16. *Curry CJ, Stevenson RE, Aughton D i sur.* Evaluation of mental retardation: recommendations of a Consensus Conference: American Colege of Medical Genetics. Am J Med Genet 1997;72:468–77.
17. *Cans C, Wihelm L, Baille MF, du Mazaubrun C, Grandjean H, Rumeau-Rouquette C.* Aetiological findings and associated factors in children with severe mental retardation. Developmental Medicine and Child Neurology 1999;41:233–239.
18. http://www.ncbi.nlm.nih.-gov/omim
19. *Partington M, Mowat D, Einfeld S, Tong B, Turner G.* Genes on the X chromosome are important in undiagnosed mental retardation. Am J Med Genet 2000;92:57–61.
20. *Chiurazzi P, Hamel BCJ, Neri G.* XLMR genes: update 2000. Eur J Hum Genet 2001;9:71–8.
21. http://homepages.go.com/~xlmr/home.html
22. *Sattler JM.* Assessment of Children 3rd Edition. San Diego: Jerome M Sattler, Publisher, Inc, 1992.
23. *Battaglia A, Bianchini E, Carey JC.* Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. Am J Med Genet 1999;82:60–6
24. *Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M.* Etiologic yield of subspecialists' evaluation of young children with global developmental delay. J Pediatr 2000;136:593–8.
25. *Hunter AG.* Outcome of the routine assessment of patients with mental retardation in a genetics clinic. Am J Med Genet 2000;90:60–8.
26. *Livet MO, Monela A, Philip N, Chabrol B, Mancini J.* Clinical approach to mental retardation of genetic origin. Rev Neurol 1999;155:593–5.
27. *Dykens E.* Introduction to the special issue on behavioral pheotypes. Am J Ment Retardation 2001;106:1–3.
28. *Kirchoff M, Rose H, Duno M, Gerdes T. Lundsteen C.* Screening of dysmorphic and mentally retarded subjects with high resolution comparative genomic hybridization. Eur J Hum Genet 2002;10:65
29. *Knight SJ Flint JA.* Perfect endings: a review of subtelomeric probes and their use in clinical diagnosis. J Med Genet 2000;37:401–9.
30. *Rosenberg MJ, Vaske D, Killoran CE i sur.* Detection of chromosomal aberrations by a whole-genome microsatellite screen. Am J Hum Genet 2000;66:419–427.
31. *Colleaux L, Rio M, Heuertz S i sur.* A novel automated strategy for screening cryptic telomeric rearrangements in children with idiopathic mental retardation. Eur J Hum Genet 2001;9:319–327.
32. *Agostini C.* Chromosomal rearrangements and mental retardation. Ped Research 2000;47:429.
33. *Petković I, Barišić I.* Application of fluorescence in situ hybridization (FISH) in clinical genetics. Paediatr Croat 2001;45:175–178.
34. *Mannens M, Alders M.* Genomic imprinting: concept and clinical consequences. An Med 1999;1:4–11.
35. *Ligutić I, Brečević L, Marković N, Grgić T.* Mentalna retardacija i X fragilno mjesto. Arhiv ZMD 1987;31:361–369.
36. *Fu YH, Kuhl DP, Pizzuti A i sur.* Variation of CGG repeat at the fragile X sute results in genetic instability: resolution of the Sherman paradox. Cell 1991;67:1047–58.
37. *Sherman SL.* Premature ovarian failure in the fragile X syndrome. Am J Med Genet. 2000;97:189–94.
38. *Hagerman PJ, Greco CM, Tassone F, Chudley A, Del Bigio MR, Jacquemont S, Leehey M, Hagerman RJ.* Neuronal intranuclear inclusions in a new cerebellar tremor/ataxia syndrome among fragile X carriers. Eur J Hum Genet 2002;10:(Suppl 1):63
39. *Hećimović S, Barišić I, Muller A i sur.* Expand Long PCR for fragile X mutation detection. Clin Genet 1997; 52:147–54
40. *Hećimović S, Vlašić S, Barišić I, Marković D, Čulić V, Pavelić K.* A simple and rapid analysis of triplet repeat diseases by Expand Long PCR. Clin Chem and Lab Med 2001;39:1259–1262
41. *Gecz J.* The FMR2 gene, FRAXE and non-specific X-linked mental retardation: clinical and molecular aspects. Ann Hum Genet 2000;64:95–106.
42. *Hećimović S, Barišić I, Pavelić K.* DNA analysis of the fragile X syndrome in an at risk pediatric population in Croatia: simple clinical preselection criteria can considerably improve the cost-effectiveness of fragile X screening studies. Hum Hered 1998;48:256–265.
43. *Willemsen R, Oostra BA.* FMRP detection assay for the diagnosis of the fragile X syndrome. Am J Med Genet. 2000;97;183–8.
44. *Molinari F, Rio M, Munnich A, Colleauy L.* Mutation in neurotrypsin is responsible for autosomal recessive non-specific mental retardation. Eur J Hum Genet 2002;10: Suppl(1):64
45. *Schwartz CE, Hahn KA, Salomons GS i sur.* Mutations in the creatine transporter gene (SLC6A8) in Xq28 cause X-linked mental retardation: the important role of creatine metabolism in brain function. Eur J Hum Genet 2002;10: Suppl(1):64
46. *Hagemann G, Redecker C, Witte OW.* Kortikale Dysgenesien. Aktuelle Klassifikation, kernspintomographische Diagnostik und klinische Übersicht. Nervenarzt 2000;616–628.
47. *Whiting S, Duchowny M.* Clinical spectrum of cortical dysplasia in childhood; diagnosis and treatment issues. J Child Neurol 1999;12:759–71
48. *Deb S.* Structural neuroimaging in learning disability. Br J Psychiatr 1997; 171:417–419.
49. *Walsh KK. Kastner TA.* Quality of health care for people with developmental disabilities: the challenge of managed care. Ment Retard 1999;37:1–15.
50. *Santosh PJ, Baird G.* Psychopharmacotherapy in children and adults with intellectual disability. Lancet 1999;354(9174):233–42.
51. *Barišić I, Clementi M, Häusler M, Gjergja R, Kern J, Stoll C.* Evaluation of prenatal ultrasound diagnosis of fetal abdominal wall defects by 19 European registries. Ultrasound in Obstet and Gynecol 2001;18:309–317.
52. *Garne E, Haeusler M, Barišić I, Gjergja R, Stoll C, Clementi M.* Congenital diaphragmatic hernia: evaluation of prenatal diagnosis in 20 European regions. Ultrasound Obstet Gynecol 2002;19:329–33
53. *Haeusler MC, Berghold A, Barišić I, Clementi M, Stoll C and EUROSCAN Study Group.* Prenatal ultrasonographic diagnosis of gastrointestinal obstruction: Results from 18 European congenital anomaly registries. Prenatal Diagn 2002;22:616–623
54. *Ye X, Mitchell M, Newman K, Batshaw ML.* Prospects for prenatal gene therapy in disorders causing mental retardation. Ment Retard Dev Disabil Res Rev. 2001;7:65–72.

