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Kronična bubrežna insuficijencija — kardiovaskularni čimbenik rizika

Chronic renal failure — cardiovascular risk factor

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SAŽETAK: *Kardiovaskularne bolesti predstavljaju glavni uzrok morbiditeta i mortaliteta u bolesnika s terminalnim stupnjem kroničnog bubrežnog zatajenja koji se liječe dijalizom. Hipertrofija lijeve klijetke, koronarna bolest srca i srčana insuficijencija su najučestalije kardiovaskularne bolesti u dijaliznih bolesnika. U bolesti dijaliznih bolesnika 10-20 puta je veći rizik razvoja kardiovaskularnih bolesti u odnosu na opću populaciju. Cilj ovog rada bio je utvrditi učestalost čimbenika rizika (tradicionalnih i netradicionalnih) za nastanak kardiovaskularnih bolesti u pacijenata na kroničnom programu dijalize. Najučestaliji tradicionalni čimbenici u ovom istraživanju bili su hipertenzija (62%) i hiperlipidemija (60%), a od netradicionalnih anemija (86%) i hiperhomocisteinemija (82%). Bolesnici na kroničnom programu dijalize trebali bi, obzirom na visoku učestalost čimbenika rizika, biti optimalna ciljna populacija za primarnu prevenciju.*

KLJUČNE RIJEČI: *kardiovaskularni morbiditet, kardiovaskularni mortalitet, dijaliza, čimbenici rizika.*

SUMMARY: *Cardiovascular diseases are a major cause of morbidity and mortality in patients at the end stage of renal disease. Left ventricular hypertrophy, coronary heart disease and heart failure are the most prevalent cardiovascular diseases in dialysis patients. The patients on chronic dialysis have a 10 to 20-fold higher risk of development of cardiovascular disease than the general population. The aim of this article was to define the frequency of risk factors (traditional and non-traditional) for cardiovascular diseases in dialysis patients. The most frequent traditional factors in this study were hypertension (62%) and hyperlipidemia (60%), while anemia (86%) and hyperhomocysteinemia (82%) were the most frequent non-traditional factors. To present the study and repeat again that dialysis patients have high risk of development of cardiovascular disease and this population should be an ideal target group for primary prevention.*

KEYWORDS: *cardiovascular morbidity, cardiovascular mortality, dialysis, risk factors.*

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Kardiovaskularne bolesti predstavljaju najčešći uzrok morbiditeta i mortaliteta u bolesnika s terminalnim stupnjem bubrežne insuficijencije[1]. Hipertrofija lijeve klijetke (HLK) javlja se u 75% bolesnika liječenih kroničnom dijalizom. Prevalencija koronarne bolesti srca (KBS) u bolesnika koji se liječe kroničnom hemodijalizom iznosi 40%. Učestalost kongestivne srčane insuficijencije u bolesnika na hemodijalizi iznosi 46%. Bolesti srca predstavljaju vodeći uzrok smrti dijaliznih bolesnika, od čega je najčešća iznenadna srčana smrt koja je odgovorna za oko 25% svih smrtnih ishoda. Stopa kardiovaskularnog mortaliteta u bolesnika na dijalizi iznosi približno 9% godišnje[2].

U bolesnika liječenih kroničnom dijalizom 10 do 20 puta je veći rizik razvoja kardiovaskularnih bolesti u odnosu na opću populaciju[3]. Uremijski milje pogoduje nastanku ateroskleroze i aterosklerotskih kardiovaskularnih komplikacija, a često je prisutan i razvoj ubrzane, galopirajuće ateroskleroze[4].

Bolesnici na kroničnoj dijalizi izloženi su tradicionalnim i netradicionalnim čimbenicima rizika za razvoj kardiovaskularnih komplikacija[5]. Tradicionalni čimbenici rizika mogu biti nepreinačivi (dob, spol, nasljeđe) i preinačivi (pušenje cigareta, hiperlipidemija, hipertenzija, pretilost, dijabetes, nedovoljna tjelesna aktivnost, stres). Netradicionalni čimbenici rizika posljedica su uremijskog miljea

Cardiovascular diseases (CVD) represent the most frequent cause of morbidity and mortality in patients at the end stage of renal diseases (ESRD)[1]. Left ventricle hypertrophy (LVH) occurs in 75% of patients treated by chronic dialysis. The prevalence of coronary heart disease (CHD) in patients who are treated by chronic hemodialysis is 40%. The frequency of congestive heart failure in patients undergoing hemodialysis is 46%. Cardiac diseases represent the leading cause of death of dialyzed patients of which sudden cardiac death is the most frequent that is responsible for around 25% of all deadly outcomes. The rate of cardiovascular mortality in patients undergoing chronic dialysis is nearly 9% per annum[2].

