

Vrednovanje D-dimer testa kod pacijenata na kroničnoj hemodijalizi

Evaluation of D-dimer test in patients on chronic hemodialysis

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SAŽETAK: Određivanje vrijednosti D-dimera rutinska je pretraga kod sumnje na tromboembolički incident. Kod pacijenata na kroničnoj dijalizi bazične koncentracije biomarkera u čestoj kliničkoj uporabi su izmjenjene što nas je navelo na mjerenje koncentracije D-dimera, zbog poremećaja hemostaze u kroničnom bubrežnom zatajenju. Evaluacijom nalaza D-dimera kod 67 pacijenata, kao i u dostupnoj literaturi, može se zaključiti da je vrijednost testa u dijagnozi tromboemboličkih incidenata znatno smanjena.

KLJUČNE RIJEČI: D-dimeri, terminalno bubrežno zatajenje, hemodijaliza.

SUMMARY: Determining the value of D-Dimer is a routine test in case of suspecting thromboembolic event. In patients on chronic dialysis, baseline concentrations for biomarkers have changed in widespread clinical use, which prompted us to measure the concentration of D-dimer, due to disorders of hemostasis in chronic kidney failure. From the evaluation of the findings of D-dimer in 67 patients and the available literature we can conclude that the value of the test in the diagnosis of thromboembolic events has significantly decreased.

KEYWORDS: D-dimer, end stage renal disease, hemodialysis.

CITATION: *Cardiol Croat.* 2013;8(7-8):254-257.

Uvod

Prema rezultatima Hrvatskog registrira nadomještanja bubrežne funkcije u 2011. godini incidencija nadomještanja bubrežne funkcije iznosila 119,3, a prevalencija je iznosila 980 bolesnika na milijun stanovnika. Međimurska županija, prema popisu stanovništva iz 2011. godine broji 114.414 stanovnika od kojih je njih 70-75 na programu kronične hemodijalize posljednjih nekoliko godina.

Kronično bubrežno zatajenje (KBZ) ima za posljedicu promjene u koncentraciji biomarkera koji se koriste u rutinskim dijagnostičkim procedurama kardiovaskularnih bolesti^{1,2}. Primjerice, poznato je da se kod ovih bolesnika susreće nivo troponina T bazično viši od referentnih vrijednosti.

Važnost D-dimer testa je u njegovoj negativnoj prediktivnoj vrijednosti za razvoj tromboze te se rutinski koristi za isključivanje duboke venske tromboze i plućne embolije^{3,4}. Vrijednosti D-dimera mogu biti povišene u različitim netrombotičkim poremećajima: kod inflamatornih bolesti, u bolestima jetre, postoperativno, u eklampsiji, krizama bolesti srpastih stanica. Bolesnici s malignitetom često imaju povišene vrijednosti D-dimera, a umjereno su fiziološki povišeni i za vrijeme trudnoće, kao i u starijoj dobi.

Smanjena aktivnost von Willebrandova čimbenika uvjetuje sniženu interakciju trombocita s endotelom krvnih žila uz

Introduction

According to the Croatian Registry for Renal Replacement Therapy in 2011, the incidence of renal replacement therapy was 119.3, while the prevalence was 980 patients per million of inhabitants. According to the 2011 population census, the Međimurje County has 114,414 inhabitants of whom 70-75 have been involved in the chronic hemodialysis program in the last few years.

Chronic renal failure (CRF) results in changes of the concentration of biomarkers used in routine diagnostic procedures of cardiovascular diseases^{1,2}. For example, it is known that in these patients we can observe the level of troponin T basically higher than the reference values.

The importance of D-dimer test lies in its negative predictive value for the development of thrombosis and is routinely used to exclude deep venous thrombosis and pulmonary embolism^{3,4}. The values of D-dimer can be elevated in different non-thrombotic disorders: in inflammatory diseases, liver diseases, postoperatively, in eclampsia, sickle cell disease crises. The patients with malignancy usually have elevated levels of D-dimer, which are moderately physiologically elevated even during pregnancy and in old age as well.

