Original Article

Association between Ophthalmological Changes and Cardiovascular Diseases in Patients with Chronic Kidney Disease Undergoing Hemodialysis

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Aims: Patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) have a high prevalence of cardiovascular diseases (CVD). Arterial sclerosis plays an important role in the pathogenesis of CVD. However, to date, there have been no reports of assessment of the association between retinal arterial sclerosis and CVD in patients with CKD on HD. The aim of this study was to assess retinal arterial sclerosis and to investigate the relationship between retinal arterial changes in patients with CKD on HD and arterial stiffness/past history of CVD.

Methods: We examined the data of 44 patients (21 female, 23 male) with CKD receiving HD treatment at Saiseikai Kurihashi Hospital. The relationship between ophthalmological changes and arterial stiffness [pulse wave velocity (PWV)] or past history of CVD was evaluated. All medications being taken were recorded, and biochemical parameters were analyzed.

Results: Significant correlations were found between the presence of arteriosclerotic retinopathy [Scheie classification S grade (grade 0: 7 patients, grade 1: 18 patients, grade 2: 14 patients, grade 3: 4 patients, and grade 4: 1 patient)] and results of the evaluation of arterial stiffness (PWV) and past history of CVD ($p=0.001$, $p=0.045$). Other ophthalmological findings were not associated with a history of CVD or arterial stiffness.

Conclusion: We showed that the classification (Scheie S grade) of retinopathy on ophthalmoscopic examination may be a useful tool for predicting arterial stiffness and its association with CVD.

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Key words: Retinal arterial sclerosis, Chronic kidney disease on hemodialysis, Arterial stiffness, Cardiovascular disease

Introduction

Arteriosclerotic retinopathy is characterized by medial layer hypertrophy, hyalinization of the intima, and hyperplasia of the endothelial layer of the vessel wall¹⁾. It is usually associated with progressive hardening of blood vessels due to the loss of elastic tissue and calcification.

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Ophthalmoscopic examination is widely used in clinical practice to examine the presence and degree of arteriolar retinopathy and offers a unique noninvasive opportunity to assess the status of systemic arteriosclerosis^{2,3)}. Presence of retinopathy has been shown to be associated with an increased risk of death in the general population^{4,6)}. Both retinal and coronary arteries raising tortuosity are characterized by blood vessel abnormalities, particularly abnormal twists and turns⁷⁾. The retinal arterioles exhibit similar anatomical and physiological characteristics to the coronary microcirculation. Therefore, retinal microvascular disease may also reflect the presence of systemic microvascular disease^{2,8)}. Factors such as smoking, inflammation, and

Table 1. Scheie Classification

(A) Atherosclerosis retinopathy	
S Grade	Observation
0	Normal
1	There is broadening of the light reflex from the arteriole, with minimal or no arteriovenous compression.
2	Light reflex changes and crossing changes are more prominent.
3	The arterioles have a copper wire appearance, and there is more arteriovenous compression.
4	The arterioles have a silver wire appearance, and arteriovenous crossing changes are most severe.
(B) Hypertensive retinopathy	
H Grade	Observation
0	Normal
1	Barely detectable arterial narrowing
2	Obvious arterial narrowing with focal irregularities plus light reflex changes
3	Grade 2 plus retinal hemorrhages and/or exudate
4	Grade 3 plus papilledema

oxidative stress that are associated with free radical formation have been identified as possible risk factors for both systemic atherosclerosis and arteriolar retinopathy^{9, 10}.

