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Original Article

Factors Related to High-sensitivity Cardiac Troponin T Levels in Pre-dialysis Chronic Kidney Disease Patients

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Abstract

Background and objectives: Cardiac troponin T (cTnT) is independently associated with cardiovascular complications in patients with chronic kidney disease (CKD). The present study aimed to determine the factors related to cTnT levels in pre-dialysis CKD patients, which result to increased cardiovascular risk.

Methods: A total of 147 patients, with a mean age of 69.1 ± 14.7 years old, were enrolled. These participants were classified to estimated glomerular filtration rate (eGFR) and albuminuria categories, according to the Kidney Disease Improving Global Outcomes 2012 criteria. The estimated pulse wave velocity (ePWV), as an index of arterial stiffness, was calculated using an equation, which included age and mean blood pressure. Coronary arterial disease (CAD) and left ventricular hypertrophy (LVH) were also recorded. The cTnT concentrations were measured by high-sensitivity immunoassay. The significant correlation between cTnT and different variables was determined, and the significant risk factors for high cTnT levels were defined.

Results: A significant correlation was observed between cTnT serum concentrations and age, triglycerides/HDL-C, ePWV, glucose, phosphate (P), intact-parathyroid hormone (i-PTH), serum uric acid and albuminuria, although the association with eGFR was shown to be significantly inverse. The multifactorial model revealed that current smoking (p = 0.03, OR = 8.3, 1.15–60.3), CAD (p = 0.001, OR = 25.2, 5.6–113.6), low eGFR (p = 0.001, OR = 0.9, 0.8–0.9), high ePWV (p = 0.04, OR = 2.6, 1.0–6.8), and primary renal disease (p = 0.001, OR = 3.8, 1.7–8.5) are independent risk factors for elevated cTnT levels, after adjusting for age, gender, obesity and albuminuria.

Conclusions: Arterial stiffness, smoking, primary renal disease and unregulated metabolic abnormalities may have an independent association between high cTnT levels and low eGFR in pre-dialysis CKD patients, with or without overt cardiovascular disease.

Keywords: Cardiac troponin T; Estimated pulse wave velocity; eGFR; Albuminuria; Hypertension.

Abbreviations: CKD, chronic kidney disease; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; ePWV, estimated pulse wave velocity; UACR, urinary albumin-to-creatinine ratio; CAD, coronary arterial disease; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; PP, pulse pressure; LDL-C, low-density lipoprotein cholesterol; P, phosphate; hsCRP, high sensitivity C reactive protein; i-PTH, intact-parathyroid hormone; ESRD, end-stage renal disease.

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Introduction

Patients with chronic kidney disease (CKD) have an increased risk of morbidity and mortality, when compared to the general population.[1,2] Although the high prevalence of cardiovascular disease in end-stage renal disease (ESRD) was identified since 1970, elevated cardiovascular risk has only been identified in patients with early-stage CKD in recent years. It has been recently reported that myocardial injury and features of coronary arterial disease (CAD) are common in early-stage of CKD patients.[3] Furthermore, it has been suggested that the severity and occurrence of coronary disease may be significantly determined by chronic renal dysfunction

and albuminuria.[4]

Interestingly, dialysis patients may have atypical symptoms of acute coronary syndrome, including isolated dyspnea, nausea and weakness. A number of these symptoms may be associated with the dialysis therapy. However, the biochemical diagnosis of acute myocardial infarction remains doubtful in this population. Cardiac damage biomarkers, including creatine kinase, creatine kinase-MB and myoglobin, have been used to detect early myocardial necrosis for many years. However, since these biomarkers are elevated in CKD patients, the reliability may be limited for these patients.[5] Furthermore, although the introduction of cardiac troponins has offered more specificity, the interpretation of elevated troponins in CKD remains problematic.

Troponin consists of three structural proteins (isoforms C, T and I), which are components of cardiac and skeletal muscles. Troponin C is mainly included (>90%) in both types of tissues, and this mitigates its usefulness. Different genes encode cardiac and skeletal troponin I and T, as district isoforms. It has been reported that up to 80–90% of dialysis patients and patients with advanced CKD have elevated plasma troponin concentrations, according to manufacturer diagnostic cut-off values, with or without the findings of myocardial ischemia.[6] The present study aimed to determine the significant factors associated with high cardiac troponin T (cTnT) serum levels in pre-dialysis CKD patients, which contribute to the increase in cardiovascular risk in these patients.

