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Original Paper

Cardio-Renal Syndrome Type 4: The Correlation Between Cardiorenal Ultrasound Parameters

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Key Words
Cardio-renal syndrome • Cronich kidney disease • Renal Resistive Index • Right ventricle dysfunction • Cardiovascular diseases

Abstract
Bakground/Aims: Cardiovascular diseases represent the leading causes of morbidity and mortality in patients with cronich kidney disease (CKD). The pathogenesis includes a complex, bidirectional interaction between heart and kidney termed cardiorenal syndrome type 4. The aim of study was to evaluate the association between renal and cardiovascular ultrasonographic parameters and identify early markers of cardiovascular risk. ***Methods:*** A total of 35 patients with CKD and 25 healthy controls, were enrolled and we have evaluated inflammatory indexes, mineral metabolism, renal function, renal and cardiovascular ultrasonographic parameters. ***Results:*** Tricuspid anular plane systolic excursion (TAPSE) and estimated pulmonary artery systolic pressure (ePAPs) showed a statistically significant difference between CKD patients and healthy controls ($p<0.001$, $p=0.05$). Also 25 hydroxyvitaminD (25-OH-VitD), parathyroid hormone (iPTH), posphorus, serum uric acid, renal resistive index (RRI) and C-reactive protein (CRP) showed a significant difference between the two groups ($p=0.002$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). Moreover the TAPSE correlated positively with estimated glomerula filtration rate (eGFR) and negatively with RRI ($p=0.05$, $p=0.008$), while ePAPs correlated negatively with eGFR and positively with RRI ($p=0.029$, $p<0.001$). ***Conclusion:*** CKD can contribute to the development and progression of right ventricle dysfunction with endothelial dysfunction, inflammation and mineral metabolism disorders. Accurate assessment of right ventricular function is recommended in patients with CKD. RRI and echocardiographic parameters can be an important instrument for the diagnosis, prognosis and therapeutic assessment of cardio-renal syndrome in these patients.

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Introduction

Chronic kidney disease (CKD) is associated with cardiovascular disease (CVD), including coronary artery disease, myocardial infarction, heart failure, arrhythmia and sudden cardiac death, increasing greatly in end-stage renal disease (ESRD) [1, 2]. The pathogenesis includes a complex, bidirectional interaction between heart and kidney, that involves traditional and nontraditional risk factors, named cardiorenal syndrome (CRS) type 4 or chronic renocardiac syndrome, defined as 'chronic abnormalities in renal function leading to heart injury ' and identify the CVD risk in patients with CKD [3]. Patients with CKD are predisposed to develop CVD from atherosclerosis and cardiomyopathy. Atherosclerotic disease in CKD patients is characterized by increase in intima-media thickness, atheromatous plaques, and diffuse vascular calcifications, determined by traditional and non traditional risk factors such as anemia, endothelial dysfunction, hypertension, haemodynamic alteration, hyperhomocysteinemia, hyperuricemia, mineral bone disorders (MBD) with deficiency of vitamin D, hyperparathyroidism and abnormal calcium-phosphate metabolism, inflammation, uremic toxins, neurohormonal activation, oxidative stress, etc. These vascular changes result in cardiomyopathy with left ventricular hypertrophy (LVH) or dilatation and decreased coronary reserve or perfusion [4, 5]. Left ventricle abnormality have been widely studied in CKD, but little is known about the early changes of the right ventricle (RV), indeed few studies in literature aimed to evaluate the parameters of right ventricular function in CKD [6, 7].

The aim of our study was to evaluate the association between renal and cardiovascular ultrasonographic parameters and identify early markers of cardiovascular risk.

Materials and Methods

The study protocol was approved by the Local Clinical Research Ethics Committee. The study conforms to the principles outlined in the Declaration of Helsinki and we obtained a written consent by each patient enrolled.

