

Važnost određivanja vrijednosti visokoosjetljivih troponina I i T u bolesnika s kroničnom bubrežnom bolesti

Significance and Measurement of High-sensitivity Troponins I and T in Patients with Chronic Kidney Disease

 Branko Lozić¹,
 Đidi Delalić¹,
 Domagoj Marković²,
 Tomo Svaguša³,
 Ingrid Prkačin^{1,4*}

¹Sveučilište u Zagrebu, Medicinski fakultet, Zagreb, Hrvatska

²Klinički bolnički centar, Split, Hrvatska

³Klinička bolnica Dubrava, Hrvatska, Croatia

⁴Klinička bolnica "Merkur", Hrvatska, Croatia

¹University of Zagreb School of Medicine, Zagreb, Croatia

²University Hospital Centre Split, Split, Croatia

³University Hospital Dubrava, Zagreb, Croatia

⁴University Hospital "Merkur", Zagreb, Croatia

RECEIVED:
February 13, 2022

ACCEPTED:
February 28, 2022



SAŽETAK: Kronična bubrežna bolest (KBB) obilježena je postupnim i progresivnim gubitkom svih bubrežnih funkcija. Petina muškaraca i četvrtina žena u dobi nakon 65 godina boluje od KBB-a. Uzimajući u obzir rastuću incidenciju dijabetesa i arterijske hipertenzije koji su glavni uzroci kroničnog gubitka bubrežne funkcije, može se zaključiti da KBB postaje globalni javnozdravstveni problem. Vodeći uzrok smrti u oboljelih od KBB-a jesu kardiovaskularne bolesti (KVB), i to ponajviše bolesti vezane uz srce poput ishemijske bolesti srca i srčanog zatajivanja. Visokoosjetljivi troponini (hs-cTnT, hs-cTnI) zlatni su standard u dijagnostici kardijalne patologije. Najčešće se rabe u detekciji akutnoga koronarnog sindroma, ali se povišene vrijednosti mogu zabilježiti u nizu drugih stanja. Poznato je da se povišene serumske vrijednosti troponina mogu zabilježiti u više od dvije trećine bolesnika s KBB-om na dijalizi, čak i u odsutnosti KVB-a. Svrha je ovoga prikaza bila ustanoviti potencijalne uzroke porasta troponina u kroničnih bubrežnih bolesnika te zaključiti postoji li veza između njihova porasta i mortalitetnih i morbiditetnih pokazatelja. Pretraživanjem literature ustanovljeno je da su bolesnici u terminalnim stadijima bubrežnog zatajenja u znatno povišenom riziku za razvoj KVB-a i smrtnoga ishoda. Istraživanja su također upozorila na snažnu povezanost između koncentracije visokoosjetljivih troponina i kardiovaskularnog, odnosno ukupnog mortaliteta u oboljelih. S druge strane, malo se zna o načinu metaboliziranja i ekskrecije troponina. Teorija prema kojoj se troponini izlučuju bubrezima postaje sve prihvaćenija unutar znanstvenih krugova. Pojedina su istraživanja, od kojih i neka hrvatska, dokazala prisutnost troponina u urinu, no potrebna su i daljnja istraživanja kako bi se ustanovilo je li moguće iskoristiti troponine u urinu kao potencijalne nove biomarkere u pravodobnom prepoznavanju KBB-a i KVB-a.

SUMMARY: Chronic kidney disease (CKD) is characterized by gradual progressive loss of all kidney functions over a period of time. One-fifth of men and one-quarter of women over the age of 65 suffer from CKD. Given the growing incidence of diabetes and hypertension, which are the main causes of this disease, CKD is becoming one of the major global public health issues. Cardiovascular diseases are the leading cause of death in people with CKD, primarily heart-related conditions such as ischemic heart disease and heart failure. High-sensitivity troponins (hs-cTnT, hs-cTnI) are crucial biomarkers used in the detection of cardiac pathology. They are mostly used in the detection of acute coronary syndrome, but elevated values can be also observed in several other conditions. Studies have shown that serum troponin levels are elevated in more than two-thirds of patients with CKD on dialysis, even in those without any cardiovascular pathology. The aim of this review was to examine the literature and to determine the reason for troponin increase in patients with CKD, and to establish whether there is a connection between their increase and the mortality rate. A literature search revealed that patients with end-stage renal disease (ESRD) are at especially high risk of cardiovascular morbidity and mortality. Studies have also found a strong association of high-sensitivity troponins with cardiovascular and all-cause mortality in those patients. On the other hand, even though the function of troponins is very well-known, little is known about their production and excretion from the body. The theory that troponins are excreted by the kidneys is becoming widely accepted in scientific circles. New studies, some of which are Croatian, have demonstrated the presence of troponins in urine, but further research is needed to determine whether it is possible to use troponins in urine as potential biomarkers for cardiovascular and kidney disease.

KLJUČNE RIJEČI: kronična bubrežna bolest, biomarkeri, troponini, mortalitet, urin.

KEYWORDS: chronic kidney disease, biomarkers, troponins, mortality, urine.