Methods

Study setting and population

The present study was approved by the Hospital Institutional Review Board, with an Institutional Review Board (IRB)/Ethics Committee approval number (A.P:7216). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee, and the 1964 Helsinki declaration. An informed oral consent was obtained from each individual participant enrolled in the study. The present study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary File 1).

Participants from the Department of Nephrology Outpatient Clinic of our hospital were included for the present single-center cross-sectional study. Patients with pre-dialysis CKD, according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria,[7] participated in the present study. The time of CKD was >3 months. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR). The participants were classified according to their albuminuria level, which was defined as a urinary albumin-to-creatinine ratio (UACR) ≥30 mg/gr[7] using a spot urine sample. The albuminuria levels should be stable for the past six months.

The primary renal disease included hypertensive nephrosclerosis, with a hypertension duration of >10 years, and the ratio of participants was 38.8%. Participants with diabetic nephropathy had a ratio of 30.6%. Patients with biopsy-confirmed acute glomerulopathy were excluded. Other exclusion criteria included acute myocardial infarction, unstable angina, and heart failure or stroke within the past year. Subjects with atrial fibrillation or other arrhythmias, and those with known myopathy were also excluded.

The demographic characteristics of these patients, including age, gender, body mass index (BMI), peripheral blood pressure, waist circumference, and lifestyle, such as current smoking, alcohol drinking and physical activity, were recorded.

A detailed individual medical history was obtained from the participants. The CAD (n = 69, 46.9%) was determined through the patient's pre-existing history of myocardial infarction, coronary artery angioplasty, or bypass surgery, and clinical signs of angina pectoris. The ischemic findings were determined by electro- and echo-cardiographical examination, and/or coronary computed angiography. For suspicious subclinical cases of CAD, provocative tests were performed to determine the classic clinical manifestations of vasospastic angina and the establishment of myocardial ischemia during spontaneous episodes. Invasive coronary angiography was performed to define the demonstration of coronary artery spasms. The presence of left ventricular hypertrophy (LVH; n = 80, 54.4%) was also considered. The initial and recurrent ischemic cardiovascular events were recorded as one event during the study period.

Regarding the present pharmaceutical therapy, all participants with diabetes mellitus received similar hypoglycemic medications. All enrolled patients received statin for hypolipidemic treatment. The anti-hypertensive therapy performed for all hypertensive participants included calcium channel blockers, diuretics, beta-blockers, and inhibitors of angiotensin II AT1 receptors.

Blood pressure measurements

Home twice-daily blood pressure measurement for systolic blood pressure (SBP) and diastolic blood pressure (DBP) was performed using an automatic sphygmomanometer (OMRON M4-I; Kyoto, Japan). The peripheral mean blood pressure was calculated, as follows: pMBP = DBP + 0.4 (SBP − DBP). The difference between SBP and DBP (PP = SBP − DBP) was defined as the pulse pressure (PP). The recent American guidelines were used for the definition of hypertension.[8]

Calculation of estimated pulse wave velocity (ePWV)

The ePWV was calculated using the equation described in the study conducted by Greve *et al*.,[9] which was derived using the Reference Values for Arterial Stiffness' Collaboration. The equation used to determine the ePWV included age and MBP: $ePWV = 9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times MBP + 3.176 \times 10^{-3} \times age \times MBP - 1.832 \times 10^{-2} \times MBP$.

Electro- and echo-cardiographical assessment

The 12-lead electro-cardiographical examination was performed to estimate the ischemic findings. A Hewlett Packard SONOS 2500 device with a 2.25-MHz transducer was used for the echo-cardiographical assessment. The participants were examined by two cardiologists using the conventional M-mode method and two-dimensional echocardiography for the ischemic findings and LVH estimation, according to the recommendations of the American Society of Echocardiography.[10] The presence of LVH was defined by an interventricular septum thickness of >11.5 mm.