Study Design and Subjects

We performed an observational study on 35 patients with CKD stage 3/4 KDOQI (aged 65,3 ± 16,4) and 25 healthy controls matched for age and sex at the University Hospital "Policlinico Umberto I" of Rome, Sapienza University of Rome, Italy. Patients were enrolled from march 2014 to June 2015.

Inclusion criteria

Patients aged >18 years and < 80 years, with CKD stage 3/4 Kidney Disease Outcomes Quality Initiative (KDOQI). Estimate Glomerular Filtration Rate (eGFR - 15-60 ml/min). The estimated glomerular filtration rate (eGFR) was calculated with the abbreviated Cronich kidney disease-epidemiology formula (CKD-EPI), as defined by Levey et al [8].

Exclusion criteria

We excluded patients affected by heart failure, chronic obstructive airway disease or other lung diseases and / or pulmonary hypertension, moreover patients with congenital heart disease, valvular disease or with left ventricular moderate-severe disfunction (ejection fraction (EF) <50%). Also patients with acute coronary syndrome within 3 months before the study were excluded. We did not enroll patients who refused to give consent and patients with missing data.

Patients

A total of 35 patients with CKD stage 3/4 KDOQI and 25 healthy controls matched for age and sex have carried out the following clinical and instrumental.

Laboratory measurements

Blood was drawn in the morning after an overnight fasting of at least 12 h. In all patients, the levels of fasting plasma glucose (mg/dL), insulin (μU/ml), total serum cholesterol (mg/dL), triglycerides (mg/dL),

high-density lipoprotein (HDL) (mg/dL), creatinine (mg/dL), serum nitrogen (mg/dL), serum uric acid (SUA) (mg/dL), calcium (mg/dL), phosphorus (mg/dL), serum electrolytes (mEq/L), C-reactive protein (CRP) (mg/dL), were measured using standard automated techniques. LDL-cholesterol was calculated using the Friedewald equation: Low-density lipoprotein (LDL) (mg/dL) = total cholesterol–HDL– (triglycerides/5). Parathyroid hormone was measured using a two-site assay that measures "intact" hormone (iPTH) (pg/ml) and 25 hydroxyvitamin D (25-OH-VitD) (ng/mL) was measured by radioimmunoassay. Serum albumin (g/dL) was determined by bromcresol purple method. Microalbuminuria/24 h (30-300 mg/24h) were carried out.

Anthropometric assessments

Body weight was determined to the nearest 0.1 kg using a calibrated digital scale. Body mass index was calculated from a person's weight and height (weight (kg)/[height (m)]2).

Blood pressure measurements

Clinic blood pressure (BP) measurements were made 3 times after 10 minutes of rest in a seated position using a standard sphygmomanometer and cuffs adapted to the arm circumference, according to the British Hypertension Society guidelines [9]. Then, the mean values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated for all participants. The systolic and diastolic BP levels were taken as the points of appearance and disappearance of Korotkoff sounds, respectively. Hypertension was defined as SBP >140 mmHg or DBP >90 mmHg on repeated measurements. Furthermore, all patients had performed the 24h ambulatory blood pressure monitoring (ABPM) with evaluation of SBP, DBP and the physiological Dipper night. This monitoring was performed with hypotensive therapy .

Renal Resistive index (RRI)

Participants were studied with the high-resolution B-mode ultrasound machine Toshiba Aplio XV (Toshiba AplioxV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with a 3-3.5 MHz convex transducer. All measurements were made by a single, blinded, experienced ultrasonographer. We used an anterior approach, in the prone position, and an oblique approach, in lateral position, for detecting the renal arteries and intra-parenchymal vessels. The interlobular, interlobar or arcuate arteries in both kidneys were identified by color-flow imaging and blood-flow profile in the artery was monitored by spectral analysis. RRI values were determined with the mean of three separate measurements in the renal superior pole, interpolar regional and inferior pole in both kidneys. Three to five reproducible and consecutive waveforms with similar aspect from each kidney are obtained. These measurements were used to calculate the average RRI value for each kidney, and then the average RRI value for each patient was calculated as the mean of the RRI in the left and right kidney [10]. We determined the peak systolic velocity and end-diastolic velocity (centimeters/second) to calculate the renal resistive index (RRI) as = [1-(end-diastolic velocity ÷ maximal systolic velocity)] x 100.