CITATION: *Cardiol Croat.* 2022;17(1-2):3-8. | <https://doi.org/10.15836/ccar2022.3>

***ADDRESS FOR CORRESPONDENCE:** Ingrid Prkačin, Klinička bolnica Merkur, Ul. I. Zajca 19, HR-10000 Zagreb, Croatia. / Phone: +385-98-406-218 / E-mail: ingrid.prkacin@gmail.com

ORCID: Branko Lozić, <https://orcid.org/0000-0002-1914-6267> • Đidi Delalić, <https://orcid.org/0000-0003-2102-2586>
Domagoj Marković, <https://orcid.org/0000-0002-9432-6882> • Tomo Svaguša, <https://orcid.org/0000-0002-2036-1239>
Ingrid Prkačin, <https://orcid.org/0000-0002-5830-7131>

TO CITE THIS ARTICLE: Lozić B, Delalić Đ, Marković D, Svaguša T, Prkačin I. Significance and Measurement of High-sensitivity Troponins I and T in Patients with Chronic Kidney Disease. *Cardiol Croat.* 2022;17(1-2):3-8. | <https://doi.org/10.15836/ccar2022.3>

TO LINK TO THIS ARTICLE: <https://doi.org/10.15836/ccar2022.3>

Srčane izoforme troponina I i T (cTnI, cTnT) zbog svoje u kardioselektivnosti najpouzdaniji biomarkeri za detekciju patoloških zbivanja kardijalnog podrijetla. Njihov se porast bilježi u različitim patološkim stanjima poput ishemijske bolesti srca, plućne embolije, miokarditisa i niza drugih stanja, što potvrđuje da su specifično povezani s oštećenjem kardiomiocita različite etiologije. U praksi se najčešće određuju u svrhu dijagnostike akutnoga koronarnog sindroma. Također, zbog dnevnog „obrtaja“ staničnih proteina kojim se stari zamjenjuju novosintetiziranim, i u krvi zdravih pojedinaca može se odrediti određena koncentracija troponina koja je vrlo niska i kreće se u rasponu od 0,1 do 0,2 ng/L.¹

Poznato je da su serumske vrijednosti troponina povišene u bolesnika s kroničnom bubrežnom bolesti (KBB) u usporedbi s općom populacijom. Navedeno je posebice izraženo u terminalnih bubrežnih bolesnika na dijalizi (ESRD).² Prema istraživanjima koja su se koristila prvom generacijom troponinskih testova, utvrđeno je da su vrijednosti cTnT-a bile povišene u do 71 % bolesnika bez kliničkih znakova akutne ishemije, dok su vrijednosti cTnI-a bile povišene u 7 % oboljelih. Prvotno je visoka koncentracija troponina opravdana snažnom križnom reaktivnošću testova prve generacije sa skeletnim izoformama troponina T i I. Razvojem troponinskih testova druge generacije u kojima je križna reaktivnost sa skeletnim izoformama smanjena na manje od 0,01 %, opovrgnute su izrazito visoke vrijednosti dobivene u prvotnim istraživanjima. U daljnjim studijama provedenima primjenom testova druge generacije, ponovno su zabilježene povišene vrijednosti troponina u bolesnika s KBB-om.³ S vremenom su testovi postali mnogo osjetljiviji pa se danas, ovisno o njihovoj osjetljivosti, govori o pet generacija troponinskih testova koji se mogu okvirno grupirati u 3 kategorije: konvencionalne, osjetljive i visokoosjetljive. Osjetljivi troponinski testovi, prema definiciji, mogu detektirati i kvantificirati troponine u 20 do 50 % zdravih pojedinaca. Visokoosjetljivi troponinski testovi (određuju hs-cTnT i hs-cTnI) mogu detektirati troponine u više od 50 % naizgled zdravih ispitanika zadržavajući koeficijent varijacije manjim od 10 % pri određivanju 99. percentile gornje granice normale (URL).⁴ Upravo je određivanje visokoosjetljivih troponina današnji dijagnostički standard. Koristeći se spomenutim testovima, istraživanja su zabilježila povišene vrijednosti hs-cTnT-a u 50 do 90 % bolesnika s ESRD-om u odnosu prema hs-cTnI koji je bio povišen u manje od 25 % oboljelih.⁵

Smatra se da bi koncentracija troponina u krvi mogla imati veliku prognostičku vrijednost u predikciji razvoja kardiovaskularnih bolesti (KVB) i smrti u oboljelih od KBB-a. Poznato je da KBB znatno povećava rizik od razvoja KVB-a te se, prema preporukama Nacionalne zaklade za bubrežne bolesti i Američkog udruženja za srce, svi bolesnici s KBB-om smatraju visokorizičnima za razvoj KVB-a.⁶ Godišnja učestalost srčanog zatajivanja u bolesnika s ESRD-om procjenjuje se između 25 i 75 %, odnosno mnogo češće nego u općoj populaciji.⁷ Tomu pridonosi i ubrzani razvoj ateroskleroze koji je potaknut općim upalnim odgovorom organizma uz dodatno volumno i tlačno preopterećenje tipično za bolesnike s KBB-om. Procjenjuje se da ESRD skraćuje očekivani životni vijek za 50 % u usporedbi s očekivanim životnim vijekom osobe iste dobi koja nema KBB.^{2,7}

