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Review article

Cardiac troponins in chronic kidney disease patients with special emphasis on their importance in acute coronary syndrome

Joanna Szczykowska[a,*], Tomasz Hryszko[b], Beata Naumnik[a]

[a] 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Bialystok, Poland
[b] 2nd Department of Nephrology and Hypertension with Dialysis Unit, Medical University of Bialystok, Bialystok, Poland

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ABSTRACT

Troponin measurement is one of crucial assessments facilitating diagnosis of acute coronary syndrome. Patients with chronic kidney disease are decimated by cardiovascular disease. Unfortunately, elevated concentration of serum troponin is commonly faced in clinical practice creating a challenge to rule out acute cardiac ischaemia in this vulnerable population. This review presents current knowlegde on analytical differences in troponin T and I measurements, their prognostic significance and their application in diagnosing acute coronary syndrome in chronic kidney disease patients. It also points out poorly known aspects and suggests directions for future research.

1. Introduction

Patients with chronic kidney disease (CKD) and particularly with end stage renal disease (ESRD) have considerably reduced life expectancy. The main cause of premature deaths is cardiovascular disease (CVD) and its adverse effects [1]. Risk of death from cardiac causes is up to 30 times increased relative to patients in gender- and age-matched population [2]. It is reported that individuals with CKD are more prone to die of CVD than to develop kidney failure [3]. Numerous studies have shown that patients with CKD have not only higher risk of CVD than their counterparts with normal kidney function, but also acute coronary syndromes (ACS) such as unstable angina and myocardial infarction (MI) are more frequently encountered in this population [4]. Notably, ESRD patients are likely to have atypical presentation of ACS with isolated dyspnoea, syncope, nausea, weakness or cardiac arrest. Many of these symptoms may be interpreted as merely dialysis-related. In a retrospective cohort-matched study, dialysis patients with ACS were less likely to present with chest pain or have ST elevation in electrocardiogram [5]. The serologic diagnosis of acute MI is also ambiguous in this population. Large trials of patients with ACS have proved the importance of cardiac troponins elevations in risk stratification, prognosis, and therapeutic utilization [6]. However, most of these studies excluded patients with elevated serum creatinine. It is noteworthy that even up to 80–90% of asymptomatic patients with advanced CKD and ESRD have elevated (above the diagnostic cut-off values provided by manufacturer) plasma troponin concentrations without signs of myocardial ischaemia [7].

Owing to these facts, the aim of this review is to consider if troponins are useful in CKD patients with acute coronary syndrome and what is the clinical significance of their chronic elevation. It is an actual and comprehensive summary of current state of knowledge concerning the topic of troponins among CKD patients, elucidating biochemical intricacies, presenting practical approach and pointing out questionable issues.

2. Review

2.1. Troponin biochemistry and high-sensitivity assays

Troponins are three proteins, which are part of cardiac and skeletal muscle. Troponin C (TnC) is identical in both types of tissue, which limits its usefulness. Skeletal and cardiac troponin I and T are distinct isoforms encoded by different genes. Thus, there is a divergence in amino acid composition between cardiac and skeletal proteins, which allows for the identification of these molecules by monoclonal antibody assays. Cardiac troponin I (cTnI) and T (cTnT) have been endorsed internationally as the standard biomarkers for detecting myocardial injury and infarction, because of their superior specifity and sensitivity comparing to other biochemical indices [8,9]. The majority of cTnT and cTnI are found in the contractile apparatus (approximately 10 mg/g and

* Corresponding author at: 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Żurawia 14, 15-540, Bialystok, Poland.
E-mail address: a.szczykowska@wp.pl (J. Szczykowska).

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4–6 mg/g tissue, respectively) with 4–8% reported to occur as a free cytosolic component [10]. Current evidence fosters the idea that the release of troponins is due to cell death caused by various conditions including trauma, myocardial necrosis, toxin exposure or inflammation and is irreversible [11]. However, cTn may also be released, in smaller amounts, due to physiological causes, e.g. apoptosis or cell turnover. The degradation of troponins remains undefined and the effect of renal clearance on circulating troponin's concentrations uncertain [12].