Recently, it was reported that among the 7640 adults from the National Health and Nutrition Examination Survey, 4.6% had retinopathy and 15% had chronic kidney disease (CKD). The prevalence of retinopathy in patients with CKD was 11%. The presence of retinopathy was a strong predictor of mortality in the adult population with CKD¹¹. However, no sub-analysis of patients with CKD undergoing hemodialysis (HD) was performed. In patients undergoing HD, atherosclerosis is usually advanced, and arterial thickening, stiffening, and calcification are accelerated by 10–20 years as compared with the rates in age-matched healthy subjects^{12, 13}. Patients with CKD undergoing HD have a very high prevalence of cardiovascular risk factors as compared to the general population and approximately 40% have clinical coronary artery disease¹⁴. The potentially life-threatening cardiovascular sequelae of uremia include vascular changes, such as tortuosity, dilatation, and calcification of arteries, and cardiac lesions, including coronary artery thrombosis and calcification of heart valves. The clustering of several risk factors in patients with end-stage renal disease (ESRD) places them at a unique risk. The risk factors in this patient population can be grouped as follows: (1) traditional risk factors, e.g., age, sex, hypertension, dyslipidemia, smoking, and diabetes, (2) factors unique to patients with ESRD, such as anemia, hormones, and an elevated calcium–phosphorus product, and (3) “emerging” risk factors,

including inflammation^{15, 16}.

To date, there have been no reports of assessment of the association between retinal arterial sclerosis in patients with CKD undergoing HD and risk of CVD. The aim of this study was to assess retinal arterial sclerosis and to investigate the relationship between retinal arterial changes in patients with CKD on HD and arterial stiffness/past history of CVD.

Methods

Subjects

We examined the data of 44 patients with CKD who were undergoing HD at Saiseikai Kurihashi Hospital between July and December 2014. The number of cases undergoing HD at this hospital during the study period determined the sample size. The Research Ethics Board of Saiseikai Kurihashi Hospital approved the study protocol. All patients gave written informed consent for participation in the study. The underlying CKD was chronic glomerulonephritis in 19 patients (43.2%); diabetic nephropathy in 7 patients (15.9%); nephrosclerosis in 6 patients (13.6%); polycystic kidney disease, lupus nephritis, and ANCA-associated vasculitis in 2 patients each; and unknown in 6 cases.

The ophthalmological changes [intraocular pressure (IOP), central corneal thickness (CCT), and ophthalmoscopic examination] in each participant were evaluated by a retinal specialist (C.S) who was unaware of the patients' backgrounds determined the classification. IOP and CCT were measured with noncontact tonometer (TX-20P, Canon Corp, Osaka, Japan). After mydriasis, a fundus photograph, including the optic

disc and macula, was taken of one eye in each participant.

Fundus photography was performed with a fundus camera with a 50° angle (TRC50LX; Topcon Corp, Tokyo, Japan). Retinal arteriosclerosis was confirmed by slit-lamp examination with super-field non-contact lens (Volk Optical Inc, Mentor, OH, USA) and fundus photography. The retinal arteriosclerosis was graded according to the Scheie classification for arteriosclerosis^{17, 18)} (**Table 1**).

We used the brachial-ankle pulse wave velocity (baPWV) as a marker of arterial stiffness. PWV was measured using an automatic waveform analyzer (form PWV/ABI; Colin, Co., Ltd., Komaki, Japan), as described previously¹⁹⁾. All individuals were examined after they had rested in the supine position for at least 5 min. The aortic calcification index (ACI) was measured on abdominal CT²⁰⁾.

The systolic and diastolic blood pressure (SBP and DBP, respectively), body mass index (BMI), serum albumin (Alb), serum total cholesterol (TC), serum low-density lipoprotein cholesterol (LDL-C), serum triglycerides (TG), fasting blood glucose (FBG), and serum Ca, P, Ca-P product (Ca × P), intact parathyroid hormone (iPTH), hemoglobin (Hb), and C-reactive protein (CRP) levels were measured at the time of ophthalmoscopic examination. The presence/absence of CVD (history of myocardial infarction, angina pectoris, stroke, or peripheral arterial occlusive disease) and information on whether patients were smokers or receiving antihypertensive medication and/or statins were obtained from medical charts and analyzed. Of the 44 patients, 13 (29.5%) were taking renin-angiotensin system blockers, including angiotensin II receptor blockers (ARBs), 12 (27.3%) were taking calcium-channel blockers, 9 (20.5%) were taking beta-blockers, and 16 (36.4%) were taking statins.