Due to their cardioselectivity, cardiac troponin isoforms I and T (cTnI, cTnT) are the most reliable biomarkers for detecting pathological events of cardiac origin. They are elevated in various pathological states, such as ischemic heart disease, pulmonary embolism, myocarditis, and a number of others, which demonstrates that they are specifically associated with cardiomyocyte damage of different etiologies. In clinical practice, they are most often measured in order to diagnose acute coronary syndrome. Additionally, due to the daily turnover of cell proteins in which old proteins are replaced by those that have been newly-synthesized, a low concentration of troponin can also be observed in the blood of healthy individuals, ranging from 0.1 to 0.2 ng/L.¹

It is well-known that serum troponin levels are elevated in patients with chronic kidney disease (CKD) in comparison with the general population. This is especially pronounced in patients with end-stage renal disease (ESRD) on dialysis.² Based on studies that used the first generation of troponin tests, it was determined that cTnT levels were elevated up to 71% in patients without clinical signs of acute ischemia, while cTnI levels were elevated in 7% of patients. High troponin concentrations were initially justified by strong cross-reactivity of the first-generation troponin tests with skeletal isoforms of T and I troponins. The development of second-generation troponin tests in which cross-reactivity with skeletal isoforms was reduced to less 0.01% disproved the extremely high values observed in the initial studies. Further studies performed with second-generation tests once again found elevated troponin levels in patients with CKD.³ Over time, the tests have become significantly more sensitive, and today there are five generations of troponin tests that can be broadly classified into 3 categories: conventional, sensitive, and highly-sensitive tests. Sensitive troponin tests can, by definition, detect and quantify troponins in 20% to 50% of healthy individuals. High-sensitivity troponin tests (determining hs-cTnT i hs-cTnI) can detect troponins in more than 50% of seemingly healthy subjects, while keeping the coefficient of variation at less than 10% when determining the 99th percentile upper reference limit.⁴ It is this high-sensitivity troponin measurement that represents the current diagnostic standard. Using the tests mentioned above, studies have found elevated hs-cTnT levels in 50% to 90% of patients with ESRD in comparison with hs-cTnI, which was elevated in less than 25% of such patients.⁵

It is believed that troponin concentrations in the blood can have significant prognostic value in predicting the development of cardiovascular diseases (CVD) and deaths in patients with CKD. We know that CKD significantly increases the risk for CVD development, and, according to the recommendations of the National Kidney Foundation and the American Heart Association, all patients with CKD are considered at high risk for developing CVD.⁶ Annual incidence of heart failure in patients with ESRD is estimated at between 25% and 75%, which is significantly higher than in the general population.⁷ This is also exacerbated by the accelerated development of atherosclerosis caused by the general inflammatory response along with the additional volume and pressure overload typical for patients with CKD. It is estimated that the life expectancy of persons with ESRD is reduced by 50% in comparison with persons of the same age without CKD.^{2,7}

Povezanost troponina s ukupnim i kardiovaskularnim rizikom

TROPONIN T

S obzirom na pandemijske razmjere problema, posljednjih 20-ak godina istražuje se povezanost serumske koncentracije troponina i KV morbiditeta i mortaliteta u oboljelih od KBB-a. U jednom od prvotnih istraživanja autorâ Dierkes *i sur.*, provedenom u 102 ispitanika na dijalizi praćenih tijekom dvije godine, pokazano je da je u skupini od 12 bolesnika u kojih su zabilježene povišene koncentracije cTnT-a više od 100 ng/L bila utvrđena mnogo veća smrtnost (>80 %).⁸ U 40 bolesnika zabilježene su koncentracije cTnT-a više od 40 ng/L te je do kraja praćenja u toj skupini preminulo 18 osoba. Svi bolesnici s nedetektibilnim cTnT-om preživjeli su razdoblje praćenja od dvije godine. Zaključno, osjetljivost povišenog cTnT-a u predikciji ukupnog mortaliteta iznosila je 83 % pri koncentracijama višima od 100 ng/L, a pri koncentracijama višima od 40 ng/L iznosila je 45 %. Specifičnost testa bila je 100 %. Ukupno su 33 bolesnika oboljela od neke KVB tijekom razdoblja praćenja. Nisu zabilježene značajnije razlike u koncentracijama cTnT-a u onih koji su oboljeli od KVB-a u usporedbi s onima koji nisu.

