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NEPHROLOGY - ORIGINAL PAPER

Statins and vitamin D: a friendly association in pre-dialysis patients

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Abstract The increased mortality rate observed in patients with chronic kidney disease is related to the high prevalence of cardiovascular disease in this population. Recently, it has been shown that interventional therapy with statins and/or vitamin D could improve the outcomes of these patients. The aim of this study was to identify the risk factors for mortality in a group of patients with chronic kidney disease (stages 4 and 5—pre-dialysis) and verify whether vitamin D and statins could change the outcome. We included 95 patients (mean age—69.4) with stages 4 and 5 (pre-dialysis) of our "low-clearance" outpatient clinic, with an average eGFR of 16.9 ml/min and a mean follow-up of 24.1 months. Several biological, nutritional, laboratory and inflammatory parameters were analysed at baseline. Our population was divided into three groups: G-I, patients not medicated with either vitamin D or statins; G-II, patients medicated with either vitamin D or statins; and G-III, patients medicated with vitamin D and statins. We found (ANOVA) that the serum levels of pre-albumin ($P = 0.018$) and PTH ($P = 0.03$) were lower in G-I. Concerning the inflammatory parameters, G-I showed higher levels of hsCRP ($P = 0.014$) and a trend to higher IL-6 levels ($P = 0.077$). We found the actuarial survival at 30 months (Kaplan–Meier), to be 56.4% in G-I, 82.3% in G-II and 100% in G-III (log rank = 13.08 $P = 0.0014$). Using the Cox proportional hazards model, we found that the existence of coronary artery disease ($P = 0.0001$) and the absence of medication with vitamin D and/or statins ($P = 0.005$) independently influenced the mortality of our patients. In conclusion, we found, in our study, that patients under vitamin D and statins (with a synergistic effect) were less inflamed and showed a lower mortality rate.

Keywords Statins · Vitamin D · Inflammation · CKD · Survival

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Introduction

Patients with chronic kidney disease (CKD) have an high prevalence of cardiovascular disease that yields a mortality risk 10–20 times superior than that of the general population [1].

Along the years, several studies showed the co-existence of classical and non-classical risk factors for cardiovascular disease in patients with CKD [2–4]. This would explain the excess in cardiovascular events and mortality risk. Cardioprotection is therefore a hallmark of CKD pre-dialysis as post-dialysis care.

Among these non-classical risk factors, hyperphosphatemia [5], a high calcium × phosphorus product [6], and secondary hyperparathyroidism [7]

that lead to vascular calcification, as well as malnutrition [8] and inflammation [9] have recently emerged as important players.

Observational studies on vitamin D administration in dialysis patients showed a reduction of mortality in "users" versus "non-users" (both with an oral as well as with an injectable formulation) and an advantage of paricalcitol over calcitriol [10, 11]. This benefit was independent of mineral bone metabolism and parathyroid hormone levels suggesting the existence of other pathways of action for vitamin D on the cardiovascular system. In fact, the vitamin D receptor is ubiquitous in the human body, and it has been also identified in the vascular endothelium and in myocytes [12]. Epidemiologic studies showed that vitamin D deficiency is associated with an increased risk for cardiovascular diseases, malignancies, chronic inflammatory and autoimmune diseases [12, 13]. In fact, calcitriol has been shown to downregulate plasma renin activity [14], to inhibit myocyte proliferation [15] and to decrease left ventricular hypertrophy [16]. Moreover, it has been shown to modulate inflammation and reduce tubulointerstitial fibrosis in a model of CKD [17], to slow the progression of chronic allograft nephropathy [18] and to decrease proteinuria in CKD [19].

The effect of statins on cardiovascular morbidity and mortality has been well established in a series of trials that started with the "4S" trial [20]. This positive effect of statin therapy was initially attributed to a cholesterol-lowering effect mediated by the inhibition of 3-hydroxy-3-methylglutaryl coenzyme (3HMGCo) A reductase [21]. However, in some of those trials, there was a discrepancy between the magnitudes of cholesterol concentration reduction and the reduction of mortality, indicating that other pathways beyond the inhibition of the 3HMGCoA reductase existed. In fact, more recently, statins were shown to have anticoagulant, anti-inflammatory and anti-oxidant properties [22].