In patients treated by chronic dialysis, the risk of development of CVD is 10-20 times higher than in general population[3]. Uremic milieu contributes to occurrence of atherosclerosis and atherosclerotic cardiovascular complications and often the development of accelerated, galloping atherosclerosis is present[4].

The patients undergoing chronic dialysis are exposed to traditional and non-traditional risk factors for the development of cardiovascular complications[5]. Traditional risk factors may be unchangeable (age, gender, inheritance) and changeable (smoking, hyperlipidemia, hypertension, obesity, diabetes, insufficient physical activity, stress). Non-traditional risk factors are the consequence of the uremic mi-

i povezani su sa samom tehnikom dijalize, a dijele se na hemodinamse i metaboličke. Hemodinamski su anemija, retencija natrija i vode, arteriovenska (AV) fistula, a metaboličke čine hiperhomocisteinemija, hipoalbuminemija, oksidativni stres, mikroinflamacija te sekundarni hiperparatiroidizam.

Pušenje cigareta spada u kategoriju glavnih čimbenika rizika za nastanak kardiovaskularnih bolesti[6]. Ateroskleroza kod pušača nastaje direktnim djelovanjem duhanskog dima na stijenku krvne žile te indirektno utjecajem na lipidan status; povisuju se trigliceridi i smanjuje razina HDL. Arterijska hipertenzija (AH) predstavlja neovisan čimbenik rizika za razvoj kardiovaskularnih komplikacija u bolesnika liječenih dijalizom[7]. U bolesnika liječenih dijalizom AH nastaje zbog volumnog opterećenja i povećanja krutosti arterija. Hiperlipidemija je također neovisan čimbenik rizika za razvoj ateroskleroze u bolesnika na hemodijalizi, a 30-50% bolesnika liječenih dijalizom ima povišene vrijednosti LDL, snižene vrijednosti HDL i povišene vrijednosti triglicerida[8]. Dijabetes jedan je od najčešćih uzročnika bubrežnog oštećenja, a ova bolest i neovisno povećava rizik od nastanka kardiovaskularnih bolesti. Rezultati dviju velikih kliničkih studija, Framinghamske studije i Multiple Risk Factor Intervention Trial pokazuju da dijabetes udvostručuje vjerojatnost nastanka KBS u muškaraca i utrostručuje rizik pojave KBS u žena[9].

Anemiju ima više od 90% bolesnika koji se liječe kroničnom dijalizom. Ova bolest pokreće nekoliko mehanizama koji povećavaju kardiovaskularni rizik: zbog smanjene oksigenacije povećava se aktivnost simpatikusa čime se povećava rad miokarda, a zbog smanjene viskoznosti dolazi do povećanog venskog priljeva u srce i posljedične HLK. Anemija zajedno s AH dovodi do HLK. Svako snižavanje vrijednosti hemoglobina za 10 g/l ispod vrijednosti od 100 g/l povisuje relativni rizik od srčane smrti za 18% u bolesnika na dijalizi[10]. Preopterećenje tekućinom predstavlja važan čimbenik za razvoj kongestivnog srčanog zatajivanja, a sam po sebi je čimbenik i za kardiovaskularni mortalitet. Nativna AV fistula predstavlja supkutanu anastomozu između arterije i vene, najčešće radijalne arterije i vene cefalike (Brescia-Cimino fistula). Protok krvi kroz AV fistulu veći od 1000 ml/min, dovodi do progresivne dilatacije lijeve klijetke i srčane insuficijencije[11].

