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Cardiac Vascular Calcification and QT Interval in ESRD Patients: Is There a Link?

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Key Words
Vascular calcification · QT interval · QT dispersion · Chronic kidney failure · Haemodialysis

Abstract
We will present our experience and our preliminary data about the correlation between cardiac calcification and QT interval (and QT dispersion) in uraemia. We studied 32 haemodialysis (HD) patients (age 69 ± 16 years, time on dialysis 32 ± 27 months) and 12 chronic kidney disease stage 4 (CKD-4) patients (age 66 ± 17 years, uraemia duration 38 ± 16 months). The patients were characterized by a good mineral control, as shown by serum phosphate levels (3.6 ± 1.3 mg/dl in CKD-4 and 4.3 ± 1.6 mg/dl in HD patients) and Ca × P product (46 ± 17 and 49 ± 16 mg^2/dl^2, respectively). The parathyroid hormone levels were higher in HD than CKD-4 patients ($p < 0.0001$). A TC score >400 was found to be highly prevalent in both groups. Significantly more HD patients (62.5%) showed cardiac calcification than CKD-4 patients (33%; $p = 0.01$). The patients were matched for TC scores higher or lower than 400. The two groups differed by gender ($p < 0.05$), age ($p = 0.026$), frequency of diabetes mellitus ($p < 0.01$), uraemia follow-up period ($p < 0.001$), low-density lipoprotein cholesterol level ($p = 0.009$), Ca × P product ($p = 0.002$), parathyroid hormone level ($p < 0.0001$), and corrected QT dispersion ($p < 0.0001$). The QT interval was higher in HD and CKD-4 patients with higher TC scores (approximately 11%), but QT interval dispersion was significantly higher in patients with TC scores >400. QT dispersion showed a linear correlation with TC scores in both groups ($r = 0.899$ and $p < 0.0001$ and $r = 0.901$ and $p < 0.0001$). Male gender, age, time (months) of uraemia, low-density lipoprotein cholesterol, albumin, calcium × phosphorus product, parathyroid hormone, and TC score are important determinants of QT dispersion. Our data show that it is possible to link dysrhythmias and cardiac calcification in uraemic patients.

Introduction

End-stage renal disease (ESRD) patients have a dramatically higher risk of death as compared with the general population [1]. These risk factors for mortality observed in dialysis patients are mainly of cardiovascular origin and have been associated with cardiovascular calcifications in ESRD patients [2–4].

Vascular calcification and arterial stiffening are independent predictors of all causes of cardiovascular mortality in chronic kidney disease (CKD). Few data are currently available comparing vascular calcification and its attendant functional cardiovascular consequences be-

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tween CKD stage 4 (CKD-4) patients and both peritoneal dialysis (PD) and haemodialysis (HD) (CKD stage 5) patients.

Recently, Sigrist et al. [5] have demonstrated vascular calcification and associated cardiovascular dysfunction in 28 PD patients, in 60 HD patients, and in 47 patients with CKD-4. Interestingly, their data show that 27% of the HD and 29% of the PD patients showed no evidence of vascular calcifications, even those initiated on dialysis for a prolonged period of time. More interestingly, Sigrist et al. [5] have shown that the process of arterial calcification has begun in most subjects prior to the initiation of dialysis. They conclude that older age, male gender, the presence of diabetes, and a high Ca × P product contribute to the occurrence of vascular calcifications.

On the other hand, echocardiographic studies have reported a high prevalence of cardiac abnormalities in CKD patients, and the prevalence of left ventricular (LV) hypertrophy (LVH) is linked to increased QT interval and QT dispersion (QTd), providing a link with the high risk of sudden death in this population [6]. QTd, defined as the difference in duration between the longest and shortest QT interval for a given set of electrocardiogram leads, was originally proposed as a direct measure of the regional heterogeneity of myocardial repolarization [7]. More recently, other authors [8, 9] have suggested that QTd reflects a difference in heart dipole projections and abnormalities of T wave loop morphology. Several studies have shown QTd to predict increased mortality or cardiovascular risk or both.

We would like to present our experience and our preliminary data about the correlation between cardiac calcification and QT interval (and QTd) in uraemia.