Statistical Analysis

Descriptive statistics are expressed as frequencies and proportions for categorical variables and means ± standard deviation for continuous variables. Differences between two groups were determined by the *t* test or the χ^2 test. The odds ratio (OR) and 95% confidence interval (95% CI) used Woolf's method to evaluate the presence of CVD compared with no CVD history. The correlations between variables were evaluated by determining the Pearson's (for parametric data) or Spearman's (for nonparametric data) correlation coefficients, as appropriate. Multiple linear regression analysis was performed to evaluate the contribution of each risk factor to the presence of CVD. *P* values of <0.05 were considered as denoting statistical

Table 2. Patients' characteristics

Parameter	
N	44
Age	65.8 ± 10.0
Sex (male, female)	m:23 f:21
Body mass index (kg/m ²)	20.0 ± 6.7
Duration of hemodialysis (y)	10.1 ± 7.5
High-flux dialysis	44
DM (n)	7
CVD (n)	6
Smokers (Current, Former: n)	12 (8, 4)
SBP (mmHg)	137.4 ± 19.7
DBP (mmHg)	78.7 ± 15.6
PWV	2035.0 ± 472.9
ABI	1.2 ± 0.2
ACI	39.7 ± 30.1
Alb (g/dL)	3.5 ± 0.3
Ca (mg/dL)	9.1 ± 0.6
P (mg/dL)	5.3 ± 1.0
PTH intact (pg/mL)	188.5 ± 187.1
CRP (mg/dL)	0.4 ± 1.0
Hb (g/dL)	10.8 ± 0.8
Ca × P	48.2 ± 10.4
Glu (mg/dL)	112.8 ± 39.9
HbA1c (%)	6.3 ± 1.0
TC (mg/dL)	145.3 ± 30.9
TG (mg/dL)	95.1 ± 42.7
LDL-C (mg/dL)	70.6 ± 25.3
Medication	
Statin (n)	16
RAS-b (n)	13
CCB (n)	12
β-b (n)	9
Insulin (n)	2
Antiplatelet agents (n)	8
Warfarin sodium (n)	4
ophthalmological examination	
IOP (mmHg)	13.8 ± 3.1
CCT (μm)	554.3 ± 28.4
Scheie classification	
H grade 0	7
grade 1	16
grade 2	18
grade 3	3
grade 4	0
S grade 0	7
grade 1	18
grade 2	14
grade 3	4
grade 4	1

DM: diabetes mellitus, CVD; cardiovascular disease, SBP; systolic diastolic blood pressure, DBP; diastolic blood pressure, PWV; pulse wave velocity, ABI; ankle-brachial pressure index, ACI; aortic calcification index, iPTH; intact parathyroid hormone, CRP; C-reactive protein, Hb; hemoglobin, Glu; glucose, TC; total cholesterol, LDL-C; low-density lipoprotein cholesterol, TG; triglycerides, RAS-b; renin-angiotensin system blockers, CCB; calcium-channel blockers, β-b; beta-blockers, IOP; intraocular pressure, CCT; central corneal thickness, H; Scheie classification H grade, S; Scheie classification S grade

Table 3-1. Number of patients in Scheie classification

	S0	S1	S2	S3	S4
H0	5	2	0	0	0
H1	2	8	6	0	0
H2	0	6	7	4	0
H3	0	2	1	0	0
H4	0	0	0	1	0

H; Scheie classification H grade, S; Scheie classification S grade

Table 3-2. Ratio of cardiovascular disease in patients with retinopathy of Scheie classification

	S0	S1	S2	S3	S4
H0	0/5 (0%)	0/2 (0%)	–	–	–
H1	0/2 (0%)	1/8 (12.5%)	1/6 (16.7%)	–	–
H2	–	0/6 (0%)	1/7 (14.3%)	2/4 (50%)	–
H3	–	0/2 (0%)	0/1 (0%)	–	–
H4	–	–	–	1/1 (100%)	–

H; Scheie classification H grade, S; Scheie classification S grade

significance. All statistical analyses were performed using statistical software JMP version 11.2 (SAS, Cary, NC, USA).