Biochemical measurements

Overnight fasting plasma creatinine, glucose, uric acid, albumin, calcium (Ca), phosphate (P), triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol

Table 1. The correlation between cardiac troponin T (cTnT) and different variables (*n* = 147)

Variables	r	*p*-value
Age (years)	0.531	0.001
BMI (kg/m^2)	0.233	0.005
WC (cm)	0.334	0.001
LDL-C (mg/dl)	−0.228	0.006
Triglyceride/HDL-C ratio	0.300	0.001
Glucose (mg/dl)	0.233	0.004
SBP (mmHg)	0.530	0.001
DBP (mmHg)	−0.122	0.100
MBP (mmHg)	0.342	0.001
ePWV (m/s)	0.571	0.001
PP (mmHg)	0.566	0.001
eGFR (mL/min/1.73 m^2)	−0.666	0.001
UACR (mg/gr)	0.429	0.001
i-PTH (pg/mL)	0.408	0.001
P (mg/dl)	0.243	0.003
hsCRP (mg/L)	0.277	0.001
Uric acid (mg/dl)	0.316	0.001

r, Spearman correlation coefficient; BMI, body mass index; WC, waist circumference; LDL-C, low density lipoprotein cholesterol; triglyceride/HDL-C, triglycerides/high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ePWV, estimated pulse wave velocity; PP, pulse pressure; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; i-PTH, intact parathormone; P, phosphate; hsCRP, high sensitivity C-reactive protein. A *p*-value of <0.05 was considered statistically significant.

(HDL-C) were recorded from the patient files using the latest results. The spectrophotometric technique was performed using a chemistry analyzer (Mindray BS-200; Diamond Diagnostics, USA) to measure the above biochemical markers, and these were expressed in mg/dL. Then, the triglyceride/HDL-C ratio was calculated.

The concentration of intact-parathyroid hormone (i-PTH) was measured by radioimmunoassay (CIS Bio International, France). The high-sensitivity C-reactive protein (hsCRP) serum concentration was measured by ELISA (Immundiagnostik AG, Bensheim, Germany).

The cTnT concentration was measured using a high-sensitivity immunoassay analyzer (Cobas e411 Roche Diagnostic), with a reference range of <14 ng/L. Three sequential measurements of cTnT were obtained from the present data, and the average value was used in the statistical analysis. Spot urine samples obtained from the first morning void were employed to measure the albumin and creatinine concentrations using the chemistry analyzer.

Statistical analysis

The SPSS 25.0 statistical package for Windows (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analysis of the present data. The results were expressed as mean ± standard deviation, or as the median value (interquartile range) for data with a skewed distribution. The differences between mean values were assessed using unpaired *t*-test for two groups, and Mann-Whitney *U*-test was used for comparisons between groups of data with a skewed distribution.

Spearman's coefficient was used to define the correlations between variables, and chi-square test was performed to determine the relationships among categorical variables. A *p*-value of <0.05 was considered statistically significant. A model was established using logistic regression analysis through the enter method, in order to investigate the important risk factors for the increase in cTnT levels after entering covariates, including age, gender, the presence of central obesity, smoking, ePWV, primary renal disease, UACR, eGFR and CAD.

Results

A total of 147 patients were enrolled. These patients included 88 male and 59 female patients, with a mean age of 69.1 ± 14.7 years old. As shown in Table 1, the bivariate correlations defined by the Spearman coefficient revealed a significantly positive correlation between cTnT serum concentrations and age, BMI, waist circumference, triglyceride/HDL-C ratio, SBP, PP, ePWV, glucose, P, i-PTH, serum uric acid, hsCRP and UACR, although the correlation with eGFR and LDL-C was significantly inverse.

Table 2 presents the characteristics and differences between groups of patients with elevated cTnT and normal cTnT concentrations. Using the average value of three sequential cTnT measurements, a cTnT value of >14 ng/L was considered high, according to the upper reference limits (URL) provided by the manufacturer. Participants with higher cTnT levels were older, and had significantly higher blood pressure, waist circumference, ePWV (Fig. 1), triglyceride/HDL ratio, PP, glucose, uric acid, UACR, i-PTH, P (Fig. 2), and hsCRP, but had significantly lower eGFR and LDL-C, when compared to participants with normal cTnT serum concentrations.