Echocardiography

M-mode 2D echocardiographic examinations by a single experienced sonographer in the echocardiography laboratory and using a standard institutional protocol were carried out [9]. Commercially available instruments (Toshiba AplioxV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with 2.5-7.5 MHz imaging transducers were used; continuous single-lead electrocardiogram (ECG) monitoring was maintained during the study; the patients were in the left decubitus position, and the sonographer was blinded to all clinical details of the patients. All echocardiographic data according to the guidelines of the American Society of Echocardiography (ASE) were recorded [11, 12]. Tricuspid Anular Plane Systolic Excursion (TAPSE), estimated pulmonary artery systolic pressure (ePASP), pulmonary capillary wedge pressure (PCWP), and right ventricular end-diastolic volume (RVEDV) were measured. The estimated pulmonary artery systolic pressure was obtained by the sum of the Doppler derived transtricuspid gradient and the estimated right atrial pressure, as assessed by the inspiratory collapse of the inferior vena cava [13].

Statistical analysis

Data management and analysis were performed using IBM® SPSS® Statistics 17 for Windows® software (IBM Corporation, New Orchard Road Armonk, New York, United States). The normality of variables was tested using the Shapiro-Wilk method for normal distributions. All continuous variables were

Table 1. Patient' s characteristics. Data are show as mean ± standard deviation. Abbreviations: BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iPTH, intact parathyroid hormone; CRP, C-reactive protein; RRI, Renal Resistive Index; TAPSE, Tricuspid Anular Plane Systolic Excursion; ePASP, estimated pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; RVEDV, right ventricular end-diastolic volume

	Cronich kidney disease group 35	Healthy controls group 25	
Age (years)	70 ± 15	54 ± 11	
Male n (%)	20 (57%)	11 (43%)	
BMI (kg/m²)	27.6 ± 5.3	28.5 ± 4.8	*n.s.*
Plasma glucose (mg/dL)	96.0 ± 28.3	91 ± 22.4	*n.s..*
Creatinine (mg/dL)	1.7 ± 0.4	0.8 ± 0.2	*p<0.001*
eGFR (ml/min/1.73m2)	39.8 ± 11.3	95.4 ± 15.5	*p<0.001*
Hb (g/dl)	11.0 ± 0.2	11.6 ± 0.4	*n.s.*
Serum Uric Acid (mg/dL)	6.8 ± 2.1	5.2 ± 1.7	*p=0.002*
Calcium (mg/dL)	9.6 ± 0.5	9.3 ± 0.5	*n.s.*
Phosphorus (mg/dL)	4.2 ± 0.6	3.4 ± 0.3	*p<0.001*
iPTH (pg/ml)	84.2 ± 45.6	45.3 ± 10.8	*p<0.001*
25 - hydroxy vitamin D (ng/mL)	19.8 ± 11.3	30 ± 5.0	*p<0.001*
CRP (mg/dL)	4.7 ± 1.6	1.6 ± 0.9	*p<0.001*
RRI	0.72 ± 0.06	0.62 ± 0.03	*p<0.001*
TAPSE (mm)	21.5 ± 3.1	25.6 ± 3.6	*p<0.001*
ePASP (mmHg)	34.1 ± 6.8	30.2 ± 5.1	*p=0.018*
PCWP (mmHg)	10.4 ± 3.3	9.8 ± 2.8	*n.s.*
RVEDV (mm)	31.8 ± 3.3	31.2 ± 3.5	*n.s.*

expressed as mean ± standard deviation, categorical variables were expressed as number (percentage). Student's t-test or-Mann-Whitney U-test were performed to determine differences between groups. Binomial Test or Chi-square test was used for comparison of categorical data. Pearson's or Spearman's Correlation was used to determine in bivariate correlation the relationship and the strength of association between the variables. A probability value of $p < 0.05$ was considered to be statistically significant.