Hiperhomocisteinemija je neovisan čimbenik rizika za razvoj ateroskleroze u bolesnika na hemodijalizi[12], a više od 80% bolesnika koji se liječe redovnim hemodijalizama ima povišenu koncentraciju homocisteina[13]. U bolesnika s terminalnim stupnjem bubrežne insuficijencije i povišenim nivoom homocisteina 2,9 puta je veći rizik od nastanka KBS nego u bolesnika s niskim vrijednostima homocisteina[14]. Oksidativni stres je također neovisan čimbenik rizika za razvoj kardiovaskularnih komplikacija u bolesnika na hemodijalizi, a malondialdehid (MDA) je pokazatelj oksidativnog stresa i razvoja kardiovaskularnih komplikacija. Infekcija/inflamacija (CRP >10 mg/l) je neovisan čimbenik rizika za razvoj kardiovaskularnih komplikacija u bolesnika na hemodijalizi i u zloćudnoj je sinergiji sa uremijom i pothranjenošću[15]. Prisutna je u 30-50% bolesnika koji se liječe redovnim hemodijalizama[16]. Sekundarni hiperparatiroidizam također predstavlja neovisan čimbenik rizika za razvoj kardiovaskularnih komplikacija[17].

lieu and are related with the dialysis technique itself, and they are divided in hemodynamic and metabolic risk factors. Hemodynamic risk factors are anemia, retention of sodium and water, arteriovenous (AV) fistula, while the metabolic risk factors are hyperhomocysteinemia, hypoalbuminemia, oxidative stress, microinflammation and secondary hyperparatiroidism.

Smoking cigarettes is included in the category of main risk factors for occurrence of CVD[6]. Atherosclerosis in smokers is caused by direct effect of tobacco smoke on the blood vessel wall and indirectly by influencing the lipid status: triglycerides are increased and HDL level is reduced. Hypertension is an independent risk factor for the development of cardiovascular complications in patients treated by dialysis[7]. In patients treated by dialysis, hypertension is caused by volume load and an increase in arterial rigidity. Hyperlipidemia is also an independent risk factor for the development of atherosclerosis in patients undergoing hemodialysis, while 30-50% of patients treated by dialysis have increased LDL, decreased HDL and incresed triglyceride[8]. Diabetes is one of the most frequent causes of renal damage, and this disease independently increases the risk of occurrence of CVD. The results of the two large clinical studies, the Framingham study and Multiple Risk Factor Intervention Trial have shown that diabetes increases the likelihood of occurrence of CHD in men twice and increases the risk of occurrence of CHD in women by three times[9].

Anemia affects more than 90% of patients who are treated by chronic dialysis. This disease is triggered by several mechanisms that increase the cardiovascular risk: reduced oxygenation causes an increase in sympaticus activity thereby increasing the myocardial action, while the reduced viscosity causes the increased venous inflow to the heart and consequential LVH. Anemia along with hypertension causes LVH. Each lowering of the hemoglobin values by 10 g/l below the value of 100 g/l increases the relative risk of cardiac death by 18% in patients undergoing dialysis[10]. Excessive fluid load represents an important factor for the development of congestive heart failure, and at the same time it is a factor for cardiovascular mortality. Native AV fistula represents the subcutaneous anastomosis between the artery and vein, most often radial artery and cephalic vein (Brescia-Cimino fistula). Blood flow through AV fistula greater than 1000 ml/min, leads to progressive dilation of the left ventricle and heart insufficiency[11].

Hyperhomocysteinemia is an independent risk factor for the development of atherosclerosis in patients undergoing hemodialysis[12], while over 80% of patients who are treated by regular hemodialysis have an increased concentration of homocysteine[13]. In patients with ESRD and increased level of homocysteine, the risk of occurrence of CHD is 2.9 times higher than the risk of occurrence of CHD in patients with low homocysteine values[14]. The oxidative stress is also an independent risk factor for the development of cardiovascular complications in patients undergoing hemodialysis, while malondialdehyde (MDA) is an indicator of oxidative stress and development of cardiovascular complications. Infection/inflammation (CRP >10 mg/l) is an independent risk factor for the development of cardiovascular complications in patients undergoing hemodialysis and is in malign synergy with uremia and malnutrition[15]. It is present in some 30-50% of patients that are treated by regular hemodialyses[16]. The secondary hyperparatiroidism is also an independent risk factor for the development of cardiovascular complications[17].

