Original Article

Association between troponin I level and cardiovascular risk factors in asymptomatic hemodialysis patients

Shahram Taheri¹, Ali Asghar Pilehvarian², Nafiseh Akbari¹, Samane Musavi², Afsoon Emami Naeini¹

ABSTRACT

Objective: Patients on hemodialysis (HD) have a high risk for cardiovascular morbidity and mortality. Cardiac troponins are biomarkers for diagnosing acute myocardial injury or infarction. There is considerable controversy that exists in the frequency and significance of cardiac troponins in predicting cardiac injury and ischemia in HD patients.

Methods: In this cross-sectional study, all HD patients more than 18-year-old, who were at least 3 months under HD, and had no sign and symptom of active cardiovascular disease (CVD), in two HD centers were enrolled. One hundred and one patients fulfilled the inclusion criteria. Blood sample for cardiac troponin I (cTnI) was drawn before the initiation of HD session during their routine monthly blood testing from patients’ vascular access arterial line. cTnI levels were measured by a high-sensitivity assay, VIDAS troponin I Ultra kit, and correlated with patients’ demographic, clinical, and laboratory results.

Findings: The patients’ different demographic and clinical characteristics had no statistically significant correlation with troponin levels except for marginal trend for past medical history of diabetes and hyperlipidemia with corresponding \( P \) values of 0.072 and 0.055. Twenty-six patients had cTnI level more than 0.01 µg/L and only two patients had cTnI level more than 0.11 µg/L. For laboratory results, only fasting blood sugar had statistically significant correlation with patients’ cTnI level (\( r = 0.357, P = 0.0001 \)).

Conclusion: Frequency of significant elevation of cTnI level in our asymptomatic HD patients was very low and if such elevation is found in this population, it may be considered as a sign of active CVD.

Keywords: Cardiovascular disease; hemodialysis; troponin I

INTRODUCTION

Patients on hemodialysis (HD) have a high risk for cardiovascular morbidity and mortality.¹ Cardiac troponins are biomarkers usually used to diagnose acute myocardial injury and infarction.² There is considerable controversy that exists in the significance of cardiac troponins in predicting cardiac injury and ischemia in chronic renal failure patients, especially in patients on HD.³⁴ In this study, we evaluated cardiac troponin I (cTnI) and its correlation to cardiovascular risk factors in our HD patients.

METHODS

In this cross-sectional study, from November 2013 to January 2014, all end-stage renal disease (ESRD)
patients under HD in two Isfahan University HD centers who fulfilled the following inclusion criteria were enrolled in this study.

All patients, who were at least 18-year-old, at least 3 months on HD, had no sign and symptoms of active cardiovascular disease (CVD), gave an informed consent to participate in this study, and used anonymously the information from this study as a research publication, were enrolled.

This study was approved by the Isfahan Kidney Diseases Research Center/Isfahan University of Medical Sciences and registered as a Grant number: 292135. From all 220 HD patients in these two HD centers, 101 patients had the above-mentioned inclusion criteria to enter into this study.

Demographic characteristics of the patients, including gender, age, predialysis body mass index (BMI), education level, cause of kidney failure, duration of HD, weekly dialysis session number, history of hypertension, hyperlipidemia, diabetes, CVD, limb-amputation, previous coronary care unit or Intensive Care Unit hospitalization, were recorded from patients’ recordings.

Laboratory data including serum albumin, calcium, phosphorus, triglyceride, cholesterol, high-density lipoprotein, low-density lipoprotein, white blood cell count, platelet count, fasting blood sugar (FBS), and hemoglobin level were also recorded from patients’ medical charts.

Blood sample for cTnI was drawn before the initiation of HD session during blood sampling for their routine monthly blood testing from patients’ vascular access arterial line, and sent immediately to the laboratory for analysis.

cTnI levels were measured by a high-sensitivity assay, VIDAS troponin I Ultra kit (Biomerieux, Marcy-l’Etoile, France) and by Vidas 12 device (Biomerieux Italia S.p.a., Ponte A Ema, Italy) in the Laboratory of Al-Zahra Hospital. The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection (ELFA).

