ORIGINAL ARTICLE

Dynamic changes of carotid artery intima-media thickness and mortality in hemodialysis patients

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Abstract
Introduction: Intima-media thickness (IMT) of the carotid artery is a widely accepted parameter for detection and quantification of atherosclerosis. The aim of the study was the evaluation of the impact of changes of IMT on the mortality of patients on hemodialysis.
Methods: The study was organized as a prospective and observational one. Intima-media thickness was determined by ultrasound in 194 patients who were evaluated every year during a three-year period. We analyzed the mortality rate of patients on hemodialysis in relation to their biochemical parameters, demographic and anthropometric characteristics, type of dialysis, smoking habits and statin therapy.
Results: Female gender and hemodiafiltration emerged as good predictors of long-term survival. Baseline IMT values were significantly lower than those at the end of the second ($p < 0.001$) and third years of the study ($p < 0.001$). The baseline values positively correlated with uric acid levels ($p = 0.027$) and body mass index ($p = 0.024$), while at the end of the second year, IMT positively correlated with LDL-cholesterol ($p = 0.037$) and triglyceride levels ($p = 0.018$) and body mass index ($p = 0.045$). Patients on hemodiafiltration had significantly higher values for erythrocytes ($p = 0.047$), hemoglobin ($p = 0.005$), creatinine ($p = 0.048$), Kt/V ($p = 0.026$), albumin ($p = 0.012$), LDL-cholesterol ($p < 0.001$), body mass index ($p < 0.001$),and lower IMT values at the end of the first year ($p = 0.039$), compared to patients on bicarbonate hemodialysis. Predictors of death were the duration of hemodialysis ($p < 0.001$), and IMT at the end of the first ($p = 0.008$) and second years of the study ($p = 0.005$).
Conclusion: Dynamic changes of IMT of the carotid arteries during the first two years were found in our study to be predictors of mortality in patients on hemodialysis. Hippokratia 2015; 19 (2):158-163.

Keywords: Dynamic changes, carotid intima media, atherogenesis, hemodialysis, mortality

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Introduction

In patients with severe forms of kidney disease, vascular changes occur most frequently in the early course of the disease and increase with disease progression[1]. Patients on hemodialysis (HD) have a higher risk of developing cardiovascular disease (CVD) and stroke, than the general population[2,3].

Changes in artery wall structure due to atherogenesis are reflected primarily by the thickening of the intima media (IM). Epidemiological population studies have established that IM thickness is a predictive morbidity risk factor in the general population. Moreover, these structural changes in the arterial wall are a reliable indicator of early atherosclerosis[4-7]. Consequently, measuring IM thickness of the carotid artery has been considered a generally accepted method for the detection and quantification of subclinical forms of cardiovascular disease. This diagnostic procedure for recording the morphology of the carotid artery is technically feasible with almost no risk to the patient; it can quantify atherosclerosis and can be used in studies of short duration. Moreover, it is not expensive and can be used with minimal financial resources[8-11].

The aim of this study was to determine the impact of dynamic changes of thickening IM of the carotid artery on the mortality of patients on HD.

Material and methods

Selection of patients

The survey was conducted at the Center of Nephrology and Dialysis, of the Clinical Center of Kragujevac, Serbia. In this prospective observational study, a total of 194 patients were monitored for a 3-year-period by the standard team of physicians.

The patient selection criteria included HD treatment for at least three months, and clinical stability as indicated by the absence of complications requiring hospitalization during the previous six months. The exclusion criteria were: previous history of cardiovascular or cerebrovascular complications, carotid artery surgery and chronic inflammation or cancer.

Most patients received HD for 10.5 to 12 hours per week, using commercially available dialysers for bicarbonate HD and hemodiafiltration (Fresenius Medical Care, Bad Homburg, Germany and Gambro AB, Lund, Sweden).