Patients and Methods

Patients

We have studied 32 HD patients (age 69 ± 16 years, time on dialysis 32 ± 27 months) and 12 CKD-4 patients (age 66 ± 17 years, uraemia duration 38 ± 16 months). All patients were eligible to enter the study. The CKD-4 patients were defined as having undergone at least two creatinine clearance measurements, with values between 15 and 30 ml/min. All HD patients had three dialysis sessions lasting at least 4 h per week. HD was performed using the same artificial system equipped with an automatic device for determining the ultrafiltration rate (E408; Fresenius Medical Care Italia, Isola della Scala, Italy), the same membrane (polysulfone 1.8 m^2, F8, Fresenius Medical Care Italia, or polymethylmethacrylate 2.0 m^2, Filtryzer B3-2, Toray-Hoechst, Milan, Italy), and the same blood flow rate (315–345 ml/min) and dialysate flow rate (500 ml/min). The dialysate composition did not differ: 39 mmol/l bicarbonate, 4.0 mmol/l acetate, 1.5 mmol/l calcium, 0.5 mmol/l magnesium, 5.6 mmol/l glucose, and 2.0 mmol/l potassium.

All patients had been dry weight stable for at least 3 months and had achieved a normotensive, oedema-free state. Throughout the study period, each patient complied with fluid and dietary restrictions and maintained a constant ultrafiltration volume. The HD patients (n = 32) had primary interstitial nephritis (n = 10), diabetic nephropathy (n = 6), polycystic kidney disease (n = 4), glomerulonephritis (n = 8), or chronic pyelonephritis (n = 4); the CKD-4 patients (n = 12) had interstitial nephritis (n = 2), diabetic nephropaty (n = 3), polycystic kidney disease (n = 1), glomerulonephritis (n = 4), or chronic pyelonephritis (n = 2). All our CKD-4 and HD patients were selected for this study. Only 32 HD patients and 12 CKD-4 patients accepted participation.

Before enrollment, the patients underwent 24-hour Holter ECG monitoring. Criteria for exclusion were ECG-detected signs of cardiac arrhythmias and ECG signs of a previous myocardial infarction. We also excluded patients with pacemakers, those on digitalis or on other drugs known to interfere with the QT interval, in conformity with the guidelines set by the Minister of Health of the Italian Government [10], and patients who had dilatational heart disease or myocardia l fibrosis or both. All HD patients, except those with polycystic kidney disease, were given intravenous erythropoietin three times a week (mean dosage 23 ± 7 IU/kg/day). Of this cohort, 22 were receiving angiotensin-converting enzyme inhibitors, 6 calcium antagonists, 28 angiotensin receptor antagonists, 2 nitrate agents, and 7 diuretics; 20 patients received vitamin D analogs, and 15 patients used sevelamer as phosphate binder. In the CKD patients, 5 were given subcutaneously erythropoietin once a week (mean dosage 35 ± 15 IU/kg/week). Of this cohort, 8 were receiving angiotensin-converting enzyme inhibitors, 2 calcium antagonists, 8 angiotensin receptor antagonists, all had diuretics, and 5 used sevelamer as phosphate binder.

Echocardiography was carried out after HD sessions in the HD patients, with the patients at dry weight, and in the CKD patients, and their mean LV ejection fraction was 60.7 ± 10.1%. Data regarding LV mass index (LVMI) and the LV cavity volume index were ascertained by two-dimensional-targed M mode (Schiller Cardiovit CS-2000; Esaote Biomedica, Florence, Italy) using the criteria and specific calculations previously described [8]. We defined LVH on the basis of a LVMI >131 g/m^2 in males and >100 g/m^2 in females and LV dilation as LV cavity volume index >90 g/m^2 [11].

Biochemistry

Patient characteristics, past medical history, comorbid conditions, and current medication were taken from the medical records, in addition to direct answers to questions regarding current conditions and phosphate-binding medication. Blood samples were collected at monthly intervals for the HD patients and at regular clinic visits for the CKD-4 patients as part of routine treatment follow-up. Serum phosphate, calcium, albumin, parathyroid hormone (PTH), lipid profile and C-reactive protein were analyzed in on-site biochemistry laboratories, using standard autoanalyzer techniques. The PTH level was assessed by standard radioimmunoassay. C-reactive protein was quantified by nephelometry.