Ciljne vrijednosti kardiovaskularnih čimbenika rizika za pacijente na kroničnoj hemodijalizi prikazane su u **Tablici 1.**

Target values of cardiovascular risk factors in patients undergoing hemodialysis are shown in **Table 1.**

Table 1. *Target values of risk factors for the prevention of development of cardiovascular diseases in patients undergoing hemodialysis (modified according to reference 18).*

Risk factors	*Target value*
Arterial hypertension	Pre-dialysis blood pressure <140/90 mmHg
Diabetes	Glycosylated hemoglobin ≤8.0%
Hyperlipidemia	LDL cholesterol <2.6 mmol/L, triglycerides < 1.70 mmol/L
Hyperchomocysteinemia	Homocysteine <15 μmol/l
Anemia	Hct = 33-36%, Hb = 110-120 g/L
Inflammation	C-reactive protein <10 mg/L
Secondary hyperparatiroidism	$[PO_4^{3-}]$ <1.8 mmol/L , $[Ca^{2+}]$ x $[PO_4^{3-}]$ <4.4 $mmol^2/L^2$, iPTH 100-300 pg/mL

CILJ RADA

Utvrditi učestalost tradicionalnih i netradicionalnih čimbenika rizika za nastanak kardiovaskularnih bolesti u bolesnika na kroničnoj dijalizi (hemodijalizi i kontinuiranoj ambulantnoj peritonealnoj dijalizi) i usporediti ih s dostupnim podacima iz drugih studija.

ISPITANICI I METODE

Na Odsjeku za dijalizu Klinike za interne bolesti Univerzitetsko-kliničkog centra Tuzla, Bosna i Hercegovina, sprovedeno je istraživanje kojim su obuhvaćeni pacijenti liječeni postupcima kronične dijalize (hemodijalizom i kontinuiranom ambulantnom peritonealnom dijalizom) od početka 1999. do kraja 2010. godine. Uključni kriterij bilo je vrijeme provedeno na kroničnom dijaliznom liječenju. U studiju nisu uključeni bolesnici koji su na kroničnom dijaliznom programu bili manje od tri mjeseca te bolesnici koji su imali malignu bolest.

Svim bolesnicima uzeti su detaljni anamnestički podaci i analizirane su sljedeće varijable: dužina i vrsta dijaliznog tretmana, standardne laboratorijske analize (KKS, GUK, CRP, urea, kreatinin, kalij, natrij, kalcij, fosfor, magnezij, željezo, lipidogram, proteinogram, parathormon), nivo serumskog homocisteina. Arterijski tlak (AT) je mjeren sfingomanometrom na prijemu, prije dijaliznog liječenja.

Hipertenzija je definirana kao sistolički AT >140 i/ili dijastolički AT >90 mmHg (1 mm Hg = 0,133 kPa). Hiperlipidemija je definirana kao vrijednosti ukupnog kolesterola >5,17 mmol/L; triglicerida >1,7 mmol/L; LDL >2,6 mmol/L. Vrijednosti HDL <1,03 mmol/L smatrane su sniženima. Anemija je definirana kao vrijednosti koncentracije hemoglobina niža od 110 g/l ili hematokrit niži od 33%. Stupanj mikroinflamacije je procjenjivan na osnovu vrijednosti CRP čija je koncentracija >10 mg/L ukazivala na povećan rizik od razvoja aterosklerotskih kardiovaskularnih komplikacija. Hiperhomocisteinemija je definirana kao koncentracija ukupnog homocisteina u plazmi viša od 15 μmol/L.

Za statističku analizu korištene su metode deskriptivne statistike.

AIM

The aim of study is to determine the frequency of traditional and non-traditional risk factors for occurrence of CVD in patients undergoing chronic dialysis (hemodialysis and continuous ambulatory peritoneal dialysis) and compare them with available published data.

PATIENTS AND METHODS

At the Dialysis Department of the Internal Disease Clinic of the University-Clinical Center in Tuzla, Bosnia and Herzegovina, the study was conducted which included the patients treated by chronic dialysis procedures (hemodialysis and continuous ambulatory peritoneal dialysis) from the beginning of 1999 to the end of 2010. The inclusive criterion was the time spent on chronic dialysis treatment. The study did not include the patients who underwent the chronic dialysis program for less than three months and patients who had a malign disease.