The X^2 test revealed a significant association between elevated cTnT levels and the presence of CAD, LVH, central obesity, hypertension, and low eGFR (Fig. 3) and UACR ($\chi^2 = 62.3$, $p = 0.001$, $\chi^2 = 48.9$. $p = 0.001$, $\chi^2 = 3.8$, $p = 0.04$, $\chi^2 = 21.6$, $p = 0.001$, $\chi^2 = 42.35$, $p = 0.001$ and $\chi^2 = 17.4$, $p = 0.001$, respectively).

The model established by logistic regression analysis using the enter method revealed that current smoking, CAD, low eGFR, high ePWV and primary renal disease, which mainly included diabetic nephropathy and hypertensive nephrosclerosis, are independent risk factors for the elevated cTnT levels in the present data, after adjusting for age, gender, UACR and central obesity (Table 3).

Discussion

The main findings of the present study were the significant association between elevated cTnT levels and renal dysfunction defined by low eGFR and/or high albuminuria, metabolic abnormalities and bone disease disorders, and the potential relationship between high cTnT serum concentrations and CAD, hypertension, LVH, smoking and ePWV. By comparing with previous studies, the significant association between high cTnT levels and CAD, LVH, hypertension, smoking, low eGFR and metabolic disorders in predialysis CKD patients was verified, and it was revealed that there is significant relationship between high cTnT levels and arterial stiffness defined by high ePWV, central obesity and albuminuria.

Cardiac troponins (cTnI and cTnT) were originally used as markers for cardiac cell death. Both proteins are presently and

Table 2. The differences between patients with cTnT levels of >14 ng/L and patients with cTnT levels of <14 ng/L

Characteristic	Patients with cTnT >14 ng/L (*n* = 77), mean ± SD	Patients with cTnT <14 ng/L (*n* = 70), mean ± SD	*p*-value
cTnT (ng/mL)	0.021 ± 0.005	0.008 ± 0.003	0.001
Age (years)	75.2 ± 11.8	62.4 ± 14.8	0.001
BMI (kg/m^2)	28.9 ± 5.3	28.09 ± 6.06	0.300
WC (cm)	106.02 ± 14.08	99.7 ± 16.3	0.010
LDL-C (mg/dl)	104.5 ± 31.4	115.75 ± 31.48	0.030
Triglyceride/HDL-C ratio	3.4 ± 1.8	2.7 ± 1.6	0.020
Glucose (mg/dl)	116.7 ± 32.0	103.9 ± 17.3	0.003
SBP (mmHg)	150.20 ± 13.03	135.6 ± 14.5	0.001
DBP (mmHg)	79.2 ± 9.6	80.4 ± 6.6	0.400
MBP (mmHg)	107.60 ± 8.45	102.5 ± 7.6	0.001
ePWV (m/s)	13.20 ± 2.09	10.60 ± 2.35	0.001
PP (mmHg)	71.06 ± 14.60	55.17 ± 14.80	0.001
eGFR (mL/min/1.73 m^2)	37.2 ± 14.5	65.4 ± 22.4	0.001
UACR (mg/gr)	280.3 ± 442.8	94.2 ± 176.5	0.001
i-PTH (pg/mL)	131.01 ± 124.10	67.3 ± 53.2	0.001
P (mg/dl)	3.70 ± 1.04	3.3 ± 0.8	0.010
hsCRP (mg/L)	3.65 ± 5.50	1.71 ± 2.30	0.007
Uric acid (mg/dl)	6.90 ± 1.65	5.9 ± 1.7	0.001
Albumin (mg/dl)	4.2 ± 0.4	4.4 ± 0.6	0.060
Category variable	***n* (%)**	***n* (%)**	
CAD (yes/no)	60.0 (77.9) / 17.0 (22.1)	9.0 (12.9) / 61.0 (87.1)	0.001
LVH (yes/no)	63.0 (81.8) / 14.0 (18.2)	17.0 (24.3) / 53.0 (75.7)	0.001
eGFR (< or > 60 mL/min/1.73 m^2)	72.0 (93.5) / 5.0 (6.5)	31.0 (44.3) / 39.0 (55.7)	0.001
UACR (< or > 30 mg/gr)	21.0 (27.3) / 56.0 (72.7)	43.0 (61.4) / 27.0 (38.6)	0.001
Hypertension (yes/no)	69.0 (89.6) / 8.0 (10.4)	39.0 (55.7) / 31.0 (44.3)	0.001
Central obesity (yes/no)	67 (87) / 10 (13)	52.0 (74.3) / 18.0 (25.7)	0.040
Primary renal disease			
Diabetes mellitus (yes/no)	27.0 (35.1)	18.0 (25.7)	0.007
Hypertensive nephrosclerosis (yes/no)	36.0 (46.8)	21 (30)	0.007
Chronic GN	5.0 (6.5)	9.0 (12.9)	0.007
Other renal disease	9.0 (11.7)	22.0 (31.4)	0.007