RENALNA DISLIPIDEMIJA U BOLESNIKA NA KRONIČNOJ HEMODIJALIZI

RENAL DYSLIPIDEMIA IN PATIENTS ON CHRONIC HAEMODIALYSIS

VEDRAN KOVAČIĆ, MILENKA ŠAIN, VALENTINA VUKMAN*

Deskriptori: Hiperlipidemija – etiologija; Bubrežno zatajenje, kronično – komplikacije; Trigliceridi – u krvi; Bubrežna dijaliza

Sažetak. Važnu ulogu u razvoju ateroskleroze u bolesnika na kroničnoj hemodijalizi (BKHD) imaju lipidni poremećaji u krvi. Ti bolesnici imaju obrazac lipida u krvi čije su osobine povišenje triglicerida i sniženje HDL-kolesterola. Fenotip poremećaja lipida u uremičnih bolesnika uglavnom je tip IV po Fredricksonu (oko 30%), a manji dio otpada na IIA i na IIB. Oko 9% lipidnih poremećaja uremičara otpada na izolirano povišenje Lp(a). Glavni uzrok hipertrigliceridemije u BKHD je smanjen metabolizam VLDL-kolesterola zbog inhibicije lipoproteinske lipaze. Također postoje aterogene promjene u sastavu lipoproteina, osobito su aterogene promjene LDL-čestice. Liječenje renalne dislipidemije treba biti odlučno, i to na početku bubrež-

* **Dom zdravlja Trogir, Centar za turističku i domicilnu hemodijalizu** (Vedran Kovačić, dr. med.; Milenka Šain, dr. med.; Valentina Vukman, dr. med.)

Adresa za dopisivanje: Dr. V. Kovačić, Dom zdravlja Trogir, Centar za turističku i domicilnu hemodijalizu, 21220 Trogir

Primljeno 17. svibnja 2001., prihvaćeno 26. rujna 2002.

nog zatajenja. Na raspolaganju nam stoje dijetalne mjere (osobito omega-3-masne kiseline), statini, gemfibrozil, intravenski L-karnitin i bikarbonati per os. U tom smislu važne su i modifikacije postupka hemodijalize kao što je visokoprotočna hemodijaliza, niskomolekularni heparin, dijalizatori obloženi vitaminom E, a za tvrdokorne slučajeve služi i LDL-afereza.

Descriptors: Hyperlipidemia – etiology; Kidney failure, chronic – complications; Triglycerides – blood; Renal dialysis

Summary. Disorder of blood lipids plays an important role in atherosclerosis progress in patients ongoing chronic haemodialysis (PCHD). These patients have specific features of blood lipids with increment of triglycerides and decrement of HDL-cholesterol. Phenotype of lipid disorder in PCHD is mostly type IV according to Fredrickson (30%), and IIA and IIB fenotypes are less frequent. About 9% of lipid disorders in PCHD are isolated increase of Lp(a). Main reason of hypertriglyceridemia in PCHD is attenuated metabolism of VLDL-cholesterol because of lipoprotein lipasis inhibition. There are changes in lipoproteins quality, specially changes in LDL particle have atherogenic potential. Renal dyslipidemia treatment must be vigorous in the early stages of renal insufficiency. Treatment can be dietary measures (specially omega-3-fatty acids), statins, gemfibrozil, intravenous L-carnitin and bicarbonate given per os. Haemodialysis modifications such as highflux haemodialysis, low molecular weight heparin, vitamin E coated dialyzers and LDL-apheresis in extreme cases have important role in renal dyslipidemia treatment.