Detailed history was taken from all patients and the following variables were analyzed: length and type of dialysis treatment, standard laboratory analyses (complete blood count, blood glucose, CRP, urea, creatinine, potassium, sodium, calcium, phosphor, magnesium, iron, lipidogram, proteinogram, parathormone), a level of serum homocysteine. Blood pressure (BP) was measured by sphygmomanometer on admission, prior to dialysis treatment.

Hypertension is defined as systolic BP >140 and/or diastolic BP >90 mmHg (1 mm Hg = 0,133 kPa). Hyperlipidemia was defined as the value of total cholesterol >5.17 mmol/L; triglycerides >1.7 mmol/L; LDL >2.6 mmol/L. The HDL values <1.03 mmol/L were considered decreased. Anemia was defined as the value of hemoglobin concentration lower than 110 g/l or hematocrit lower than 33%. The microinflammation level was evaluated on the basis of CRP value whose concentration of >10 mg/L indicated a higher risk of development of atherosclerotic cardiovascular complications. Hyperhomocysteinemia is defined as the concentration of total homocysteine in plasma over 15 μmol/L.

The descriptive statistical methods were used for statistical analysis.

REZULTATI

Uključeno je ukupno 50 bolesnika: 22 muškarca (44%) i 28 žena (56%). 35 bolesnika (70%) liječena su hemodijalizom, a 15 bolesnika (30%) kontinuiranom ambulantnom peritonealnom dijalizom (CAPD). Prosječna životna dob iznosila je 47,33±12,74 godina. Prosječna dužina trajanja dijaliznog tretmana iznosila je 42,6±17,2 mjeseci.

Učestalost tradicionalnih čimbenika iznosila je: arterijska hipertenzija (62%), hiperlipidemija (60%), dijabetes (25%) te pušenje (24%). Anemija je bila prisutna u 86% ispitanika. Od netradicionalnih metaboličkih čimbenika rizika hiperhomocisteinemija je bila prisutna u 82% ispitanika, mikroinflamacija u 26%, hipoalbuminemija u 30% te sekundarni hiperparatireoidizam u 36%. Vrijednosti ostalih varijabli prikazane su u **Tablici 2.**

RESULTS

50 patients were included: 22 men (44%) and 28 women (56%). 35 patients (70%) treated by hemodialysis, while 15 patients (30%) were treated by continuous ambulatory peritoneal dialysis (CAPD). The average life was 47.33±12.74 years. The average length of dialysis treatment was 42.6±17.2 months.

The frequency of traditional factors was: hypertension (62%), hyperlipidemia (60%), diabetes (25%) and smoking (24%). Anemia was present in 86% patients. From non-traditional metabolic risk factors, 82% hyperhomocysteinemia was present in 82% of patients, microinflammation in 26%, hypoalbuminemia in 30% and secondary hyperparatireoidism in 36%. The values of the remaining variables are shown in **Table 2.**

Table 2. *Values of blood pressure and laboratory results.*

Variable (unit)	*Mean value ± standard deviation*
Systolic blood pressure (mmHg)	158.74 ± 19.21
Diastolic blood pressure (mmHg)	95.12 ± 10.31
Mean pressure (mmHg)	119.06 ± 14.15
Hemoglobin (g/L)	100.60 ± 24.75
Hematocrit (%)	0.31 ± 0.064
Total proteins (g/L)	66.98 ± 6.78
Serum albumin (g/L)	30.39 ± 7.62
Cholesterol (mmol/L)	6.10 ± 1.34
LDL-cholesterol (mmol/L)	3.57 ± 0.91
HDL-cholesterol (mmol/L)	1.00 ± 0.22
Triglycerides (mmol/L)	2.64 ± 1.60
C-reactive protein (mg/L)	15.56 ± 2.38
Homocystein (μmol/L)	27.36 ± 12.58
[Ca^{2+}]mmol/L	2.37 ± 0.22
Parathormone-iPTII pg/ml	261.27 ± 295.09