High-sensitivity cardiac troponin (hs-cTn) assays measure the levels of the same protein as the conventional assays, though in much lower concentrations. The term 'high-sensitivity' reflects only the assay's analytical characteristics but there is no difference in the form of detected cardiac troponin. To be classified as 'high-sensitivity', an assay has to meet two criteria. First, an assay should have a coefficient of variation (CV) of < 10% at the 99th percentile value. Second, measureable concentrations below the 99th percentile should be dectectable above the assay's limit of detection for > 50% of healthy individuals in the population of interest [10]. The diagnostic cut-off values have been reduced from 500 ng/L in the first generation assays to currently possible levels as low as 14 ng/L (hs-cTn). It means that the term 'negative troponin' becomes relatively meaningless as troponin at low levels can almost always be detected, even in healthy people. At the same time, it should be mentioned that these very low concentrations might be difficult to quantify due to pre-analytical errors such as haemolysis, which even at mild degree, may reduce hs-cTnT values [13]. Also, elevation of troponins caused by skeletal muscle pathology (e.g. rhabdomyolisis) is more often detected by hs-cTnT assays than by conventional ones [14]. Moreover, many experts and guideline documents support the use of sex-specific cut-off values, because the 99th percentile among normal population differs between men and women [15,16]. With higher sensitivity comes the responsibility of understanding and interpreting these very small elevations of hs-cTn levels in the clinical context. No troponin assay alone allows a clinician to determine the etiology of myocardial cell necrosis. However, these extremely sensitive tests allow earlier and faster recognition of patients with acute myocardial infarction (AMI). Two large prospective studies have shown that in successful diagnosis of acute MI, within 3 h since the onset of symptoms, the hs-cTn assays are more accurate than the previously used assays [17,18].

2.2. Causes of stable elevated troponins in CKD patients

Numerous studies have shown that stably elevated troponin concentrations are commonly found in patients with decreased glomerular filtration. Up to 80% of patients with eGFR < 60 ml/min/1.73m^2 and no history of acute coronary syndrome or congestive heart failure, test positively for cTnT [7]. Contrarily, one large study including more than 700 patients found the prevalence of cTnI to be only 0.4–6%, depending on the chosen cut-off value [19]. Using the most current high sensitivity assays does not change this phenomenon. Elevated hs-cTnI level is still detected less frequently than that of hs-cTnT [20], therefore cTnI may be a more specific marker of acute coronary syndrome in patients with renal failure. Nonetheless, consensus guidelines do not specify a preference for cTnI in CKD patients [15].

Higher levels of cTnT than cTnI may be caused by important differences in myocyte biology and protein chemistry. In brief, the cTnT content per gram of myocardium is almost twice as that of cTnI. Additionally, the same relations concern the free cytosolic troponin, which is released earlier in case of myocyte death [10]. Moreover, troponin T and I are released from damaged myocytes in different forms: free cTnT, cTnI-TnC and cTnT-cTnI-TnC complex. The last one is quickly degraded into cTnT and cTnI-TnC (Fig. 1). Free cTnI is extremely unstable and as a result of its hydrophobicity it is suggested to bind to other proteins, which potentially mask its epitopes recognized by antibodies [21]. Also TnC, protecting cTnI from proteolytic degradation, competes with assay antibodies for binding to cTnI, and only

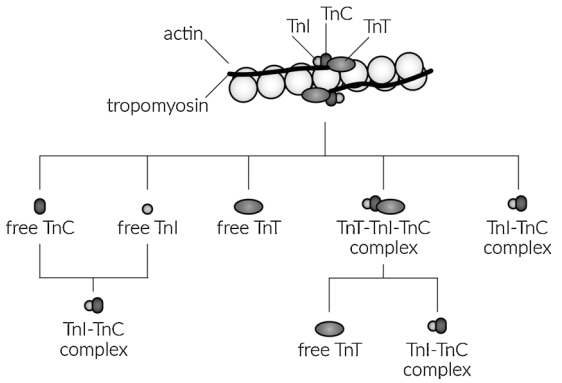

Fig. 1. Troponin release profile.