Biochemical tests

Blood samples were obtained in Vacutainer® tubes, in the middle of the week before dialysis. Plasma samples were stored at -20°C. Biochemical analyses were made using the flow cytometric method (Beckman Coulter Inc., Fullerton, CA, USA) or spectrophotometrically on an ILAB-600 instrument (Diamond Diagnostics - 333 Fiske Street Holliston, MA, USA) using original reagents. Low-density lipoprotein (LDL) was calculated using the Fridewold formula[12]. Serum iPTH was determined by radiometric immunoassay using a WIZARD® Gamma Counter (PerkinElmer, USA). Biochemical parameters represent average values of laboratory tests at the beginning, the middle and the end of the study.

Clinical, demographic and anthropometrical parameters

The age, sex and duration of HD expressed in months, were registered for all patients. The type of HD (bicarbonate/hemodiafiltration), the history of smoking habits and statin therapy were recorded. Adequacy of HD was calculated by the urea kinetic model Kt/V, according to the formula of Daugirdas[13].

Ultrasonography of the carotid arteries

Artery imaging was done on a SHIMADZU SDU-2200 instrument (Tokyo, Japan), using a 7.5 MHz high-resolution linear phased array, color imaging transducer. Wall thickness was not determined at the plaque containing sites. Standard measurements were made two cm above and below the carotid bifurcation, with three measurements on each side. IMT was derived as the mean of these six measurements[14]. Ultrasound measurements of IMT were performed at baseline (IMT0), and at the end of the first (IMT1), second (IMT2) and third years of observation (IMT3).

Statistics

Descriptive statistical parameters included mean, median and standard deviation (SD). The continuous variables were compared using either Student's t-test (for normal distribution) or the Mann-Whitney test (for non-normal distribution). The Wilcoxon rank sum test was deployed to estimate the statistical significance of the changes in IMT. Variables differing at a probability level of p<0.05 were included in Pearson's correlation and multiple linear regression analysis, to determine the relationship between the predictors and the survival rate (dependent variable). The Cox regression model was used for survival analysis and Kaplan-Meier analysis to determine the cumulative survival rates. The criterion for statistical significance was set at p <0.05. The statistical analysis was made using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and INSTAT software programs (GraphPad Software Inc., La Jolla, CA, USA).

Results

Out of a total of 194 patients with mean age 59 ± 11.2 years, 130 (67%) were men and 64 (33%) women. The average duration of HD was 94 ± 64 months. A total of 139 (71.6%) patients were active, or former smokers, and 34 (17.5%) received statin therapy. Less than two-thirds of the patients received bicarbonate HD while the rest were treated by hemodiafiltration (40%). The average value of IMT0 was 0.89 ± 0.19 mm, increasing to 0.93 ± 0.20 mm at the end of the first year, 1.06 ± 0.17 mm at the end of the second year and 1.12 ± 0.21 mm at the end of the study. Of note, 117 patients (60.3%) died during the three years of observation, most of them [67 patients (57%)] as a result of a cardiovascular event (Table 1).

A statistically significant, moderate-range correlation (r =0.365, p =0.02) was found between IMT0 and uric acid levels; an inverse, statistically significant, but weak correlation (r =-0.270, p =0.025) was observed between IMT0 and BMI. IMT1 values positively correlated with circulating uric acid concentration (r =0.342, p =0.027), while IMT2 was associated with LDL-cholesterol (r =0.605, p =0.037) and triglyceride levels (r =0.693, p =0.018) (Table 2).

Variables significant at p <0.05 were included in the multiple linear regression model to determine the relationship between these predictors and the duration of survival (dependent variable). The multiple linear regression model was not statistically significant (F =0.870; p =0.594).

The patients treated by hemodiafiltration were significantly younger (p <0.001), with a longer duration of HD (p =0.006), compared to patients receiving bicarbonate HD. The patients treated by hemodiafiltration had significantly higher value erythrocyte (p =0.047), hemoglobin (p =0.005), creatinine (p = 0.048), Kt/V (p =0.026), albumin (p =0.012) and LDL levels (p <0.001), as well as BMI (p <0.01), and lower average values of IMT1 (p = 0.039), compared to patients receiving bicarbonate HD (Table 3).