The decreased activity of von Willebrand factor causes reduced interaction of platelets with the endothelium of blood

smanjenu adhezivnu i agregacijsku sposobnost. U bolesti ma bubrega s razvojem nefrotskog sindroma raste sinteza fibrinogena uz gubitak antitrombina III⁵⁻⁷.

Svrha ovog istraživanja bilo je mjerenje bazične koncentracije vrijednosti D-dimera kod pacijenata na kroničnoj dijalizi zbog poremećaja hemostaze u bolesnika s KBZ. Zanimalo nas je da li KBZ ima utjecaja na vrijednosti D-dimer testa jer su D-dimeri raspadni produkt fibrina koji u sebi sadržava poprečnu vezu nastalu djelovanjem FXIII na fibrinske niti prilikom nastajanja ugruška.

Pacijenti i metode

Odabrani su pacijenti Djelatnosti za hemodijalizu Županijske bolnice Čakovec s uredno funkcionirajućom nativnom arteriovenskom fistulom, bez kliničkih znakova tromboze ili infekcije u posljednjih šest mjeseci te bez antikogulantne terapije u vandijalitičkom periodu. U studiju nisu bili uključeni pacijenti s trajnim ili privremenim endovenskim kateterom te pacijenti s umjetnom fistulom — graftom.

Uzorci su prikupljeni tijekom 2 mjeseca kod uzastopnih pacijenata bez isključnih kriterija tijekom redovnih termina dijalize. Krv je vađena prije samog postupka dijalize u smislu izbjegavanja heparinizacije. Uzorci krvi su izvađeni vacutainerom u 2,7 mL epruvetu s 3,2% natrij-citratom. Nakon zaprimanja, uzorci su centrifugirani na 1.500 g tijekom 15 minuta. Samo izvođenje testa na analizatoru traje oko 5 minuta. Svi uzorci su obrađeni u maksimalnom vremenu od 60 minuta od zaprimanja^{8,9}.

D-dimeri su mjereni na BCS automatskom analizatoru pomoću D-Dimer Innovance testa (Siemens Healthcare Diagnostics). Princip testa je imunoturbidimetrijska metoda, pri čemu se na dva epitopa D-dimer produkta vežu 8D3 monoklonalna protutijela te nastaje agregacija koja se očituje povišenom adsorbancijom, koja omogućuje izračunavanje kvantitativnih vrijednosti. Vrijednosti D-dimer testa izražavaju se kao $\mu\text{g/L}$ FEU (Fibrinogen equivalent unit). Prema specifikacijama D-dimer Innovance testa cut-off iznosi 500 $\mu\text{g/L}$ FEU. Specifičnost testa je 35,8-38,2%, osjetljivost 98,0-99,4%, a negativna prediktivna vrijednost 98,6-99,5%. Ovaj test je trenutno u širokoj rutinskoj uporabi.

Kod 52 pacijenata je učinjena transtorakalna ehokardiografija (CV 70 Siemens) prema standardnom protokolu. Kao kriterij koncentrične hipertrofije lijeve klijetke uzet je indeks mase lijeve klijetke $>131\text{g/m}^2$ za muškarce i $>100\text{g/m}^2$ za žene. Ejekcijska frakcija lijeve klijetke (EF) mjerena je metodom po Teicholtzu i Simpsonu.

Rezultati

Mjerene su bazične vrijednosti D-dimera kod 67 pacijenata (37 žena i 30 muškaraca) na kroničnoj dijalizi u dobi od 17 do 80 godina (medijan 66 godina) i duljinom liječenja dijalizom od 3 do 216 mjeseci (medijan 94 mjeseca). Na terapiji sredstvima koja stimuliraju eritropezu su bila 42 pacijenta s prosječnim vrijednostima hemoglobina od 108 g/L.

U 68,3% pacijenata bazične koncentracije D-dimera su bile dvostruko i više iznad gornje granice normalne vrijednosti. Rezultati testa su bili u referentnim granicama za normalu kod 31,6% pacijenata (**slika 1**). Pratili smo povezanost rezultata s dobi i spolom pacijenata, vremenom provedenom na liječenju dijalizom, no nismo našli povezanost dobi, spola kao ni utjecaj duljine liječenja dijalizom s dobivenim rezultatima.

vessels with reduced adhesive and aggregation capability. Fibrinogen synthesis accompanied by antithrombin III deficiency rises in kidney diseases with the development of nephrotic syndrome⁵⁻⁷.

