CrossMark

NEPHROLOGY - ORIGINAL PAPER

Coronary risk score for mineral bone disease in chronic non-diabetic hemodialysis patients: results from a prospective pilot study

Cristiana David[1,2] · Jordi Bover[3] · Cornelia Voiculet[4,5] · Ileana Peride[1,2] ·
Lucian Cristian Petcu[6] · Andrei Niculae[1,2] · Adrian Covic[7,8] ·
Ionel Alexandru Checherita[1,2]

Abstract

Introduction Chronic kidney disease-mineral bone disorder enhances coronary artery impairment (often occult and difficult to diagnose) in hemodialysis (HD) patients. The *aim of the study* was to correlate biochemical and imagistic parameters of MBD with the degree of documented coronary artery disease (CAD) in non-diabetic HD patients, in order to obtain a *MBD-coronary risk score* as a screening algorithm.

Methods A 3-year prospective study was conducted on 168 non-diabetic HD patients, evaluating MBD biochemical parameters along with pulse wave velocity (PWV) determination and valve/coronary calcification assessment; coronary angiography was performed in symptomatic patients. Correlations between noninvasive parameters and the degree of coronary obstruction were assessed using *IBM SPSS Statistics* 20 *software, Chi-square test and the determination of odds ratio*.

Results Significant differences in serum calcium ($p < 0.001$), phosphates ($p = 0.03$), bicarbonate ($p < 0.001$), albumin and iPTH ($p = 0.002$), percentage of deviations from PWV normal values ($p = 0.004$), average doses of phosphate binders and vitamin D and the number of vascular/valve calcifications were noted between the study group (angina, $n = 17$) and control group (asymptomatic, $n = 151$). After applying *MBD-coronary risk score* in control group, coronary angiography was performed in high-score patients.

Conclusion A noninvasive screening algorithm for early diagnosis of CAD in asymptomatic HD patients with altered MBD parameters is necessary. Applying *MBD-coronary risk score* might be an important step in the prevention of major coronary episodes by extending the indication for further investigations, early diagnosis and treatment management.

Keywords Chronic hemodialysis · Mineral bone disorder · Coronary risk score · Coronary angiography

✉ Andrei Niculae
niculaeandrei@yahoo.com

1 Department of Nephrology and Dialysis, "St. John" Emergency Clinical Hospital Bucharest, 37th Dionisie Lupu StreetSector 2, 020021 Bucharest, Romania

2 Clinical Department No. 3, "Carol Davila" University of Medicine and Pharmacy Bucharest, Bucharest, Romania

3 Department of Nephrology, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

4 Department of Internal Medicine, "St. John" Emergency Clinical Hospital Bucharest, Bucharest, Romania

5 Clinical Department No. 1, "Carol Davila" University of Medicine and Pharmacy Bucharest, Bucharest, Romania

6 Department of Biostatistics and Biophysics, Faculty of Dental Medicine, "Ovidius" University Constanta, Constanta, Romania

7 Department of Nephrology, "Dr. C. I. Parhon" Clinical Hospital Iasi, Iasi, Romania

8 Department of Internal Medicine I, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Iasi, Romania

Introduction

Cardiovascular diseases are the most important causes for morbidity and mortality in patients on chronic hemodialysis (HD) [1–5]. Among others, severe coronary events are responsible for 40–50% of deaths, with an incidence of 30% in the first year after initiation of dialysis and 52% in the first 2 years [6–8]. The elevated lethal potential of

ischemic coronary lesions in dialysis patients justifies the concern for an early diagnosis of this pathology, even more because we refer to a double-risk population: a recognized predisposition for multifactorial vascular impairment and a high risk of asymptomatic evolution. Late-/underdiagnosed significant coronary obstructions in dialysis patients were documented by numerous clinical studies and proven to be responsible for a high number of sudden deaths in which autopsies have been made, even in patients without coronary symptoms [1, 8–11].