Table 1
Biochemical differences between cardiac troponin T (cTnT) and I (cTnI).

	cTnT	cTnI
Content (mg/g tissue)	10	4–6
Cytosolic component (%)	6–8	2–8
Molecular weight (kDa)	37	21–24
Half-life	120 min	free – very unstable
Form of release	free cTnT, cTnT fragments, cTnT-cTnI-TnC complex	free cTnI – small amounts cTnI-TnC complex, cTnT-cTnI-TnC complex

a few assays using antibodies specific to the central part of cTnI can recognize the cTnI-TnC complexed form [10]. Detailed biochemical differences are listed in Table 1. Although these theses can explain a discordance between the stable cTnT and cTnI elevations, they do not answer the question why troponins' concentrations are elevated in patients with CKD. The etiology of stably increased cTnT in renal failure conditions remains elusive, but is certainly multifactorial. There are some hypotheses, which are considered:

- loss of integrity of cardiac myocyte membrane, which is observed in renal failure, is found to cause continual release of cardiac troponins from cytosolic compartment into the circulation [22];
- presence of clinically silent microinfarctions. Patients with CKD and, especially, ESRD are known for high incidence of coronary artery disease, so they are more likely to undergo asymptomatic necrosis of small areas of myocardium. There is pathological evidence documenting this phenomenon in patients with elevated troponins and no clinical signs of MI [23].
- concomitance of heart failure (HF) even without acute ischemia. When using hs-cTn assays, detectable troponin is found in nearly 100% of this population, with a significant majority above the 99th percentile [24]. The prevalence of HF among patients with declining renal function is high. In a large, population-based Atherosclerosis Risk in Communities study, the incidence of HF was 3-fold higher in a group with eGFR < 60 mL/min/1.73 m^2 compared to the reference group with normal renal function [25]. In addition, patients with renal failure frequently have left ventricular hyperthrophy [26], the presence of which is also significantly correlated with the increased circulating cTn levels, even more strongly than cardiac ischemia or diabetes [27].
- cross-reactivity with skeletal muscle troponin T was also taken into consideration as a cause of elevated cTnT levels in ESRD patients. Even the expression of cTnT isoforms in the skeletal muscles of patients with ESRD has been discussed [28]. However, these assumptions were true only for the first generation troponin T assays, as currently used assays have not shown the cross-reactivity [29].
- troponins accumulation due to decreased clearance, which is the most controversial and questionable explanation [30]. A few small

studies, carried out on a population with congestive HF, have shown that elevated cTnT occurs as a result of impaired renal function rather than injury of myocardial cells, leading to even 2-fold higher concentrations in patients with concomitant CKD [31,32]. Other studies have not confirmed this association [33]. The latest study concerning the origin of cTn elevations in CKD patients indicates that diminished renal clearance is not the main cause of elevation, because diurnal cTnT rhythm is preserved in this population. If the accumulation of troponin due to renal failure was the key driver of elevated cTn in this population, its concentration would be steadily at the same level. Yet, the study showed that the cTnT concentrations among CKD patients are decreasing during daytime and increasing throughout nighttime with amplitudes similar to those observed in the reference group [34]. Moreover, intact troponins are relatively large molecules, with molecular weight similar to creatine kinase, which is cleared by the reticuloendothelial system [35], what makes them improbable to be removed primarily by the kidneys.