cTnT, cardiac troponin T; BMI, body mass index; WC, waist circumference; LDL-C, low density lipoprotein cholesterol; triglyceride/HDL-C, triglycerides/high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ePWV, estimated pulse wave velocity; PP, pulse pressure; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; i-PTH, intact parathormone; P, phosphate; hsCRP, high sensitivity C-reactive protein; CAD, coronary arterial disease; LVH, left ventricular hypertrophy; Chronic GN, chronic glomerulonephritis.

widely used to diagnose acute myocardial infarction, unstable angina, post-surgery myocardium trauma, and other diseases related to cardiac muscle injury, due to superior specificity and sensitivity, when compared to other biochemical indices.[11] Furthermore, cardiovascular events and all-cause mortality are significantly associated with the increase in cTnT serum concentrations in patients with CKD.[12] It has been suggested that cTnT serum concentrations above the cut-off for the reference (normal) population are independently predictive of the subsequent death in ESRD patients, in combination with the increase in hsCRP and cTnI levels, although merely the tertile analysis for N-terminal pro-B-type natriuretic peptide (NT-proBNP) has a prognostic value.[13] In the present study, merely pre-dialysis CKD patients were included, and the significant association between high cTnT levels and the presence

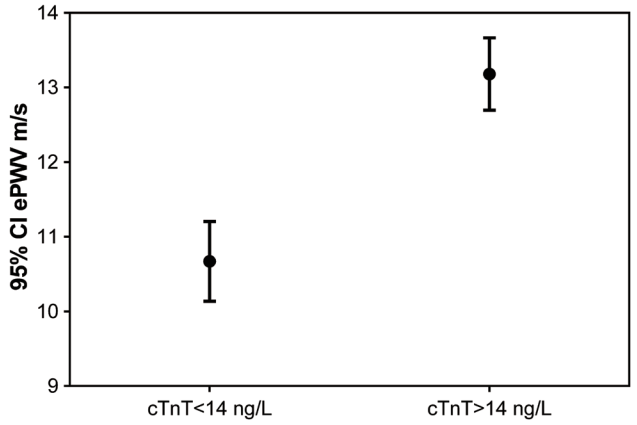

Fig. 1. Estimated pulse wave velocity (ePWV) in patients with elevated concentrations of high sensitivity cardiac troponin T (cTnT) levels, when compared to patients with normal cTnT serum concentrations ($p < 0.05$).

of CAD was verified. Furthermore, in the established multifactorial adjusted model, CAD was the strongest independent risk factor for elevated cTnT serum concentrations.

A number of previous studies have reported that the level of troponins stably increases in patients with decreased eGFR. In agreement with these reports, the present study revealed that eGFR was significantly lower in patients with high cTnT levels, when compared to patients with normal cTnT levels. It was also observed that there is a significantly inverse bivariate correlation between the cTnT and eGFR value. In the present multifactorial model, low eGFR was proven to be a strong independent risk factor for high cTnT, in consent to a larger previous study that enrolled 2,464 participants.[14] Furthermore, it was observed that there is an important association between high cTnT levels and high UACR, which are additional markers for renal dysfunction. However, this observation is in relative disagreement with a similar previous study, in which the UACR did not have a linear association with hs-cTnT, and merely participants with a UACR of >1,000 mg/gr had a higher cTnT.[14] Furthermore, albuminuria was not noted to be an important risk factor for elevated cTnT levels in the established adjusted model. Albuminuria appeared to lose its significance after adjustment, and there may be a need for more increased levels