Deegan *i sur.* tijekom petnaestomjesečnog praćenja utvrdili su smrt u 13 od 20 dijaliziranih bolesnika s koncentracijama cTnT-a >100 ng/L te u 8 od 53 bolesnika s koncentracijama <100 ng/L.⁹ Mallamaci *i sur.* navode kako su inicijalne koncentracije cTnT-a tijekom trogodišnjega praćenja bile više u preminulih s obzirom na preživjele te također među preminulima od KVB-a s obzirom na preminule od ostalih bolesti.¹⁰ U jednogodišnjem praćenju 94 bolesnika na dijalizi Stolar *i sur.* zabilježili su značajne razlike u preživljenju, pri čemu su oni s koncentracijama cTnT-a >100 ng/L imali mnogo lošije ishode.¹¹

Novija su istraživanja temeljena na određivanju hs-cTnT-a s pomoću testova četvrte i pete generacije. Hassan *i sur.* pratili su kohortu od 393 ispitanika na dijalizi tijekom jedne godine.¹² Medijan hs-cTnT-a iznosio je 57 ng/L bez značajnije razlike između bolesnika na peritonealnoj dijalizi i hemodijalizi. Porast ukupnog mortaliteta i učestalosti infarkta miokarda pratio je porast vrijednosti hs-cTnT-a. Dokazano je da je hs-cTnT neovisni prediktor ishoda (smrti odnosno fatalnog KVB-a), pri čemu je povišenje rizika bilo posebice značajno pri vrijednostima hs-cTnT-a višima od 49 ng/L.¹³

TROPONIN I

Rezultati istraživanja vezanih za cTnI mnogo su varijabilniji u usporedbi s istraživanjima s cTnT-om. Naime, pojedina istraživanja nisu zabilježila povezanost između vrijednosti cTnI-a i KV rizika u šestomjesečnom razdoblju praćenja.¹⁴ Druga istraživanja navode da su novi hs-cTnI testovi podjednako precizni u predikciji KV rizika kao i oni koji mjere hs-cTnT.¹⁵ Prema jednoj metaanalizi, lošija prediktivnost cTnI-a mogla bi biti posljedica neadekvatne standardiziranosti testova.¹⁶

Pojedini izvori navode kako bi proces hemodijalize mogao pospješivati eliminaciju cTnI-a te posljedično utjecati na njegovu postdijalizu koncentraciju i time na prediktivni potencijal.² Da bi se istražio utjecaj hemodijalize na koncentraciju troponina, provedeno je pilot-istraživanje temeljeno na mjerenju koncentracije cTnT-a i cTnI-a u dijalizatu anuričnih

The association between troponin and total and cardiovascular risk

TROPONIN T

Given the pandemic scale of the issue, the association between serum concentrations of troponin and CV morbidity and mortality in patients with CKD has been vigorously investigated over the last 20 years. In one of the initial studies conducted by Dierkes et al., 102 patients on dialysis were followed over the course of two years, and it was demonstrated that the group of 12 patients who had increased concentrations of cTnT, above 100 ng/L, had significantly higher mortality (>80%).⁸ A group of 40 patients had cTnT concentrations above 40 ng/L, and 18 persons died in this group during the study period. All patients with undetectable cTnT survived the study period of two years. In conclusion, the sensitivity of elevated cTnT for the prediction of total mortality was 83% for concentrations above 100 ng/L and 45% for concentrations above 40 ng/L. The test specificity was 100%. A total of 33 patients developed some form of CVD during the follow-up period. No significant differences in cTnT concentration were observed in those patients who developed CVD in comparison with those who did not.

Over the course of 15-month study, Deegan et al. reported deaths in 13 of 20 patients on dialysis with cTnT concentrations >100 ng/L and in 8 out of 53 patients with cTnT concentrations <100 ng/L.⁹ Mallamaci et al. reported that initial cTnT concentrations during three-year follow-up were higher in patients who died in comparison with those who survived, and were also higher in patients who died of CVD in comparison with those who died of other diseases.¹⁰ In a one-year follow-up of 94 patients on dialysis, Stolar et al. observed significant differences in survival rates, with those patients who had cTnT concentrations >100 ng/L having significantly poorer outcomes.¹¹

Newer studies are based on measuring hs-cTnT using fourth- and fifth-generation tests. Hassan et al. followed a cohort of 393 patients on dialysis for a period of one year.¹² Median hs-cTnT was 57 ng/L, with no significant difference between patients on peritoneal dialysis and those on hemodialysis. Total mortality and incidence of myocardial infarction increased along with increased hs-cTnT levels. It has been demonstrated that hs-cTnT is an independent outcome predictor (of death or fatal CVD), with an especially significant risk increase for hs-cTnT values above 49 ng/L.¹³

TROPONIN I

The results of studies conducted on cTnI are much more variable in comparison with studies on cTnT. Namely, some studies did not find an association between cTnI values and CV risk in a six-month follow-up period.¹⁴ Other studies reported that new hs-cTnI had a similar level of precision in predicting CV risk as those that measure hs-cTnT.¹⁵ According to one metaanalysis, poorer predictivity of cTnI could be a consequence of inadequate test standardization.¹⁶