Liječ Vjesn 2003;125:77–80

Kardiovaskularne, cerebrovaskularne i periferne vaskularne bolesti najčešći su uzrok smrti i pobola u bolesnika s kroničnim zatajenjem bubrega.[1] Čak 42,5% bolesnika na kroničnoj hemodijalizi umire od srčanih i cerebrovaskularnih bolesti.[2]

Najvažniji uzroci ateroskleroze u bolesnika na kroničnoj hemodijalizi (BKHD) jesu hipertenzija, hiperlipidemija, šećerna bolest, hiperparatiroidizam, stanje kronične upale, pušenje, hiperhomocisteinemija.[3–5] Pušenje je dokazani čimbenik aterosklerotskog rizika u općoj populaciji, a osobito je važan aterogeni čimbenik u populaciji bolesnika na dijalizi.[6]

Hiperhomocisteinemija je dokazani čimbenik rizika ateroskleroze u ljudi, a razina homocisteina je povišena u bolesnika s kroničnim zatajenjem bubrega i u nekim nasljednim metaboličkim bolestima kao što je homocistinurija.[7] Homocistein dovodi do proizvodnje i lučenja elastaza u arterijskoj stijenci sudjelujući tako u procesu smanjenja elastičnosti arterija, što dovodi do povišenog krvnog tlaka i ateroskleroze.[8] Također postoje dokazi da je povišen nivo homocisteina u krvi povezan sa slabijim odgovorom endotela na dušični oksid (NO) i s povećanom proliferacijom glatkih mišića u arterijama.[9,10]

Dokazano je da je hiperhomocisteinemija nezavisan čimbenik rizika za kardiovaskularne bolesti u bolesnika na hemodijalizi.[11] Zato se bolesnicima s kroničnim zatajenjem bubrega preporučuje davanje folne kiseline, vitamina B6, vitamina B12 i betaina, koji dokazano snizuju razinu homocisteina u krvi jer su kofaktori/supstrati u metabolizmu homocisteina.[12] Folna kiselina u dozi od 2,5 do 5 mg snizuje povišenu koncentraciju homocisteina u krvi u uremičnih bolesnika, a što je viša razina homocisteina u krvi, to folna kiselina ima bolji učinak na nj.[13] Ipak, dokazano je da su za bolesnike na dijalizi učinkovitije doze tih vitamina koje premašuju fiziološke dnevne doze, primjerice doze od 15 mg folne kiseline, 100 mg vitamina B6 i 1 mg vitamina B12 na dan.[14]

Vrlo važnu ulogu u razvoju ateroskleroze u BKHD imaju lipidni poremećaji.[15] BKHD i predijalizni bolesnici imaju specifičan obrazac poremećaja lipida u krvi (uremička ili renalna dislipidemija), a ti poremećaji postoje i u bolesnika na peritonejskoj dijalizi.[16,17] Glavne osobine uremičke dislipidemije su:

- povišeni trigliceridi plazme
- normalan ukupni kolesterol i LDL-kolesterol
- smanjen HDL-kolesterol u plazmi
- nakupljanje lipoproteina koji sadržavaju apo-B i bogati su trigliceridima (tzv. Lp-Bc), a to su VLDL i IDL zajedno sa svojim ostatnim česticama
- LDL-kolesterol najčešće nije povišen, ali pokazuje promjene u veličini i sastavu, što je dodatni rizik za razvoj ateroskleroze
- nakupljanje ostatnih lipoproteina (djelomično metaboliziranih lipoproteina), što predstavlja rizik od ateroskleroze.[18]

Takav obrazac nije specifičan samo za uremične bolesnike već i za dijabetičku hiperlipidemiju pa su u uremičara s dijabetičkom nefropatijom ove promjene lipida u krvi još naglašenije, a glavna strukturalna promjena lipoproteina u dijabetičke nefropatije jest povećanje relativnog udjela apoproteina C (ApoC) u VLDL, IDL i LDL-česticama.[19]

Fenotip poremećaja lipida u uremičnih bolesnika uglavnom je tip IV po Fredricksonu (oko 30%), a manji dio otpada na IIA i na IIB, najmanji dio otpada na izdvojenu hipoalfalipoproteinemiju i na hiper-ApoB fenotip. Oko 9% lipidnih poremećaja u uremičara otpada na izdvojeno povišenje Lp(a).[20,21] Glavni lipidni poremećaj u uremičara je hipertrigliceridemija uz snižen HDL (između povišenja triglicerida i sniženja HDL-a postoji negativna korelacija).[22]

