Evaluation of Troponin I Serum Level in Patients With Peritoneal Dialysis and Relationship Between Troponin I and Cardiovascular Risk Factors

Shahram Taheri[1], Ali Asghar Pilehvarian[2], Afsoon Emami Naeini[1], Fariba Kushki[2], Firouzeh Moeinzadeh[1,3]

[1] *Department of Nephrology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

[2] *Department of Biology, Payame Noor University, Isfahan, Iran*

[3] *Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

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Abstract- End-stage renal disease is a situation that predisposes the patients to cardiovascular disease, especially myocardial infarction (MI). A valuable biomarker for the diagnosis of this event is cardiac troponin. Although some asymptomatic patients show high plasma levels of cardiac troponin I, it is still the most sensitive variable in MI. All patients more than 18-year-old, on chronic ambulatory peritoneal dialysis (CAPD) for at least three months, and did not have a history of acute myocardial infarction or hospitalization for CVD during last month are included in a cross-sectional descriptive study. Troponin I serum level was measured by VIDAS Troponin I Ultra (TNIU) Assay. Correlation between serum troponin level and cardiovascular risk factors are evaluated. In this study, 52% of patients were male. The mean cTnI level was 0.025±0.044 ng/mL, less than 0.11 ng/mL, and only five patients had cTnI level more than the laboratory threshold. The cut-off level of cTnI for diagnosing cardiovascular disease must be re-evaluated and maybe increase to 0.3 ng/mL. Indeed, the asymptomatic patient may need more close observation for cardiovascular disease.

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Keywords: Cardiac troponin I; Peritoneal dialysis; Cardiovascular risk factors

Introduction

Cardiovascular disease (CVD) is the most common cause of mortality and morbidity in end-stage renal disease (ESRD) patients. The mortality rate of patients with ESRD is about 15-20 times higher than the general population (1,2). Some investigations indicate that CVD in peritoneal dialysis (PD) patients are similar to hemodialysis (HD) patients (3). Nevertheless, some believe that ultrafiltration in HD can exert ischemia in the myocardium and left ventricular wall motion abnormality (4,5). Due to its continuous pattern, PD may be a safer modality for the cardiovascular system, and some reports indicate PD can improve ventricular hypertrophy, blood pressure, and volume status (6). Cardiac troponin T and I (cTnT, cTnI) and B-type (Brain) natriuretic peptide (BNP) may be utilized in predicting cardiovascular disease, prognosis, and outcome stratification in PD patients (7). Measuring circulating cTnT and cTnI levels have become the current gold standard approach in detecting myocardial injury and in diagnosing acute myocardial injury (8,9). Cardiac troponins were frequently elevated in the absence of acute coronary syndrome among patients with varying degrees of kidney disease (10,11), and cTnT was more frequently increased compared to cTnI in asymptomatic ESRD patients (12). Indeed the lower incidence of cTnI elevations and lack of expression of cTnI in non-cardiac tissues has led to the initial suggestion that cTnI may be a more specific diagnostic and prognostic marker in reflecting myocardial injury in patients with renal failure (13,14,15). We decided to evaluate cTnI in asymptomatic CAPD patients and its relationship to known cardiovascular risk factors.

Materials and Methods

This cross-sectional descriptive study was done in two PD centers in Isfahan University of Medical Sciences from November 2013 to January 2014. All patients more than 18-year-old, on chronic ambulatory peritoneal dialysis (CAPD) for at least three months, who did not have a history of acute myocardial infarction or hospitalization for CVD during last month and who gave

Corresponding Author: F. Moeinzadeh
Department of Nephrology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Tel: +98 31 38226713, Fax: +98 31 36691510, E-mail address: f_moinzade@med.mui.ac.ir

informed consent to use their data anonymously, enrolled in the study. From 190 patients, 103 patients fulfilled the inclusion criteria. Demographic characteristics including age, sex, body mass index (BMI), cause of kidney failure, time on CAPD, marital and employment status, education level and history of hypertension, diabetes, hyperlipidemia, ischemic cardiovascular disease, limb ischemia due to peripheral vascular disease, hospital admission for cardiovascular disease and laboratory data including complete blood cell count (CBC), lipid profile and electrolytes were extracted from patient medical files. All measurements were done in the university laboratory, Al-Zahra Hospital, Isfahan, IRAN.