Some sources state that hemodialysis could improve cTnI elimination and consequently influence its post-dialysis concentration and thus also its predictive potential.² In order to study the influence of hemodialysis on troponin concentrations, a pilot study was conducted based on measuring cTnT

bolesnika na programu kronične hemodijalize.² Medijan dobi iznosio je 70 godina. Nitko od ispitanika nije bolovao od srčanog zatajivanja. U svih se ispitanika koncentracija troponina određivala prema unaprijed određenom vremenskom obrascu. Prvi uzorak dijalizata uzimao se pola sata nakon početka dijalize, drugi nakon 120 minuta, a treći nakon 180 minuta od početka. cTnT je dokazan u svim uzorcima dijalizata, za razliku od cTnI-a koji je dokazan u 53,3%, pri čemu su koncentracije cTnT-a bile više s obzirom na cTnI. Razlike u koncentraciji troponina na kraju dijalize u odnosu prema prosječnoj koncentraciji troponina u dijalizatu nisu bile statistički značajne. Sukladno rezultatima, prvi put je dokazana prisutnost troponina T i I u dijalizatu anuričnih bolesnika na hemodijalizi.² Također je dokazano da je koncentracija troponina u dijalizatu stabilna tijekom izvođenja procesa hemodijalize. Veća koncentracija cTnT-a s obzirom na cTnI mogla bi se objasniti vezanjem cTnI-a za membranu dijalizatora.¹⁷

Metabolizam i ekskrecija troponina

Građa i sinteza troponina i troponinskog kompleksa, kao i njihova cirkulacija u krvi, dobro su poznate. No nedovoljno se zna o procesu metaboliziranja i samoj ekskreciji troponina iz organizma. Upravo bi se u načinu metaboliziranja troponina mogao potencijalno kriti razlog zbog kojega se u oboljelih od KBB-a bilježe njihove povišene vrijednosti. U istraživanju E. Michielsena utvrđena je i opisana degradacija troponina nakon ireverzibilnog oštećenja kardiomiocita.¹⁸ Lancel *i sur.* govore o degradaciji troponina unutar kardiomiocita kao posljedici djelovanja proteaza osjetljivih na stanično oštećenje.¹⁹ Druga istraživanja navode da porast unutarstaničnog kalcija za vrijeme ishemijske i rane reperfuzije miokarda dovodi do aktivacije o kalciju ovisnih proteaza poput kalpaina I i II koje potom degradiraju troponine.²⁰ Communal *i sur.* upućuju na enzimatsku razgradnju putem kaspaza u *in vitro* eksperimentima.²¹ S druge strane, pojedini izvori navode kako retikuloendotelni sustav ima ključnu ulogu u metaboliziranju troponina.²²

Bubrezi i ekskrecija troponina

Istraživanja su sve sklonija teoriji prema kojoj su bubrezi ključni organi putem kojih se troponini eliminiraju iz krvi. S obzirom na veliku molekularnu masu intaktnih troponina te kompleksa u čijem se sastavu oslobađaju u krv, malo je vjerojatno da bi se tako velike molekule izlučivale bubrezima.³ Uzimajući u obzir rezultate prethodno spomenuta istraživanja u kojemu je dokazana degradacija troponina u manje fragmente, može se pretpostaviti da bi takvi mnogo manji degradacijski produkti mogli biti podložni izlučivanju putem bubrega.¹⁸ Pervan *i sur.* odredili su preliminarni referentni interval za visokoosjetljivi troponin I (hs-cTnI) u urinu zdravih ispitanika.¹ Uzorak je činilo 60 zdravih ispitanika (30 muškaraca i 30 žena) koji su odabrani prema sljedećim kriterijima: nepušači u dobi od 25 do 65 godina, indeks tjelesne mase <30 kg/m², odsutnost akutnih i kroničnih bolesti te izostanak teške tjelesne aktivnosti unatrag 7 dana i noćnog rada unatrag 30 noći od trenutka uzorkovanja. Istraživanjem je dokazana prisutnost troponina I u urinu te je određena preliminarna 99. percentila URL-a uzorkovane skupine koja se smatra referentnom. Ta je vrijednost za muškarce iznosila 39,3 ng/L, a za žene 35,2 ng/L. Time je potvrđena pretpostavka da se troponini u zdra-

and cTnI concentrations in the dialysate of patients with anuria participating in a chronic hemodialysis program.² The median age in the study was 70 years. None of the participants suffered from heart failure. Troponin concentrations in all participants were measured according to a previously determined schedule. The first dialysate sample was taken half an hour after the start of the dialysis procedure, the second after 120 minutes, and the third after 180 minutes from the beginning of the procedure. cTnT was found in all dialysate samples, as opposed to cTnI, which was found in 53.3%, with higher cTnT concentrations in comparison with cTnI. The differences in troponin concentrations at the end of dialysis in comparison with average troponin T and I concentrations in the dialysate were not statistically significant. These results represent the first demonstration of the presence of troponins T and I in the dialysate of patients with anuria on hemodialysis.² Additionally, it was demonstrated that the concentration of troponin in the dialysate was stable during hemodialysis. The higher concentration of cTnT in comparison with cTnI might be explained by the binding of cTnI to the dialysis membrane.¹⁷