U renalnoj dislipidemiji ukupni kolesterol obično nije poremećen, kao ni LDL, a povećani su omjeri ukupni kolesterol/HDL i LDL/HDL, što znači rizik od ateroskleroze.[23]

Rasprava

Glavni uzrok hipertrigliceridemije u BKHD je smanjen metabolizam VLDL-kolesterola. Uzrok toga je povišenje ApoC-III i sniženje ApoC-II. ApoC II je kofaktor lipoproteinske lipaze (LPL), dok ApoC-III koči njezinu aktivnost. ApoC-III je povišen u uremičnih bolesnika, a vrijednosti mu značajno koreliraju s vrijednostima triglicerida i LP-Bc, vjerojatno preko inhibicije LPL-a.[24] Smanjena LPL-aktivnost, kao i smanjena aktivnost hepatičke trigliceridne lipaze (HTGL) uzrokuju smanjeni katabolizam hilomikrona, VLDL i IDL-čestica.[25,26] Citokini koji su povišeni u uremiji (TNFα, IL-1, IL-2) također inhibiraju LPL.[27] Važno je i smanjenje zaliha LPL-a zbog ponavljane primjene konvencionalnoga nefrakcioniranog heparina koji se rabi u postupku hemodijalize.[28] Sveukupni učinak inhibicije djelovanja LPL-a je smanjena pretvorba VLDL-a u LDL. Posljedica toga je povišenje VLDL-a i triglicerida.

Sniženje koncentracije HDL-a čest je nalaz u BKHD osobito u prisutnosti hipertrigliceridemije. Naime, u BHDK smanjena je aktivnost lecitin kolesterol aciltransferaze (LCAT) i HTGL-a koji sudjeluju u konverziji HDL-čestice.[25] Za sniženje HDL-a bitno je i sniženje ApoA-I i ApoA-II proteina.[29] Dokazano je da uremičke srednje molekule veličine 500–2000 iz seruma uremičnih bolesnika inhibiraju lučenje ApoA-I u hepatocitima.[30] HDL je u uremičara drugačijeg sastava, veće je gustoće i sadržava manje kolesterola.[31]

Iako LDL-kolesterol i ukupni kolesterol nisu povišeni, u BKHD i predijaliznih bolesnika LDL-čestice su manje gustoće, manje veličine, bogatije trigliceridima, a siromašne kolesterolom. Te promjene u sastavu i veličini LDL-čestica, unatoč njihovoj normalnoj koncentraciji u plazmi, dodatni su čimbenik rizika za razvoj ateroskleroze jer su takve LDL-čestice atero-

genije, javljaju se rano u bubrežnome zatajenju, a prisutne su i nakon presađivanja bubrega.[19,22,32,33] Takve LDL-čestice podložne su lipidnoj peroksidaciji, čiji je proizvod osobito aterogen oksidirani LDL (O×LDL).[34,35] Sve te promjene LDL-čestice dovode do smanjenog klirensa LDL-čestica putem ApoB/E-receptora u fibroblastima i hepatocitima i njihova pojačanog katabolizma u glatkim mišićnim stanicama arterija i makrofazima, što je fiziološka osnova ateroskleroze.[36]

Promjene u sastavu i strukturi lipoproteina javljaju se i pri normalnim ili čak niskim vrijednostima lipida u plazmi.[25,31] Karakteristična promjena sastava apoproteina u plazmi uremičara je povišena koncentracija ApoB i ApoC-proteina, a snižena koncentracija ApoA-I i ApoA-II.[37] Uremični bolesnici u odnosu na zdravu populaciju imaju u VLDL, IDL i LDL-česticama veći udio ApoB, a u VLDL i IDL-česticama veći udio ApoC-II i III i ApoE. U LDL-u povišen je udio ApoC-II i ApoC-III, a u HDL-u smanjen je udio ApoA-I, ApoA-II i ApoC.[38]

Lipoprotein-a [Lp(a)] neovisni je čimbenik rizika za kardiovaskularne bolesti koji u osoba s aterogenim rizikom (kao što su uremični bolesnici) dodatno pridonosi kardiovaskularnom pobolu.[39] Dokazana je povišena koncentracija Lp(a) u BKHD i u predijaliznih bolesnika neovisno o vrijednostima ostalih lipida.[37] Lp(a) je osobito visok u bolesnika koji se liječe peritonejskom dijalizom, a uspješna bubrežna transplantacija dovodi do brzog smanjenja Lp(a).[40]