Measurement of Vascular Calcification

In order to quantify presence and extent of arterial calcification, each patient underwent a multislice spiral CT scan. All studies were performed using a GE Medical Systems (Milwaukee, Wisc., USA) LightSpeed 16 multislice spiral CT scanner. The images were acquired, when the patient was supine; no contrast was used. A standardized section of the cardiac muscle was performed. This image allowed accurate, reproducible quantification of calcium load in this section of coronary and cardiac muscle. The investigator scored each of the 20 slices individually. The score has been found to be reproducible from CT scanner to CT scanner regardless of the scan protocol [12]. Calcification was considered to be present, if an area >1 mm^2 displayed a density >400 Hounsfield units (HU). Scoring was performed using GE Medical Systems Advantage Workstation software, as described by Agatston et al. [13].

ECG Measurements

ECGs were obtained during mid-dialysis by means of a 12-channel recorder (Esaote Biomedica) at a paper speed of 25 mm/s (gain 10 mm/mV). To analyze the QT interval, the 12-lead tracings were enlarged, always on the same photocopier, by a factor of three; and a minimum of 10 leads were studied in each patient. For each lead, three consecutive cardiac cycles were measured and averaged. The QT intervals were measured manually with callipers by one observer, from the beginning of the QRS complex to the end of a T wave. If the T wave was indistinct, the reading was excluded from the analysis. Moreover, for each derivation, the lengths of the minimum and maximum QT intervals and the differences between them were measured. Each QT interval was corrected for heart rate using Bazett's formula: $QTc = QT/RR^{1/2}$.

The difference between maximum and minimum QTc provided the corrected QTd (QTcd). Inter- and intra-observer reliabilities of QTd and QTcd measurements were also assessed. To ensure intra-observer reliability, 40 randomly selected ECGs were re-measured by the principal investigator. The mean differences between the first and the second reading for QTd and QTcd were 2.91 ms (SD 5.80; range from –7.4 to 10.1 ms) and 2.70 ms (SD 5.36; range from –8.4 to 10.65 ms; intraclass correlation coefficient $r = 0.92$; $p < 0.001$). To ensure interobserver reliability, a second blinded observer re-measured 40 ECGs. The mean differences between the measurements made by the two observers for QTd and QTcd were 1.76 ms (SD 16.12; range from –33.5 to 31.1 ms) and 2.06 ms (SD 17.80; range from –33.6 to 40.3 ms; intraclass correlation coefficient $r = 0.85$; $p < 0.01$). Measurements of potassium, calcium, and magnesium were performed. The local Ethics Committee approved the study protocol.

Statistics

Data are expressed as mean values ± SD, unless otherwise specified. $p < 0.05$ was considered significant. The t test and the chi-square test were used for continuous and categorical variables to compare baseline characteristics between the CKD-4 and HD groups with QTcd values above and below the study median of 41 ms. Associations between continuous variables were evaluated using Pearson's correlation coefficients controlling for confounding variables with general linear regression modeling. The statistically significant variables, analyzed initially by univariate analysis, were chosen for multivariate analysis. Multivariate analysis was used to estimate the independent effect of TC score on QTd and QTcd.

Table 1. Characteristics of the study population

	CKD-4	HD	p
n	12	32	
Male gender, %	67	62	0.75
Age, years	66 ± 17	69 ± 16	0.41
Body mass index, kg/m^2	26 ± 2	25 ± 2	0.59
Smokers, %	25	28	0.28
Diabetes mellitus, %	50	40	0.125
Time on dialysis, months	–	32 ± 27	
Uraemia, months	38 ± 16	76 ± 41	0.001
PAS, mm Hg	136 ± 18	141 ± 30	0.65
PAD, mm Hg	81 ± 7	84 ± 16	0.45
Total cholesterol, mg/dl	196 ± 37	169 ± 46	0.53
HDL cholesterol, mg/dl	36 ± 7	41 ± 10	0.411
LDL cholesterol, mg/dl	104 ± 21	119 ± 16	0.79
Albumin, g/dl	3.7 ± 0.7	3.6 ± 1.0	0.33
Haemoglobin, g/dl	11.4 ± 0.4	11.9 ± 0.6	0.45
Ca × P product, mg^2/dl^2	45 ± 17	49 ± 16	0.51
Na, mmol/l	140 ± 2.1	140 ± 2.4	0.88
K, mmol/l	5.0 ± 1.2	5.1 ± 1.4	0.75
Mg, mEq/l	1.0 ± 0.5	0.9 ± 0.4	0.39
PTH, pg/ml	126 ± 37	225 ± 41	0.0001
C-reactive protein, mg/l	11 ± 7	12 ± 6	0.71
Lipid-lowering therapy, %	67	62	0.66
Use of vitamin D, %	17	31	0.121
Use of sevelamer phosphate binders, %	42	47	0.444
QT interval, mm	431 ± 51	440 ± 47	0.61
QTd, mm	37.5 ± 11.1	40.4 ± 18.0	0.57