CTnI analysis method

For cTnI measurement, blood samples were obtained during their routine medical laboratory sampling in the morning and centrifuged to separate the serum, which was stored at −20° C. CTnI was measured with VIDAS Troponin I Ultra (TNIU) Assay (bioMérieux, Marcy L'Etoile, France) (16,17), Enzyme-linked Fluorescent Immunoassay (ELFA) technique for the quantitative detection of human cardiac troponin I (17,18). All assay steps and assay temperatures are controlled by the instrument. Pipette tip-like disposable device, the Solid Phase Receptacle (SPR), selves as the solid phase as well as a pipettor for the assay were used. Reagents for the assay are in the sealed TNI Reagent Strips. The sample is transferred into the wells containing anti-cardiac troponin I antibodies labeled with alkaline phosphatase (conjugate). The sample/conjugate mixture is cycled in and out of the SPR for a specified length of time. Troponin I present in the specimen will bind to the anti-cardiac troponin I immunoglobulin coating the interior of the SPR. Unbound sample components are washed away. A fluorescent substrate, 4-methylumbelliferyl phosphate, is introduced into the SPR. Enzyme remaining on the SPR wall will catalyze the conversion of the substrate to the fluorescent product 4-methylumbelliferone. The optical scanner in the instrument measures the intensity of fluorescence. When the VIDAS TNIU essay is completed, the results are analyzed automatically by the computer, a test value is generated, and a report is printed for each sample (18). Analytical characteristics for this cTnI assay, established by the manufacturer, were as follows: The measurement values of the VIDAS cTnI Ultra kit limit of detection is less than 0.01 ng/mL; range from 0.01 to 30 ng/mL, and the smallest measurable concentration of cTnI with an inter-lot coefficient of value≤10% is 0.11 ng/mL (16,17). For statistical analysis, we used One-way ANOVA, independent sample t-test, and analysis of covariance (ANCOVA). Two-tailed $P<0.05$ was considered significant. SPSS software version 20 (SPSS, Inc., Chicago, IL) is used (15,16).

Results

A total of 103 patients (52.4% male and 47.6% female) were enrolled in the study. Demographic characteristics and laboratory data of all patients showed in tables 1 and 2.

According to this study, the mean cTnI level was 0.025±0.044 ng/mL, less than 0.11 ng/ml, and only five patients had cTnI level more than laboratory threshold, ranged from 0.11 to 0.3 ng/mL. According to Pearson correlation test, patients' age, BMI, time on CAPD, total serum cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, fasting blood sugar (FBS), calcium, phosphorus, albumin, and white blood cell and platelet count and hemoglobin level had no significant correlation with serum cTnI level. One-way ANOVA test showed that employment, educational status, cause of renal failure, and unpaired sample t-test showed that marital status, history of hypertension, diabetes, hyperlipidemia, cardiovascular disease, and limb ischemia had no statistically significant effect on serum cTnI level.

By unpaired sample t-test, mean serum cTnI was significantly higher in patients with a history of hospital admission due to CVD (0.042±0.07 ng/mL and 0.018±0.02 ng/mL, $P=0.015$).

By using ANCOVA test, after adjusting for age, BMI, serum lipids, FBS, albumin, hemoglobin, educational and marital status, history of hypertension, diabetes, hyperlipidemia, cardiovascular disease and limb ischemia, only history of hospital admission due to CVD had a significant effect on serum cTnI level ($\beta=0.038$, 95% CI, 0.012- 0.063, $P=0.004$).

Table 1. Demographic characteristics of CAPD patients

Body Mass Index (Mean±SD)		24.07± 4.48
Age (Mean±SD)		58.28±14.73
Sex	**Male, no(%)**	54(52.4)
	Female, no(%)	49(47.6)
Marital status	**Married, no (%)**	85(82.5)
	Unmarried, no (%)	18(17.5)
Employment status	**Housekeeper, no (%)**	40 (38.8)
	Retired, no (%)	32 (31.1)
	Employed, no (%)	16 (15.5)
	Unemployed, no (%)	15 (14.6)
Educational status	**Illiterate, no (%)**	34 (33)
	Undergraduate, no (%)	53 (51.5)
	Graduate & more, no (%)	16(15.5)
Cause of renal failure	**Diabetes, no (%)**	46 (48.5)
	Hypertension, no (%)	30 (29.1)
	Others, no (%)	23 (22.3)
History of Hypertension, no (%)		86 (81.6)
History of Diabetes, no (%)		48 (46.6)
History of hyperlipidemia, no (%)		55 (53.4)
History of Cardiovascular disease, no (%)		50 (48.5)
History of limb ischemia, no (%)		4 (3.9)
Hospital admission history due to cardiovascular diseases, no (%)		29 (28.2)

Table 2. Laboratory data of CAPD patients.