There are also other non-ischemic clinical conditions associated with troponin elevation, where the exact mechanism of myocardial damage is uncertain or multifactorial. Chronic elevation of troponin levels may be found in patients with tachy/bradyarrhythmias, aortic valve disease, rhabdomiolysis with cardiac injury or infiltrative diseases such as amyloidosis [36]. Patients with CKD can suffer from all of these disorders as isolated chronic renal failure is rare and multimorbidity is the norm in this population [37]. For instance, the prevalence of the most common arrhythmia - atrial fibrillation (AF) among CKD patients was found to be even 2- to 3-fold higher than in the general population [38,39] In the Chronic Renal Insufficiency Cohort study the overall prevalence of AF among CKD patients was 18% and even > 25% in a group of patients ≥ 70 years old [39].

Rhabdomyolysis is worth special attention, as myopathies and muscle wasting in CKD, although underestimated, are common and concern about 50% of dialysis patients [40]. An early study showed that cTnI and cTnT levels may be elevated in patients with rhabdomyolysis [41]. Other studies have found that cTnT level is more commonly elevated than cTnI [14]. However, the most recent data suggest, that elevated cardiac troponins' level in the course of rhabdomyolysis is more associated with cardiac involvement rather than with cardiac troponins expression in the skeletal muscles [42]. A short summary of causes of elevated troponins is presented in Table 2.

2.3. Interference of cTn levels with CKD and dialysis

Patients with ESRD are more likely to have elevated cardiac troponins than patients with earlier stages of CKD mainly due to chronic myocardial injury. The cardiac workload of these patients is increased by several factors, such as chronic volume overload, hypertension, and the presence of arteriovenous fistula or anemia. All these conditions induce alteration in cardiac structure and may lead to steady troponin release [43]. Moreover, hemodialysis sessions induce cardiac stress caused by circulatory variations and may trigger myocardial damage [44]. However, the most important issue is if dialysis may change circulating cTn levels. At least two scenarios should be considered: concentration could potentially increase due to hemoconcentration or decrease due to clearance or absorption by dialysis membrane. Studies on hemodialysed (HD) patients yielded different results and there is still a lack of consensus. An increase [45], a decrease [46] and no changes in post-HD concentrations of cTn [47] were observed. The most recent study supports the idea that HD does not significantly affect cTn levels [48]. A connection between post-HD cTn level fluctuactions and the type of utilised dialyser membrane have also been researched. Each membrane has a molecular weight cut-off for the largest molecules that can pass through it. High-flux dialyzers have molecular weight cut-offs ranging from 3 kDa even up to 65 kDa [49]. Although cardiac troponins, as mentioned above, are relatively large molecules, they theoretically may be removed during HD, because the molecular weight of cTnI is 21 to 24 kDa [50], cTnT 37 kDa, and its circulating fragments - 8 to 25 kDa [51], respectively. Alas, numerous studies present conflicting results. In the study by Wayand et al. [52] the authors concluded that cTnT increased with dialysis regardless of the HD membrane. Lippi et al. [53] confirmed the hypothesis that high-flux HD membranes clear both cTnT and cTnI from serum more efficiently than low-flux membranes. In 2014, one study using an in vitro model of dialysis found that cTnI is not dialysed from vascular compartment but adheres to the polysulphone dialyser membrane [54]. These novel results provided, for the first time, a presumable mechanism by which cTnI decreases after dialysis. However, it must be mentioned, that many different membranes are used clinically, so the adsorption of cTnI to these surfaces may differ and variously impact on post-HD concentrations. Undoubtedly, the influence of utilised dialysis membranes on cTn concentrations requires further research. Anyway, to determine the baseline cTn concentration in dialysis-dependent patients, it is suggested to obtain the samples pre-HD to overcome discrepancies.

There are no data concerning the influence of peritoneal dialysis on cardiac troponins.

Table 2
Causes of stable elevation of cardiac troponins in patients with chronic kidney disease.