Metabolism and excretion of troponin

The structure and synthesis of troponins and the troponin complex as well as their circulation in the blood is well-established. However, not enough is known on the metabolism and excretion of troponin from the body. Troponin metabolism could potentially be the reason for higher troponin values in patients with CKD. A study by E. Michielsen found and described the degradation of troponins after irreversible cardiomyocyte damage.¹⁸ Lancel et al. described the degradation of troponins within cardiomyocytes as a consequence of the action of proteases sensitive to cellular damage.¹⁹ Other studies have claimed that the increase in intracellular calcium during ischemia and early myocardial reperfusion leads to the activation of calcium-dependent proteases such as calpain I and II, which subsequently degrade troponins.²⁰ Communal et al. pointed to enzymatic troponin degradation by caspase *in vitro*.²¹ On the other hand, some sources have claimed that the reticuloendothelial system plays a key role in troponin metabolism.²²

The kidneys and troponin excretion

Studies have been increasingly leaning towards the theory that the kidneys are the crucial organ for the elimination of troponin from the blood. Given the large molecular mass of intact troponins and the complexes in which they are released into the blood, it is unlikely that such large molecules would be excreted via the kidneys.³ Based on the results of the abovementioned studies that demonstrated degradation of troponin into smaller fragments, it can be assumed that such significantly smaller products of degradation could be susceptible to excretion via the kidneys.¹⁸ Pervan et al. determined the preliminary reference intervals for high-sensitivity troponin I (hs-cTnI) in the urine of healthy subjects.¹ The sample comprised 60 healthy subjects (30 men and 30 women) who were selected according to the following criteria: non-smokers between the ages of 25 and 65, body-mass index <30 kg/m², absence of acute and chronic diseases, and absence of strenuous physical activity in the previous 7 days and night

vih ljudi, barem jednim dijelom, izlučuju bubrežima.¹ U prilog teoriji da se troponini izlučuju putem bubrega ide i činjenica da bolesnici s ESRD-om imaju povišene koncentracije troponina čak i bez suspektne KV patologije, kao i djeca na dijalizi.^{2,23} Stoga je u dijagnostici ishemijske bolesti srca u takvih bolesnika važno obratiti pažnju na kliničku sliku i dinamiku troponina tijekom vremena kako se ne bi pribjegavalo pogrešnom dijagnostičiranju akutnoga koronarnog sindroma (AKS). Fridén *i sur.* utvrdili su na životinjskom modelu (štakor) da se cTnT pri niskim i stabilnim koncentracijama u krvi pojačano izlučuje bubrežima, dok pri izrazitom povišenju koncentracije (npr. nakon infarkta miokarda) dominiraju ekstrarenalni putevi metaboliziranja.²⁴ Time bi se moglo objasniti zašto se koncentracija troponina povećava u krvi bolesnika s oslabljenom bubrežnom funkcijom u fazi kada se u njih još nije razvila AKS ili neka druga KV patologija. U istraživanju Ziebiga *i sur.* dobiveni su podaci o eliminaciji troponina urinom, u kojima se može uočiti podudarnost s teorijom V. Fridéna, prema kojoj se način metaboliziranja troponina razlikuje ovisno o njihovoj koncentraciji u krvi.²⁵

Marute *i sur.* dokazali su prisutnost hs-cTnI-a u urinu ispitanika s oštećenjem miokarda.²⁶ Za ispitanike su izabrani bolesnici s akutnim infarktom miokarda bez elevacije ST-segmenta (NSTEMI) te bolesnici podvrgnuti invazivnim kardiološkim zahvatima. Rezultati su pokazali da su plazmatske vrijednosti hs-cTnI bile znatno povišene u bolesnika s NSTEMI-jem, kao i u onih podvrgnutih invazivnim postupcima, u usporedbi sa zdravim kontrolama. Također u usporedbi sa zdravim kontrolama, ispitanici su imali i znatno povišene vrijednosti hs-cTnI-a u urinu, uz napomenu da su dobivene koncentracije bile 1000 do 10 000 puta od plazmatskih.

Poseban je osvrt potreban u populaciji s dijabetesom koja također poprima pandemijske razmjere, a koji čine većinu bolesnika u ESRD-om, pa je potrebno sustavno razumjeti složenu situaciju povezanosti više organskih sustava, a posebno utjecaja HbA1c i troponina na konačan ishod.

Zaključak

Uzimajući u obzir globalno starenje populacije i kontinuirani porast incidencije kroničnih nezaraznih bolesti, poput arterijske hipertenzije i dijabetesa, očekivan je pandemijski problem povećanja udjela oboljelih od KBB-a u svakodnevnoj kliničkoj praksi. Iako je uvriježeno mišljenje da bolesnici u terminalnim stadijima bubrežne bolesti na dijalizi umiru zbog bubrežne bolesti, stvarnost je drukčija. Istraživanja jasno upućuju na to da su KVB vodeći uzrok smrti u oboljelih od KBB-a, a posebice ESRD-a. U većini slučajeva riječ je iznenadnoj srčanoj smrti u podlozi ishemijske bolesti srca te o srčanom zatajivanju. Nerijetko se viđaju moždani udar i periferna arterijska bolest. Nepobitna je činjenica da su vrijednosti visokoosjetljivih troponina povišene u bolesnika s KBB-om i ESRD-om te da su u izravnoj korelaciji s kardiovaskularnim i ukupnim mortalitetom, odnosno povišenim rizikom od smrtnog ishoda.