	Mean±SD
Total Cholesterol (mg/dL)	159.6±43.7
Triglyceride (mg/dl)	133.3±71.7
HDL- Cholesterol (mg/dL)	46.6±10.0
LDL- Cholesterol (mg/dL)	89.4±31.7
Fasting Blood Sugar (mg/dL)	125.4±55.7
White blood cell count (n/µL)	7528±2688
Hemoglobin(g/dL)	10.8±2.1
Platelet (n/µL)	214766±58050
Calcium (mg/dL)	8.8±0.6
Phosphorus (mg/dL)	4.39±1.06
Albumin (g/dL)	3.4±0.6
Cardiac Troponin I (ng/mL)	0.025±0.045
Cardiac Troponin I >0.11 (ng/mL), no (%)	5 (4.85)

Discussion

Troponin is a biomarker that increases myocardial damages, including myocardial infarction. Nearly 20-90% of ESRD patients have increase in serum cTnT concentration but it is about 0-19% in cTnI concentrations (17,18,19).

Although some variations in dialysis equipment like different membranes and vascular access types influence the concentration of cardiac troponins (20), but probable causes that are suggested for increasing in troponin level in ESRD patients include: altered protein clearance, abnormal protein metabolism, left ventricular hypertrophy (LVH), probably due to cardiac troponin release into circulation (21), uremic myopathy, silent myocardial injury due to uremic neuropathy, microinfarctions, inflammatory conditions related to primary kidney disease or uremia itself and non-ischemic damage to the myocardium(22).

Goicoechea (23) demonstrated that serum level of cTnT increased in about 11.3% of chronic kidney disease, not on dialysis patients enrolled in their study. Abaci *et al.*, (24) evaluated the serum cTnI level in ESRD patients and declared an elevated level in 24% of their patients. They suggested that although cardiac troponins derive from the heart and correlate with left ventricular mass index, but had no prognostic value.

In concordance to other studies done in CKD patients (17,18,19), serum level of cTnI was positive in five (4.85%) patients in our study, but none of them was more than 0.3, maybe it is better to define a new upper limit threshold for positive results in this specific population.

Taheri *et al.,* (25) have shown low repetition in an increased level of cTnI in hemodialysis patients, but they concluded that it could be a clue for active CVD.

In a study done in stage 3-5 CKD patients, Abbas *et al*., (10) revealed a positive correlation between cTnI level and age, LVH, left ventricular mass index, history of diabetes mellitus and CVD, but negative correlation with estimated glomerular filtration rate. They found no correlation with sex, BMI, and arteriopathic disease. In our study, all of our patients were in CKD stage 5, and there was no relationship between cTnI level and age, sex, BMI, and history of diabetes mellitus.

Lo¨wbeer *et al*., (26) carried out another study and evaluated cTnT level in dialysis patients, hemodialysis, and PD. They found a positive correlation between cTnT level with age and diabetes mellitus. Also, they found that serum cTnT levels of more than 0.1 µg/L correlate with increased mortality. In concordance with our results, Ninan *et al.,* evaluated cTnI level in forty-six HD and twenty-nine PD patients and found that cTnI levels were below significant levels in 92% of patients and had no correlation with BMI, gender and age (27). They concluded that the cTnI level could be used as a good indicator of ischemic heart injury. More in our study, that history of hospital admission due to cardiovascular diseases was correlated with cTnI level.

To increase the accuracy of cardiac troponins, new sensitive assay has been developed with a lower detection limit and coefficient of variation less than 10% at the 99th percentile (28,29). Artunc *et al*., in a cross-sectional study, analyzed plasma concentrations of sensitive cTnI in stable ambulatory hemodialysis patients and investigated its association with clinical factors and mortality (30). In a multivariate linear regression analysis, they found that cTnI level independently correlated with age, duration of an HD session, systolic left ventricular failure, pulse pressure, and time on dialysis. But the history of hospital admission due to CVD is the only variable that is significantly correlated with elevated cTnI levels in our study.

With regarding this point, Artunc *et al.*, suggested that cTnT level more than 38 pg/mL was associated with increased risk of mortality, but they could not define clear cut-off cTnI level due to gradual association with death (30). Ryu *et al*., evaluated the clinical usefulness of cTnT in ESRD patients with the acute coronary syndrome (31). They suggested a new cTnT cutoff level of more than 0.35 ng/mL for diagnosis of acute coronary syndrome in ESRD patients, and urgent diagnosis and treatment is indicated in dialysis patients with ACS when the initial cTnT levels exceed this level.

Although we did not evaluate mortality risk in association with cTnI, our results also suggest that the new cut-off point should be defined for cTnI in the ESRD patients population, especially PD patients. For confirmation, more investigations must be conducted to validate this hypothesis.

A high level of cTnI in PD patients may need more attention to CVD. These measures probably indicate at-risk patients.

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