The aim of our study was to evaluate the effect of therapy with vitamin D and statins on the survival of patients with stage 4 and 5 CKD.

Subjects and methods

This is an observational and prospective study conducted at Serviço de Nefrologia of Hospital de Faro, Portugal. The study received the approval of the local ethical committee.

We included patients with CKD stages 4 and 5 (according to the National Kidney Foundation classification) [23] followed at our *Low-Clearance* outpatient clinic. The inclusion criterion was an estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2 (Modification of Diet in Renal Disease equation [24]). Exclusion criteria included the presence of clinical signs of infection, malignancy, psychiatric disease or chronic liver disease.

A clinical history and a physical examination were performed, and all medications were registered at baseline and during the follow-up period. The following visits were done every 2–3 months or depending on the patients' necessities. During those visits, a clinical examination and laboratory analysis were made and the medication was adjusted according to the findings. Several clinical, laboratory and inflammatory parameters were considered including gender, age, presence of diabetic nephropathy (DN), hypertension, medication with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), coronary artery disease (CAD), eGFR, serum haemoglobin (Hb), creatinine, blood urea nitrogen (BUN), uric acid, albumin, pre-albumin, cholesterol (total and HDL), triglycerides, uric acid, calcium (Ca), phosphate (Pi), Ca × Pi, intact parathormone (iPTH), interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP). eGFR was calculated using the MDRD equation [24].

Hypertension was considered to be present when the sitting blood pressure (BP) was ≥140/90 mmHg or when, regardless of BP values, the patient was under antihypertensive therapy. CAD was defined by a history of classical exertional angina, myocardial infarction, coronary percutaneous angioplasty or bypass grafting. Asymptomatic coronary disease was also considered whenever there was a positive result for coronary disease on a treadmill stress test, echocardiography, myocardial scintigraphy or coronariography.

Nutritional status was assessed by the body mass index (kg/m^2) and the subjective global assessment (SGA) [25]. The patients were medicated with vitamin D analogues or statins according to the KDOQI Guidelines [26, 27].

Plasma, collected using heparin as anticoagulant, was separated (within 30 min of drawing) and stored at −80°C until analysis for the measurements of CRP (chemiluminescent immunometric assay—Immulite® 2000 High Sensitivity CRP) and IL-6 (solid-phase, enzyme labelled, chemiluminescent sequential immunometric assay—Immulite®). During follow-up, we aimed at keeping the haemoglobin levels between 11 and 13 g/dl, using once-weekly subcutaneous darbepoetin alpha.

Our population was first divided into three groups: G-I, patients not medicated with either vitamin D or statins; G-II, patients medicated with either vitamin D or statins; and G-III, patients medicated with statins and vitamin D. These three groups were compared regarding the parameters described above and also regarding the 30-months actuarial survival. Secondly, the whole population was divided into two other groups: survivors (S) and non-survivors (NS). Similarly, these two groups were compared regarding the several parameters already described. Finally, we tried to identify the risk factors for mortality in our population. The patients were followed for 3 years or until death even if it occurred after the beginning of renal replacement therapy.

Statistical analysis

For comparisons between groups, ANOVA test, Student's *t*-test and chi-square test were used. Cox proportional hazards regression was used to assess the effects of individual factors on mortality, controlling for differences in other factors possibly affecting for mortality. The 95% CI for the hazard ratio is expressed. Several independent variables were used. As continuous variables, we used age, eGFR, BMI, SGA, albumin, Ca × Pi and Hb. As categorical variables, we used gender, the presence of DN (yes/no), the presence of CAD (yes/no) and therapy with vitamin D or statins (none/vitamin D or statin/both). We used the Kaplan–Meier method to evaluate the influence of vitamin D and statins on survival and to assess the 30-months survival of the three groups.

SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL) was used to perform the statistical analysis. Data are expressed as means ± SDs. The null hypothesis was rejected below the 5% level.

Results

We evaluated 95 patients (41 women and 54 men) with a mean age of 69.4 ± 14.6 (age range 25–96) and a mean eGFR of 16.1 ml/min/1.73 m^2. The mean follow-up was 24.1 ± 9.8 months. Original disease was unknown in 24.2% ($n = 23$); diabetic nephropathy was present in 31.5% ($n = 30$), hypertensive renal disease in 20% ($n = 19$), chronic interstitial disease in 15.8% ($n = 15$), chronic glomerulonephritis in 5.3% ($n = 5$) and polycystic kidney disease in 3.2% ($n = 3$) of patients. The prevalence of hypertension in our population was 80% (76 patients) with 55.8% (53 patients) under ACEIs and/or ARBs therapy. The mean Hb level was 11.6 ± 1.6 g/dl with a darbepoetin mean dose of 0.467 μg/kg/week.

Oral vitamin D (alfacalcidol or calcitriol) daily dose ranged from 0.25 to 1.0 μg with a median of 0.5 μg. Statins (simvastatin or pravastatin) daily dose ranged from 20 to 40 mg with a median dose of 20 mg/day. In our population, the majority (54.7%) of the patients were under statin and/or vitamin D (G-II and G-III) therapy with 18.9% of patients taking both medications (Table 1). Table 1 also shows the comparison between the three groups of patients according to therapy with vitamin D and statins. The serum levels of pre-albumin, iPTH and hs-CRP were significantly lower in patients under therapy (G-II and G-III) when compared to those without (G-I). Total cholesterol and IL-6 levels were also lower, though not significantly, in those groups. Furthermore, these effects were maximal in G-III (patients on double therapy). No other differences were observed between G-I, G-II and G-III. At the end of this study, 66.3% of the patients were still alive and regarding the actuarial survival at 30 months, patients under double therapy presented the highest survival rate (Fig. 1): G-I = 56.4%; G-II = 82.3% and G-III = 100% (log rank = 13.08, $P = 0.0014$).

We also compared, regarding the several parameters evaluated at baseline, patients who were still alive at the end of the follow-up with those who died (Table 2). The use of vitamin D and statins was more common among survivors than in non-survivors. Non-survivors were also older and had a higher prevalence of cardiovascular atherosclerotic disease, as evidenced by a higher prevalence of CAD. This

Table 1 Demographic, clinical and laboratorial parameters according to medication groups: G-I—patients not medicated with statins or vitamin D, G-II—patients medicated with statins or vitamin D, G-III—patients medicated with statins and vitamin D

	G-I ($n = 43$)	G-II ($n = 34$)	G-III ($n = 18$)	P
Age (years)	71.3 ± 14.5	68.9 ± 15.6	65.7 ± 11.6	NS
Gender (female/male)	21/22	12/27	8/10	NS
DN (yes/no)	17/26	9/25	8/10	NS
CAD (yes/no)	11/32	10/24	3/15	NS
eGFR (ml/min)	16.6 ± 5.0	15.8 ± 5.1	15.4 ± 5.1	NS
BUN (mg/dl)	70 ± 29	72 ± 28	83 ± 21	NS
Hb (g/dl)	11.6 ± 1.9	11.7 ± 1.3	11.6 ± 1.6	NS
Darbepoetin (μg/kg/week)	0.48 ± 0.52	0.44 ± 0.49	0.48 ± 0.31	NS
Uric acid (mg/dl)	8.5 ± 2.7	8.3 ± 2.12	8.4 ± 2.5	NS
Albumin (mg/dl)	4.2 ± 0.5	4.2 ± 0.4	4.3 ± 0.5	NS
Pre-albumin (mg/dl)	28.9 ± 8.5	31.6 ± 7.5	36 ± 9.7	0.018
Calcium (mg/dl)	9.6 ± 1.2	9.9 ± 0.7	9.9 ± 0.6	NS
Phosphate (mg/dl)	4.6 ± 1.5	4.9 ± 1.6	4.8 ± 1.0	NS
Ca × Pi (mg^2/dl^2)	45 ± 15	49 ± 17	48 ± 10	NS
iPTH (pg/ml)	267 ± 193	358 ± 310	511 ± 329	0.03
Total cholesterol (mg/dl)	197 ± 47	212 ± 47	235 ± 72	0.065
Triglycerides (mg/dl)	135 ± 60	170 ± 104	170 ± 102	NS
BMI (kg/m^2)	23.8 ± 5.7	24.9 ± 3.5	25.9 ± 4.6	NS
SGA score	13.2 ± 3.8	11.4 ± 3.2	11.3 ± 3.6	NS
hs-CPR (pg/ml)	2.10 ± 3.6	0.76 ± 0.78	0.32 ± 0.29	0.014
IL-6 (pg/ml)	6.8 ± 7.1	4.7 ± 3.5	3.7 ± 1.4	0.077

