

The role of cardiac troponin T in detection of cardiac damage and long term mortality in children with chronic renal disease

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In this study, we aimed to evaluate the role of cardiac troponin T (cTnT) in detecting myocardial involvement in children with chronic kidney disease (CKD) and to investigate whether it contributes to predicting cardiac involvement and mortality at follow-up. Echocardiographic evaluations were performed on a sample of 69 patients, of which 33 (47.8%) were female, with grade 3, 4 and 5 chronic renal failure and end-stage renal failure. Patients with normal cTnT levels and patients with high cTnT levels were compared. cTnT levels were observed to be high in 13 (19%) of the 69 patients. The comparison between the patients with normal cTnT levels and patients with high cTnT levels with regards to the echocardiographic findings revealed that in the latter group, the average ejection fraction and fractional shortening levels were lower ($p=0.003$ and $p=0.013$, respectively), the detection rate of left ventricular systolic dysfunction was 5.5 times higher and the rate of detection of left ventricular hypertrophy (LVH) was 3 times higher ($p=0.004$, $p=0.011$). In this study, it was shown that it is possible to obtain information about cardiac effects by examining the serum cTnT level before clinical symptoms occur in children with CKD, and that cTnT can be used for screening purposes.

Key words: chronic kidney disease, cardiac troponin T, cardiac influence.

Cardiovascular diseases are still the prominent cause of death in cases of end-stage renal disease and account for about 45% of deaths.¹ In these patients, electrocardiography (ECG) and echocardiography are the main methods of evaluating the heart.² However, it is believed that cardiac troponin I (cTnI) and cardiac troponin T (cTnT) may be more important diagnostic tests to demonstrate myocardial influence, especially in cases where echocardiographic evaluation is not possible.²

Cardiac troponins (cTnI, cTnT, cTnC) are regulatory proteins involved in myocardial contraction by regulating the relationship of actin and myosin with calcium. Since cTnI and cTnT are genetically differently

encoded compared to the skeletal muscle troponins, their specificity and sensitivity in demonstrating myocardial damage are very high.³

Although some studies on patients with chronic kidney disease (CKD) have revealed conflicting results, many studies have shown that cTnT levels may be associated with mortality as well as cardiac involvement determinations in adult CKD cases.^{4,5-7}

In this study, we aimed to evaluate the role of cTnT in demonstrating myocardial efficacy in patients with CKD in the childhood age group, and to investigate whether it contributes to predicting cardiac involvement and mortality at follow-up.

Material and Methods

This study was conducted between March 2008 and June 2013 at Izmir Dr. Behcet Uz Children's Hospital as a cross-sectional cohort observational study. The research procedure was approved by the local ethical committee (2008/14-16). Parents were informed about the study and each parent provided a written consent to allow their child to participate in the study.

The patient group consisted of stage 3, 4 and 5 chronic renal failure and end stage renal failure⁸ (stage 3: moderate renal injury, moderate decrease in glomerular filtration rate (GFR), GFR: 30-59 ml/min/1.73m²; stage 4: serious kidney damage, severe reduction in GFR, GFR: 15-29 ml/min/1.73m²; stage 5: renal failure, GFR <15 ml/min/1.73m² or initiation of renal replacement), and the control group consisted of cases who were evaluated for murmur and diagnosed with innocent murmurs at the pediatric cardiology clinic. The cases with active infections and congenital heart disease that was not associated with CKD at the time of the examinations were not included in the study.