Connected with myocardial ischemia:
asymptomatic microinfarctions [23]
hypoxia, hypoperfusion (e.g. due to anemia) [36]
heart failure [24]
severe aortic valve disease [36]
arrhythmias [36]
hypertension [36]
Non-ischemic causes:
chronic volume overload [43]
left ventricular hypertrophy [27]
loss of integrity of cardiac myocyte membrane [22]
presence of arteriovenous fistula [43]
myopathies including rhabomyolysis with cardiac injury [41]
infiltrative diseases [36]

2.4. Diagnostic utility of troponins in ACS patients with CKD

As mentioned above, new generation hs-cTn assays yeld mild troponin elevations commonly in asymptomatic patients with CKD [55] not necessarily due to acute ischemia. The latest study on patients presenting to the Emergency Department with signs of AMI showed that patients with renal dysfunction had at least one positive troponin nearly twice as often as patients without kidney disease. However, the incidence of AMI was found to be comparable in both investigated cohorts [55].

The evaluation of CKD patients becomes more challenging, when we realise, that the troponin upper reference limits (URL) were originally derived from healthy general population. According to The Third Universal Defition of MI, among CKD patients who are suspected of AMI, a rise of cTn values, with at least one value above the 99th percentile, the URL provided by the manufacturer of the assay should be used rather than a single value obtained on presentation [15]. However, the consensus does not specify particular thresholds and the degree of cTn elevation required for the diagnosis of MI among patients with impaired renal function. Nonetheless, it seems reasonable to consider higher threshold values in patients with CKD, because, as noted before, cTn values above the URL are a common finding in this population. Some studies attempted to define the optimal cut-offs specifically for CKD patients. Twerenbold et al. [56] examined the clinical utility of 7 more sensitive cTn assays in a population presenting with symptoms of AMI. Their findings point out that clinical decision levels are assay-specific and need to be determined for each assay

Table 3
Summary of prognostic and diagnostic utility of cTn among patients with CKD.

	Stable chronic kidney disease	Suspicion of acute coronary syndrome	Myocardial infarction
Significance of elevated troponin	increased risk of cardiovascular events and poor long-term survival [62]	dynamic change in concentration in 3-hours interval for high sensitivity assays and 6-hours for conventional ones with at least one measurement above the 99th percentile URL to establish the diagnosis of MI [15]	the higher elevation the grater risk for major adverse cardiovascular outcomes [30] and mortality [61]

individually. The optimal receiver-operator characteristic curve-derived cutoff levels in patients with renal impairment were 1.9–3.4 times higher than the levels in patients with normal renal function for all investigated hs-cTn assays [56]. Another study [57] of 75 patients with eGFR < 60 ml/min/1.73m^2 reported that an initially high hs-cTnT was an accurate predictor of MI when the used cut-off was more than 2.5-fold higher than the 99th percentile establihed by the manufacturer (36 ng/L compared with 14 ng/L). Although this higher threshold resulted in higher specificity compared to lower threshold (86% vs. 54%, respectively), an unacceptable loss of sensitivity was observed (94% compared to 100%). In these circumstances, it seems that the diagnosis of MI in CKD patients should rely more heavily on the assessment of serial changes of hs-cTn levels. The problem is how to define a significant change (or "delta"), which has been found as assay- and interval-dependent. A recommendation has been made in general population for hs-cTnT assay to use a 50% change when the first measurement is near the 99th percentile URL and a 20% change when the baseline value increased over the 99th percentile within a 3 h interval [58]. Unfortunately, studies have shown that higher delta values increase the specificity for diagnosing AMI, but at the cost of clinical sensitivity [59]. Unfortunately, there are still no recommendations to support a specific threshold of change in patients with CKD and the additional studies are needed in this area.