Results

The characteristics of the study population are shown in table 1. Relevant serum biochemistry and relevant prescribed medications of the study population are also shown. The CKD-4 and HD patients do not show differences in age, arterial blood pressure, haemoglobin, cholesterol, PO_4, and Ca × P product and in the use of sevelamer phosphate binders, lipid-lowering therapy, and vitamin D. Overall, this patient population was characterized by good mineral control, as shown by serum phosphate (3.6 ± 1.3 mg/dl in CKD-4 patients and 4.3 ± 1.6 mg/dl in HD patients) and Ca × P product (46 ± 17 and 49 ± 16 mg^2/dl^2, respectively). The PTH level was higher in the HD patients than in the CKD-4 patients ($p < 0.0001$). The HD patients had a longer history of CKD ($p < 0.001$).

A TC score >400 was found to be highly prevalent in both groups, as shown in figure 1. Significantly more HD patients (62.5%, median TC score 306) demonstrated calcification than CKD-4 patients (33%, median TC score

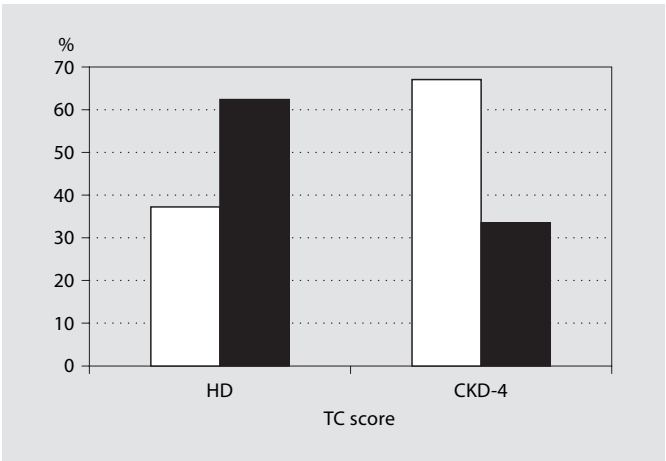

Fig. 1. Percentages of HD and CKD-4 patients with TC scores lower (open columns) and higher (dark columns) than 400. $p < 0.01$ HD vs. CKD-4 patients.

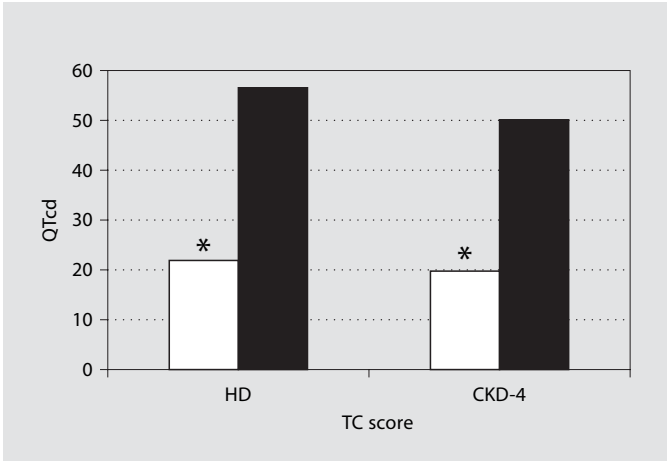

Fig. 2. QTcd in HD and CKD-4 patients with TC scores lower (open columns) and higher (dark columns) than 400. * $p < 0.01$.