DISKUSIJA

Kardiovaskularne bolesti predstavljaju glavni uzrok smrtnosti u bolesnika na kroničnoj dijalizi. Ovi pacijenti, osim uobičajenih, tradicionalnih čimbenika rizika za nastanak kardiovaskularnih bolesti (dob, dijabetes, pušenje cigareta, AH, pozitivna obiteljska anamneza), imaju i dodatne čimbenike karakteristične za uremični sindrom, koji su podijeljeni na hemodinamske (anemija, retencija Na i H_2O, AV fistula) i metaboličke (hipoalbuminemija, hiperhomocisteinemija, oksidativni stres, mikroinflamacija, sekundarni hiperparatireoidizam).

Svim uključenim ispitanicima određena je učestalost tradicionalnih i netradicionalnih čimbenika rizika. Pušenje je bilo prisutno u 24% ispitanika, što je manje od 40% ispitanika koji su bili pušači u studiji Foley i suradnika[19]. Hipertenzija je bila prisutna u 62% bolesnika, a hiperlipidemija u 60% bolesnika, što je u skladu sa rezultatima istraživanja drugih autora[20]. Blaga inflamacija je jedan od najvažnijih čimbenika koji doprinosi visokoj stopi kardiovaskularnog morbiditeta i mortaliteta u bolesnika s kro-

DISCUSSION

CVD represent the main cause of mortality in patients on chronic dialysis. These patients, besides some usual, traditional risk factors for occurrence of CVD (age, diabetes, smoking cigarettes, hypertension, positive familiary anamnesis), have additional factors characteristic for uremic syndrome, that are divided in hemodynamic (anemia, retention of Na and H_2O, AV fistula) and metabolic (hypoalbuminemia, hyperhomocysteinaemia, oxidative stress, microinflammation, secondary hyperparatireoidism).

Frequency of traditional and non-traditional risk factors has been determined for all included patients. Smoking was present in 24% patients, which is less than 40% who were smokers in the article by Foley et al[19]. Hypertension was present in 62% of patients, while hyperlipidemia was present in 60% of patients, which is in compliance with published results[20]. Slight degree of inflammation is one of the most important factors that contributes to a high rate of cardiovascular morbidity and mortality in patients with chronic renal failure[21]. In this study, microinflammation was determined in 26% of patients.

ničnom bubrežnom insuficijencijom[21]. U ovom istraživanju mikroinflamacija je bila utvrđena kod 26% bolesnika.

U toku dvogodišnjeg praćenja bolesnika na redovnim hemodijalizama, značajno je veća stopa smrtnosti u onih s koncentracijom ukupnog homocisteina (tHcy) >33,6 μmol/L, u odnosu na one sa tHcy <24,1 μmol/L[22]. Hiperhomocisteinemija je bila prisutna u 82% ispitanika.

ZAKLJUČAK

Učestalost tradicionalnih i netradicionalnih rizičnih čimbenika za nastanak kardiovaskularnih bolesti u dijaliznih bolesnika je veoma visoka. Najučestaliji tradicionalni čimbenici u ovom istraživanju bili su hipertenzija (62%) i hiperlipidemija (60%), a od netradicionalnih anemija (86%) i hiperhomocisteinemija (82%).

Ranom detekcijom i primjenom odgovarajuće terapije za postizanje ciljnih vrijednosti čimbenika rizika, smanjuje se učestalost kardiovaskularnog morbiditeta i mortaliteta u bolesnika liječenih postupcima dijalize.

During the two-year monitoring of patients on regular hemodialyses, the mortality rate in those with concentration of total homocystein (tHcy) >33.6 μmol/L is much higher compared to those with tHcy <24.1 μmol/L[22]. Hyperhomocysteinemia was present in 82% patients.

CONCLUSION

The frequency of traditional and non-traditional risk factors for occurrence of CVD in dialyzed patients is very high. The most frequent traditional factors in this study were hypertension (62%) and hyperlipidemia (60%), while anemia (86%) and hyperhomocysteinemia (82%) were the most frequent non-traditional factors.

The early detection and application of relevant therapy for the achievement of target values of risk factors reduces the frequency of cardiovascular morbidity and mortality in patients treated by dialysis procedures.

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