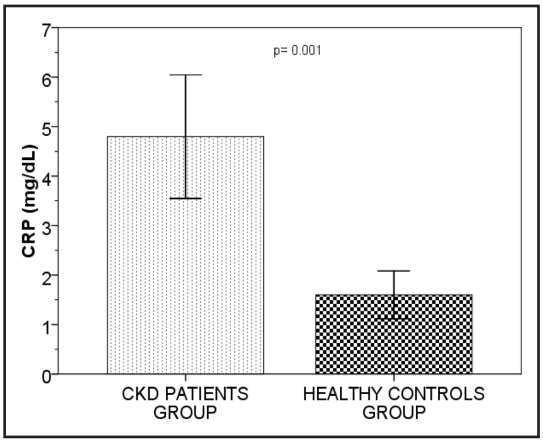

Fig. 1. Bar charts with error bars. The mean value of CRP was significantly different between two groups (4.7 ± 1.6 vs 1.6 ± 0.9, p<0.001). Boxes represent means; error bars indicate confidence interval (CI). Abbreviations: CRP, C-reactive protein; CKD, chronic kidney disease.

Results

Table 1 shows patients' characteristics. Our results evidenced no statistically significant differences in age, sex and BMI, between CKD patients and healthy controls group, while the ePASP and TAPSE showed a statistically significant difference between two groups (p=0.018, p<0.001; respectively) (Table 1). We observed in CKD patients a significant reduction in 25-OH-VitD (p<0.001) (Table 1) and a significant increase in iPTH, phosphorus, SUA, RRI and CRP (p<0.001, p<0.001, p=0.002, p<0.001, p<0.001; respectively) (Table 1; Figure 1) respect to healthy controls group, while there were no statistically significant differences between two groups for PCWP and RVEDV (p=0.463, p=0.501; respectively) (Table 1). Also ePAPs correlates negatively with eGFR (r=-0.329, p=0.029) (Figure 2) and positively with RRI (r=-0.486, p=0.001) and TAPSE correlates positively with eGFR (R=0.412, p=0.05) and negatively with RRI (r=-0.394, p=0.008) (Figure 3). Our study also showed a significant negative correlation between RRI and eGFR (r = -0.705, p <0.001) and CRP and eGFR (r=-0.429, p=0.004)(Figure 4) and a significant positive correlation between CRP and RRI (r=-0.391, p=0.009) (Figure 5).

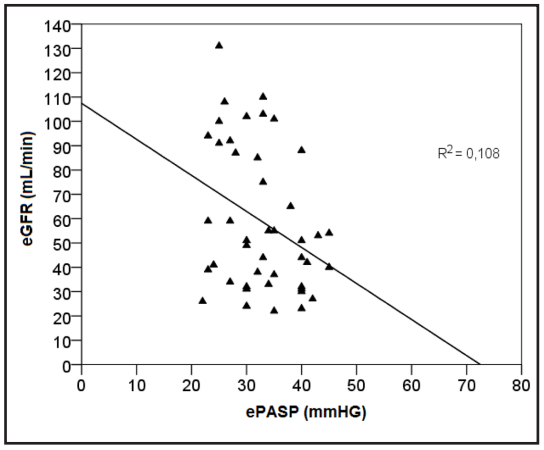

Fig. 2. Linear regression plot. Correlation between eGFR (mL/min) and ePAPs (mmHg), r=-0.329; p=0.029. Abbreviations: eGFR, estimated glomerular filtration rate; ePASP, estimated pulmonary artery systolic pressure.