325; p = 0.01). Table 2 shows our population matched for TC score higher or lower than 400: 20 patients (12 HD and 8 CKD-4) showed TC scores <400 (median 129), and 24 patients (20 HD and 4 CKD-4) had TC scores >400 (median 600). The two groups differed in gender ($p < 0.05$), age (p = 0.026), frequency of diabetes mellitus ($p < 0.01$), uraemia follow-up ($p < 0.001$), low-density lipoprotein cholesterol (p = 0.009), Ca × P product (p = 0.002), PTH ($p < 0.0001$), and QTcd ($p < 0.0001$). The QT interval was longer in patients with higher TC scores in HD and CKD-4 patients (approximately 11%), but QTd was significantly more frequent in patients with TC scores >400 (fig. 2). QTd showed a linear correlation with TC score ($r = 0.899$, $p < 0.0001$, and $r = 0.901$, $p < 0.0001$) in both groups (fig. 3). The median QTcd values were 37.5 in CKD-4 patients and 44.6 in HD patients; the median TC score <400 in all patients was 129, and the median TC score >400 was 55.6.

In order to identify possible determinants of QTd, a multivariate regression analysis was performed using all the factors shown in table 1 (except time on dialysis) as independent variables and the QTd as the dependent variable. Table 3 shows the results: male gender, age, diabetes, time of uraemia, low-density lipoprotein cholesterol, albumin, Ca × P product, PTH, and TC score were important determinants of QTd.

Finally, 50% of the CKD-4 patients and 66% of the HD patients (p = NS) showed LVH defined on the basis of a LVMI >131 g/m^2 in males and one >100 g/m^2 in females, and no patient showed LV dilation defined as LC cavity volume index >90 g/m^2 [11]. The LVMI showed no significant correlation with TC score or/and QT interval.

Table 2. Characteristics of the population with a TC score <400 (12 HD and 8 CKD-4 patients) and a TC score >400 (20 HD and 4 CKD-4 patients)

	TC score <400	TC score >400	p
n	20	24	
Male gender, %	42	75	0.05
Age, years	55 ± 22	71 ± 24	0.026
Smokers	29	25	0.24
Diabetes mellitus, %	70	20	0.01
Time on dialysis, months	30 ± 29	34 ± 31	0.33
Uraemia, months	79 ± 35	31 ± 36	0.001
PAS, mm Hg	138 ± 22	143 ± 29	0.62
PAD, mm Hg	80 ± 10	85 ± 19	0.48
Total cholesterol, mg/dl	188 ± 42	206 ± 64	0.51
HDL cholesterol, mg/dl	42 ± 11	38 ± 12	0.5
LDL cholesterol, mg/dl	101 ± 25	122 ± 26	0.009
Albumin, g/dl	3.8 ± 0.9	3.4 ± 1.1	0.22
Haemoglobin, g/dl	11.7 ± 0.5	11.4 ± 0.8	0.11
Ca × P product, mg^2/dl^2	41 ± 19	59 ± 16	0.002
PTH, pg/ml	115 ± 42	306 ± 61	0.0001
Na, mmol/l	139 ± 1.9	141 ± 2.2	0.31
K, mmol/l	5.1 ± 0.9	5.0 ± 1.0	0.55
Mg, mEq/l	1.1 ± 0.4	1.1 ± 0.6	0.66
C-reactive protein, mg/l	10.1 ± 9	12.8 ± 9	0.55
Lipid-lowering therapy, %	71	60	0.41
Use of vitamin D, %	21	30	0.25
Use of sevelamer phosphate binders, %	50	30	0.21
LVMI >131 g/m^2, %	50	66	0.3
LV cavity volume index >90 g/m^{2,} %	0	0	0.9
QT interval, mm	411 ± 43	461 ± 54	0.33
QT dispersion, mm	26.8 ± 10	54.1 ± 8	0.0001