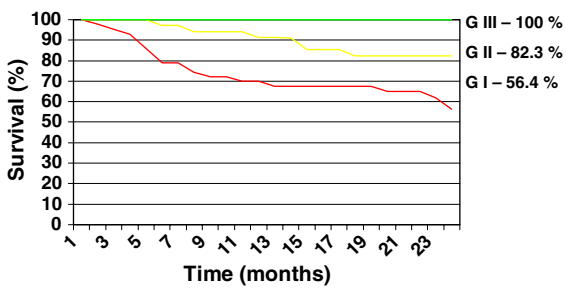

Fig. 1 Actuarial survival curve

group also showed a worse nutritional status (higher SGA score) and more inflammation (higher hs-CRP and IL-6 levels).

Using the Cox proportional hazards model, we found that CAD ($P = 0.0001$) and the absence of vitamin D and/or statin therapy ($P = 0.005$) were independent risk factors of mortality. The age of the patients, in our study, only showed a trend to influence the mortality ($P = 0.081$) (Table 3).

Discussion

The increased prevalence of cardiovascular disease in patients with CKD is responsible for the excess mortality observed in this population [1, 28, 29]. Classical and non-classical cardiovascular risk factors have been identified as targets for intervention [2–4]. Recently, several studies revealed the benefit of vitamin D therapy on survival of haemodialysis patients [10, 11]. On the other hand, observational studies analysing the effect of statin therapy on haemodialysis patients pointed towards an improvement on survival, in accordance with the results of trials from the general population [20, 30, 31]. However, the results of randomized controlled studies in renal patients are controversial. The "4D" study (atorvastatin) failed to show a significant benefit of statin therapy on survival of haemodialysis diabetic patients [32]. On the other hand, Tonelli et al. [33] have shown a decrease in the incidence of major coronary events, but not in mortality, with

Table 2 Patient's demographic, clinical and laboratorial parameters according to outcome groups: S—survivors, NS—non-survivors