The impressing prevalence and advanced degree of coronary artery calcification in long-term dialysis patients are based on the presence of mutually reinforcing factors [12–15]. Besides traditional risk factors on coronary circulation (e.g., smoking, obesity, diabetes, dyslipidemia, blood pressure) [16], which are amplified by chronic kidney disease (CKD) and produce intimal calcifications, in end-stage renal disease (ESRD) patients we confront with associated medial calcifications (*Monckeberg's arteriosclerosis*) promoted by uremic endothelial dysfunction, hyperhydration and oxidative stress, chronic inflammation, increased stiffness and extra-skeletal calcifications [17–22]. Among others, the role of calcium phosphate imbalance and the effects of its treatment are still difficult to assess, with an incomplete quantified impact.

Biochemical and radiological findings attesting the presence and degree of chronic kidney disease-mineral bone disorders (CKD-MBD) in ESRD patients are rarely correlated by the practitioner with the risk of major coronary events. Noninvasive screening methods for coronary artery disease (CAD) in a population with low tolerance for physical exercise and high prevalence of autonomic neuropathy should help us to perform early diagnosis and establish therapeutic measures to avoid severe cardiovascular events in these patients.

The primary objective of the study was to correlate CKD-MBD biochemical and imagistic parameters with the presence of symptomatic significant coronary obstructions in non-diabetic hemodialysis patients, in order to obtain a *MBD-coronary risk score. A secondary objective* was the validation of this risk score as a noninvasive screening algorithm for extending coronary angiography indications in asymptomatic patients with mineral metabolism disturbances.

Methods

Over a 3-year period, March 2013–March 2016, 168 chronic dialysis patients (receiving hemodialysis for longer than 6 months) from two private dialysis centers in Bucharest were recorded for the survey, after they expressed their willingness to participate. Severe valve disease,

arrhythmias, systemic vasculitis, dyslipidemia and tobacco addiction were excluded from the study because these conditions might have a major impact on vascular wall quality and the accuracy of correlations; diabetic subjects were excluded as well, and in this manner a uniform cohort was obtained. Patients with previous coronary angiography, with or without stent implants were also excluded (Fig. 1).

The study was approved by the Ethical Committee (No. 25151/18.03.2013) of our hospital, and patients were enrolled after verbal informed consent. Patients selected for coronary angiography examination signed an informed consent.

The following laboratory tests were recorded: urea, creatinine, calcium, phosphate, intact parathormon (iPTH), alkaline phosphatase, serum bicarbonate and albumin obtained by calculating the average of the last 12-month values registered in the routine monthly monitoring program for the maintenance dialysis patient. Test values were provided by the dialysis centers registries, with the consent of the chief physician. The average weekly doses for phosphate binders and vitamin D were calculated and noted for each patient. Both centers prescribed only calcium-based phosphate binders (for financial reasons) with 498 mg calcium carbonate per tablet, and 0.25 µg per tablet (calcitriol) as vitamin D supplement.

Every cardiac angina episode (minutes of frank substernal pain or tightness, after exertion/emotional stress/dialysis session, relieved by rest/medication), diagnosed according to American College of Cardiology/American Heart Association (ACC/AHA), was monitored [23]. We did not consider other angina equivalents (e.g., unexplained arrhythmias, left ventricular failure symptoms) because they can also be produced by dyselectrolytemia or hypertension during the dialysis session. Patients with stable angina episodes were referred to cardiologist in a maximum 48-h interval, and the appointment for coronary angiography was made. For unstable angina patients were immediately admitted in the cardiology department of our hospital; coronary angiography was performed in emergency for diagnosed myocardial infarctions, following the ACC/AHA guidelines [23]. Electrocardiography was performed monthly in all patients, and ischemic lesions (e.g., persistent ST–T-wave inversions, left bundle-branch block or bifascicular block) were registered [23]. Pulse wave velocity (PWV) determination, chest X-ray for the detection of coronary calcifications and cardiac ultrasound for valve calcification assessment were performed once in the study interval for each patient. Patients with at least one episode of angina during the study (representing the study group) underwent coronary angiography (only two patients refused the investigation and were excluded from the study).