Blood sample serums from the patient and control groups were separated and stored at -20 °C. Serum cTnT level was evaluated with Modular Analytics E170 by using ELECSYS-2010 kit (Roche diagnostic kit) and "electro-chemiluminescence immunoassay" method. With reference to a study on healthy volunteers with the Elecsys 2010 kit, where the 99th percentile value was found to be 0.01 ng/ml, the cutoff value for cardiac troponin T was assumed to be ≤0.01 ng / ml and the evaluations were made accordingly.⁹

The same pediatric cardiology specialist performed the echocardiographic examination by using Vivid 3 Ultrasound System and S 5-1, S 12-4 probes. Patients with congenital and/or acquired heart disease were excluded from the study. Conventional echocardiographic measurements were made according to the American Echocardiography Society standards.¹⁰ The dimensions of the left ventricle in the parasternal long axis on M mode tracing, and ejection fraction (EF) and fractional shortening (FS) were analyzed by using the

Teicholz formula.¹¹ Left ventricular mass index was calculated by using the Devereux formula, division of the left ventricular mass by 2.7 degrees of the height.¹² Left ventricular mass index (LVMI) >38 g/m^{2.7} was evaluated as left ventricular hypertrophy (LVH), and LVMI > 51 g/m^{2.7} was evaluated as severe.¹³

In the study, the relationship between cTnT and echocardiographic findings was evaluated based on the comparison of echocardiographic findings of patients with normal cTnT levels and those with high cTnT levels. Echocardiographic findings and cTnT levels of the patients who received dialysis treatment and those who did not were compared. The effect of dialysis treatment on cardiac findings and cTnT levels was evaluated on this basis. Echocardiographic findings and cTnT levels of patients of peritoneal dialysis and hemodialysis were also compared and the effect of the type of dialysis on cardiac findings and cTnT levels were investigated.

In the study echocardiographic findings and mortality of the patients were monitored during a five years follow up process. Survival rates and recent echocardiographic findings were obtained from the Dialysis Unit and Nephrology Clinic records and interviews with the patients' relatives. The relationship of initial cTnT level with the cardiac changes and mortality in the follow-up was evaluated.

Statistical analysis

Data obtained during the study were evaluated using the Statistical Package for Social Sciences (SPSS) 17.0 statistical program. Averages and standard deviations of numerical values were calculated. The student's t test was used in comparison of the means of two independent groups, and the Mann-Whitney U test was used when the distribution was not homogeneous. The categorical data were compared by using chi-square test, and by using the Fisher exact test when the expected numbers were small. Findings were considered significant when p <0.05.

Results

The patient group consisted of a total of 69 patients, 33 (47.8%) of them being female,

and the control group consisted of a total of 20 patients, 8 (40%) of them being female. The mean ages of the patient and control groups were 12.3 ± 4.9 and 9.9 ± 3.5 years, respectively; and there was no difference in age and sex between the two groups ($p: 0.543$, $p: 0.213$, respectively). Patient group consisted of chronic renal disease patients who were not receiving dialysis treatment (28 patients, 40.6%), who were receiving peritoneal dialysis (31 patients, 44.9%) and who were receiving hemodialysis (10 patients, 14.5%). The comparison between echocardiographic findings and cTnT levels of the patients in the study and control groups is shown in Table I.

In 69 patients, the cTnT score was found to be as high as 13 (19%). When echo findings of patients with normal and high cTnT levels

were compared, the average EF and FS values were found to be lower in the group with higher cTnT levels ($p: 0.003$, $p: 0.013$, respectively). Furthermore, in patients with high cTnT levels, the rate of systolic dysfunction detection in the left ventricle was 5.5-fold and the rate of severe LVH detection was 3-fold higher ($p: 0.004$, $p: 0.011$) (Table II).

Echocardiographic findings and cTnT levels were compared between those patients who received dialysis and those who did not. Echocardiographic findings and cTnT levels did not differentiate between the two groups. Dialysis treatment was found to have no effect on cardiac findings in the patients of the study (Table III).

Echocardiographic findings and cTnT levels of those patients who received peritoneal dialysis

Table I. Comparison of the Echocardiographic Findings and Troponin T Levels between the Control and Patient Group.