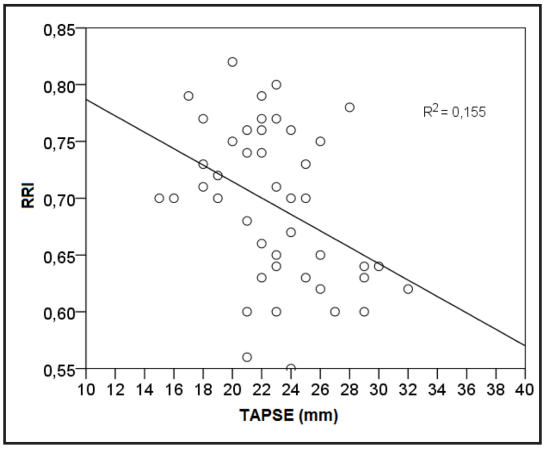

Fig. 3. Linear regression plot. Correlation between RRI and TAPSE (mm), r=-0.394; p=0.008. Abbreviations: TAPSE, Tricuspid Anular Plane Systolic Excursion; RRI, Renal Resistive Index.

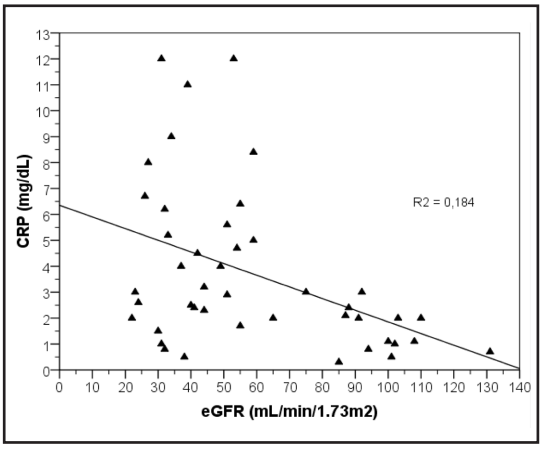

Fig. 4. Linear regression plot. Correlation between CRP (mg/dL) and eGFR (mL/min/1.73m2), (r=-0.429; p=0.004). Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

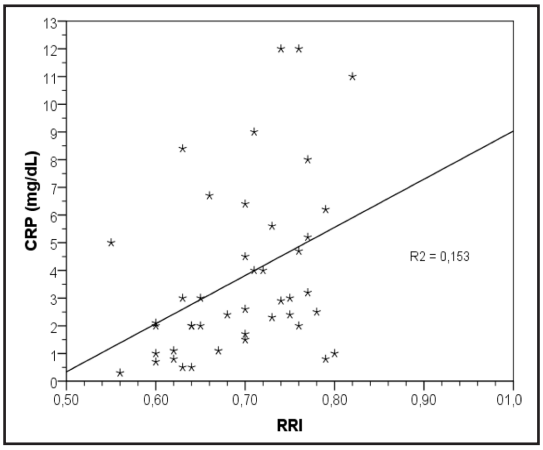

Fig. 5. Linear regression plot. Correlation between CRP (mg/dL) and RRI, (r=-0.391; p=0.009). Abbreviations: CRP, C-reactive protein; RRI, renal resistive index.

Discussion

Chronic kidney disease can contribute to the development and progression of CVD with multiple pathophysiological processes, also if not fully characterized. Renal and cardiac function are closely related and communication between these organs occurs through multiple common pathogenetic mechanisms that determines the development of CRS type 4. However, little is known as to whether specific renal disorders, such as MBD, endothelial dysfunction, fluid retention or activation of the renin-angiotensin-aldosterone-system (RAAS) and neuro-endocrine systems could contribute to RV dysfunction [7, 14]. Cardiovascular disease is an important predictor of poor survival in patients with CKD, right heart failure also contributes to morbidity and mortality and increased mass of the RV has been associated with incident heart failure and cardiovascular mortality, as shown by Dini et al. [7]. The left and right ventricles have a different embryologic origin, geometry and fiber

