



## Dislipidemija u kroničnom bubrežnom zatajenju

## Dyslipidemia in chronic kidney failure

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**K**ronično bubrežno zatajenje (KBZ) predstavlja jedan od vodećih javnozdravstvenih problema u svijetu. Bolje razumijevanje bubrežnog zatajenja, praćenog tehnološkim i znanstvenim pretpostavkama dijalizne tehnike i transplantacije bubrega, značajno je poboljšalo prognozu i preživljavanje bolesnika sa završnim stadijem bubrežne bolesti (ZSBB). Unatoč poboljšanju tehnologije te kliničkom i znanstvenom napretku u liječenju metodama nadomještanja bubrežne funkcije (NBF), sve je veća učestalost nebubrežnih komplikacija ZSBB koje bitno utječu

**C**hronic kidney failure (CKF) represents one of the leading public health issues in the world. A better understanding of kidney failure followed by technological and scientific assumptions of dialysis techniques and kidney transplantation has significantly improved diagnosis and patient survival at the end stage of renal diseases (ESRD). Despite advancement of technology as well as clinical and scientific advances in treatment methods for compensating kidney functioning (CKF), there is an increasing frequency of non-kidney related complications at



na pobol i smrtnost bolesnika. Najvažnije su srčanožilne komplikacije koje najviše utječu na ishod liječenja. Brojni su čimbenici rizika od kojih samo opći, nazočni i u općoj populaciji, ne mogu objasniti visoku pojavnost srčanožilnih bolesti u bolesnika sa ZSBB. Osim općih čimbenika rizika, značajni su i rizični čimbenici specifični za KZB i ZSBB, a često se označuju i kao "uremijski" čimbenici rizika.

Dislipidemija je čimbenik napredovanja bubrežne bolesti, kako u populaciji bez poznate bolesti bubrega, tako i u bolesnika s dijabetesom. Osim toga, dislipidemija pridonosi napredovanju oštećenja bubrega u osoba s već postojećom bolesti. Značajna je povezanost između srčanožilnih bolesti i kronične bubrežne bolesti i može se usporiti s onom u bolesnika s uznapredovalom aterosklerozom ili sa šećernom bolesti. Dislipidemija neovisno ili udružena s hipertenzijom i proteinurijom oštećuje bubrežnu funkciju. Nazočna je u bubrežnih bolesnika, a obilježena povišenom razinom triglicerida i LDL kolesterola u serumu, te sniženom razinom HDL kolesterola. U bolesnika sa KBZ je aterogena, a javlja se rano i pogoršava s njegovim napredovanjem. I u bolesnika sa ZSBB su opisani tipični poremećaji lipida koji se očituju hipertrigliceridemijom, povećanom koncentracijom lipoproteina vrlo male gustoće, normalnim ili sniženim kolesterolom, normalnom koncentracijom lipoproteina niske gustoće kao i smanjenom koncentracijom lipoproteina visoke gustoće. Takva lipoproteinska slika je povoljna za nastanak ateroskleroze. U bolesnika na liječenju peritonealnom dijalizom lipidni je profil još aterogeniji zbog veće prevalencije povišenog ukupnog i LDL-kolesterola. Postoje dokazi da se u bolesnika na hemodijalizi primjenom biokompatibilnih visokoprotocnih dijalizatora, niskomolekularnog heparina i ultračistog dijalizata može usporiti napredovanje ateroskleroze povoljnim djelovanjem na lipidni profil. Slični su učinci opaženi i primjenom biokompabilnih otopina za peritonealnu dijalizu.

U bolesnika s bubrežnim presatkom primjena nekih imunosupresivnih lijekova dovodi do nepovoljnog lipidnog profila. U tih bolesnika to predstavlja dodatni srčanožilni čimbenik rizika.