Results

The profile of patients and ophthalmological changes are shown in **Table 2**. According to Scheie's classification, 7 (15.9%), 18 (40.9%), 14 (31.8%), 4 (9.1%), and 1 (2.3%) of the 44 patients showed grade 0, 1, 2, 3, and 4 arteriosclerotic (S) changes, respectively, and 7 (15.9%), 16 (36.4%), 18 (40.9%), and 3 (6.8%) of the 44 patients showed grade 0, 1, 2, and 3 hypertensive (H) changes, respectively. In addition, combination H and S was shown in **Table 3-1**.

We examined the factors related to ophthalmological changes. Correlations were found between arteriosclerotic retinopathy (Scheie classification S grade) and age and PWV [$p=0.026$, and $p=0.001$, respectively (**Table 4-1**)], and association between arteriosclerotic retinopathy (Scheie classification S grade) and history of CVD was significantly different [$p=0.045$ (**Table 4-2**)]. On the other hand, the presence of hypertensive retinopathy (Scheie classification H grade) was significantly correlated with male gender, smoking, and RAS blocker use ($p=0.0002$, $p=0.038$, and $p=0.017$, respectively) (**Fig. 1** and **Table 4**). There were no statistically significant associations between other ophthalmological parameters (IOP and CCT) and presence of arteriosclerotic retinopathy or atherosclerotic risk factors. No correlation was found between a

history of CVD and PWV, age, gender or smoking status (data not shown).

We performed a multivariate logistic regression analysis to identify determinants of the presence of CVD using the S grade, H grade, PWV, age, gender, smoking status, and diabetes mellitus, and only the S grade was found to be significantly associated with the presence of CVD ($p=0.04$) (data not shown). The association between the presence of CVD and severity grades on Scheie classification are shown in **Table 3-2**. There were six patients with CVD, including one of the eight patients with H1S1 [$p=0.92$, OR 0.88 (95% CI 0.04–6.76)], one of the six patients with H1S2 [$p=0.82$, OR 1.32 (95% CI 0.82–10.82)], one of the seven patients with H2S2 [$p=0.96$, OR 1.07 (95% CI 0.05–8.38)], two of the four patients with H2S3 [$p=0.06$, OR 9 (95% CI 0.89–95.33)], and one patient with H4S3 [$p=0.04$, OR 3*107 95% CI 1.19–)].

Discussion

Among the noninvasive and direct diagnostic tests for arterial sclerosis, fundus examination is the most useful. The Keith Wagener classification of fundoscopic changes is not very helpful as it combines the arteriosclerotic and hypertensive changes. In 1953, Scheie classified arteriosclerotic and hypertensive changes separately^{17, 18, 21}), as shown in **Table 1**. Therefore, we estimated the severity of arteriosclerotic and hypertensive changes according to Scheie's classification. In general, hypertensive changes parallel the clinical sever-

Table 4-1. Associations between ophthalmological changes and factors for atherosclerosis

parameter	Hypertensive retinopathy (H)		Arteriosclerosis retinopathy (S)	
	σ	p value	σ	p value
Age	0.248	0.105	0.335	0.026 *
Dry Weight	-0.304	0.059	-0.185	0.246
Body mass index (kg/m ²)	-0.095	0.551	0.068	0.671
Duration of hemodialysis	0.120	0.439	0.046	0.768
SBP	0.264	0.104	0.303	0.061
DBP	0.130	0.430	0.148	0.367
PWV	0.271	0.087	0.488	0.001 *
ABI	0.171	0.279	-0.201	0.202
ACI	-0.039	0.829	0.063	0.729
Alb	-0.102	0.510	-0.085	0.585
Ca	-0.058	0.706	-0.033	0.832
P	-0.083	0.594	-0.190	0.218
iPTH	-0.042	0.787	0.113	0.464
CRP	-0.138	0.372	0.047	0.764
Hb	0.262	0.099	0.071	0.661
Ca $\times$ P	-0.128	0.408	-0.159	0.302
Glu	-0.075	0.635	0.108	0.490
Tcho	0.029	0.855	-0.143	0.361
TG	-0.154	0.326	-0.183	0.241
LDL	-0.001	0.993	-0.145	0.354
IOP	-0.017	0.913	0.073	0.636
CCT	-0.266	0.081	-0.092	0.554