The Wilcoxon rank test showed significantly lower IMT1 than IMT2 values (z =-4.321, p <0.001). The difference between IMT2 and IMT3 was not statistically significant (z =-1.865, p =0062). On the other hand, the difference between IMT1 and IMT3 value was signifi-

Table 1: Basic demographic, anthropometric and clinical characteristics of the 194 patients on hemodialysis that were prospectively monitored for a 3-year-period.

Parameters	Total number of patients n = 194
Age [(months), (mean ± SD)]	59 ± 11.2
Gender (M/F)	130/64
Duration of HD [(months), (mean ± SD)]	94 ± 64
BMI (kg/m^2)	21 ± 5
Smoking history (yes/no)	139/55
Statin therapy (yes/no)	34/160
Type of HD (bicarbonate/hemodiafiltration)	116/78
IM thickness (mean ± SD)	
IMT0	0.89 ± 0.19
IMT1	0.93 ± 0.20
IMT2	1.06 ± 0.17
IMT3	1.12 ± 0.21
Exitus letalis (n/%)	117/60.3
Cause of death (n/%)	
Cardiovascular diseases	67/57.2
Infectious disease (sepsis)	19/16.3
Diabetes mellitus complication	13/11.1
Malignant diseases	18/15.4

SD: standard deviation, M: male, F: female, n: number, BMI: body mass index, IM: intima media, IM_0: baseline value for IM thickness, IM_1: IM at the end of the first year of study, IM_2: IM thickness in the middle of the study, IM_3: final IM thickness, HD: hemodialysis.

Table 2: Correlation of intima media thickness of the carotid artery, biochemical and clinical parameters, performed at baseline and at the end of the first, second and third years of observation.

	Correlation	P	HDL	Ur. acid	LDL	PTH	Urea	Creat	Glyc	Choles	Trigl	BMI	Ca x P
	r	-0.089	0.192	-0.365	-0.012	0.039	0.033	-0.104	-0.101	0.071	-0.200	-0.270	0.070
IM0	p	0.634	0.236	0.02*	0.950	0.753	0.792	0.402	0.417	0.665	0.216	0.025*	0.579
	n	30	30	30	30	30	30	30	30	30	30	30	30
	r	0.069	0.172	0.342	0.023	0.028	0.002	-0.175	-0.086	0.070	-0.186	0.266	0.047
IM1	p	0.576	0.277	0.027*	0.896	0.818	0.988	0.147	0.480	0.660	0.237	0.024*	0.699
	n	194	97	97	90	194	194	190	190	97	97	194	194
	r	-0.089	0.177	-0.159	0.605	0.132	0.110	-0.074	-0.059	-0.454	0.693	0.319	0.026
IM2	p	0.588	0.602	0.640	0.037*	0.430	0.505	0.653	0.722	0.161	0.018*	0.045*	0.860
	n	40	40	40	40	40	40	40	40	40	40	40	40
	r	-0.089				0.273	0.184	0.079	0.324			0.009	0.032
IM3	p	0.634				0.152	0.322	0.673	0.075			0.964	0.829
	n	33				33	33	33	33			33	33

IM: intima media, IM0: baseline value for IM thickness, IM_1 IM at the end of the first year of study, IM2: IM thickness in the middle of the study, IM3: final IM thickness, P: inorganic phosphorus, HDL: high density cholesterol, Ur. acid: uric acid, LDL: low density cholesterol, PTH: parathormone, Creat: creatinine, Glyc: glycemia, Choles: cholesterol, Trigl: triglycerides, BMI: body mass index, Ca x P, product of Ca and P, *statistically significant parameters, n: number.

cant ($z = -3.587$, $p < 0.001$).

Survival time was significantly shorter in male (95% CI: 40.01-56.41) than for female patients (95% CI: 52.74-74.13), $p < 0.05$ (Figure 1).

The bicarbonate dialysis patients (95% CI: 33.41-48.12) had a higher mortality rate when compared to patients on hemodiafiltration (95% CI: 73.09-84.56), $p < 0.001$ (Figure 2).

Discussion

It is generally accepted[1] that patients on HD have 10-20 times higher risk for cardiovascular disease and 5-10 fold higher incidence of stroke. These result from an atherogenic process, caused by a variety of metabolic disbalances, and can only partly be explained by the well-known reasons connected with the final stage of renal failure or the treatment method[15]. Some authors suggest that HD treatment leads to induction of the complement

Table 3: Examined parameters of the 194 patients on hemodialysis, according to type of hemodialysis.