In the *study group*, the average level of the monitored parameters was calculated from the 12-month values prior

Fig. 1 Study design diagram
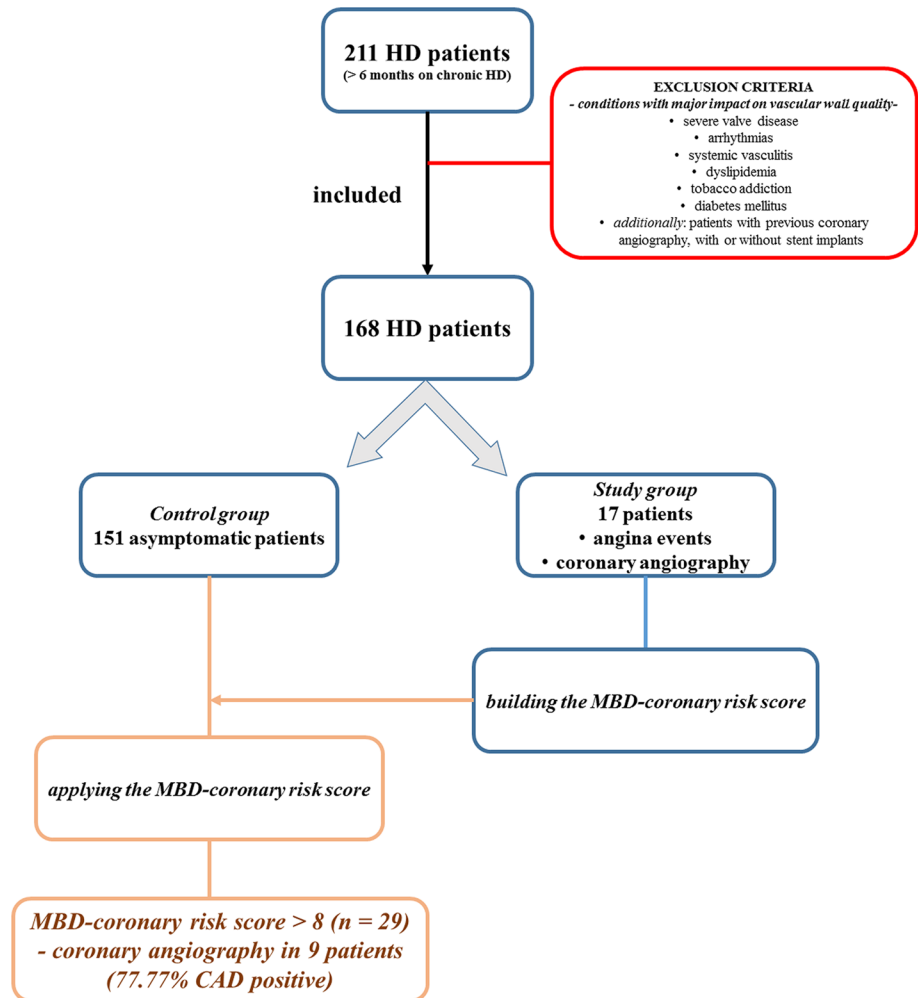
the angiography. For the *control group*, the average value of the biochemical test was obtained from the last 12-month levels before the last trial month. As required by the standard procedure for hemodialysis patients monitoring, biochemical tests were collected before the dialysis session, in a midweek day; for all the studied patients the tests were performed by the same laboratory. Routine parameters were carried out on *Mindrayassay device*; iPTH was determined using *ELISA immunoassay*. For cardiac ultrasound investigation a two-dimensional M-mode *Mindray DC-6 Expert* device was used, in a midweek non-dialysis day, carried out by the same cardiologist. Coronary arteries calcifications were objectied using a low-radiation chest radiography *PI30 DB* device. PWV evaluations were performed using *Mobil-O-Graph* (*Industrielle Entwicklung Medizintechnik, Germany*) and *IEM-Hypertension Management Software*; after the measurements were recorded, for each patient we calculated the deviation from the normal maximum value of PWV, based on the displayed normal ranges of aortic PWV included in the software (adjusted for age, body mass index (BMI) and blood pressure (BP) levels).