	S ($n = 63$)	NS ($n = 32$)	*P*
Age (years)	62.2 ± 14.9	75.7 ± 11.1	0.002
Gender (female/male)	28/35	13/19	NS
eGFR (ml/min)	16.4 ± 6.7	15.5 ± 7.7	NS
Diabetic nephropathy (yes/no)	20/43	10/22	NS
Hypertension (yes/no)	50/13	26/6	NS
ACEIs and/or ARBs (yes/no)	35/28	18/14	NS
CAD (yes/no)	8/55	16/16	0.0001
Vitamin D (yes/no)	32/31	8/24	0.016
Statins (yes/no)	26/38	4/28	0.004
BMI (kg/m^2)	25.2 ± 4.9	23.5 ± 4.5	NS
SGA score	11.8 ± 3.5	13.1 ± 3.8	0.09
BUN (mg/dl)	74 ± 27	72 ± 29	NS
Uric acid (mg/dl)	8.3 ± 2.6	8.6 ± 2.5	NS
Hb (g/dl)	11.6 ± 1.5	11.6 ± 1.9	NS
Darbepoetin (μg/kg/week)	0.48 ± 0.52	0.44 ± 0.49	NS
Calcium (gm/dl)	9.9 ± 0.7	9.4 ± 1.3	0.016
Phosphate (mg/dl)	4.9 ± 1.6	4.5 ± 1.2	NS
Ca × Pi (mg^2/dl^2)	49 ± 16	43 ± 11	NS
iPTH (pg/ml)	355 ± 294	309 ± 235	NS
Albumin (g/dl)	4.3 ± 0.5	4.1 ± 0.5	NS
Pre-albumin (mg/dl)	32.1 ± 8.3	29.3 ± 9.2	NS
Total cholesterol (mg/dl)	211 ± 57	208 ± 48	NS
HDL cholesterol (mg/dl)	51 ± 18	55 ± 23	NS
Triglycerides (mg/dl)	152 ± 73	161 ± 117	NS
hs-CPR (pg/ml)	0.46 ± 0.48	2.9 ± 3.9	0.0001
IL-6 (pg/ml)	4.4 ± 3.0	7.6 ± 7.8	0.005

pravastatin in patients with chronic kidney disease and not in dialysis. Recently, the AURORA study [34], a large prospective randomized double-blinded controlled trial, did not show any benefit of rosuvastatin over placebo on the survival of haemodialysis patients. In spite of this, statins have lowered the LDL cholesterol and decreased inflammation; there were no differences regarding the several cardiovascular endpoints between the groups under observation. One possible explanation was that almost 30–40% of those patients were already under statin therapy at the start of the study. We must also realize that cardiovascular disease in renal patients has a complex physiopathology, and other players, such as the mineral metabolism must be taken into consideration. In our study, 33.6% of patients with CKD died. As expected, the major cause of death (50%) was cardiovascular disease (cardiac and cerebrovascular). Patients who died were older, presented a higher prevalence of atherosclerotic cardiovascular disease, a worse nutritional status and higher inflammatory parameters. All of these parameters have already been associated with higher mortality rates in patients with CKD [8, 35–38]. Finally, in the survivors group, there was a higher proportion of patients under vitamin D and statins, already pointing out to a clear benefit of these therapies.

In fact, in our population, the majority of patients (54.7%) were under therapy with vitamin D and/or a statin. These patients presented lower levels of inflammatory markers (hs-CRP, IL-6), and this effect was maximal in patients under therapy with both drugs. Several studies in different populations have already shown that statins [39, 40] and vitamin D [41, 42] lowered inflammatory markers.

Similarly to other reports in literature [10, 11, 20, 30, 31, 43], in our study, patients under therapy with a statin and/or vitamin D had a better survival. Once again, patients under combined therapy showed the maximal benefit.

Furthermore, when risk factors for mortality were analysed, only the absence of vitamin D/statin therapy emerged as an independent factor, besides the already expected presence of CAD. Concerning the factor age, in our study, we found only a trend to influence the mortality. This can be explained by the high mean age of the sample and/or by the low number of patients included in the study.

We think that the beneficial effect of improved survival in our patients with CKD was mediated by a synergistic reduction in inflammation induced by statins and vitamin D. The mechanism behind this interplay has not yet been well elucidated. The hypothesis that statins could be vitamin D analogues exerting their effect through the vitamin D receptor generated much controversy, but some authors thought it deserved further investigation [44]. Very recently, atorvastatin was shown to increase the levels of vitamin D in patients with ischaemic heart disease [45], and the benefit of vitamin D analogues on the survival of pre-dialysis CKD patients was also reported [46].