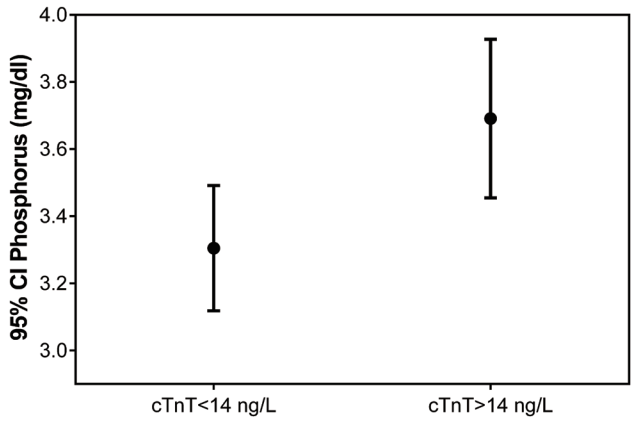

Fig. 2. Serum phosphate (P) in patients with elevated concentrations of high sensitivity cardiac troponin T (cTnT) levels, when compared to patients with normal cTnT serum concentrations ($p < 0.05$).

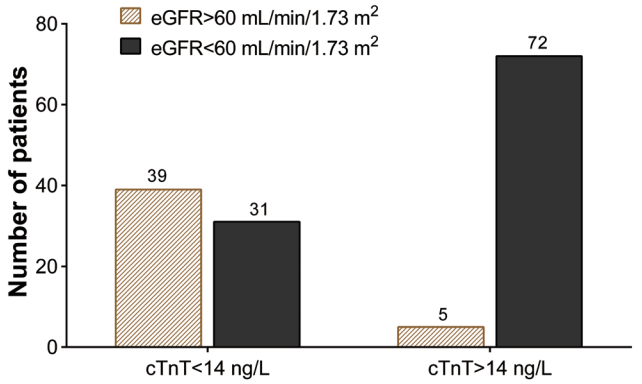

Fig. 3. The association between high sensitivity cardiac troponin T (cTnT) and estimated glomerular filtration rate (eGFR) using Chi-square, Phi and Cramer's V correlation test ($\chi^2 = 42.35$, $p = 0.001$).

of albuminuria. Thus, this is an independent risk factor for high cTnT, which is in agreement with the above reported previous study.[14] Studies have revealed that patients with renal dysfunction have at least 2-folds more frequent incidences of high troponin, when compared to patients without kidney disease, although the incidence of myocardial infarction was found to be comparable in both investigated cohorts of patients.[15] In addition, it has been shown that left ventricle mass is associated with hs-TnT levels, independent of eGFR.[16] It has been interestingly established that cTnT independently predicts cardiovascular mortality, even in the general population, with or without cardiac disease.[17]

The association between low eGFR and high TnT levels could be in part due to the reduced renal clearance of troponin T.[16] However, the general consensus does not specify the particular thresholds and degree of cTnT elevation required for the diagnosis of myocardial infarction in patients with impaired renal function. Some studies have attempted to determine the optimal cTnT cut-off, particularly for CKD patients, but the guidelines remain unclear.[18] It appears that the diagnosis of myocardial infarction in CKD patients should mainly rely on the assessment of sequential changes in hs-cTnT levels.[19]

Even though the cTnT levels may be high, which is partly due to

Table 3. Logistic regression analysis for the prediction of high cTnT levels in the present data ($n = 147$)

Variables in Model	*p*-value	Odds ratio	Confidence interval
Age (years)	0.100	0.9	0.70–1.03
Gender (males/females)	0.200	0.5	0.1–1.6
Smoking (yes/no)	0.030	8.3	1.1–60.3
Central obesity	0.100	3.9	0.7–21.3
eGFR (mL/nin/1.73 m^2)	0.001	0.9	0.80–0.95
UACR (mg/gr)	0.800	1.0	0.900–1.003
ePWV (m/s)	0.040	2.6	1.008–6.800
CAD (yes/no)	0.001	25.2	5.6–113.6
Primary renal disease	0.001	3.8	1.7–8.6

cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; ePWV, estimated pulse wave velocity; CAD, coronary arterial disease.

the low clearance in kidney disease, the real reasons for the stable increase in cTnT in renal disease remains unclear, and the etiology is certainly multifactorial. Some of the hypotheses included myocardial stress, which leads to the release of cTnT, injury and loss of integrity of the myocyte membrane in the myocardium, silent microinfarctions, the co-existence of heart failure (HF) even without acute ischemia, the presence of LVH, non-ischemic clinical conditions, including tachy/bradyarrhythmias, and aortic valve disease, or infiltrative diseases such as amyloidosis and myopathies. Rhabdomyolysis is a more worthy disorder in this population of patients.