Liječenje renalne dislipidemije

U liječenju renalne dislipidemije vrlo su važne dijetalne mjere kao što je smanjenje kolesterola u prehrani, a korisnim se u BKHD pokazalo riblje ulje, omega-3-masne kiseline i uzimanje 20–50 i. j. vitamina E na dan, što smanjuje podložnost LDL-čestice oksidaciji.[41] Na Lp(a) dijeta nema učinka.[42] Statini su se pokazali učinkoviti u renalnoj dislipidemiji (peroralni pravastatin ili simvastatin) snižavajući trigliceride, još više kolesterol i LDL, povisujući HDL i ApoA, a snizujući ApoB. Simvastatin davan u dozi od 10 mg imao je terapijski učinak i bio je odlično podnošljiv u BKHD.[43] Ispitivanjem farmakokinetike pravastatina, koji je davan bolesnicima na dijalizi u dozi od 20 mg na dan, pokazano je da nema promjene u njegovoj farmakokinetici te da može biti davan sigurno i bez promjene doze.[44] Gemfibrozil manje snižava kolesterol i LDL i manje podiže HDL u odnosu na statine, a nema učinka na ApoA. Na sniženje ApoB, ApoE i ApoC-III gemfibrozil i statini djeluju podjednako, a ne djeluju na Lp(a).[45–47] Gemfibrozil se u BKHD daje u dozi od 300 do 600 mg i dokazano je da nema povećane opasnosti od oštećenja skeletnih mišića.[48] Korisnim se u BKHD s hipertrigliceridemijom pokazalo i intravensko davanje L-karnitina u dozi od 25 mg/kg nakon dijalize, tri puta na tjedan.[49]

Ako se niskomolekularni heparin (LMWH) rabi u postupku dijalize umjesto konvencionalnoga nefrakcioniranog heparina, dolazi u BKHD s renalnom dislipidemijom do sniženja kolesterola, LDL, ApoB, triglicerida, Lp-Bc, a do povišenja HDL-a.[50,51] Isto tako postoje izvještaji o poboljšanju lipidnih pokazatelja u krvi ako se snizi doza konvencionalnoga nefrakcioniranog heparina koji se rabi za postupak hemodijalize.[52] Pokazano je da i peroralnim uzimanjem $NaHCO_3$ (smanjenjem metaboličke acidoze) dolazi do sniženja triglicerida, ali to nema učinka na kolesterol i HDL.[53]

Korisne su se pokazale i dijalizne membrane obložene vitaminom E, koje smanjuju oksidaciju LDL i HDL-čestica.[54]

Nekoliko studija pokazalo je poboljšanje lipidnih pokazatelja u BKHD koji su liječeni visokoprotočnom hemodijalizom (high flux – HF) u odnosu na niskoprotočnu hemodijalizu (low flux – LF).[55–58] Razlog tomu je u sposobnosti HF-hemodijalize u uklanjanju jednog ili više uremičkih toksina veće molekularne mase koji djeluju kao inhibitori LPL-a. Pokazano je *in vitro* da serum uremičnih bolesnika inhibira LPL.[59] Isto tako je pokazano da HF-dijaliza značajno uklanja i ApoC-III koji je također (lipoproteinski) inhibitor LPL-a.[57] Učinak HF-dijalize bio je najizraženiji u sniženju triglicerida (sniženi su čak 30–50%). Taj pozitivni učinak HF-hemodijalize nije posljedica veće biokompatibilnosti membrana, nego veće protočnosti membrana. HF-dijaliza je učinkovita i u uklanjanju niskomolekularnih AGE (advanced glycation endproducts) koji su vezani na ApoB (AGE-ApoB).[60] Tako izmijenjeni ApoB u LDL-čestici smanjuju klirens LDL-čestica, a niskomolekularni AGE mogu *in vitro* inhibirati LPL.[61]

Niskoprotočni dijalizatori od celuloze acetata s boljim klirensom za veće molekule također snizuju trigliceride, povisuju HDL i pojačavaju aktivnost LPL-a.[62]

Ima dokaza da peritonejska dijaliza više pridonosi aterogenosti nego hemodijaliza. Tako su kod bolesnika liječenih peritonejskom dijalizom nađene više koncentracije ukupnog kolesterola, VLDL, LDL, apoA-I, apo B i lipoproteina (a) u krvi u odnosu na bolesnike liječene hemodijalizom.[63,64]

Neke su studije proučavale i učinak rekombinantnog humanog eritropoetina na lipide u krvi u BKHD, ali su dale proturječne rezultate.[65,66]

Za najteže slučajeve hiperlipidemije može poslužiti i LDL-afereza. Tim se postupkom snizuje ukupni kolesterol, ukupni trigliceridi, LDL-kolesterol, apoprotein B te smanjuje oksidacija LDL-čestica.[67]

Zaključak

Zaključno, renalna dislipidemija značajno pridonosi smrtnosti i pobolu BKHD, a liječenje tog stanja treba biti odlučnije, i to još u ranim stupnjevima bubrežnog zatajenja. Osim lijekova, dijetalnih mjera i prestanka pušenja stoje nam na raspolaganju i neka poboljšanja postupka hemodijalize, osobito HF-dijalizatori i niskomolekularni heparin. Potrebna je veća hrvatska multicentrična studija koja bi dala ujednačene smjernice za liječenje renalne dislipidemije. Osobito pažljiv treba biti pri stratifikaciji skupina s obzirom na osobine ispitanika (spol, pušenje, način prehrane, liječenje anemije eritropoetinom itd.) jer to značajno može utjecati na rezultate istraživanja.