orientation, indeed the left ventricle (LV) originates from the primary heart field whereas the RV arises from the anterior heart field, the LV is elliptical whereas the RV is triangular. Moreover the LV is thicker and has more mass than the RV and therefore is better appropriate to manage pressure overload, while the more compliant RV is better equipped to manage volume overload. Therefore, given their inherent differences, specific renal abnormalities affect each ventricle differently [4, 6]. Among the several echo-Doppler measures of RV function, TAPSE index, is the one that has been more extensively studied and together with ePAPs have been associated with adverse outcomes [11]. High ePASP estimated by echocardiography is an established cardiovascular (CV) risk factor in the general population but little is known about ePASP in early CKD stages [5, 15]. The prevalence of high ePASP was estimated in two large population-based studies, the Olmsted county study [16] and the Armadale echocardiography study [17] and was about 5% in the first study and 9.1% in the second study. In patients with advanced CKD (stage 5 KDOQI), the prevalence of high ePASP largely exceeds estimates in the general population, ranging from 9-39% in patients on conservative therapy, 18.8-68.8% in hemodialysis patients [18] and 0-42% in individuals on peritoneal dialysis therapy [19]. Pulmonary hypertension (PH) in CKD, may be related to multiple risk factors, such as anemia, sleep apnea, increased sympathetic activity, inflammation, vascular calcification and endothelial dysfunction but in early stages of CKD patients, the pathogenesis of PH remains unclear [5]. In our study TAPSE and ePASP showed a significant difference between CKD patients and healthy controls group (Table 1). Moreover ePAPs correlates negatively with eGFR (Figure 2), showing a progressive increase with the worsening of renal function, while there were no statistically significant differences between two groups for PCWP and RVEDV (Table 1). We observed, also, in CKD patients a significant reduction in 25-OH-VitD and a significant increase in iPTH and phosphorus (Table 1) respect to healthy controls group. These results might suggest that, atherosclerotic disease, endothelial damage, and MBD, may determine alterations in renal blood flow, and also in the RV and in pulmonary circulation with reduction of TAPSE and an increase of ePASP. Altered mineral metabolism, common in CKD, may contribute to CVD by promoting adverse cardiac remodeling. Indeed, hyperparathyroidism and vitamin D deficiency, have direct effects on LV growth in experimental models, but the impact of mineral metabolism on the RV is poorly studied [6, 19, 20]. Mineral bone disorders with hyperparathyroidism, hyperphosphatemia, vitamin D deficiency and vascular calcification, has been associated to the CRS type 4, even in the early stages of CKD, as shown by Mathew et al. [6]. In fact, hyperparathyroidism is associated with pulmonary vascular calcification and PH in a CKD dog model, and increased prevalence of PH, and a PH-hyperparathyroidism relationship in pre-dialysis CKD, and hemodialysis patients, are reported [19]. Insufficient Vitamin D receptor (VDRs) activation also may contribute to CRS type 4, indeed VDRs are expressed not only in the classical target organs but also in other non-classical targets including arteries, heart, immune system, endocrine organs, and nervous system. The myocardium is an important target of vitamin D and its deficiency predisposes to up-regulation of the RAAS and hypertrophy of ventricle and vascular smooth muscle cells, indeed VDRs knockout mice show myocardial renin overexpression and marked cardiomyocyte hypertrophy [21, 22]. Vitamin D deficiency is associated with increased cardiovascular-related morbidity and mortality, possibly by modifying cardiac structure and function, but while its effects on the LV, have been extensively studied, little is known about its effects on the RV [23, 24]. We observed also in CKD patients a significant increase of SUA (Table 1) respect to healthy controls group. Hyperuricemia is highly prevalent in CKD, and is associated to LVH, worsening of renal function and increased cardiovascular morbidity and mortality [25, 26], but effects on the RV are still poorly investigated. In our study, SUA is associated with an increase in the ePAPs and TAPSE, but are required extensive clinical trails to explain this findings. Hyperuricemia might play a causative role in oxidative stress, inflammation, and atherosclerosis even if its role is controversial. Increased SUA levels may contribute to the echocardiographic abnormalities through effects on endothelial function, indeed it has been shown to inhibit nitric oxide production and also the proliferation and migration of vascular endothelial cells. These effects may be partly related to activation of the RAAS, that has been proposed to determine