Variables	Type of hemodialysis								p
	Bicarbonate hemodialysis				Hemodiafiltration				
	Mean	SD	Med	Min-Max	Mean	SD	Med	Min-Max	
Age	62.4	11.3	62.0	36-86	54.7	9.3	56.5	28-74	<0.01*
Duration of hemodialysis	81.2	58.8	69.5	8-300	112.3	67.9	92.0	18-299	<0.01*
IM0	0.9	0.2	0.9	0.6-1.5	0.8	0.2	0.8	0.6-1.3	0.053
IM1	1.0	0.2	0.9	0.6-1.5	0.9	0.2	0.9	0.6-1.4	0.039*
IM2	1.1	0.2	1.1	0.8-1.4	1.0	0.2	1.0	0.7-1.3	0.060
IM3	1.2	0.2	1.3	0.8-1.5	1.1	0.2	1.1	0.7-1.4	0.070
Leukocytes	6.9	2.2	6.6	2.9-19.6	6.7	2.0	6.5	2.4-12.9	0.467
Erythrocytes	3.1	0.5	3.2	1.3-4.5	3.2	0.5	3.2	2.3-4.5	0.047*
Hemoglobin	98.2	14.8	101.0	46-135	104.2	12.8	104.0	70-138	<0.01*
Urea	24.3	6.6	24.0	10.6-45.6	22.6	5.1	22.8	12.0-33.7	0.056
Creatinine	887.9	223.4	886.0	356-1564	958.3	254.9	951.0	354-1683	0.048*
Kt/V	1.0	0.2	1.0	0.7-1.6	1.1	0.2	1.0	0.8-1.6	0.026*
Glycemia	6.4	2.2	6.0	2.8-19.4	6.5	3.3	5.5	3.7-26.6	0.163
Total cholesterol	4.3	1.2	4.2	1.7-6.6	4.5	1.3	4.6	2.8-5.9	0.813
Triglycerides	2.0	1.3	1.7	0.5-7.1	2.0	1.1	2.2	0.8-3.0	0.898
Total protein	67.0	6.3	67.0	48-88	66.3	5.5	66.5	46-80	0.277
Albumin	38.2	4.2	38.5	24-50	40.6	5.3	40.0	26-67	0.012*
Na	139.7	3.5	140.0	131-149	139.7	3.3	140.0	128-152	0.958
K	5.2	0.7	5.2	3.1-7.3	5.2	0.7	5.2	3.9-7.6	0.976
Ca	2.3	0.2	2.3	1.7-2.8	2.4	0.2	2.4	2.0-3.0	0.368
P	1.5	0.6	1.5	0.6-4.7	1.7	0.6	1.5	0.4-3.2	0.086
HDL	1.0	0.2	1.0	0.5-1.5	1.0	0.1	1.0	0.9-1.1	0.80
Uric Acid	344.3	98	350.5	3.0-573.0	356.8	71.3	327.5	310-462	0.807
LDL	3.5	1.9	2.7	0.8-7.4	7.0	1.1	6.6	6.3-8.9	<0.001*
PTH	358.8	438.5	193.0	2.4-2908.0	509.0	598.8	206.0	1.6-2138.0	0.164
Ca x P	9.7	64.0	3.3	1.3-675.0	3.8	1.4	3.5	1.0-7.6	0.140
BMI	20.6	4.4	20.0	14.0-34.8	24.0	5.6	24.0	15.1-42.0	<0.001*

IM: intima media, IM0: baseline value for IM thickness, IM1: IM at the end of the first year of study, IM2: IM thickness in the middle of the study, IM3: final IM thickness, Kt/V: adequacy hemodialysis, Na: sodium, K: potassium, Ca: calcium, P: inorganic phosphorus, HDL: high density cholesterol, LDL: low density cholesterol, PTH: parathormone, BMI: body mass index, Ca x P: product of Ca and P, *statistically significant difference.