LITERATURA

1. *Parfrey PS, Harnett JD, Barre PE.* The natural history of myocardial disease in dialysis patients. J Am Soc Nephrol 1991;2:2–12.
2. *Held PJ, Port FK, Webb RL, Turenne MN, Wolfe RA, Holzman E i sur.* The USRDS 1994 Annual Data Report Am J Kidney Dis 1994;24:1–181.
3. *Collins A, Ma J, Herzog C.* Acute and chronic survival of dialysis patients with acute myocardial infarction. J Am Soc Nephrol 1996;7:1476.
4. *Rostand SG, Brunzell JD, Cannon RO, Victor RG.* Cardiovascular complications in renal failure. J Am Soc Nephrol 1991;2:1053–62.
5. *Bachmann J, Tepel M, Raidt H, Riezler R, Graefe U, Langer K i sur.* Hiperhomocysteinemia and the risk for vascular disease in hemodialysis patients. J Am Soc Nephrol 1995;6:121–5.
6. *Biesenbach G, Zazgornik J.* Influence of smoking on the survival rate of diabetic patients requiring hemodialysis. Diabetes Care 1996;19:625–8.
7. *Kang SS, Wong PWK, Malinow MR.* Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. Annu Rev Nutr 1992;12:279–98.
8. *Jourdheuil-Rahmani D, Rolland PH, Garcon D.* Homocysteine induces synthesis and secretion of serine-elastase in isolated smooth muscle cells from human normal arteries. Ir J Med Sci 1995;15:164.
9. *Celermajer DS, Sorensen K, Ryalls M, Robinson J, Thomas O, Leonard JV, Deanfield JE.* Impaired endothelial function occurs in the systemic arteries of children with homozygous homocystinuria but not in their heterozygous parents. J Am Coll Cardiol. 1993;22:854–8.
10. *Rolland PH, Friggi A, Barlatier A, Piquet P, Latrille V, Faye MM, Guillou J, Charpiot P, Bodard H, Ghiringhelli O, Calaf R, Luccioni R, Garcon D.* Hyperhomocysteinemia induced vascular damage in the minipig. Circulation. 1995;91:1161–74.
11. *Sutton-Tyrrell K, Bostom A, Selhub J, Zeigler-Johnson C.* High homocysteine levels are independently related to isolated systolic hypertension in older adults. Circulation 1997;96:1745–9.
12. *Bostom A, Shemin D, Verhoef P, Nadeau M, Jacques P, Selhub J i sur.* Elevated fasting total plasma homocysteine levels and cardiovascular