The purpose of this study was to measure the baseline concentrations of D-dimer in patients on chronic dialysis due to disorders of hemostasis in patients with CRF. We wondered whether CRF impacts the value of the D-dimer test because the D-dimers are the fibrin degradation products containing the transverse link created as a result of FXIII action on fibrin threads at the time of clot formation.

Patients and methods

The patients of the Hemodialysis Department of the Čakovec County Hospital with normally functioning native arteriovenous fistula without clinical manifestations of thrombosis or infection in the last six months' period and without anticoagulant therapy during the period when they were not subject to hemodialysis were selected. Patients with permanent or temporary endovenous catheter and patients with artificial fistula — graft were not included in the study.

Samples were collected during the two months' period with consecutive patients without excluded criteria during the regular terms of dialysis. Blood was taken prior to the procedure of dialysis for the purpose of avoiding heparinization. Blood samples were taken by Vacutainer in 2.7 mL tube with 3.2% sodium citrate. Upon the receipt, the samples were centrifuged at 1,500 g in 15 minutes. Performing the test on the analyzer takes about 5 minutes. All samples were processed in a maximum time of 60 minutes from the receipt^{8,9}.

D-dimers were measured in the BCS automatic analyzer by using the Innovance D-Dimer assay (Siemens Healthcare Diagnostics). The principle of the test is the immunoturbidimetric method, whereas 8D3 monoclonal antibodies are bonded to the two epitopes of the D-dimer product to form the aggregation manifested as elevated adsorbency, which allows the calculation of the quantitative values. The values of D-dimer test are expressed as $\mu\text{g/L}$ FEU (Fibrinogen equivalent unit). According to the specifications of the D-dimer Innovance test cut-off is 500 $\mu\text{g/L}$ FEU. The specificity of the test is 35.8-38.2%, sensitivity 98.0-99.4%, while the negative predictive value is 98.6-99.5%. This test is currently widely routinely used.

Transthoracic echocardiography (CV 70 Siemens) was performed in 52 patients according to standard protocol. Left ventricular mass index $>131\text{g/m}^2$ for men and $>100\text{g/m}^2$ for women was taken as a criterion of concentric left ventricular hypertrophy. Left ventricular ejection fraction (EF) was measured by Teicholtz method and Simpson method.

Results

Baseline values of D-dimer were measured in 67 patients (37 women and 30 men) on chronic dialysis at the age from 17 to 80 years (median 66 years) and the length of dialysis treatment from 3 to 216 months (median 94 months). 42 patients with average hemoglobin values of 108 g/L were on the therapy by agents that stimulate erythropoiesis.

In 68.3% of patients the baseline D-dimer concentrations were twice or more above the upper limit of the normal value. The test results were within normal reference limits in 31.6% of patients (**Figure 1**). We followed-up how the results are related to the patients' age and sex, the time spent on dialysis treatment, but we found no relation between the

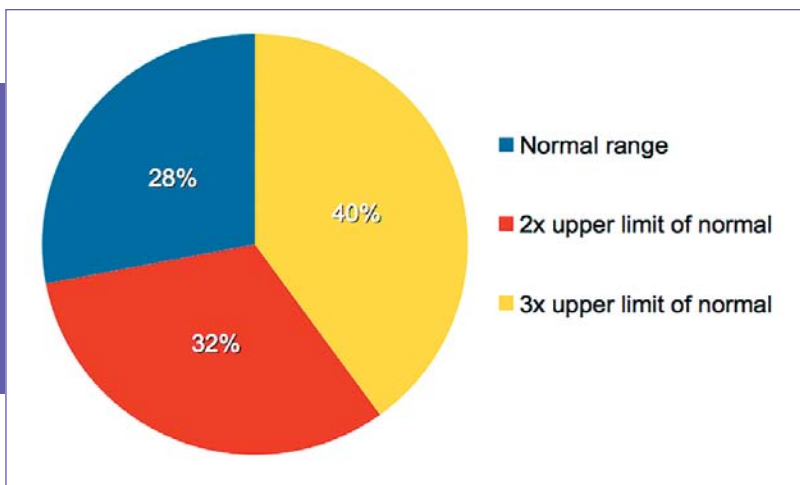


Figure 1.
Distribution of the D-dimer test results.