Table 3 Independent risk factors for mortality in the Cox proportional hazard model

	β	Wald	P	Exp (β)	Upper limit	Lower limit
Gender	−0.201	0.261	0.609	0.818	0.379	1.765
Age	0.036	3.046	0.081	1.306	0.996	1.079
GFR	−0.024	0.395	0.530	0.977	0.907	1.051
DN	0.187	0.138	0.710	1.205	0.450	3.226
CAD	1.461	12.627	0.0001	4.311	1.926	9.652
BMI	−0.007	0.011	0.917	0.993	0.878	1.124
SGA	−0.032	0.138	0.710	0.968	0.817	1.148
Albumin	−0.468	0.932	0.334	0.626	0.242	1.619
Ca × Pi	0.004	0.045	0.832	1.004	0.971	1.037
Hb	0.048	0.144	0.705	1.049	0.848	1.345
Statin/vitamin D	−0.944	8.017	0.005	0.389	0.202	0.748

Notwithstanding, we are not aware of any other study reporting a synergistic benefit of therapy with vitamin D and statin on the survival of patients with pre-dialysis stages 4/5 CKD. Further studies involving a larger number of patients with a stronger methodology are needed to confirm our results.

References

1. Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal failure. Am J Kidney Dis 32(suppl 5):S112–S119
2. Cheung AK, Sarnak MJ, Yan G et al (2000) Atherosclerotic cardiovascular disease risks in chronic haemodialysis patients. Kidney Int 58:353–362
3. Kaysen GA (2001) The microinflammatory State in Uremia: causes and potential consequences. J Am Soc Nephrol 12:1549–1557
4. Stuveling EM, Bakker SJL, Hillege HL et al (2005) Biochemical markers: a novel area for better prediction of renal risk? Nephrol Dial Transplant 20:497–508
5. Block GA, Hulbert-Shearon TE, Levin NW, Port FK (1998) Association of serum phosphorus and calcium × phosphorus product with mortality risk in chronic hemodialysis patients. Am J Kidney Dis 31:607–617
6. Jung HH, Kim S-W, Han H (2006) Inflammation, mineral metabolism and progressive coronary artery calcification in patients on haemodialysis. Nephrol Dial Transplant 21:1915–1920
7. Kovesdy CP, Ahmazadeh S, Anderson JE, Kalantar-Zadeh K (2008) Secondary hyperparathyroidism is associated with higher mortality in men with moderate to severe chronic kidney disease. Kidney Int 73:1296–1302
8. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH (2001) A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 38:1251–1263
9. Stenvinkel P, Alvestrand A (2002) Inflammation in end-stage renal disease: sources, consequences, and therapy. Semin Dial 15:329–337
10. Shoji T, Shinohara K, Kimoto E et al (2004) Lower risk for cardiovascular mortality in oral 1α hidroxy vitamin D3 users in a hemodialysis population. Nephrol Dial Transplant 19:179–184
11. Teng M, Wolf M, Ofsthun MN et al (2005) Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol 16:1115–1125
12. Napgal S, Na S, Rathnachalam R (2005) Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 26:662–687
13. Patel S, Farragher T, Berry J et al (2007) Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum 56:2143–2149
14. Li YC, Kong J, Wei M et al (2002) 1, 25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 110:229–238
15. Xiang W, Kong J, Chen S et al (2005) Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab 288(1):E-125–E-132
16. Achinger SG, Ayus JC (2005) The role of vitamin D in left ventricular hypertrophy and cardiac function. Kidney Int Suppl (95):S37–42
17. Tan X, Li Y, Liu Y (2006) Paricalcitol attenuates renal interstitial fibrosis in obstructive nephropathy. J Am Soc Nephrol 17(12):3382–3393
18. O'Herrin JK, Hullet DA, Heisy DM et al (2002) A retrospective evaluation of 1, 25-dihydroxyvitamin D (3) and its potential effects on renal allograft function. Am J Nephrol 22:515–520
19. Agarwal R, Acharya M, Tian J et al (2003) Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidney Int 68:2823–2828
20. Scandinavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin study (4S). Lancet 344:1383–1389