disease outcomes in maintenance dialysis patients. Arterioscler Thromb 1997;17:2554–8.
13. *Dierkes J, Domröe U, Ambrosch A, Bosselmann HP, Neumann KH, Luley C.* Response of hyperhomocysteinemia to folic acid supplementation in patients with end-stage renal disease. Clin Nephrol 1999;51:108–15.
14. *Bostom AG, Shemin D, Lapane KL, Hume AL, Yoburn D, Nadeau MR, Bendich A, Selhub J, Rosenberg IH.* High dose B-vitamin treatment of hyperhomocysteinemia in dialysis patients. Kidney Int 1996;49:147–52.
15. *Ma KW, Greene EL, Raij L.* Cardiovascular risc factors in chronic renal failure and hemodialysis populations. Am J Kidney Dis 1992;19:505–13.
16. *Senti M, Romero R, Pedro-Bottet J, Pelegri A, Nogues X, Rubies-Prat J.* Lipoprotein abnormalities in hyperlipidemic and normolipidemic men on hemodialysis with chronic renal failure. Kidney Int 1992;41:1394–9.
17. *Joven J, Vilella E, Ahmad S, Cheung MC, Brunzell JD.* Lipoprotein heterogenity in end-stage renal disease. Kidney Int 1993;43:410–8.
18. *Oda H, Yorioka N, Okushin S, Nishida Y, Kushihata S, Ito T i sur.* Remnant-like particles cholesterol may indicate atherogenic risk in patients on chronic hemodialysis. Nephron 1997;76:7–14.
19. *Zambon S, Zambon A, Stabellini N, Tarroni G, Gilli P, Crepaldi G i sur.* Lipoprotein abnormalities in hypertriglyceridemic patient on long-term haemodialysis. J Intern Med 1993;234:217–21.
20. *Samuelsson O, Attman PO, Knight-Gibson C, Kron B, Larsson R, Mulec H i sur.* Lipoprotein abnormalities without hyperlipidemia in moderate renal insuffiency. Nephrol Dial Transplant 1994;9:1580–5.
21. *Elisaf MS, Bairaktari HT, Tziallas CS, Germanos NK, Siamopoulos KC.* Atherogenic lipid and lipoprotein parameters in hemodialysis patients. Dial Transplant 1995;24:642–60.
22. *Moberly JB, Attman PO, Samuelsson O, Johansson AC, Knight-Gibson C, Alaupovic P.* Apolipoprotein C-III, hypertriglyceridemia and triglyceride-rich lipoproteins in uremia. Miner Electrolyte Metab 1999;25:258–62.
23. *Tomura S, Nakamura Y, Doi M, Ando R, Ida T, Chida Y i sur.* Fibrinogen, coagulation factor VII, tissue plasminogen activator, plasminogen activator inhibitor-1, and lipid as cardiovascular risk factors in chronic hemodialysis and continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis 1996;27(6):848–54.
24. *Attman PO, Knight-Gibson C, Tavella M, Samuelsson O, Alaupovic P.* The compositional abnormalities of lipoproteins in diabetic renal failure. Nephrol Dial Transplant 1998;13:2833–41.
25. *Shoji T, Nishizawa Y, Nishitani H, Yamakawa M, Morii H.* Impaired metabolism of high density lipoprotein in uremic patients. Kidney Int 1992;41: 1653–61.
26. *Havel RJ, Hamilton RL.* Hepatocytic lipoprotein receptors and intracellular lipoprotein catabolism. Hepatology 1988;8:1689–704.
27. *Querfeld U, Ong JM, Prehn J.* Effects of cytokines on production of lipoprotein lipase in cultured human macrophages. J Lipid Res 1990;31: 1379–86.
28. *Attman PO, Alaupovic P.* Lipid and apolipoprotein profiles of uremic dyslipoproteinemia-relation to renal function and dialysis. Nephron 1991; 57:401–10.
29. *Sakurai T, Oka T, Hasegawa H, Igaki N, Miki S, Goto T.* Comparison of lipids, apoproteins and associated enzyme activities between diabetic and nondiabetic endstage renal disease. Nephron 1992;61:409–14.
30. *Kamanna VS, Kashyap ML, Pai R.* Uremic serum subfraction inhibits apolipoprotein A-I production by human hepatoma cell line. J Am Soc Nephrol 1994;5:193–200.
31. *Deckelbaum RJ, Granot E, Oschry Y, Rose L, Eisenberg S.* Plasma triglyceride determines structure-composition in low- and high-density lipoproteins. Arterioslerosis 1984;4:225–31.
32. *O'Neal D, Lee P, Murphy B, Best J.* Low-density lipoprotein particle size distribution in end-stage renal disease treated with hemodialysis or peritoneal dialysis. Am J Kidney Dis 1996;27:84–91.
33. *Keane WF.* Lipids and kidney. Kidney Int 1994;46:910–20.
34. *Sutherland W, Walker RJ, Ball MJ, Stapley S, Robertson MC.* Oxidation of low-density lipoproteins from patients with renal failure or renal transplants. Kidney Int 1995;48:227–36.
35. *Maggi E, Bellazzi R, Falaschi F, Frattoni A, Perani G, Finardi G.* Enhanced LDL oxidation in uremic patient an additional mechanism for accelerated atherosclerosis? Kidney Int 1994;45:876–83.
36. *Reiner Z, Tedeschi-Reiner E.* Pathophysiology of atherosclerosis. The morphology and developmental levels of atherosclerotic changes. Liječ Vjesn 1990;112:118–23.
37. *Elisaf M, Bairaktari H, Tzallas C, Germanos N, Koulouridis E, Pappas M i sur.* Lipid parameters including Lp(a) in hemodialysis patients. Renal Failure 1994;16:501–9.
38. *Attman PO, Alaupovic P, Tavella M, Knight-Gibson C.* Abnormal lipid and apolipoprotein composition of major lipoprotein density classes in patients with chronic renal failure. Nephrol Dial Transplant 1996;11:63–9.
39. *Cressman MD, Heyaka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF.* Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. Circulation 1992;86:475–82.
40. *Kandoussi AM, Hugue V, Cachera C, Hazzan M, Dracon M, Tacquet A i sur.* Apo(a) phenotypes and Lp(a) concentrations in renal transplant patients. Nephron 1998;80(2):183–7.