In the present study, it was observed that there is a significant relationship between the increase in cTnT levels and LVH occurrence. In agreement with this, it was shown that hs-TnT is strongly associated with the alterations of the left ventricular structure and diastolic dysfunction in pre-dialysis CKD patients, and the baseline hs-TnT levels were predictive of new LVH on follow-up.[20] Furthermore, it was shown that hs-TnT is independently associated with LVH in the participants of the Chronic Renal Insufficiency Cohort (CRIC) study, who did not have self-reported cardiovascular disease.[21]

CKD results in accelerated atherosclerosis and vascular calcification associated to high blood pressure. In the present study, it was observed that there is a significant association between high cTnT levels and the occurrence of hypertension, which is in agreement with previous reports.[14] It was also noted that there is a significant correlation between cTnT levels and blood pressure, hsCRP, PP and ePWV. In the present study, participants with high cTnT had significantly higher blood pressure, hsCRP, PP and ePWV, when compared to participants with normal cTnT levels. In addition, ePWV, as an index of arterial stiffness, was found to be a significant risk factor for high cTnT levels in the present adjusted model. Few previous studies have reported the association between cTnT levels and arterial stiffness markers. A previous study reported the significant association between cTnT concentrations and the brachial-ankle vascular index.[22] It has been also reported that cTnT has a positive correlation with carotid intima-media thickness (cIMT), and a reverse association with brachial artery flow mediated dilation (baFMD) in pre-dialysis CKD patients.[23] Meanwhile, it has been established that dialysis patients with high cTnT levels have significantly higher carotid IMT and PWV values.[24] Furthermore, it has been shown that increased levels of hsCRP are a prognostic value for high mortality in ESRD patients.[13] In the present study, a significant association between high cTnT levels and high hsCRP serum concentrations was observed.

CKD may lead to myocardial injury via endothelial dysfunction, and the microvascular disease caused by inflammation and mediators of oxidative stress.[25] In the present study, the primary renal disease, which mainly included diabetic nephropathy and hypertensive nephrosclerosis, was a potential risk factor for the increase in cTnT levels, in combination with low eGFR, coronary syndrome, current smoking, and arterial stiffness defined by ePWV. A previous study reported that cTnT is independently associated with renal risk, rather than with cardiovascular risk, in diabetic patients with nephropathy.[26] Reports have also supported the significant association between smoking and high cTnT levels, due to the contribution of smoking in atherosclerosis and cardiovascular risk,[27] which is in agreement with the present findings.

The increased severity of vascular calcification in CKD is the result of the complex interactions between changes in vascular function, mineral metabolites, and other uremic factors.[28] In the present study, it was noted that there is a significant correlation between cTnT and the markers of bone disease, including serum P and i-PTH, which is in agreement with a previous report.[14] High serum P concentrations have been connected to adverse health outcomes in CKD, including cardiovascular disease, the progression of kidney disease and all-cause mortality, and this is mainly due to the vascular calcification, endothelial dysfunction, and elevated levels of fibroblast growth factor 23 (FGF23) induced by phosphorus.[29] In addition, it has also been reported that there is a connection between elevated serum P and adverse outcomes, even in subjects who apparently have normal kidney function, and this is mainly caused by the elevated concentrations of FGF23 linked to genetic variants in genes of mineral metabolism.[30] This concept could be used to explain why cTnT can be employed to independently predict cardiovascular mortality in the general population, with or without cardiac disease. Therefore, attention should be given in maintaining the serum P levels in the normal range, even in normal populations.