Cardiac ultrasound, chest X-ray and PWV assess for the study group were performed before angiography; for the control group these investigations were made at the end of the survey.

Angiography was performed by an experienced angiographer using a *Philips Allura Clarity Xper FD 20 System* device, iso-osmolar iodinated contrast media, and a 75% or greater lumen narrowing was considered significant (severe).

Statistical analysis

The assessed results were processed using Microsoft Excel and IBM SPSS Statistics 20 software. Continuous clinical variables were expressed as means and standard deviations (SD) or medians and interquartile ranges and compared between groups. The following tests were applied: Mann–Whitney test for two independent samples, Chi-square test for associations of two categorial variables, and the determination of odds ratio (OR) and relative risk (Rr). Logistic regression analysis was used to determine the relationship between

independent categorical/continuous variables and nominal/binary dichotomous-dependent variable in which values were coded 0/1. A *p* value of <0.05 was considered significant. The *MBD-coronary risk score* values were assigned using transform rank of ORs (rank type; *N* tiles = 5).

Results

During follow-up there were 19 symptomatic patients (typical angina) and 17 of them consented to perform coronary angiography—*study group* (*n* = 17; 10 men); the mean age was 60.4 ± 7.9 years, and average dialysis interval was 80.5 ± 31.1 months. The *control group* (151 patients; 83 men) consisted of all non-diabetic patients without angina episodes during the study, with a mean age 57.4 ± 13.5 years and mean dialysis vintage 51 ± 51.7 months. Demographic and other data are shown in Table 1.

Only the dialysis vintage presented significant differences between groups—patients experiencing angina were at the same age as the asymptomatic ones, but they were on renal replacement treatment for a longer period. BMI and BP values were similar in groups.

Table 1 Demographic and other parameters in both groups

Parameter	Study group (*n* = 17)	Control group (*n* = 151)	*p*
Age	60 ± 7.9 59.73 [53.5, 67.5]	57 ± 13.5 61.00 [48.00, 69.00]	0.78
Dialysis vintage	80.59 ± 31.18 88.00 [47.50, 99.50]	51.01 ± 51.76 34.00 [2.00, 95.00]	0.02
BMI	22.48 ± 2.488	22.134 ± 2.238	0.43
Systolic BP	144.117 ± 14.430	147 ± 12.288	0.57

The results are expressed as mean ± SD and/or median [25, 75%], respectively

Coronary angiography findings in CAD symptomatic patients

Significant CAD lesions were found in 16 patients investigated in the study group. The affected blood flow in one case was justified by the presence of a muscle bridge, but the patient had also discrete coronary lesions, with 45% degree of stenosis. There were two patients with left main coronary disease diagnosed, and they were referred to surgery for coronary artery bypass grafting (CABG). In other two cases CABG was performed for two vessel diseases in patients known with altered left ventricular function (cardiologist decision). In nine cases percutaneous transluminal coronary angioplasty (PTCA) was performed, using drug-eluting stents. Three patients necessitated more than one stent implant. No complications were registered in the perioperative period. One patient from the CABG subgroup died at 3 months after the procedure, by sudden death, one hour after a common dialysis session.

Correlations between symptomatic coronary lesions and CKD-MBD parameters

Average values of laboratory tests are shown in Table 2, with statistically significant differences regarding serum calcium, phosphate, bicarbonate, albumin and iPTH between the two groups. 20.2% of patients were found to have mean 12-month serum calcium levels under 8.5 mg/dL, and 36.3% showed mean calcium levels above 9.5 mg/dL.