LV hypertrophy and cardiac fibrosis though direct action of angiotensin II and aldosterone on cardiac myocytes [27]. Moreover an accepted source of elevated SUA in heart failure patients is breakdown of ATP to adenosine and hipoxanthine and increase in the generation of uric acid by xanthine dehydrogenase and xanthine oxidase. In addition, lactic acid generated during hypoxia can result in the urinary excretion of lactate that increases the absorption of urate in the proximal tubule [28]. In different randomized controlled trials, allopurinol treatment resulted in improvement of oxidative stress, endothelial function, and progression of kidney disease. In another study of patients with CKD stage 3/4 KDOQI, hyperuricemia appeared to be an independent risk factor for all cause and cardiovascular mortality. Furthermore, hyperuricemia is easily detected using an inexpensive blood test, facilitating its use as a target for screening and risk stratification [29]. Also inflammation is one of the pathogenetic events that can contribute to the development and progression of CVD, as confirmed in our study, that showed a significant increase of CRP in CKD patients (Figure 1) with a significant positive correlation with RRI (Figure 5) and negative correlation with eGFR (Figure 4). Wang et al. [30] showed that chronic microinflammation, is associated with progressive arteriosclerosis, and several studies reported an inverse relationship between inflammatory markers and renal function, suggesting that CKD per se may contribute to the inflammatory response, although the exact mechanism is not completely clear [31]. In our study also RRI, measured by Doppler ultrasonography, was significantly increased compared to the healthy controls group; it resulted negatively associated with eGFR and TAPSE (Figure 3) and positively associated with ePASP. These results, could partly explain the changes observed in RV, indeed RRI is a marker of atherosclerosis and is associated with cardiovascular events and mortality in CKD patients [32]. Originally, Resistive Index (RI) was proposed by Pourcelot [33] to define the resistance of blood flow in peripheral arteries but currently, even if there is no agreement, RRI is widely considered a renal and systemic vascular damage marker that reflects the vascular atherosclerotic changes [34]. Many studies [35-37] confirm the impact of systemic, and local intrarenal vascular changes on RRI value. In fact clinical trials in patients with CVD showed significant and independent association of RRI with all-cause mortality and cardiovascular event, without significant impact of renal function and kidney disease with the exception of atherosclerosis. Additional and large clinical trials on pathophysiological mechanisms involved in CRS type 4 are needed to allow a more accurate diagnosis and better therapeutic strategies in these patients [2].

Limitations of the study

The sample size of this study is relatively small, and so there are required large multicenterstudies to confirm our findings. Pulmonary systolic artery pressure was non invasively measured using Doppler echocardiography without obtaining right heart catheterization. In addition, our study is based on the associations between surrogate end points; thus the generated hypothesis needs further prospective cohort studies powered to show causality with hard end points.

Conclusion

Chronic kidney disease can contribute to the development and progression of RV dysfunction, also in early stages of CKD. The ultrasound can be a valuable tool for the nephrologist in the diagnosis of CRS type 4, in fact echocardiographic indexes, as TAPSE and ePAPs, represents a useful tool for investigation of RV function [13], and RRI, could be a useful marker of cardiovasculorenal changes [32]. Mineral bone disorders and inflammation should be monitored and treated already in the early stages of CKD. SUA can be used as a marker of endothelial dysfunction and a target for risk stratification, indeed is easily detected using an inexpensive blood test. However our study shows that the management of CRS type 4 requires a multidisciplinary approach, and further studies are needed to understand the common pathophysiological processes, that promote CRS type 4, for more appropriate therapeutic strategies to improve outcomes in these patients [7].

Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The manuscript has been seen and approved by all authors.

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