21. Endo A (1992) the discovery and development of HMG-CoA reductase inhibitors. J Lipid Res 33:1569–1582
22. Davignon J (2004) Beneficial cardiovascular effects of statins. Circulation 109(Suppl III):III39–III43
23. National Kidney Foundation (2002) NKF-K/DOQI clinical practice guidelines for chronic kidney disease. Am J Kidney Dis 39(Suppl 1):S76–S110
24. Levey AS, Bosh JP, Lewis JB, Greene T, Rogers N, Roth D (1999) For the Modification of Diet in Renal Disease Study Group: a more accurate method to estimate glomerular filtration rate from serum creatinine. A new prediction equation. Ann Intern Med 130:461–470
25. Kalantar-Zadeh K, Kleiner M, Dunne E et al (1999) A modified quantitative subjective global assessment of nutrition for dialysis patients. Nephrol Dial Transplant 14:1732–1738
26. National Kidney Foundation (2003) K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42(4 suppl 3):S52–S130
27. (2003) K/DOQI Clinical practice guidelines for managing of dyslipidemias in patients with kidney disease. Am J Kidney Dis 41(suppl 3):39–58
28. Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE (1995) Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int 47:884–890
29. US Renal Data System (2005) USRDS 2005 annual data report: morbidity and mortality. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
30. Shepherd J, Cobbe SM, Ford I et al (1995) For the West of Scotland coronary prevention study group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 333:1301–1307
31. (1998) The long-term Intervention with pravastatin in ischemic disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Eng J Med 339:1349–1357
32. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E (2005) German diabetes and dialysis study investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 353: 238–248
33. Tonelli M, Isles C, Curhan GC et al (2004) Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 21:1557–1563
34. Fellstrom BC, Jardine AG, Schiemedler E et al (2009) Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 360:1395–1407
35. Bradbury BD, Fissell RB, Albert JM et al (2007) Predictors of early mortality among incident US Hemodialysis patients in the dialysis outcomes and practice patterns study (DOPPS). Clin J Am Soc Nephrol 2:89–99
36. Kovesdy CP (2007) Regional mortality differences in end-stage renal disease: how far can observational studies take us. Kidney Int 71:11–12
37. Stenvinkel P, Lindholm B, Heimbürger M, Heimbürger O (2000) Elevated serum levels of soluble adhesion molecules predicts death in predialysis patients: association with malnutrition, inflammation, and cardiovascular disease. Nephrol Dial Transplant 15:1624–1630
38. Honda H, Qureshi A, Heimbürger O et al (2006) Serum albumin, C-reactive protein, interleukin-6, and fetuin A as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis 47: 139–148
39. Panichi V, Paoletti V, Manterano E et al (2006) In vivo and in vitro effects of simvastatin on inflammatory markers in predialysis patients. Nephrol Dial Transplant 21:337–344
40. Arnaud C, Burger F, Steffens S et al (2005) Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. Arterioscler Thromb Vasc Biol 25:1231–1236
41. Türk S, Akbulut M, Yildiz A et al (2002) Comparative effect of oral pulse and intravenous calcitriol treatment in hemodialysis patients: the effect on serum IL-1 and IL-6 levels and bone mineral density. Nephron 90:188–194
42. Giulietti A, van Etten E, Overbragh L et al (2007) Monocytes from type 2 diabetic patients have a pro-inflammatory profile 1, 25-dihydroxyvitamin D(3) works as anti-inflammatory. Diabetes Res Clin Pract 77:47–57
43. Seliger SL, Weiss NS, Gillen DL et al (2002) HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. Kidney Int 61:297–304
44. Grimes DS (2006) Are statins analogues of vitamin D? Lancet 368:83–86
45. Pérez-Castrillón JL et al (2007) Effects of atorvastatin on vitamin D levels in patients with acute ischemic heart disease. Am J Cardiol 99:903–905
46. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K (2008) Association of activated vitamin D treatment and mortality in chronic kidney disease. Arch Intern Med 168:397–403