In 2000, the Consensus Committee of the European Society for Cardiology and the American College of Cardiology recommended that the diagnosis of myocardial necrosis can be made when the level of cardiac troponin is > the 99th percentile of a reference control group with imprecision <10%. The imprecision study result with the smallest measurable concentration of cTnI, with an inter-lot coefficient of variation <10%, is 0.11 μg/L. [5]

The measurement values of the VIDAS troponin I Ultra kit range from 0.01 to 30 μg/L. The analytical detection limit, defined as the smallest concentration of cTnI which is significantly different from the zero concentration with a probability of 95%, is <0.01 μg/L.

Data were reported as frequencies and means ± standard deviations (SDs) for patients’ demographic and clinical variables. The statistical analysis including one-way analysis of variance (ANOVA) and unpaired sample t-test was used to compare the cTnI level between different clinical parameters. Pearson correlation test was performed to find any correlation between demographic and laboratory parameters with cTnI level by using SPSS software for windows (SPSS, Chicago, IL, USA) version 20.

RESULTS

One hundred and one patients treated by HD were contributed and entered into the final analysis study. The difference of patients’ different demographic and clinical characteristics with troponin levels was analyzed by unpaired sample t-test and ANOVA [Table 1]. None of the mentioned parameters had statistical significance except for marginal trend for past medical history of diabetes and hyperlipidemia with corresponding P values of 0.072 and 0.055.

Range of cTnI levels was 0.01–0.19 (mean ± SD: 0.02 ± 0.026). Frequency of the cTnI levels in our patients is shown in Figure 1. Twenty-six patients had cTnI level more than 0.01 μg/L and only two patients had cTnI level more than 0.11 μg/L.

Table 2 shows the correlation of troponin level with different patients’ laboratory parameters

![Figure 1: Distribution of cardiac troponin I level in our study population. The numbers at the top of each bar indicate absolute patients’ number in each of the cardiac troponin I level measurement](image-url)
It has been shown that cardiac troponins were not only released after cardiac myocyte necrosis, but also were detected in circulation in some clinical situation without any apparent cardiac injury.[6] High level of cTnI with complementary clinical presentation and other parameters such as electrocardiogram indicate acute myocardial infarction.[7]

Some authors stated that increases in cardiac troponins in patients with renal failure have reduced the sensitivity to predict adverse outcome.[8] The main coronary artery stenosis, microvascular lesions, silent plaque, rupture or subclinical myocardial fibrosis, and necrosis may cause high levels of troponin in blood circulation.[9]

The reason for cTnI elevation in HD patients is not clear.[10,11] In addition, the precise mechanism for raised cardiac troponin concentrations in the kidney failure patients is uncertain.[7] In fact, little is known about the route of degradation of cTnI; furthermore, the kinetics of decreases and the catabolic pathways of cTnI in HD patients are not known.[9,12]

Some mechanical manifestations may create controversy, for example, the dialysis membrane may also adsorb cTnI and alter its level after each HD session.[13] ESRD patients have increased mortality and morbidity due to cardiovascular events.[14] These patients also have neuropathy,[15] so they may not experience classical chest pain, and clinical presentation during coronary events is atypical. Risk for atherosclerosis has been increased in uremic patients,[16] and silent ischemia is common among ESRD patients because of associated autonomic neuropathy.[16,17] Due to simultaneous reduction of coronary artery oxygen delivery and increasing myocardial oxygen demand, both symptomatic and silent ischemic heart disease may occur frequently during HD.[16,18]

McLaurin et al. showed that some patients with chronic kidney disease have high cTnI levels in

using Pearson correlation test. Only FBS had statistically significant correlation with patients’ cTnI level ($r = 0.357, P < 0.001$).

**DISCUSSION**

It has been shown that cardiac troponins were not only released after cardiac myocyte necrosis, but also were detected in circulation in some clinical situation without any apparent cardiac injury.[6] High level of cTnI with complementary clinical presentation and other parameters such as electrocardiogram indicate acute myocardial infarction.[7]

Some authors stated that increases in cardiac troponins in patients with renal failure have reduced the sensitivity to predict adverse outcome.[8] The main coronary artery stenosis, microvascular lesions, silent plaque, rupture or subclinical myocardial fibrosis, and necrosis may cause high levels of troponin in blood circulation.[9]