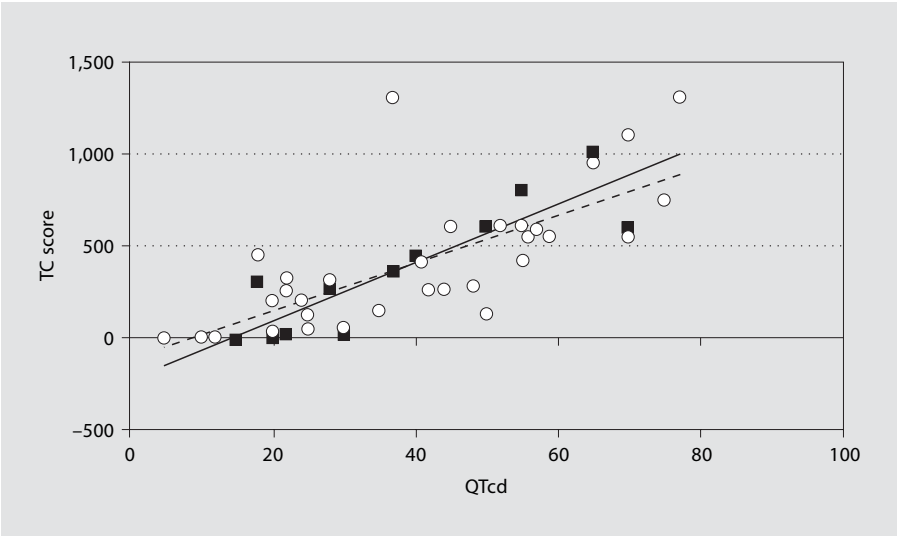

Fig. 3. Linear correlation of TC score and QTcd in HD patients (○) and CKD-4 patients (■). HD: r = 0.899, p < 0.0001; CKD-4: r = 0.901, p < 0.0001.

Table 3. Multivariate regression analysis: determinants of QTd

	Coefficients	p	RR (95% CI)
Male gender	–2.01	0.001	0.85 (0.81–0.76)
Age	0.099	0.001	1.2 (1.01–1.44)
Diabetes mellitus	70	0.01	1.41 (1.31–5.07)
Duration of uraemia	1.671	0.001	7.29 (6.21–9.01)
LDL cholesterol	–0.44	0.003	0.76 (0.70–0.047)
Albumin	–0.045	0.0028	0.95 (0.96–0.88)
Ca × P product	0.715	0.05	2.2 (1.51–3.0)
PTH	0.811	0.05	4.2 (3.41–7.01)
TC score	1.571	0.0001	11.2 (8.22–16.7)

Discussion

Despite improvements in dialysis therapy, patients with ESRD have a significantly decreased life expectancy. Although this marked decrease in life expectancy may be explained partially by concomitant malnutrition, impaired immunity, bleeding diathesis, and comorbid diseases common to dialysis patients [14], cardiac disease continues to be the predominant cause of death. Data from the United States Renal Data System show that more than half of the ESRD mortality is cardiovascular, an incidence ten times that of age-matched and sex-matched controls [15, 16], with myocardial infarction, heart failure, and sudden death comprising most of these deaths, although multiple physiological changes encountered in ESRD patients may explain this increased incidence, including anaemia, left LVH, ischaemic heart disease, and electrolyte shifts [17]. So, patients on HD present arrhythmias which can cause sudden death [1]. HD appears to cause ECG changes [18], and dysrhythmias and arrhythmias frequently occur after the start of a HD session and may persist for at least 5 h after dialysis [19].

This phenomenon appears to have different causes, including dialysis-induced electrolyte alterations. In a recent study [20], we demonstrated how using a dialysis bath with a higher calcium concentration reduced QT intervals and QTd. These intervals and their increased dispersions have been linked to the occurrence of arrhythmias in ESRD patients on HD [7, 21].

On the other hand, arterial calcification and arterial stiffening are independent predictors of all-cause and cardiovascular mortality in CKD stage 5 patients [22]. It is well recognized that the cardiovascular mortality is responsible for around 50% of all deaths in the dialysis population [1]. The reasons for this high incidence of cardiovascular mortality are incompletely understood in that they mostly cannot be explained by traditional risk factors [23]. In fact, CKD patients have a reverse association with some traditional risk factors; obesity, hypercholesterolaemia, and hypertension have been associated with a reduction in the relative risk of death in epidemiological studies of dialysis patients [24]. Inflammation, malnutrition, oxidative stress, and abnormal mineral metabolism are risk factors for vascular disease specific to CKD [25].

Our observational study presents data comparing cardiac calcification and associated functional ECG parameters between CKD-4 and CKD-5 patients and confirm the data reported by Sigrist et al. [26].

These authors demonstrated that the process of arterial calcification has begun in almost 50% of subjects prior to the initiation of dialysis. In addition, morphological changes of the arterial wall caused by arterial calcification are associated with stiffening of the arterial tree, and the process is highly prevalent in CKD-4 patients. Our data show that only 33% of the CKD-4 patients have TC scores >400 in comparison with 67% in the HD population.