	Patient group (n: 69)	Control group (n: 20)	P
Mean EF, %	71.9 ± 10.0	78.6 ± 5.0	0.005
Mean FS, %	37 ± 7.4	40.4 ± 4.1	0.054
Mean LV mass, grams	84.1 ± 40.0	75 ± 32.9	0.36
LVH, n (%)	35 (50.7%)	2 (10.0%)	0.001
Severe LVH, n (%)	18 (26.1%)	0 (0)	0.011
Systolic dysfunction, n (%)	9 (13.0%)	0 (0)	0.045
Troponin T >0.01 ng/ml, n (%)	13 (18.8%)	0 (0)	0.036

EF: ejection fraction, FS: fractional shortening, LVH: left ventricular hypertrophy

Table II. Echocardiographic Findings, Mean Follow-up Time and GFR Comparisons According to Troponin T Levels.

Findings	Troponin T ≤ 0.01 ng/ml (n: 56)	Troponin T >0.01 ng/ml (n: 13)	P
Follow-up period, months	48.0 ± 40.4	34.1 ± 35.0	0.26
GFR, ml/min/1.73m ²	22.2 ± 14.5	13.4 ± 7.3	0.038
Mean EF, %	73.6 ± 9.3	64.7 ± 10.1	0.003
Mean FS, %	38.1 ± 7.2	32.5 ± 6.6	0.013
Mean LV mass, grams	86.1 ± 36.2	75.6 ± 54.3	0.40
Systolic dysfunction, n (%)	4 (7.1%)	5 (38.5%)	0.004
LVH, n (%)	26 (46.4%)	9 (69.2%)	0.14
Severe LVH, n (%)	11 (19.6%)	7 (53.8%)	0.011

EF: ejection fraction, FS: fractional shortening, GFR: glomerular filtration rate, LV: left ventricular, LVH: left ventricular hypertrophy

Table III. Comparison of Echocardiographic Findings and Troponin T Levels in Patients on Dialysis or not.

Findings	No dialysis (n: 28)	On dialysis (n: 41)	P
Mean EF, %	73.9±10.4	70.6±9.6	0.18
Mean FS, %	37.3±7.7	36.9±7.3	0.84
Mean LV mass, grams	87.1±34.8	82±43.6	0.61
LVH, n (%)	10 (35.7%)	25 (61.0%)	0.034
cTnT >0.01 ng/ml, n (%)	3 (10.7%)	10 (24.4%)	0.15

EF: ejection fraction, FS: fractional shortening, LVH: left ventricular hypertrophy

Table IV. Comparison of Echocardiographic Findings and Troponin T levels in Patients with Peritoneal Dialysis versus Hemodialysis.

Findings	Peritoneal dialysis (n: 31)	Hemodialysis (n: 10)	P
Mean EF, %	73.9±10.4	70.6±9.6	0.23
Mean FS, %	37.3±7.7	36.9±7.3	0.83
LVH, n (%)	21 (67.7%)	4 (40.0%)	0.15
cTnT >0.01 ng/ml, n (%)	8 (25.8%)	2 (20.0%)	0.54

EF: ejection fraction, FS: fractional shortening, LVH: left ventricular hypertrophy

and those who received hemodialysis were compared. There was no difference between the two groups in terms of echocardiographic findings and cTnT levels. It was found that dialysis type had no effect on cardiac findings of the patients in the study (Table IV).

During the five-year follow-up, 5 (7.3%) of 69 patients died (2 had sudden cardiac death), 4 (5.8%) developed systolic dysfunction, and 21 (30.4%) had renal transplantation. The initial cTnT values of both the 2 patients who died due to sudden cardiac death and the 4 patients who developed systolic dysfunction in the follow-up were found to be normal.

Discussion

This study shows that cTnT can be used for detecting cardiac involvement in cases with CKD, when echocardiographic evaluation is not possible, or before echocardiographic evaluation.