SBP; systolic diastolic blood pressure, DBP; diastolic blood pressure, PWV; pulse wave velocity, ABI; ankle-brachial pressure index, ACI; aortic calcification index, iPTH; intact parathyroid hormone, CRP; C-reactive protein, TC; total cholesterol, LDL-C; low-density lipoprotein cholesterol, TG; triglycerides, IOP; intraocular pressure, CCT; central corneal thickness

Table 4-2. Associations between ophthalmological changes and factors for atherosclerosis

parameter	Hypertensive retinopathy (H)		Arteriosclerosis retinopathy (S)	
	kai ²	p value	Kai ²	p value
Sex (male, female)	19.683	0.0002 *	8.137	0.087
DM	1.690	0.639	6.356	0.174
CVD	3.925	0.270	9.743	0.045 *
Smoker	8.447	0.038 *	5.166	0.271
statin	8.294	0.04 *	2.833	0.586
RAS-b	10.228	0.017 *	1.460	0.834
CCB	2.646	0.449	5.354	0.253
Beta-blocker	0.566	0.904	2.133	0.711
insulin	1.090	0.772	1.366	0.850
antiplatelet agents	2.949	0.400	5.290	0.266
Warfarin sodium	1.077	0.783	6.062	0.195
H			29.136	0.004 *
S	29.136	0.004 *		

DM; diabetes mellitus, CVD; cardiovascular disease, RAS-b; renin-angiotensin-system blockers, CCB; calcium-channel blockers, β -b; beta-blockers, H; Scheie classification H grade, S; Scheie classification S grade

Fig. 1-1. Relationship between the PWV level and retinal hypertensive degree (Scheie classification H grade). There was no correlation between the PWV level and retinal hypertensive degree (Scheie classification H grade).

Fig. 1-2. Relationship between the PWV level and retinal arteriosclerosis degree (Scheie classification S grade). There was a direct linear correlation between the PWV level and retinal arteriosclerotic degree (Scheie classification S grade) ($r^2=0.68$, $p=0.001$ by Spearman's correlation coefficients)

ity of hypertension, while atherosclerotic changes give an indication about the sequential morphological changes of blood vessels associated with prolonged or severe hypertension. The former is potentially more reversible than the latter²²). In this study, we revealed the presence of a significant relationship between the presence of CVD and arteriosclerotic retinopathy but not hypertensive retinopathy.

According to the HEMO study in the United States, evaluated morbidity and mortality of HD patients, the uremic milieu, and the hemodialysis procedure itself were likely to be contributory to CVD. High-flux dialysis might have a beneficial effect on cardiac outcomes²³). On the other hand, high blood pressure or high cholesterol levels are not risk factors for CVD²⁴).

Of the 44 patients, while 39 (88.6%) had arteriosclerotic or hypertensive retinopathy, only six patients (13.6%) had CVD. As among the reasons for this finding, we speculated that the percentage of patients with diabetes mellitus in our study population was low (15.9%) and that the patients were adequately treated with RAS blockers and high-flux dialysis. While we could identify that age is a traditional risk factor for atherosclerosis, we could not identify any risk factors unique to patients with ESRD, such as anemia or an elevated Ca-P product or any "emerging" risk factors.

The limitations of this study were that it was not a single-center trial and the number of patients enrolled was small.

We are the first to report on the assessment of the correlation between retinal arterial sclerosis in patients with CKD undergoing HD and the presence of CVD. There was a significant relationship between retinal changes in patients with CKD on HD and arterial stiffness and past history of CVD. Fundus examination was found to be a useful tool for determining arteriosclerotic changes and may be considered as a radical tool for prognostic factor of CVD for HD patients.

Conflicts of Interest

None.