## Liječenje dislipidemije

Sasvim je razumljivo da promjena načina ishrane povoljno utječe na lipidni profil. Ipak, brojna su istraživanja pokazala da nefarmakološke mjere nisu dovoljne u sprječavanju pogubnih učinaka dislipidemije kako u općoj populaciji, tako i u bolesnika sa KBZ. Već je prošlo četvrt stoljeća od prvih dokaza o korisnosti primjene statina u liječenju bolesnika s hiperkolesterolemijom. Tijekom godina, kako je rastao broj predstavnika skupine, narastao je i broj dokaza o korisnosti i sigurnosti primjene statina u sekundarnoj prevenciji bolesnika s dokazanom ishemijskom bolesti srca, perifernom žilnom bolesti, preboljelom moždanom udaru, kao i u primarnoj prevenciji bolesnika visokog rizika zbog nazočnosti čimbenika rizika (šećerna bolest, arterijska hipertenzija, pušenje). Iako primjena statina ima veću učestalost nuspojava u odnosu na placebo,

ESRD that significantly affect the morbidity and mortality rate of patients. The most important are cardiovascular complications that affect the treatment outcome the most. There are numerous risk factors of which only general, present and in the general population, cannot not explain the high occurrence of cardiovascular diseases in patients with ESRD. Besides general risk factors, significant risk factors are also specific for CKF and ESRD, and are often designated as "uremic" risk factors.

Dyslipidemia is a factor in the advancement of kidney disease, not just in a population without known kidney disease, but also in diabetic patients. Furthermore, dyslipidemia contributes to the advancement of kidney injury in persons with an existing disease. The relationship between cardiovascular diseases and chronic kidney disease is significant and can be compared to diseases in patients with advanced atherosclerosis or diabetes. Dyslipidemia independently or associated with hypertension and proteinuria damages kidney functioning. It is also present in kidney patients and is marked by an increased level of triglycerides and LDL cholesterol in serum, including lowered level of HDL cholesterol. In patients with CKF, it is atherogenic, appearing early and degenerating with its advancement. Also, in patients with ESRD, typical lipid disorders are described which appear with hypertriglyceridemia, increased concentrations of lipoproteins with very little density, normal or lowered level of cholesterol, normal concentrations of lipoproteins of a low density and lowered concentration of lipoproteins of high density. Such lipoprotein characteristics are favourable for the development of atherosclerosis. In patients treated with peritoneal dialysis, the lipid characteristic is more atherogenic due to a higher prevalence of increased total and LDL cholesterol. There is evidence that patients treated with haemodialysis using biocompatible high flow dialyzer, low molecular heparin and ultra-clean dialysate can slow down the advancement of atherosclerosis through the favourable impact on the lipid profile. Similar effects are observed using biocompatible solutions for peritoneal dialyses.

In patients with kidney transplants, administering some of the immunosuppressive medications leads to an unfavourable lipid profile. In such patients this represents an additional cardiovascular risk factor.

## Treating dyslipidemia

It is altogether understandable that changes in food habits affect lipid profile. However, numerous researches have shown that non-pharmacological measures are not adequate in preventing the serious consequences of dyslipidemia, not only in the general population, but also in patients with CKF. A quarter of century has passed since the first evidence of the benefits of administering statins, in treating patients with hypercholesterolemia. During the years, as the number of group representatives grew, the amount of evidence of the benefits and safety in the administration of statins in secondary prevention of patients with proven ischemic heart disease, peripheral arterial disease, strokes, as well as primary prevention in high risk patients due to the presence of risk factors (diabetes, arterial hypertension, smoking) also increased. Even though the use of statins exert more frequent negative side-effects



učestalost značajnih mišićnih nuspojava i toksičnog jetrenog učinka rijetka je kod primjene umjerenih i visokih doza statina. U bolesnika s KBZ primjena statina napredovala je od sporadične do preporučene primjene, ne samo kao lijekova s povoljnim učinkom na lipidni profil, već i kao lijekova s utjecajem na napredovanje kronične bubrežne bolesti. Osim očitog učinka na inhibiciju sinteze kolesterola, statini imaju značajan protuupalni učinak. Unatoč sve većem broju dokaza o blagotvornim učincima statina u ZSBB bolesnika, osobito protuupalnih, potrebna su daljnja istraživanja za potvrdu tog potencijala ovih lijekova. U tijeku je nekoliko kliničkih istraživanja koja bi mogla dati značajne odgovore (AURORA i SHARP studije). Rezultati tih studija se očekuju 2008. i 2010. godine.