PWV assessment revealed deviations from normal ranges of values in both groups, with a number of 15 patients (88.23%) outside limits in the imaging investigated group (average value 16.04 ± 6.96 m/s) and 117 patients (77.48%) in the control group (average value 11 ± 7.26 m/s), *p* = 0.004.

Vascular calcification rate showed on X-ray was significantly higher in the study group—15 patients (88.23%)

Table 2 Biochemical parameters in both groups

Parameter	Study group (*n* = 17)	Control group (*n* = 151)	*p*
Calcium	9.68 ± 0.49 9.73 [9.58, 9.91]	9.00 ± 0.65 8.92 [8.53, 9.59]	0.00004
Phosphate	5.87 ± 1.22 6.03 [5.18, 6.59]	5.20 ± 1.23 5.40 [4.28, 6.19]	0.03
Serum bicarbonate	18.32 ± 1.63 17.6 [17.1, 19.5]	20.32 ± 1.91 19.8 [18.6, 21.7]	0.000059
Albumin	3.94 ± 0.89 3.7 [3.5, 3.9]	4.71 ± 1.17 5.2 [3.7, 5.7]	0.02
iPTH	649 ± 513 420.0 [317.8, 1073.0]	338 ± 306 261.8 [154.1, 391.4]	0.002
Total alkaline phosphatase	28.00 ± 7.96 28.0 [23.5, 33.0]	24.34 ± 8.96 23.0 [16.0, 33.0]	0.10

The results are expressed as mean ± SD and median [25, 75%], respectively

Table 3 Risk estimation of coronary lesions in both groups

Parameters	Risk value*	OR (study group/control group)	95% Confidence interval	
			Lower	Upper
Serum bicarbonate (mEq/L)	<18	18.182	5.790	57.099
	<20	6.835	1.511	30.929
Valvular calcification (echocardiography)	Positive	12.093	1.563	93.544
Serum calcium (mg/dL)	>9.5	10.326	2.832	37.650
Ischemic modifications on EKG	Positive	10.261	1.325	79.432
Calcium phosphate binders therapy (tablets)	>9	7.273	1.991	26.560
	≥9	2.906	1.004	8.410
PWV$^\delta$ (m/s)	>10%	5.696	1.572	20.641
Serum albumin (g/dL)	<4	5.258	1.451	19.049
Vascular calcification	Positive	5.225	1.153	23.665
Serum phosphate (mg/dL)	>6.5	4.338	1.193	15.780
iPTH (pg/mL)	>800	3.778	1.171	12.192
Dialysis vintage (months)	>60	3.352	1.125	9.994
Vitamin D therapy$^\gamma$ (tablets)	>7	1.085	0.317	3.716

The parameters are presented according to the decreasing OR

* Values considered from literature data and our personal clinical observations

$^\delta$ OR was calculated depending on the percentage of deviations from PWV normal values

$^\gamma$ Equal risk for both groups

versus 89 (58.94%) from the control group, $p = 0.01$. In 16 cases (94.11%) of study group and 86 (56.95%) from the control group, cardiac valve calcifications were detected by ultrasound determinations, $p = 0.002$. In addition, ischemic lesions observed on electrocardiogram (EKG) were higher in the study group than in the control one—16 patients (94.12%) versus 92 (60.93%), $p = 0.007$.

Regarding the influence of therapy with calcium-based phosphate binders and vitamin D on the prevalence of symptomatic vascular calcifications, there were significant differences between groups in the average doses of both drugs: The average dose of calcium carbonate as phosphate binder in the study group was 9 tablets/day (4.4 g/day)—significantly different from the average dose in the control group—7 tablets/day or 3.4 g/day ($p = 0.003$). The average dose of vitamin D in the study group was 1.75 versus 0.75 mcg/week in the control group, $p = 0.03$. In 65 newly initiated patients (dialysis started in the last year of our trial) we had no evidence over the treatment plan followed before dialysis; these patients were excluded from the medication-calcification correlations.

CAD risk calculation and the MBD-coronary risk score constitution

To assess the risk of vascular lesions and further to establish a coronary risk score in hemodialysis patients with altered mineral metabolism, OR was calculated for each parameter (Table 3).