Furthermore, it was observed that there is a potential relationship between high cTnT levels and the components of metabolic syndrome, including the presence of central obesity, BMI, triglyceride/HDL-C ratio, serum glucose and serum uric acid. The LDL-C serum concentrations were lower in patients with higher cTnT, which is in agreement with a previous report.[14] In contrast, a previous study did not find a significant association between cTnT levels and the characteristics of metabolic syndrome.[22] In the present study, it was observed that the association between central obesity and high cTnT levels was significantly mitigated by the adjustment. It has been reported that obesity contributes to the development of cardiovascular disease in the general population, and in patients with CAD, which is mainly due to its association with metabolic syndrome components.[31] However, a study suggested the presence of an obesity paradox phenomenon, with respect to mortality, in subjects with established CAD.[32] Furthermore, a recent study reported that for hemodialysis patients with obesity, the lipids profile is unfavorable, and that although these patients had higher levels of inflammation, they did not have an increased risk of atherosclerotic cardiovascular disease.[33]

The findings of the present study support the notion that cellular injury of the myocardium, as defined by the elevated concentrations of cTnT, is strongly associated with low eGFR and arterial stiffness defined by a high ePWV in pre-dialysis CKD patients, with or without overt CAD. Smoking and primary renal disease, which mainly include diabetic nephropathy and hypertensive nephrosclerosis, contribute in vascular diseases. Disordered bone disease and unregulated metabolic abnormalities may be the pathophysiological pathways that lead to the poor prognosis in this population of patients. Furthermore, stable high cTnT concentrations, with or without apparent cardiovascular disease, can reflect the increased risk of worsened renal function.

Limitations

The main limitation of the present study was the inability to consider the cause-effect relationships, due to the single-center cross-sectional nature of the study. Furthermore, the definition of CAD using the CT calcification score and the direct measurement of PWV was unavailable in the present study.

Clinical significance

Elevated cTnT levels in CKD patients should be given concern. This can be employed to predict the worse prognosis due to its association with potential risk factors for cardiovascular disease, in-

cluding low eGFR, vascular stiffness, bone disease and metabolic abnormalities. Although several theories can be used to determine what levels of troponin increased in CKD patients, the significance of particular sequential changes in cTnT levels should not be ignored. Concerns for the management of the above risk factors should also be included in the therapy of CKD patients, due to the relationship with elevated cTnT levels. That is, these should be regulated.

Future directions

More research should be conducted to determine the pathophysiological mechanisms connected to high cTnT serum concentrations in CKD patients. High protein intake, particularly through animal sources, is significantly associated with chronic renal disease progression, worsened albuminuria, and elevated cardiovascular morbidity. Although it has been reported that higher intake of total protein is associated with lower risk of all-cause mortality, and that the intake of plant protein is associated with lower risk of cardiovascular disease mortality, high dietary protein intake affects the renal hemodynamic state, and results in metabolic derangements in CKD, such as metabolic acidosis and hyperphosphatemia. This is a well-known risk factor for cardiovascular disease and bone abnormalities in CKD patients. Metabolic abnormalities and bone disease are associated with high cTnT levels, according to the results of the present study. High protein intake can also influence the elevated levels of cTnT in CKD patients. This can be used as a new research hypothesis.

Conclusions

Arterial stiffness, smoking, primary renal disease, and unregulated metabolic abnormalities may have an independent association between high cTnT serum concentrations and low eGFR in pre-dialysis CKD patients, with or without overt cardiovascular disease.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2021.00074.

Supplementary File 1. STROBE checklist.

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Conflict of interest

The authors declare no conflict of interests.

Author contributions

Research plan, data collection, biostatistic analyses and manuscript writing (VDR); Electro- and echo-cardiographical assessments (GV); Biochemical measurements (DK); Research plan, data collection and manuscript writing (SG). All authors made a significant contribution to the study, and approved the final manuscript.

Ethics statement

The study was approved by the Hospital Institutional Review Board, with an Institutional Review Board (IRB)/Ethics Committee approval number (A.P:7216). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee, and the 1964 Helsinki declaration. An informed oral consent was obtained from each individual participant enrolled in the study. The authors obtained a consent to publish from the participant (or legal parent) and report the individual patient data.

Data sharing statement

No additional data are available.

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