I u bolesnika sa presađenim bubregom ispitani su i dokazani blagotvorni učinci statina. Prema podacima ALERT istraživanja, dosada najvećeg po broju uključenih ispitanika s bubrežnim presatkom, primjenom fluvastatina broj koronarnih intervencija i smrtnost općenito nisu se statistički značajno smanjili u odnosu na skupinu koja je primala placebo. Ipak u skupini liječenih fluvastatinom u odnosu na skupinu na placebo broj bolesnika umrlih zbog srčanožilnih uzroka kao i broj nesmrtonosnih infarkta miokarda bio je manji ( $P = 0,05$ ). Istraživanje je nastavljeno još dvije godine kao ALERT Extension Study. Nakon ukupno 6,7 godina prosječnog vremena praćenja, liječenjem fluvastatinom smanjilo je rizik velikih srčanožilnih događaja za 21% odnosno srčanu smrt i nesmrtonosni infarkt miokarda za 29%. Temeljem tih rezultata opravdana je primjena fluvastatina za sprječavanje srčanožilnih bolesti u bolesnika sa bubrežnim presatkom. Osim primjene statina, značajno je spomenuti da primjena nekalcijskog vezača fosfora, sevelamer hidroklorida, dovodi do smanjenja ukupnog i LDL-kolesterola uz sniženje razina serumskog fosfora u randomiziranom istraživanju provedenom na 200 dijaliznih bolesnika. Taj je lijek originalno i razvijen kao hipolipemik, a tijekom istraživanja opažena su izvrsna svojstva vezivanja fosfata, što mu predstavlja današnju glavnu indikaciju primjene.

**Zaključak:** *dyslipidemija je značajan čimbenik srčanožilnog rizika u svim populacijama kroničnih bubrežnih bolesnika. Liječenje dyslipidemije značajno utječe na ishod srčanožilnih komplikacija u tih bolesnika. Postoje saznanja o specifičnom proaterogenom lipidnom profilu u bolesnika sa ZSBB. U bolesnika liječenih dijalizom primjena biološki primjerene dijalize te lijekova koji utječu na lipidni profil i čimbenike napredovanja ateroskleroze predstavlja razumni postupak.*

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compared to placebo, the frequency of significant muscle side-effects and toxic liver consequences is rare when normal and high doses of statins are administered. In patients with CKF, the administration of statins has advanced from sporadic to recommended application, not only as medications with a favourable effect on lipid profile, but also as a medication affecting the advancement of chronic kidney disease. Despite an evident effect on an inhibition of cholesterol synthesis, statins have a significant anti-inflammatory effect. Despite the increasing evidence of the mild effects of statin in patients with ESRD, especially anti-inflammatory ones, it is necessary to verify the potential of such medications in further researches. Currently, in progress are a number of clinical tests that might offer important answers (AURORA and SHARP studies). The results of these studies are expected in 2008 and 2010.

In patients with kidney transplants, the proven mild effects of statin have been tested. Based on ALERT research data, up until now the largest number of respondents with kidney transplants, the use of fluvastatin has not generally led to a significant statistical reduction in the number of coronary interventions and mortality rates in comparison to the group receiving the placebo. However, in the group treated with fluvastatin when compared to the placebo group, the number of patients dying from cardiovascular events as well as the number of non-fatal myocardium infarction was less than ( $P=0.05$ ). The research was continued for another two years as the ALERT Extension Study. Following a total of 6.7 years of average monitoring time, the treatment by using fluvastatin reduced the risk of large cardiovascular events by 21% and cardiac death and non-fatal myocardium infarction by 29%. Based on these results, the administration of fluvastatin is justifiable in preventing cardiovascular diseases in patients with kidney transplants. Besides administering statin, it is also important to mention that the administration of non-calcium phosphate binder, sevelamer hydrochloride, leads to a reduction in the total and LDL cholesterol along with a reduction in the levels of serum phosphorus in randomized research conducted on 200 dialyzed patients. This medication was originally developed as a hypolipemic, and during the research, its excellent properties in binding phosphate were observed, which represents today's main indicated application.

**Conclusion:** *dyslipidemia is an important cardiovascular risk factor in all populations of chronic kidney patients. Treatment of dyslipidemia significantly affects the result of cardiovascular complications in such patients. There are discoveries of the specific proatherogenic lipid profile in patients with ESRD. In patients being treated with dialysis, the application of biological appropriate dialysis and medications which affect the lipid profile and factors in the advancement of atherosclerosis represent a reasonable procedure.*

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