The reason for cTnI elevation in HD patients is not clear.[10,11] In addition, the precise mechanism for raised cardiac troponin concentrations in the kidney failure patients is uncertain.[7] In fact, little is known about the route of degradation of cTnI; furthermore, the kinetics of decreases and the catabolic pathways of cTnI in HD patients are not known.[9,12]

Some mechanical manifestations may create controversy, for example, the dialysis membrane may also adsorb cTnI and alter its level after each HD session.[13] ESRD patients have increased mortality and morbidity due to cardiovascular events.[14] These patients also have neuropathy,[15] so they may not experience classical chest pain, and clinical presentation during coronary events is atypical. Risk for atherosclerosis has been increased in uremic patients,[16] and silent ischemia is common among ESRD patients because of associated autonomic neuropathy.[16,17] Due to simultaneous reduction of coronary artery oxygen delivery and increasing myocardial oxygen demand, both symptomatic and silent ischemic heart disease may occur frequently during HD.[16,18]
their blood and it may correlate with their poor prognosis.[19] Hence, high cTnI could be either an innocent marker and may overdiagnose myocardial infarction in renal failure patients or may be an excellent test to find out the increased risk of HD patients for future cardiovascular event.[16,18,20]

Our finding shows that although cTnI levels are more than 0.01 μg/L in 26% of our patients, elevated level (more than 0.11 μg/L) was seen only in two persons of our asymptomatic patients.

Hussein et al. in their study on 93 asymptomatic HD patients showed that cTnI has a high specificity for the diagnosis of myocardial infarction in dialysis patients and it was found to be significantly correlated with the outcome of all-cause mortality at 1 year.[20] Resic et al. reported that periodical hemodynamics or underlying cardiac disease with specific alterations of cardiac musculature in uremia would be some possible reasons for cTnI elevation.[9]

In our study, we determined the correlation of cTnI levels in HD patients and its association with some demographic, clinical, and laboratory parameters, which only had significant positive correlation with FBS and marginally correlated with history of diabetes.

It has been shown that in diabetic patients with multiple associated cardiovascular risk factors, troponin may be used as a CVD biomarker.[21] Lin-Tan et al. showed that basal fasting glucose levels play an important role in short-term mortality of diabetic maintenance HD patients.[22]

According to our study, despite a history of diabetes which did not correlate with the level of troponin, higher cTnI level was detected in patients with higher FBS; it may suggest that patients with uncontrolled diabetes are at risk for cardiovascular events, and also may conclude that with better glycemic control in patients with ESRD, future cardiovascular events can be decreased.[23,24]

Interestingly, in patients with positive history of hyperlipidemia, reduced levels of cTnI were observed even if it did not reach statistical significance. It is consistent with previous reports stating that ESRD patients with hyperlipidemia had better protection from cardio-vascular events.[25,26]

Frequency of significant elevation of cTnI level in our asymptomatic HD patients was very low and if such elevation is found in this population, it may be considered seriously and should be followed more intensely for active CVD to prevent cardiovascular events.

AUTHORS’ CONTRIBUTION
All authors contributed the idea of research, design of study, data analysis and manuscript preparation.