shit work in the past 30 days from the time the sample was collected. The study demonstrated the presence of troponin I in urine, and a preliminary 99th percentile upper reference limit of the sampled group was determined. This value was 39.3 ng/L for men and 35.2 ng/L for women. This confirms the hypothesis that troponins are, at least in part, excreted via the kidneys in healthy individuals.¹ The theory that troponin is excreted via the kidneys is also supported by the fact that patients with ESRD have elevated troponin concentrations even without suspected CV pathology, as do children on dialysis.^{2,23} It is thus important that diagnosis of ischemic heart disease in such patients include considering the clinical picture and dynamics of troponin over time, to avoid misdiagnosis of acute coronary syndrome (ACS). Fridén *et al.* used an animal model (rats) to determine that cTnT secretion via the kidneys is increased at low and stable concentrations in the blood, but when the concentration of cTnT is extremely elevated (for instance after myocardial infarction), extrarenal metabolism pathways become dominant.²⁴ This could explain why troponin concentration is elevated in the blood of patients with weakened renal function in the phase when they have not yet developed ACS or some other CV disease. The study by Ziebig *et al.* provided data on the elimination of troponin through urine that seem to corroborate the theory of V. Fridén, according to which troponin metabolism changes depending on the concentration in the blood.²⁵

Marute *et al.* demonstrated the presence of hs-cTnI in the urine of patients with myocardial damage.²⁶ Study participants were selected among patients with non-ST-elevation myocardial infarction (NSTEMI) and patients subjected to invasive cardiological procedures. The results showed that plasma hs-cTnI levels were significantly elevated in patients with NSTEMI and in those who underwent invasive procedures in comparison with healthy controls. In comparison with healthy controls, study subjects also had significantly elevated urine hs-cTnI values, with these values being 1000 to 10 000 times lower in comparison with plasma levels.

The population of patients with diabetes, which is also reaching a pandemic scale, deserves special attention, as these patients comprise the majority of patients with ESRD, and it is thus necessary to systematically examine this complex interconnectedness of multiple organ systems, especially the influence of HbA1c and troponin on final outcomes.

Conclusion

Given the global aging of the population and the continuously increasing incidence of chronic non-infectious diseases such as arterial hypertension and diabetes, we can expect a pandemic-level issue of increasing prevalence of CKD in everyday clinical practice. Although it is widely believed that patients in the end stages of kidney disease who are on dialysis die of kidney disease, the reality is different. Studies have clearly shown that CVDs are the leading cause of death in patients with CKD, especially those with ESRD. In most cases, these are sudden cardiac deaths with underlying ischemic heart disease and heart failure. Stroke and peripheral arterial disease are also common. It is indubitable that high-sensitivity troponin levels are elevated in patients with CKD and ESRD and that they are directly correlated with cardiovascular and total mortality, and thus with increased risk of a fatal outcome.