41. *Panzetta O, Cominacini L, Garbin U, Fratta Pasini A, Gammaro L, Bianco F i sur.* Increased susceptibility of LDL to in vitro oxidation in patients on maintence hemodialysis: Effect of fish oil and vitamin E. Clin Nephrol 1995;44:303–9.
42. *Bartens W, Wanner C.* Lipoprotein(a): New insights into an atherogenic lipoprotein. Clin Invest 1994;72:558–67.
43. *Walker RJ, Sutherland WHF, Walker HL, MacMahon S, Robson RA.* Effect of treatment with simvastatin on serum cholesteryl ester transfer in patients on dialysis. Nephrol Dial Transplant 1997;12(1):87–92.
44. *Gehr TWB, Sica DA, Slugg PH, Hammett JL, Raymond R, Ford NF.* The pharmacokinetics of pravastatin in patients on chronic hemodialysis. Eur J Clin Pharmacol 1997;53(2):117–21.
45. *Nishizawa Y, Shoji T, Emoto M, Kawasaki K, Konishi T, Tabata T i sur.* Reduction of intermediate density lipoprotein by pravastatin in hemo- and peritoneal dialysis patients. Clin Nephrol 1995;43:268–77.
46. *Samuelsson O, Attman PO, Knight-Gibson C, Kron B, Larsson R, Mulec H i sur.* Effect of gemfibrozil on lipoprotein abnormalities in chronic renal insuffiency. A controled study in human chronic renal disease. Nephron 1997; 75:286–94.
47. *Nishikawa O, Mune M, Miyano M, Nishide T, Nishide I, Maeda A i sur.* Effect of simvastatin on lipid profile of hemodialysis patients. Kidney Int Suppl 1999;71:219–21.
48. *Thompson CH, Irish A, Kemp GJ, Taylor DJ, Radda GK.* Skeletal muscle metabolism before and after gemfibrozil treatment in dialysed patients with chronic renal failure. Clin Nephrol 1996;45(6):386–9.
49. *Elisaf M, Bairaktari E, Kaptopodis P, Pappas M, Sferopoulos G, Tziallas C i sur.* Effect of L-carnitine supplementation on lipid parameters in hemodialysis patients. Am J Nephrol 1998;18:416–21.
50. *Vlassopoulos D, Noussias C, Hadjipetrou A, Arvantis D, Logothetis E, Magana P i sur.* Long term effect of low molecular weight heparin on serum lipids in hypertrigliceridemic chronic hemodialysis patients. J Nephrol 1997;10:111–4.
51. *Leu JG, Liou HH, Wu SC, Yang WC, Huang TP.* Low molecular weight heparin in diabetic and nondiabetic hypercholesterolemic patients receiving long term hemodialysis. J Formos Med Assoc 1998;97:49–54.
52. *Sperschneider H, Deppisch R, Beck W, Wolf H, Stein G.* Impact of membrane choice and blood flow pattern on coagulation and heparin requirement-potential consequences on lipid concentrations. Nephrol Dial Transplant 1997;12(12):2638–46.
53. *Mak RH.* Effect of metabolic acidosis on hyperlipidemia in uremia. Pediatr Nephrol 1999;13:891–3.
54. *Bonnefont-Rousselot D, Lehman E, Jaudon MC, Delattre J, Perrone B, Rechke JP.* Blood oxidative stress and lipoprotein oxidizability in haemodialysis patients: effect of the use of vitamin E-coated dialysis membrane. Nephrol Dial Transplant 2000;15:2020–8.
55. *Seres DS, Strein GW, Hashim S, Goldberg IJ, Levin NW.* Improvement in lipoprotein profiles during high flux dialysis. J Am Soc Nephrol 1993;3: 1409–15.
56. *Josephson MA, Pellner SK, Dasisgupta A.* Improved lipid profiles in patient undergoing high flux dialysis. Am J Kidney Dis 1992;20:361–6.
57. *Blankestijn PJ.* Hemodialysis using high flux membranes improves lipid profiles. Clin Nephrol 1994;42:48–51.
58. *Goldberg IJ, Kaufman AM, Lavarias VA, Vann-Reyes T, Levin NW.* High flux dialysis membranes improve plasma lipoprotein profiles in patients with end-stage renal disease. Nephrol Dial Transplant 1996;11:104–7.
59. *Crawfor GA, Mahony JF, Stewart JH.* Impaired lipoprotein lipase activation by uraemic and posttransplant sera. Clin Sci 1981;60:73–80.
60. *Fishbane S, Bucala R, Pereira B, Founds H, Vlassara H.* Reduction of plasma apolipoprotein-B by effective removal of circulating glycation derivates in uremia. Kidney Int 1997;52:1645–50.
61. *Makita Z, Bucala R, Rayfield EJ, Friedman EA, Kaufman AM, Korbet SM i sur.* Reactive glycosylation endproducts in diabetic uremia and treatment of renal failure. Lancet 1994;343:1519–22.
62. *Ingram AJ, Parbtani A, Churcill DN.* Effects of two low-flux celulose acetate dialysers on plasma lipids and lipoproteins – A cross-over trial. Nephrol Dial Transplant 1998;13:1452–7.
63. *Horkko S, Huttunen K, Laara E, Kervinen K, Kesaniemi YA.* Effects of three treatment modes on plasma lipids and lipoproteins in uraemic patients. Ann Med 1994;26(4):271–82.
64. *Avram MM, Goldwasser P, Burrell DE, Antignani A, Fein PA, Mittman N.* The uremic dyslipidemia: A cross-sectional and longitudinal study. Am J Kidney Dis 1992;20(4):324–35.
65. *Allegra V, Martimbianco L, Vasile A.* Lipid and apolipoprotein patterns during erythropoietin therapy: Roles of erythropoietin, route of administration, and diet. Nephrol Dial Transplant 1997;12(5):924–32.
66. *Prata MM, Madeira C, Vicente O, Miguel MJP.* Lipid profile in haemodialysis patients treated with recombinant human erythropoietin. Nephrol Dial Transplan 1998;13(9):2345–7.
67. *Turk Z, Mrzljak V, Turk N, Metelko Z.* Changes of autoantibodies against oxidatively modified low density lipoproteins during long-term LDL-apheresis. Diabetes Nutr Metab 1999;12(6):413–7.