Moe et al. [27] found that 28% of the HD and 32% of the transplant patients had no evidence of coronary calcification using multislice CT. Chertow et al. [28], in their treat-to-goal study, found that 17% of the HD patients had no coronary calcification and that 20% had no aortic calcification using electron beam CT. London et al. [22] found 36% of the HD patients to be free from vascular calcification using plain radiography. In addition, this latter group had a lower cardiovascular mortality than an age-matched cohort. Development and progression of vascular calcification are multifactorial processes. Potentially differing factors may exert their maximum influence during either predisposition, initiation, and continuation phases of the process [5]. Sigrist et al. [5] have recently demonstrated that HD is associated with higher Ca and PO_4 levels during the long intradialytic period as compared with the short intradialytic period. Sigrist et al. [26] hypothesized that such cyclic changes in serum mineral levels, which are not characteristic of PD, may be important in the pathogenesis of vascular calcification.

The associations among valvular calcification, inflammation, carotid atherosclerosis, and arterial calcification suggest that valvular calcification is a marker of atherosclerosis and arterial calcification in patients with ESRD, and disturbance of the mineral metabolism appears to contribute to progressive calcification, not only by passive precipitation but by actively inducing changes in vascular smooth muscle cell behaviour towards an osteoblast-like phenotype [29–33].

In our population, male gender, old age, long uraemia follow-up, high levels of low-density lipoprotein cholesterol, a high Ca × P product, high PTH levels, and a high QTd differentiate patients with a TC score >400 and those with a TC score <400. QTd and TC score have a high linear correlation in HD and CKD-4 patients.

Qunibi [34] showed that the aetiology of cardiovascular calcification is multifactorial and that the beneficial effect of sevelamer on the progression of calcification was thought to be due to lower calcium loading during its use and that a possibly more likely mechanism involves sevelamer-induced lowering of low-density lipoprotein cholesterol. In our population, patients with a high score of cardiac calcification showed higher low-density lipoprotein cholesterol levels than patients with a low cardiac calcification score, and the difference was statistically significant. This can represent a novel risk factor in uraemia [35].

Patients on HD present different cardiovascular diseases and have a higher mortality rate which is often due to the high incidence of events such as arrhythmias which can cause sudden death. HD appears to cause ECG changes [18]. Dysrhythmias and arrhythmias frequently occur after the start of a HD session and persist for at least 5 h after dialysis. This phenomenon appears to have different causes, including dialysis-induced electrolyte alterations [16]. Several studies demonstrated how using a dialysis bath with a higher calcium concentration reduces the dispersion of QT and QTc intervals [20]. These intervals and their increased dispersions have been linked to the occurrence of arrhythmias in ESRD patients on HD [7, 20]. This effect could have various causes: regional differences in ventricular wall stress (mechanic-electric or contraction-excitation feedback) caused by ventricular dilation, fibrosis, and calcification, autonomic failure caused by uraemic autonomic neuropathy, decreased circulatory volume, rapid correction of metabolic acidosis, and rapid changes in serum K levels. Most patients on HD present morphological and structural cardiac alterations that may predispose to alterations of ECG parameters [36].

The presence of ectopic calcifications in CKD has been frequently described in the literature since the 1970s [37]. The development of imaging techniques such as electron beam CT and multislice spiral CT scanning allowed accurate quantification of calcification in vivo. Recent studies using these techniques have highlighted the extent of coronary artery calcification among patients with CKD-5, particularly focusing on those receiving HD as a treatment modality [2, 7, 27], but Sharples et al. [38] stated that coronary artery calcification measured with multislice spiral CT scanning is not an accurate marker of the degree of vessel stenosis in coronary artery disease in uraemic patients and should not be used as a single screening test for atherosclerotic coronary disease. These authors showed that the method has a specificity of 48% and a positive predictive value of 53%, but also that a calcification score <20 strongly correlates with absence of significant luminal narrowing and that a zero calcification score has a negative predicitive value of 87.5%.

A bimodal distribution of vascular calcification is consistently observed in quantitative studies of vascular calcification. Interestingly, our data show that 37% of the

HD patients and 67% of the CKD-4 patients showed no evidence of vascular calcification, even those initiated on dialysis for a prolonged period of time. Our data show that the hypothesis of a link between dysrhythmias and cardiac calcification in uraemic patients is possible.