In cases with CKD, the cardiovascular system should be regularly examined in order to determine the high risk factors for mortality and morbidity. It is very important to detect cardiac changes with early and effective

evaluations and to take measures to reduce mortality and morbidity.¹⁴ In our study, it was observed that the cardiac involvement was more significant in patients with higher cTnT levels because the lower mean EF and FS levels and the higher rate of advanced hypertrophy and systolic dysfunction detection in the left ventricle. It was revealed that the cardiac troponin T level may be helpful for the clinician to detect cardiac effects. In the literature, high levels of cardiac troponins are thought to be an indicator of chronic cardiac damage.¹⁵ One study revealed the association of cTnT levels with left ventricular hypertrophy and systolic dysfunction in 150 patients with end-stage renal disease.¹⁶

In our study, a significant increase in the detection of high levels of cTnT in 18 patients with advanced LVH was observed. It was found that in patients with CKD, left ventricular hypertrophy is mostly observed and this is associated with increased levels of cTnT.¹⁷ In a study, cTnT levels were found to be higher in patients with left ventricular hypertrophy.¹⁸

At the end of the five-year follow-up, although the contribution of cTnT with regards to cardiac involvement (LVH and systolic

dysfunction) at the time was shown, it was unclear whether it would be beneficial in predicting mortality. This was thought to be related to the patients' young age (the cardiac effect has not yet begun or minor), successful management (the same cardiac findings for patients who needed dialysis and those who did not) as well as the low rate of mortality (7%) due to the high rate of kidney transplantation (30.4%) in those with a high risk. It has been seen in the literature that in similar studies, conflicting results were obtained in predicting the mortality of cTnT. It has been found that in many studies most of which were undertaken on adults, some studies provided evidence that cTnT contributed to predicting mortality.^{4,6,16,17} Some studies such as our own, found that although patients with high cTnT levels were found to have a significantly higher incidence of adverse cardiovascular events, it was not an independent indicator of adverse cardiovascular event development.^{7,19}

Recent studies in this area continue with serum high-sensitivity cardiac troponin T (hs-cTnT) in adult patients.²⁰⁻²² In a study conducted on 143 patients of CKD that underwent long term dialysis with hs-c cTnT, hs-cTnT was found to be a better predictor of mortality in a group of dialysis patients.²¹ Some studies where CKD patients were treated with high sensitive detection method showed that hs-cTnT was associated with LVH and LV dysfunction and was an independent predictor of cardiovascular events, cardiovascular mortality and all-cause mortality.²² In another study conducted on 577 CKD cases that did not receive dialysis in 2016, hs-cTnT and NT-proBNP were found to be valuable for evaluating LVH, left ventricular systolic dysfunction and left ventricular diastolic dysfunction and it was observed that the LVH increased 6 fold and diastolic dysfunction increased 18-fold in the patients with high level hs-cTnT compared to those with low levels of hs-cTnT.²² This research put forward that periodic monitoring of serum hs-cTnT levels may be beneficial for detection of high risk cardiovascular events, and for taking prompt intervention for prevention.²² Although studies recently being conducted in the field continue to produce good results, a biomarker that clearly shows morbidity and mortality has not yet been detected.

Our study is one of the rare studies conducted in childhood age group in this field.^{4,6,7,16,17,19-22} During the study the cTnT was found to be a marker that can be used in routine controls because cardiac involvement (lower mean EF and FS values, increased systolic dysfunction and a higher detection rate of LVH) is more prominent in cases with high cTnT levels despite the absence of cardiac complaints and physical examination findings. It has been shown that cTnT can be a significant contributor to the determination of cardiac involvement especially in cases where echocardiographic evaluation is not possible or before echocardiographic evaluation where possible.

The relatively small sample size and the single center design of the study can be counted as the limitations to this study. Future studies examining the efficacy of cTnT and new generation cardiac markers on the prognosis of children with chronic renal failure can be conducted on a larger sample. Despite these shortcomings, the study contributed to the literature by demonstrating that higher cTnT levels is an important early finding in children with chronic renal failure.

In conclusion, it has been shown that assessment of serum cTnT levels in children with chronic and end-stage renal disease who have a long life expectancy, may be beneficial in order to obtain information about cardiac effects before clinical symptoms occur and cTnT can be used for screening purposes. The observations in this study highlight the need for further research to investigate the association of cTnT with mortality and the potential of these biomarkers to contribute to active intervention programs that aim to improve clinical outcomes.

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