Reference

- 1) Teikari JM, Laatikainen L, Rapola JM, Virtamo J, Haukka J, Liesto K, Taylor P, Heinonen OP: Retinal vascular changes following supplementation with alpha-tocopherol or betacarotene. *Acta Ophthalmol Scand*, 1998; 76: 68-73
- 2) Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ: Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol*, 2001; 46: 59-80
- 3) Luo BP, Brown GC: Update on the ocular manifestations

- of systemic arterial hypertension. *Curr Opin Ophthalmol*, 2004; 15: 203-210
- 4) Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM: Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*, 2003; 110: 933-940
 - 5) Kramer CK, Rodrigues TC, Canani LH, Gross JL, Azevedo MJ: Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: meta-analysis of observational studies. *Diabetes Care*, 2011; 34: 1238-1244
 - 6) Hirai FE, Moss SE, Kundtson MD, Klein BE, Klein R: Retinopathy and survival in a population without diabetes: the BeaverDam Eye Study. *Am J Epidemiol*, 2007; 166: 724-730
 - 7) Owen CG, Rudnicka AR, Nightingale CM, Mullen R, Barman SA, Sattar N, Cook DG, Whincup PH: Retinal arteriolar tortuosity and cardiovascular risk factors in a multi-ethnic population study of 10-year-old children; the Child Heart and Health Study in England (CHASE) *Arterioscler Thromb Vasc Biol*, 2011; 31: 1933-1938
 - 8) Hu R, Zhang XX, Wang WQ, Lau CP, Tse HF: Smoking, homocysteine and degree of arteriolar retinopathy. *Atherosclerosis*, 2005; 183: 95-100
 - 9) Yung LM, Leung FP, Yao X, Chen ZY, Huang Y: Reactive oxygen species in vascular wall. *Cardiovasc Hematol Disord Drug Targets*, 2006; 6: 1-19
 - 10) Ambrose JA, Barua RS: The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*, 2004; 43: 1731-1737
 - 11) Ricardo AC, Grunwald JE, Parvathaneni S, Goodin S, Ching A, Lash JP: Retinopathy and CKD as Predictors of All-Cause and Cardiovascular Mortality: National Health and Nutrition Examination Survey (NHANES) 1988-1994. *Am J Kidney Dis*, 2014; 64: 198-203
 - 12) Goldsmith DJA, Covic A, Sambrook PA, Ackrill P: Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. *Nephron*, 1997; 77: 37-43
 - 13) Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int*, 1995; 48: 820-826
 - 14) Sarnak MJ, Levey AS: Cardiovascular disease and chronic renal disease: A new paradigm. *Am J Kidney Dis*, 2000; 35: S117-S131
 - 15) Zoccali C, Mallamaci F, Tripepi G: Inflammatory proteins as predictors of cardiovascular disease in patients with end-stage renal disease. *Nephrol Dial Transplant*, 2004; 19: v67-72
 - 16) Gungor OI, Kircelli F, Voroneanu L, Covic A, Ok E: Hormones and arterial stiffness in patients with chronic kidney disease. *J Atheroscler Thromb*, 2013; 20: 698-707
 - 17) Scheie HG: Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. *AMA Arch Ophthalmol*, 1953; 49: 117-138
 - 18) Murphy RP, Lam LA, Chew EY: Hypertension. In: Ryan SJ, Hinton DR, Schachat AP, Wilkinson P, editors. *Retina*. Philadelphia: Mosby; 2006. p. 1377-1382
 - 19) Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res*, 2002; 25: 359-364
 - 20) Kimura K, Saika Y, Otani H, Fujii R, Mune M, Yukawa S: Factors associated with calcification of the abdominal aorta in hemodialysis patients. *Kidney Int*, 1999; 71: S238-S241
 - 21) Spencer WH: An Atlas and Textbook (CD-ROM). In: *Systemic diseases with retinal involvement: Vascular diseases*. Based on: *Ophthalmic Pathology*. WB Saunders Co: 1995
 - 22) Chatterjee S1, Chattopadhyay S, Hope-Ross M, Lip PL: Hypertension and the eye: changing perspectives. *J Hum Hypertens*, 2002; 16: 667-675
 - 23) Cheung AK, Levin NW, Greene T, Agodoa L, Bailey J, Beck G, Clark W, Levey AS, Leypoldt JK, Ornt DB, Rocco MV, Schulman G, Schwab S, Teehan B, Eknoyan G: Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. *J Am Soc Nephrol*, 2003; 14: 3251-3263
 - 24) Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, Teehan BP, Levey AS: Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int*, 2000; 58: 353-362