In addition, logistic regression analysis was applied on all MBD parameters. Among predictor factors included in the initial regression model, only serum bicarbonate and valvular calcification were considered variables having a high significant contribution ($p < 0.05$). However, we could not use these results due to the small number of patients in the study group.

Based on OR values obtained for each parameter that were descendently ranked and consequently transformed (rank type; N tiles = 5), we elaborated a MBD-*coronary risk score* in HD patients, which we consider that it should be a supplementation to existing indication for coronary angiography in chronic dialysis patients (Table 4).

MBD-coronary risk score validation

By applying the *MBD-coronary risk score* in the control group, 29 patients (19.20%) obtained a grade **over 8** but only 9 agreed to perform coronary angiography. In seven patients (77.77%) coronary obstructions were found, five of them severe (71.4%); obstruction degrees are presented in Table 5.

There were four PTCA performed in this subgroup of patients, with no incidents reported.

The findings proved that the *MBD-coronary risk score* is not a marker for symptomatic CAD, but, in fact, a tool for assessing coronary obstructions regardless of angina.

Table 4 Assigning grades to MBD parameters based on their OR for CAD symptoms

Parameters	OR	Assigned score
Serum bicarbonate (mEq/L)	18.180	5
Valvular calcification (echocardiography)	12.090	4
Serum calcium (mg/dL)	10.330	4
Ischemic modifications on EKG	10.260	3
Calcium phosphate binders therapy (tablets)	7.270	3
PWV$^\delta$ (m/s)	5.700	3
Serum albumin (g/dL)	5.260	2
Vascular calcification	5.230	2
Serum phosphate (mg/dL)	4.340	2
iPTH (pg/mL)	3.780	1
Dialysis vintage (months)	3.350	1
Total		30

A score of 8 and greater should represent an indication for coronary angiography, even in asymptomatic hemodialysis patients

Discussion

Our study found strongly statistical correlations and, based on them, established a mathematical relation between altered CKD-MBD parameters and the risk of coronary artery obstructions in chronic dialysis patients. Furthermore, it pleads for the extension of coronary angiography indications in asymptomatic patients with high *MBD-coronary risk score* levels.

CAD is very common in patients on long-term dialysis [1–6, 12–15, 21, 22]. In our study, coronary angiography conducted in symptomatic patients highlighted a percentage of 94.11% of significant coronary lesion. In one patient the degree of obstruction was below 75%, aggravated by a muscle bridge. The incidence of "blind" coronary angiography in CKD stage 5D patients in the literature is around 25%; angina is likely to be caused by a small vessel malfunction or by the presence of muscle bridges [24].

This high prevalence of CAD in dialysis patients is due to the CKD-induced magnification of traditional risk factors and by the additional effect of vascular calcifications. The development of vascular calcifications in CKD patients was firstly mentioned in the nineteenth century and ever since it was addressed directly or collaterally, in multiple clinical trials [12, 19, 25–33]. Despite this continuous preoccupation, the connection between the degree of MBD and coronary artery impairment is still unquantifiable, although variations in serum calcium, phosphate and PTH have documented major negative impact on arterial wall elasticity and integrity [27–34]. The importance of CKD-specific factors in CAD development is emphasized by Goodman et al. [35] study that observed coronary artery calcifications in 88% of the chronic dialysis patients under 30 years old, even in the absence of age-determined atherosclerosis. A study conducted by Garland et al. [36] pointed out the importance of high calcium level as a risk factor for CAD in CKD stages 3–5, excluding dialysis. Continuing this idea, Nakamura et al. [17] highlighted that calcium phosphate product and the use of calcium-containing phosphate binders favored medial coronary calcification found in autopsied chronic renal patients with history of angina.

The connection between the biochemical disturbances of mineral bone disease and the presence of documented coronary stenosis was proved by our findings: high calcium, phosphate and iPTH levels were positively correlated with the coronary angiography subgroup. Likewise, PWV and vascular/valve calcifications were significantly higher in these patients.