2.5. Prognostic utility of troponins in CKD patients

In addition to their use in diagnosing ACS, cardiac troponins were found to be independent predictors of short-term adverse cardiac outcomes in CKD patients diagnosed with AMI (Tabl.3.). Aviles et al. [30] noticed that higher elevation of cTnT concentration means a greater risk for major adverse cardiovascular outcomes within 30 days after ACS. A meta-analysis of three studies showed that the risk of cardiac ischemia, AMI, dysrhythmia, congestive heart failure or a combination of these outcomes was increasing with cTnT level elevation [60]. Additionally, another study found [61] that the same association is observed among both dialysis-dependent patients and those with less advanced CKD. Low-strength evidence also suggested a proportional increase in short-term all-cause mortality after ACS in patients with elevated cTnT. As for cardiac troponin I, in two studies [52,61], elevation of baseline cTnI was found to be associated with higher risk of short-term cardiovascular effects after an episode of unstable angina or MI only in patients suffering from ESRD. Troponins are also a prognostic marker of mortality in non-CKD patients with an acute coronary episode. However, there is still lack of research comparing the level of prognostic utility of cardiac troponins in these two populations.

Moreover, baseline cardiac troponins can aid defining mortality risk in patients with ESRD. Stably elevated troponin concentrations are bound to a poor long-term survival among CKD patients, even when the degree of elevation is small. The most potent data derives from a study by Michos et al. [62]. The meta-analysis of 11 studies showed that increased cTnT was linked to a 3-fold higher risk of overall mortality. Concurrently, similar results were reported in the meta-analysis of 7 studies, in which elevated cTnI concentration was associated with a 2.7-fold increase in the risk of death. The study concluded also baseline elevated troponin level is associated with a higher risk (approximately 2- to 4-fold) of cardiovascular mortality and risk of major cardiovascular event among patients without suspected ACS who were receiving dialysis. Similar observations were made for patients with CKD who were not receiving renal replacement therapy, but fewer studies were identified for this subgroup. Thus, elevation of cardiac troponin levels among CKD patients is not spurious but foreshows a worse prognosis. Hovewer, the wide variety of assays and cutoffs prevents drawing clear conclusions on how these associastions should change the management and the cardiac risk stratification process in CKD population.

It is necessary to mention, that not only the troponins concentrations are the acknowledged markers of prognosis in stable ESRD population. Different studies have shown that N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and bioimpendace-derived fluid status assessment are strong predictors of overall mortality in asymptomatic haemodialysis patients [63–65]. Moreover, a combined use of NT-proBNP and galectin 3 (Gal-3) may improve risk stratification for death and cardiovascular events in this population [66]. Alas, this issue goes beyond the scope of the paper.

3. Conclusions

Elevated troponins are not an isolated phenomenon among CKD patients with no signs of acute ischemia and with the advent of high-sensitivity troponin assays this finding is even more common. Stable elevation of cTn levels in this population may be caused by different, also non-ischemic conditions. Although challenging, cardiac troponins have several important diagnostic and prognostic roles in evaluating patients with CKD (Table 3). Firstly, they are still a preferred biomarker of ACS and are recommended for diagnosing AMI by consensus guidelines, even among ESRD patients. Establishing the diagnosis of MI requires repeated measurement of cTn to demonstrate temporal changes of its concentration, although the magnitude of change is currently unknown. Secondly, baseline serum cTn levels at the onset of ACS are independent predictors of short- and long-term cardiac adverse outcomes after the episode. Thirdly, baseline troponin concentration in asymptomatic patient is closely related to mortality due to cardiac causes in patients with CKD. The more the advanced renal failure is the stronger the relation between increased basal cTn level and mortality becomes. Nonetheless, there are still gaps in our knowledge. The research must forge ahead to answer such burning question as accurate cut-offs and delta values of cTn, which enable precise diagnosis of MI in patients with decreased renal function. There should also be some investigations on the influence of dialysis procedure on troponin levels. Future randomized studies should investigate if early intervention for minor, but significant, changes in cTn concentrations improves patient outcomes in the CKD population. These doubts should set the direction for future nephrocardiological research.

Conflict of interests

The authors declare no conflict of interests.

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Author contribution

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