In fact, QTd, defined as the difference in duration between the longest and shortest QT interval for a given set of electrocardiogram leads [8], originally was proposed as a direct measure of the regional heterogeneity of myocardial repolarization. It was thought that increased repolarization heterogeneity or QTd predisposed to re-entrant pathways and ventricular arrhythmias. More recent studies [9] disprove this theory, however, and suggest that QTd instead reflects differences in heart dipole projections and abnormalities of T wave loop morphology. It has been proposed that QTd should be viewed more as an approximation for repolarization abnormalities rather than a true measure for regional heterogeneity of myocardial refractoriness. Regardless of its true meaning, several clinical studies have shown QTd consistently to predict increased mortality or cardiovascular event risk or both in non-uraemic patients with peripheral vascular disease, ischaemic heart disease, dilated and hypertrophic cardiomyopathies, and hypertension [9]. Beaubien et al. [39] showed that the value of QTd predicts arrhythmias or cardiovascular mortality in uraemia. These authors demonstrated that the QTd is an independent marker for cardiovascular risk in uraemic patients. They did not demonstrate how QTd and QTcd can be altered in ESRD patients. Our study showed that cardiac calcification is an independent determinant of QTd, with gender, age, diabetes mellitus, uraemia follow-up, low-density lipoprotein cholesterol, albumin, Ca × P product, and PTH (the last two factors, also, are important determinants of cardiac calcification).

Recently, Stewart et al. [6] presented the data of 296 non-diabetic renal disease patients with LVH (>80% of their population) and increased QTd in HD as well as CKD patients. These authors concluded that QT interval and QTd provide a link to a high risk of sudden death in this population. Honda et al. [40] have recently shown that cardiovascular disease in uraemia is also associated with malnutrition, inflammation, and mortality.

Our data show that 50% of the CKD-4 and 66% of the HD patients (p = NS) showed LVH, but they show no significant correlation with TC score and/or QT interval. The absence of a correlation between LV mass and QT interval parameters is puzzling in view of the existing literature on the subject with resistant hypertension [41–43]. These studies described that QT interval parameters have mainly been associated with the LV mass. The association of QT interval parameters and LVH may reflect different and complementary aspects of the same physiopathological process [41], although two studies [44, 45] suggested that they are no better than simple electrocardiographic voltage criteria for LVH detection. Surely, renal patients have different causes of LVH, and arterial hypertension is not alone. Foley et al. [1], first, showed that 25- to 35-year-old renal patients have the same cardiovascular mortality risk as 75- to 80-year-old patients without renal disease. Successively, several authors [1, 46–49] have shown that the cardiovascular risks in CKD patients depend on anaemia, hypercholesterolaemia, inflammation, diabetes, homocysteine, and several factors that are simultaneously present in the same patients. In our study population, the differences between CKD patients and hypertension patients can be due to the absence of a correlation between LV mass and QT interval parameters.

Unfortunately, this study has a lot of biases, Including its small sample size. Glancy et al. [50] demonstrated that the reproducibility of the mean QT interval was good: the intrasubject error was 6 ms, the interobserver error was 7 ms, and observers' versus automatic measurement errors were 10 and 11 ms, respectively. However, QTcd measurements had large errors for all methods: the intrasubject error was 15 ms, and observers' vs. automatic measurement errors were 30 and 28 ms, respectively. The poor reproducibility of QTd measurements limits its usefulness [50]. Thus, the concept of using ECG indices of ventricular repolarization to assess the arrhythmogenic risk of individual patients remains an important research objective [51]. It is generally accepted that a HD session induces prolongation of QT interval parameters, and Raizada et al. [52] showed an association of QT interval parameters with renin-angiotensin system polymorphisms.

Finally, in our study, male gender, age, diabetes, low-density lipoprotein cholesterol, PTH, Ca × P product, and TC scores are determinants of QTd. TC score and QTd can be the link between cardiovascular disease and cardiac calcification. Our population did not show malnutrition and/or inflammation (see albumin levels, body mass index, C-reactive protein levels).

The observational nature of our study might have contributed to bias. We have no data regarding the mortality, but we will examine the mortality in this population in the near future.

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