Na ehokardiografskom pregledu kod 72,7% nađena hipertrofija lijeve kljetke, a srednja vrijednost ejectiveske frakcije iznosila je $53.9\% \pm 12\%$. Kod jednog je ispitanika nađen manji perikardijalni izljev, bez hemodinamskih reperkusija. Intrakavitarna tvrbe nisu zabilježene.

Diskusija i zaključak

Relativno velika prevalencija pacijenata sa smanjenom bubrežnom funkcijom (oko 11%) zabilježena u epidemiološkim istraživanjima, s ukupnom prevalencijom trećeg, četvrtog i petog stupnja (glomerularna filtracija manja od 59 do <15 ml/min/ 1.73 m²) od 8,5% daje ovoj skupini pacijenata sve veći značaj i specijalizacijama izvan područja nefrologije, a osobito dijabetozima i kardiolozima.

Kronična bubrežna bolest je usko povezana s kardiološkim bolestima, pa je ovaj komorbiditet njihov najčešći uzrok i posljedica. Od ranije je iz literature poznata činjenica da su kod bolesnika na hemodijalizi prisutne višestruke abnormalnosti koagulacijskog sustava, dominantno kao posljedica endotelne disfunkcije, kao i da su povišene vrijednosti D-dimera neovisan prediktor prevalencije ishemijske bolesti srca¹⁰⁻¹³.

D-dimeri su odraz prokoagulantnog stanja kod pacijenata s kroničnom bubrežnom insuficijencijom te se povišene vrijednosti kod pojedinih pacijenata na dijalizi bez simptoma tromboemboličkog zbivanja, koje su utvrdili rezultati ovog istraživanja, mogu smatrati njihovim bazičnim vrijednostima.

Kod pacijenata na kroničnoj hemodijalizi vrijednost D-dimer testa u dijagnozi tromboemboličkih incidenata je značajno smanjena, no pretragu je potrebno provoditi te pratiti dinamiku nalaza i u ovoj specifičnoj populaciji, a nalaze tumačiti "cum grano salis".

Received: 3rd Mar 2013; Updated 10th May 2013

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age, sex or the influence of the dialysis treatment to the results obtained.

Left ventricular hypertrophy was found by echocardiography in 72.7% of patients, while the mean ejection fraction value was $53.9 \pm 12\%$. A small pericardial effusion was found in one of the patients without hemodynamic repercussions. Intracavitary formations were not recorded.

Discussion and Conclusion

The relatively high prevalence of patients with reduced renal function (11%) observed in epidemiological studies, with an overall prevalence of the third, fourth and fifth stage (glomerular filtration rate lower than 59 to 15 ml/min/ 1.73 m²) of 8.5% makes this group of patients increasingly important including the specializations which are not nephrology, especially diabetologists and cardiologists.

Chronic renal disease is closely associated with heart diseases, so this comorbidity is their common cause and consequence. There is a fact that has been known from the literature for some time, that multiple abnormalities of the coagulation system are present in patients undergoing hemodialysis, predominantly as a result of endothelial dysfunction, and that the elevated levels of the D-dimer are an independent predictor of the prevalence of ischemic heart disease¹⁰⁻¹³.

D-dimers are the reflection of procoagulant condition in patients with chronic renal insufficiency and the elevated values in some patients on dialysis without symptoms of thromboembolic events as determined by the results of this study can be considered to be their baseline values.

In patients on chronic hemodialysis, the value of the D-dimer test in the diagnosis of thromboembolic events has reduced significantly, but the test needs to be performed and it is necessary to follow up the dynamics of the results in this specific population as well. The results need to be interpreted according to the principle "cum grano salis — grain of salt".

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