system and increased levels of proinflammatory cytokines, which can stimulate atherogenesis. On the other hand, hemodiafiltration might be a way to reduce inflammation in chronic HD patients, although the findings of certain studies[16] do not support a protective role for hemodiafiltration in regard to inflammation. However, studies based on sophisticated parameters of endothelial dysfunction have clearly shown a reduction of inflammatory process and better preservation of the endothelial function as compared with HD[17]. The field of atherogenesis events in chronic uremia is even more focused on metabolic changes, in response to major injury of the endothelial and smooth muscle cells of the arterial walls[18,19]. The results of many clinical investigations[14], including our previous research[14], have shown that measuring the thickness of the IM is useful for the noninvasive assessment of cardiovascular risk. Brzosko et al[20] and Kablak-Ziembicka et al[21] found greater thickness of IM in men, which was confirmed in the current study.

As shown by the results of the Cox regression model, male gender was related to a shorter life expectancy, although other authors have reported different findings[22]. Survival of our patients on hemodiafiltration was significantly longer than those who were given bicarbonate HD, which is consistent with the results from recent clinical trials. This is probably due to the enhanced clearance of small and medium-sized molecules, improved hemodynamic stability and reduced activation of the complement system during hemodiafiltration[23-27].

The CONTRAST study[28] indicated an influence of hemodiafiltration on IM thickness of the carotid arteries. This effect improves the biocompatibility of the dialysis system and reduces its inflammatory impact, and this is reflected by a lessening of the atherogenic profile, which ultimately reduces the possibility of progressive thickening of the carotid artery IM.

Many studies have indicated that uric acid may be a relevant parameter and an independent risk factor for CVD, but the mechanism remains unclear. It is assumed that endothelial dysfunction could predispose to oxida-

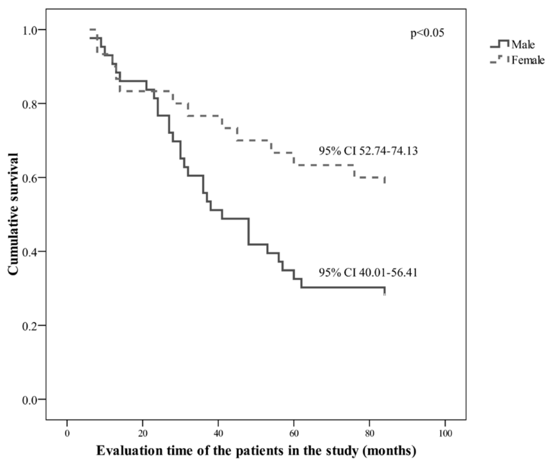

Figure 1: Kaplan-Meier survival curves of of the 194 patients on dialysis in relation to their gender.

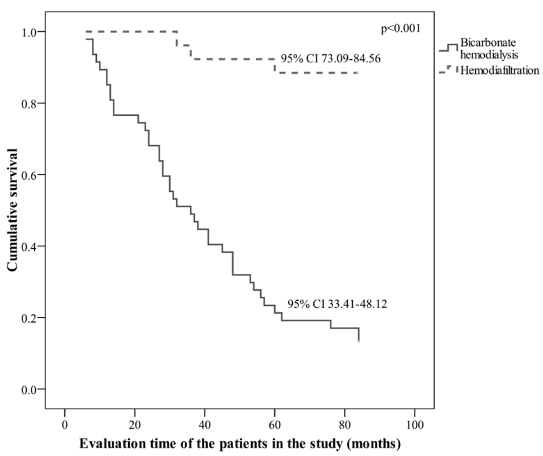

Figure 2: Kaplan-Meier survival curves of the 194 patients in relation to type of dialysis.

tive stress. A high concentration of uric acid in patients with arterial hypertension is considered to be an integral part of the complex biochemical changes that characterize the metabolic syndrome[29]. Our results, which showed a positive correlation between IM thickness of the carotid arteries and uric acid concentration, support the view that both these parameters should be included among the components of the metabolic syndrome.