LITERATURE

- Pervan P, Svaguša T, Prkačin I, Vuković J, Radeljak A, Perkov S. Urine concentrations of high-sensitivity cardiac troponin I in healthy adults - preliminary reference intervals. *Acta Medica Croatica* 2018;72(4):461-465. <https://hrcak.srce.hr/216412>
- Prkačin I, Jureković Ž, Perkov S, Savuk A, Pikivaca T, Golub A et al. High sensitive troponin concentration stability in dialysate of anuric patients on hemodialysis. *Signa Vitae*. 2018; 14(Suppl 1):35-38. <https://hrcak.srce.hr/195361>
- Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol*. 2002;40(12):2065-2071. [https://doi.org/10.1016/S0735-1097\(02\)02608-6](https://doi.org/10.1016/S0735-1097(02)02608-6)
- Holzmann MJ. Clinical implications of high-sensitivity cardiac troponins. *J Intern Med*. 201 8;284(1):50-60. <https://doi.org/10.1111/joim.12779>
- Sandoval Y, Herzog CA, Love SA, Cao J, Hu Y, Wu AHB, et al. Prognostic Value of Serial Changes in High-Sensitivity Cardiac Troponin I and T over 3 Months Using Reference Change Values in Hemodialysis Patients. *Clin Chem*. 2016;62(4):631-638. <https://doi.org/10.1373/clinchem.2015.251835>
- Ivošević A, Jakopović MM, Stanković M, Prkačin I. MicroRNA in Chronic Kidney Disease and Heart Failure. *Cardiol Croat*. 2018;13(9-10):270-6. <https://doi.org/10.15836/ccar2018.270>
- Maruta T, Li T, Morrissey J, Blood J, Macy E, Bach R et al. Urinary cardiac troponin i is detectable in patients with myocardial injury using a high-sensitive immunoassay: *Critical Care Med*.2012;40(12):1-328. <https://doi.org/10.1097/01.ccm.0000424470.26633.42>
- Dierkes J, Domröse U, Westphal S, Ambrosch A, Bosselmann HP, Neumann KH, et al. Cardiac troponin T predicts mortality in patients with end-stage renal disease. *Circulation*. 2000;102(16):1964-1969. <https://doi.org/10.1161/01.CIR.102.16.1964>
- Deegan PB, Lafferty ME, Blumsohn A, Henderson IS, McGregor E. Prognostic value of troponin T in haemodialysis patients is independent of co-morbidity. *Kidney Int*. 2001;60: 2399-2405. <https://doi.org/10.1046/j.1523-1755.2001.00076.x>
- Mallamaci F, Zoccali C, Parlongo S, Tripepi G, Benedetto FA, Cutrupi S, et al. Troponin is related to left ventricular mass and predicts all-cause cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis*. 2002;40:68-75. <https://doi.org/10.1053/ajkd.2002.33914>
- Stolar JC, Georges B, Shita A, Verbeelen D. The predictive value of cardiac troponin T measurements in subjects on regular haemodialysis. *Nephrol Dial Transplant*. 1999;14:1961-1967. <https://doi.org/10.1093/ndt/14.8.1961>
- Hassan HC, Howlin K, Jefferys A, Spicer ST, Aravindan AN, Suryanarayanan G, et al. High-Sensitivity Troponin as a Predictor of Cardiac Events and Mortality in the Stable Dialysis Population. *Clin Chem*. 2014;60(2):389-398. <https://doi.org/10.1373/clinchem.2013.207142>
- Chen T, Hassan HC, Qian P, Vu M, Makris A. High-Sensitivity Troponin T and C-Reactive Protein Have Different Prognostic Values in Hemo- and Peritoneal Dialysis Populations: A Cohort Study. *J Am Heart Assoc*. 2018 Feb 24;7(5):e007876 <https://doi.org/10.1161/JAHA.117.007876>
- Peetz D, Schütt S, Sucké B, Faldum A, Wandel E, Hafner G, et al. Prognostic Value of Troponin T, Troponin I, and CK-MBmass in Patients with Chronic Renal Failure. *Med Klin*. 2003;98(4):188-192. <https://doi.org/10.1007/s00063-003-1243-3>
- Wildi K, Twerenbold R, Mueller C. How acute changes in cardiac troponin concentrations help to handle the challenges posed by troponin elevations in non-ACS-patients. *Clin Biochem*. 2015 Mar;48(4-5):218-22. <https://doi.org/10.1016/j.clinbiochem.2014.09.003>
- Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. *Circulation*. 2005;112(20):3088-3096. <https://doi.org/10.1161/CIRCULATIONAHA.105.560128>
- 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(1):e000108. <https://doi.org/10.1136/openhrt-2014-000108>
- Michielsen, E. C. H. J. Implications of cardiac troponin T degradation. *Maastricht: Universitaire Pers Maastricht*; 2008;1-123. <https://doi.org/10.26481/dis.20080229em>
- Lancel S, Joulin O, Favory R, Goossens JF, Kluza J, Chopin C, et al. Ventricular myocyte caspases are directly responsible for endotoxin-induced cardiac dysfunction. *Circulation*. 2005 May 24;111(20):2596-604. <https://doi.org/10.1161/CIRCULATIONAHA.104.490979>
- Atsma DE, Bastiaanse EM, Jerzewski A, Van der Valk LJ, Van der Laarse A. Role of calcium-activated neutral protease (calpain) in cell death in cultured neonatal rat cardiomyocytes during metabolic inhibition. *Circ Res*. 1995 Jun;76(6):1071-8. <https://doi.org/10.1161/01.RES.76.6.1071>
- Communal C, Sumandea M, Tombe P de, Narula J, Solaro RJ, Hajjar RJ. Functional consequences of caspase activation in cardiac myocytes. *Proc Natl Acad Sci* 2002; 99(9):6252-6256. <https://doi.org/10.1073/pnas.092022999>
- Tarapan T, Musikatavorn K, Phairatwet P, Takkavatakarn K, Susantitaphong P, Eiam-Ong S, et al. High Sensitivity Troponin-I Levels in Asymptomatic Hemodialysis Patients. *Renal Failure* 2019;41:393-400. <https://doi.org/10.1080/0886022X.2019.1603110>
- Mohamed H, Youssef M, Abdel.Salam M, Mohammed SA. The Influence of Regular Hemodialysis on the Highly Sensitive Troponin-I Level in Children without Any Symptoms. *Open Journal of Nephrology* 2021; 11: 183-198. <https://doi.org/10.4236/ojneph.2021.112015>
- Fridén V, Starnberg K, Muslimovic A, Ricksten SE, Bjurman C, Forsgard N, et al. Clearance of cardiac troponin T with and without kidney function. *Clin Biochem*. 2017;50 (9):468-474. <https://doi.org/10.1016/j.clinbiochem.2017.02.007>
- Ziebig R, Lun A, Hocher B, Priem F, Altermann C, Asmus G, et al. Renal elimination of troponin T and troponin I. *Clin Chem*. 2003 Jul;49(7):1191-3. <https://doi.org/10.1373/49.7.1191>
- Šimić S, Svaguša T, Prkačin I, Bulum T. Relationship between hemoglobin A1c and serum troponin in patients with diabetes and cardiovascular events. *J Diabetes Metab Disord*. 2019 Nov 11;18(2):693-704. <https://doi.org/10.1007/s40200-019-00460-9>