Financial support and sponsorship
This study was approved by the Isfahan Kidney Diseases Research Center/Isfahan University of Medical Sciences and registered as a Grant number: 292135. This study was funded by the Vice-chancellery for Research and Technology, Isfahan University of Medical Sciences.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Su WS, Clase CM, Brimble KS, Margetts PJ, Wilkieson TJ, Gangji AS. Waist-to-hip ratio, cardiovascular outcomes, and death in peritoneal dialysis patients. Int J Nephrol 2010;2010:831243.
2. Babuin L, Jaffe AS. Troponin: The biomarker of choice for the detection of cardiac injury. CMAJ 2005;173:1191-202.
3. Buiten MS, de Bie MK, Rotmans JL, Dekker FW, van Buren M, Rabelink TJ, et al. Serum cardiac troponin-I is superior to troponin-T as a marker for left ventricular dysfunction in clinically stable patients with end-stage renal disease. PLoS One 2015;10:e0134245.
4. Badero OJ, Salifu MO. Prediction of hemodynamically significant coronary artery disease using troponin I in hemodialysis patients presenting with chest pain: A case-control study. Cardiology 2009;114:292-7.
5. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined – A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.
6. Hickman PE, Potter JM, Aroney C, Koerbin G, Southcott E, Wu AH, et al. Cardiac troponin may be released by ischemia alone, without necrosis. Clin Chim Acta 2010;411:318-23.
7. Sharma S, Jackson PG, Makan J. Cardiac troponins. J Clin Pathol 2004;57:1025-6.
8. Van Lente F, McErlean ES, DeLuca SA, Peacock WF, Rao JS, Nissen SE. Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: A case-matched study. J Am Coll Cardiol 1999;33:471-8.
9. Resic H, Ajanovic S, Kukavica N, Masnic F, Coric A. Plasma levels of brain natriuretic peptides and cardiac troponin in hemodialysis patients. Bosn J Basic Med Sci 2009;9:137-41.
10. Ie EH, Klooftwijk PJ, Weimar W, Zietse R. Significance of acute versus chronic troponin T elevation in dialysis patients. Nephron Clin Pract 2004;98:e87-92.
11. Alivianis P, Giannikouris I, Kaligas G, Arvanitis A, Volanaki M, Vogiatzis P, et al. Influence of different dialysis membrane types on cardiac-specific troponin T levels. PROCEEDINGS of the 6th BANTAO Congress. BANTAO J 2003;1:89-90.
12. Iliou MC, Fumeron C, Benoit MO, Tuppin P, Courvoisier CL,
Calonge VM, et al. Factors associated with increased serum levels of cardiac troponins T and I in chronic haemodialysis patients: Chronic haemodialysis and new cardiac markers evaluation (CHANCE) study. Nephrol Dial Transplant 2001;16:1452-8.

13. Gaze DC, Collinson PO. Cardiac troponin I but not cardiac troponin T adheres to polysulfone dialyser membranes in an in vitro haemodialysis model: Explanation for lower serum cTnI concentrations following dialysis. Open Heart 2014;1:e000108.

14. Wright RS, Reeder GS, Herzog CA, Albright RC, Williams BA, Dvorak DL, et al. Acute myocardial infarction and renal dysfunction: A high-risk combination. Ann Intern Med 2002;137:563-70.

15. Brouns R, De Deyn PP. Neurological complications in renal failure: A review. Clin Neurol Neurosurg 2004;107:1-16.

16. Xanthos T, Ekmektzoglou KA, Papadimitriou L. Reviewing myocardial silent ischemia: Specific patient subgroups. Int J Cardiol 2008;124:139-48.

17. Marchant B, Umachandran V, Stevenson R, Kopelman PG, Timmis AD. Silent myocardial ischemia: Role of subclinical neuropathy in patients with and without diabetes. J Am Coll Cardiol 1993;22:1433-7.

18. Mohi-ud-din K, Bali HK, Banerjee S, Sakhua V, Jha V. Silent myocardial ischemia and high-grade ventricular arrhythmias in patients on maintenance hemodialysis. Ren Fail 2005;27:171-5.

19. McLaurin MD, Apple FS, Falahati A, Murakami MM, Miller EA, Sharkey SW. Cardiac troponin I and creatine kinase-MB mass to rule out myocardial injury in hospitalized patients with renal insufficiency. Am J Cardiol 1998;82:973-5.

20. Hussein M, Mooij J, Roujouleh H, Al Shenawi O. Cardiac troponin-I and its prognostic significance in a dialysis population. Hemodial Int 2004;8:332-7.

21. Segre CA, Hueb W, Garcia RM, Rezende PC, Favarato D, Strunz CM, et al. Troponin in diabetic patients with and without chronic coronary artery disease. BMC Cardiovasc Disord 2015;15:72.

22. Lin-Tan DT, Lin JL, Wang LH, Wang LM, Huang LM, Liu L, et al. Fasting glucose levels in predicting 1-year all-cause mortality in patients who do not have diabetes and are on maintenance hemodialysis. J Am Soc Nephrol 2007;18:2385-91.

23. Snit M, Dwornicki M, Zukowska-Szczechowska E, Grzeszczak W. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: A 7-year observational study. Diabetes Care 2007;30:189.

24. Oomichi T, Emoto M, Tabata T, Morioka T, Tsujimoto Y, Tahara H, et al. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: A 7-year observational study. Diabetes Care 2006;29:1496-500.

25. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol 2007;18:293-303.

26. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int 2003;63:793-808.