A potential explanation for the lack of effectiveness of statin therapy to reduce CVD in HD patients suggests that cholesterol does not have crucial atherogenic potential in this population[30-33]. Thus, results of the AURORA study[34] showed that lowering the peripheral cholesterol level with statin therapy does not necessarily reduce cardiovascular risk and this state is known as an inconsistent (or inverse) relationship between cholesterol concentration and outcomes in patients undergoing HD. However, hypertriglyceridemia is a major feature of uremic dyslipidemia, and many studies support the idea of the extreme atherogenic capacity of triglycerides and their contribution to atherosclerosis[30-34]. Our results showed a positive correlation between triglyceride concentrations and carotid artery IM thickness, confirming that triglycerides had a significant atherosclerotic capacity.

Progression of the mean IM thickness was more apparent during the second year of our study than during the final year. Elevated levels of creatinine, albumin, LDL-cholesterol and BMI in hemodiafiltration patients, compared to those treated by bicarbonate dialysis, probably indicate the impact of favorable nutritional parameters - an important survival factor for patients on HD, as pointed out earlier[35]. The lower mortality and the reduced progression of IM thickness between the second and third year were probably due to the introduction of hemodiafiltration treatment, which may also significantly decelerate the course of atherogenesis.

Limitations

The present study has some limitations. Inclusion criteria were very strict (aforementioned in the methodology), thus limiting the size of the examined group.

A comprehensive approach to the problem of atherosclerosis in HD patients requires further engagement with the aim of organizing a well-stratified study, with a larger number of respondents, especially through evaluation of survival rates of patients in relation to carotid artery IMT. Our results may represent a rational basis for a larger study aimed at assessing the clinical relevance and the impact of progressive thickening of the carotid artery IM on mortality of HD patients.

Conclusion

Women and patients on hemodiafiltration have a higher survival rate. Elevated concentrations of lipid fractions were positively correlated with carotid IMT. Dynamic changes in IMT characterized the patients who died during our study. Thus, increasing IMT of carotid arteries, and duration of dialysis were significant predictors of mortality among patients in our study.

Conflict of interest

The authors state no conflict of interest.

References

1. London GM. Cardiovascular calcifications in uremic patients: clinical impact on cardiovascular function. J Am Soc Nephrol. 2003; 14: S305-S309.
2. Segura J, Campo C, Roldán C, Christiansen H, Vigil L, García-Robles R, et al. Hypertensive renal damage in metabolic syndrome is associated with glucose metabolism disturbances. J Am Soc Nephrol. 2004; 15 Suppl 1: S37-S42.
3. Dursun B, Dursun E, Suleymanlar G, Ozben B, Capraz I, Apaydin A, et al. Carotid artery intima-media thickness correlates with oxidative stress in chronic haemodialysis patients with accelerated atherosclerosis. Nephrol Dial Transplant. 2008; 23: 1697-1703.
4. Szeto CC, Chow KM, Woo KS, Chook P, Ching-Ha Kwan B, Leung CB, et al. Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. J Am Soc Nephrol. 2007; 18: 1966-1972.

5. Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM, et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. Eur Heart J. 2007; 28: 2094-2101.
6. Modi N, Kapoor A, Kumar S, Tewari S, Garg N, Sinha N. Utility of carotid intimal medial thickness as a screening tool for evaluation of coronary artery disease in pre-transplant end stage renal disease. J Postgrad Med. 2006; 52: 266-270.
7. Sánchez-Alvarez JE, Delgado-Mallén P, González-Rinne A, Hernández-Marrero D, Lorenzo-Sellare V. [Carotid ultrasound: prevention of heart disease and mortality on haemodialysis]. Nefrologia. 2010; 30: 427-434.
8. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N,et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis. 2007; 23: 75-80.
9. Baroncini LA**,** de Oliveira A**,** Vidal EA**,** França GJ**,** Stahlke PS**,** Alessi A, et al. Appropriateness of carotid plaque and intima-media thickness assessment in routine clinical practice. Cardiovasc Ultrasound. 2008; 6: 52.
10. Lundby-Christensen L, Almdal TP, Carstensen B, Tarnow L, Wiinberg N. Carotid intima-media thickness in individuals with and without type 2 diabetes: a reproducibility study. Cardiovasc Diabetol. 2010; 9: 40.
11. Espeland MA, O'leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. Curr Control Trials Cardiovasc Med. 2005; 6: 3.
12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18: 499-502.
13. Daugirdas JT. Chronic haemodialysis prescription: A urea kinetics approach. Daugirdas J, Ing TS (eds). Handbook of Dialysis. Little Brown, Boston, 1994, 92-120.
14. Stolić R, Trajković G, Jovanović A, Stolić D, Perić V, Sovtić S, et al. Carotid ultrasonographic parameters as markers of atherogenesis and mortality rate in patients on hemodialysis. Vojnosanit Pregl. 2010; 67: 916-922.
15. Seliger SL, Gillen DL, Tirschwell D, Wasse H, Kestenbaum BR, Stehman-Breen CO. Risk factors for incident stroke among patients with end-stage renal disease. J Am Soc Nephrol. 2003; 14: 2623-2631.
16. Oates T, Pinney JH, Davenport A. Haemodiafiltration versus high-flux haemodialysis: Effects on phosphate control and erythropoietin response. Am J Nephrol. 2011; 33: 70-75.
17. Ramirez R, Carracedo J, Merino A, Nogueras S, Alvarez-Lara MA, Rodríguez M, et al. Microinflammation induces endothelial damage in hemodialysis patients: the role of convective transport. Kidney Int. 2007; 72: 108-113.
18. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int. 2001; 59: 407-414.
19. van den Berg E, Biessels GJ, Stehouwer CD, Kappelle LJ, Heine RJ, Nijpels G, et al. Ten-year time course of risk factors for increased carotid intima–media thickness: the Hoorn Study. Eur J Cardiovasc Prev Rehabil. 2010; 17: 168-174.
20. Brzosko S, Lebkowska U, Malyszko J, Hryszko T, Krauze-Brzosko K, Mysliwiec M. Intima media thickness of common carotid arteries is associated with traditional risk factors and presence of ischaemic heart disease in hemodialysis patients. Physiol Res. 2005; 54: 497-504.
21. Kablak-Ziembicka A, Przewlocki T, Tracz W, Pieniazek P, Musialek P, Sokolowski A. Gender differences in carotid intima-media thickness in patients with suspected coronary artery disease. Am J Cardiol. 2005; 96: 1217-1222.
22. Szeto CC, Chow KM, Woo KS, Chook P, Ching-Ha Kwan B, Leung CB, et al. Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. J Am Soc Nephrol. 2007; 18: 1966-1972.
23. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006; 69: 2087-2093.
24. Pedrini LA, De Cristofaro V, Pagliari B, Samà F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000; 58: 2155-2165.
25. van der Weerd NC, Penne EL, van den Dorpel MA, Grooteman MP, Nube MJ, Bots ML, et al. Haemodiafiltration: promise for the future? Nephrol Dial Transplant. 2008; 23: 438-443.
26. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009; 4: 1944-1953.
27. Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nubé MJ, et al; the CONTRAST study group. Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis patients - the Dutch CONvective TRAnsport STudy (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN38365125]. Curr Cont Trials Cardiovasc Med. 2005; 6: 8.
28. Zoccali C, Maio R, Mallamaci F, Sesti G, Perticone F. Uric acid and endothelial dysfunction in essential hypertension. J Am Soc Nephrol. 2006; 17: 1466-1471.
29. Bots ML, Baldassarre D, Simon A, de Groot E, O'Leary DH, Riley W, et al. Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? Eur Heart J. 2007; 28: 398-406.
30. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham study. JAMA. 1986; 256: 2835-2838.
31. Kannel WB, Neaton JD, Wentworth D, Thomas HE, Stamler J, Hulley SB, et al. Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. Multiple Risk Factor Intervention Trial. Am Heart J. 1986; 112: 825-836.
32. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA. 1988; 260: 641-651.
33. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med. 2001; 161:1413-1419.
34. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009; 360: 1395-1407.
35. Stolic R, Trajkovic G, Stolic D, Peric V, Subaric-Gorgieva G. Nutrition parameters as hemodialysis adequacy markers. Hippokratia. 2010; 14: 193-197.