Numerous studies have demonstrated the role of hypercalcemia in favoring the osteochondrocytic transformation of vascular smooth muscle cells (VSMC) through a mechanism still unclear, while, in the same time, inducing cell apoptosis trough calcium phosphate nanocrystals [26, 37–45]. In our study hypercalcemia appears to increase the risk of symptomatic coronary lesions with a calculated OR of 10.33. The conclusion is supported by observational study conducted by Kalantar-Zadeh et al. [46, 47] on 58 058 subjects in chronic hemodialysis who claimed that hyperphosphatemia and hypercalcemia are strong predictors of mortality by cardiovascular events. Serum calcium elevation with 1 mg/dL is associated with an increased relative risk of death between 12 and 22%, according to an analysis carried out by Covic et al. [48].

DOPPS study included 25 588 subjects undergoing dialysis and concluded that the risk of general mortality and cardiovascular death increases by 10–14% by a calcium elevation of 1 mg/dL, but also by 4–9% for a phosphate levels elevation of 1 mg/dL and by 1–2% for PTH elevation of 100 pg/mL [49, 50]. In our study high phosphate levels were depicted with significantly higher prevalence in the group of patients with angina and coronary stenosis: Average serum phosphate level in the study group was 5.87 ± 1.22 mg/dL, significantly different from the mean

Table 5 Degrees of coronary obstruction in asymptomatic patients with high *MBD-coronary risk score*

Patient	1	2	3	4	5	6	7	8	9
Coronary obstruction degree (%)	80	75	55	80	45	85	75	75	40

value of control group. Although the direct action of PTH on the morphological changes of cardiovascular structures remains a debate, its mean value was significantly higher in group of patients with cardiac complaints in our study, with an OR of 3.78.

Some data suggest that severe hypophosphatemia may also be associated with increased risk of death; low phosphate levels are recorded at 5% of dialysis patients and are caused by improper diet and/or association of inflammation [51]. It was not possible for us to make a correlation regarding this subject, as we had only one patient with low abnormal phosphate levels.

PWV is still the most recommended parameter for assessing vascular elasticity [52]. The development of vascular stiffness is favored by many traditional factors along with CKD associated factors: high calcium phosphate product, PTH increased levels, marked metabolic acidosis, oxidative stress [53–59]. We observed a significant positive correlation between the presence of angiographic objectified coronary calcifications and PWV levels.

There were no differences found between the mean values of alkaline phosphatase between the two groups, although other studies describe this enzyme as a predictor for the presence of vascular calcifications when it exceeds the upper limit of normal [34, 46, 60]. In the control group we recorded 30 cases (19.86%) of alkaline phosphatase levels above normal. Coronary artery stenosis could not be objectified or disproved in these patients.

Albumin is the most widely used indicator of nutritional status, in a complex relation with inflammation [61]. A study on uremic rats undergoing a low-protein diet concluded that this diet applied without additional essential amino acids is detrimental to the subject because it calls forth *inflammation* and vascular calcifications [62]. The significantly lower albumin mean value in the study group highlights the unfavorable malnutrition-hyperphosphatemia association, recently shown to be an important promoter of morphological changes in the arterial walls, by decreased fetuin-A levels [62, 63].

The clinical trial conducted by Nam et al. [64] on chronic dialysis patients established a correlation between vascular/valve calcifications objectified on X-ray and the severity of coronary lesions shown on angiography; they concluded that further studies are required to confirm the predictive value of vascular calcification score detected through noninvasive methods. Going further, Adragao et al. [65] correlated plain pelvis and hands X-ray results with PWV determinations and mortality in dialysis patients. Our results showed a significantly higher number of X-ray coronary calcifications and ultrasound detected valve calcifications in patients who required coronary angiography compared with patients without angina episodes ($p = 0.018$; $p = 0.002$). The risk calculated for US detected valve calcifications was the second most important value in the score, after low serum bicarbonate.

