6.2778 ± 17.83 mmHg). On the contrary there was a substantial invariance in average proteinuria (Delta proteinuria: 0.0477 ± 0.69 mg/24h) and a slight increase in average glycated haemoglobin (Delta glycated haemoglobin: 1.3667 ± 2.61%) (Table 2).

Hence these data were analyzed in order to know what were the parameters whose variation could be significantly associated with the abovementioned change in resistance indices.

Statistical analysis showed statistically significant correlations ($p < 0.05$) between Delta RRI and Delta weight ($p < 0.03$), Delta BMI ($p < 0.02$) and Delta systolic blood pressure ($p < 0.05$).

Table 2.
Variation (Delta) of the variables between basic and final evaluation.

Parameter	Average	Standard deviation	N.
Delta RRI	-0.0182	0.08	84
Delta Weight	-1.9548	5.26	84
Delta BMI	-0.7643	2.10	84
Delta GFR	0.8738	10.95	84
Delta proteinuria	0.0477	0.69	84
Delta HbA1c	1.3667	2.61	84
Delta systolic blood pressure	-8.8333	25.19	84
Delta diastolic blood pressure	-5.0000	15.76	84
Delta mean arterial pressure	-6.2778	17.83	84

DISCUSSION

It has to first point out that the population enrolled for our study was composed by chronic kidney failure patients with an average glomerular filtration rate of 43 ± 18 ml/min/1.73 m^2 that should be considered as a moderate stage of CKD and not as an advanced stage of CKD, since it is known that patients with advanced stages of CKD (GFR < 30 ml/min/1.73 m^2) do not show differences in RRI values, because advanced local alterations (vascular and interstitial) on RRI exceed systemic factors like pulse pressure (20, 21).

Furthermore, in order to explain the correlation of the RRI with systolic blood pressure, we underline that it is widely known that systemic hemodynamics and peripheral arterial resistance and compliance have been demonstrated to affect the Doppler arterial waveform signal obtained in the intrarenal arteries.

More in detail a number of studies explored the association of the RRI with aortic (central) pulse pressure or peripheral (brachial) pulse pressure. All these studies consistently demonstrated a significant and direct association between the RRI and central or peripheral pulse pressure independent of other covariates (15, 22-26).

More in detail when renal resistance is increased, renal blood flow declines for a given perfusion pressure and because the decline is more prominent in diastole than in systole it leads to an increase in RRI (27).

It was also known that stiffening of the aorta and large conduit arteries wall, that is characteristic of the chronic renal failure patients (28) as well as of aging (29), increases systolic blood pressure and decreases diastolic blood pressure, thereby increasing pulse pressure (that is the difference between systolic and diastolic blood pressure) and is a strong predictor of cardiovascular and cerebrovascular mortality (29).

More in detail *Verhave et al.* (29), in a cohort of 212 patients with never treated isolated systolic hypertension, found an inverse relationship between pulse pressure and glomerular filtration rate that was only present in patients of 60 years of age or older as the population of our study that was with an average age of 74.5 ± 11 years.

In effect the calcium can be deposited into either the intimal (as a rule for older patients with a clinical history of atherosclerosis and conventional risk factors for atherosclerotic disease) or medial layers of the vasculature and calcium deposition in the medial layer, a common finding in end-stage renal disease, is associated with stiffening of the vasculature, resulting in adverse cardiovascular outcomes (28).

It is also known that insulin resistance, which is highly prevalent in diabetes mellitus type 2 and hypertension, is associated with several metabolic abnormalities, namely, obesity, essential hypertension, dyslipidemia, inflammation and impaired glucose metabolism (30).

More in detail, since 1996 *Steinberg et al.* (31) first demonstrated that obesity is associated with peripheral endothelial dysfunction, which may be related to insulin resistance.

As then insulin resistance is closely related with systemic atherosclerosis (32) and increased RRI is related with atherosclerotic renal artery damage too (33) so that RRI it is considered a sensitive marker of atherosclerosis and it is believed that an increased insulin resistance may be independently related with increased RRI (30).

In this way since a relevant component of the insulin resistance is the overweight (34) and in fact our population showed BMI values close to the obesity with an aver-

age basal BMI of 29 ± 4.1 kg/m^2, we suppose that the reduction of weight and BMI obtained during the study by the dietetic therapy, which led a final average BMI of 28.3 ± 4.1 kg/m^2, may have reduced the entity of the insulin resistance so obtaining a reduction of the RRI.

About the lack of correlation between RRI and proteinuria it is possible that RRI could be correlated with albumin excretion only in later stages when albumin excretion reaches a certain limit. These observations may also account for the common finding of an increase in RRI values in patients with diabetes even if with normal urinary albumin (10, 35).

Therefore since RRI significantly correlates with the degree of proteinuria by resulting higher in patients with macroalbuminuria (> 300 µg/mg creatinine) than in patients with normal urinary albumin or with microalbuminuria (35) and being in our study proteinuria of a modest entity (average basal proteinuria: 0.49 ± 0.97 gr/24h) with a substantial invariance over the course of the study, this could explain why we did not find a statistically correlation between RRI and proteinuria.

Finally about the lacking relationship between RRI and glycated haemoglobin we note that poor control of blood glucose, as represented by increased HbA1c, affected the magnitude of decrease in RRI in patients with type 2 diabetes (36). In fact RRI is mainly influenced by renal microcirculation and systemic factors such as atherosclerosis of big vessel and pulse pressure and in our population we recorded a slightly increase of Delta HbA1c too (10).

Conclusions

About the relationship between Delta RRI and Delta blood systolic pressure our data are in line with the already known concept that a strict blood pressure control is necessary for renoprotection and clearly suggest a beneficial effect of a similar intensive blood pressure reduction. In effect it was already demonstrated that a significant blood pressure lowering to recommended values is associated with a significant improvement of intrarenal arterial functional properties and renal function (14).

Similarly obesity is a major risk factor for essential hypertension, diabetes, and other comorbid conditions that contribute to the development of chronic kidney disease (37). In fact obesity among the his many adverse effects raises blood pressure by increasing renal tubular sodium reabsorption, impairing pressure natriuresis, and causing volume expansion via activation of the sympathetic nervous system and renin-angiotensin-aldosterone system ultimately leading to glomerular injury that exacerbates hypertension and worsens renal injury (37).

In accordance with *Hall et al.* (37) we suppose therefore that a body weight reduction, via caloric restriction and increased physical activity, is an important first step for the management of obesity, hypertension, and chronic kidney disease.

Despite its many limitations our study clearly identifies the targets (yet widely known) to act on in order to prevent glomerulosclerosis, arteriosclerosis and tubule interstitial lesions that have shown to be related to RRI more than to others morphologic parameters like renal length and cortex area (3, 38). Furthermore it provides further evidence, if any, of the utility of RRI as a key parameter in monitoring patients with chronic renal failure (38) and as a valuable tool to drive the clinical efforts to contrast the kidney disease.

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