In the study group there were significantly higher prescribed doses for both vitamin D and phosphate binders ($p = 0.03$, $p = 0.003$), although the value calculated for OR regarding vitamin D was 1, meaning that vitamin D administration did not influence vascular lesion appearance in our study. These doses are adjusted monthly in response to variations in phosphate, calcium and PTH levels (depending mainly on the phosphates ingested by the patients). The attempt of maintaining bone metabolism parameters within normal limits may become a two-edge sword, especially in countries with limited resources for the use of non-calcium phosphate binders. We should focus more on nutritional education for convincing the patient to comply with the low-phosphate diet, insisting on avoiding additives and food preservatives, since calcium-based phosphate binders use revealed an important contribution to the *MBD-coronary risk score* (OR = 7.27) [66–68]. Nevertheless, a daily high dose of phosphate binders reveals a noncompliant type of patient, with uncontrolled diet and high interdialysis fluid gains, producing BP elevations and left ventricular hypertrophy which favors arterial stiffness. This is an important issue in the developing countries that do not fully reimburse expensive drugs in CKD patients (e.g., in Romania, vitamin D receptor activators are reimbursed by prescriptions for predialysis only). Despite the drawback of having only calcium-based phosphate binder prescribed for the studied population, this aspect adds uniformity to the study.

DOPPS study concluded that severe acidosis increases the mortality risk and establishes the safest serum bicarbonate range between 20 and 22 mEq/L [49, 69]. The study of this parameter in the two groups revealed that the average bicarbonate level in the subgroup of patients who had at least one episode of angina was much lower than the average serum bicarbonate in the control group (18.32 ± 1.63 versus 20.32 ± 1.91 mEq/L), a correlation with high statistical significance ($p < 0.001$). Bicarbonate levels showed the most important influence on the formation of coronary lesions (OR = 18.18 for the values found under 18 mEq/L and 6.84 for values under 20 mEq/L). In CKD, the influence of acidosis on the vascular wall calcification process is now highly disputed. Many authors emphasize the protective effect of acidosis by uprising the solubility of hydroxyapatite solubility and blocking the effect of matrix Gla protein and sodium-dependent phosphate cotransporter [70, 71]. On the other hand, acidosis strongly promotes arterial wall inflammation and releases pro-calcification cytokines; it favors bone dissolution and raises the serum calcium levels; mineral phosphate is released to buffer the acidosis and restore the pH [70, 72]. We also presume that the large serum pH variations during the dialysis

sessions (from severe initial acidosis to alkalosis in the end of the dialysis session) may produce important harmful changes in vascular cells function and endothelial mediated vascular tone, favoring arterial stiffness.

Electrocardiography showed ischemic type modifications in symptomatic (94.12%) and asymptomatic (60.93%) patients, with a significant difference in the favor of the study group. The electrocardiography recording suggesting CAD proved to be an important risk factor for the finding of coronary obstruction (OR = 10.26).

In summary, all these correlations found in symptomatic CAD-documented dialysis patients outline a pattern for coronary obstruction presence and lead us to the construction of this screening algorithm—the *MBD-coronary risk score*. The major problems in the diagnosis of CAD for patients on renal replacement therapy are the lack of symptoms and the limitations of noninvasive screening methods. We considered that out *MBD-coronary risk score* can help us overcome these obstacles.

Asymptomatic coronary artery obstructions are not uncommon in dialysis patients [24, 31, 73–75]. A recent investigation, conducted on 30 chronic dialysed patients (with no history of angina or myocardial infarction) to whom coronary angiography was performed, has showed the presence of over 50% coronary lumen narrowing in 53.5% of them. The percentage of obstruction was correlated with dialysis vintage [74, 76].

Occult type or atypical symptoms of coronary artery disease in patients on renal replacement therapy delays the diagnosis of vascular lesions and their treatment [76–78]. The noninvasive screening methods used for patients not on dialysis are difficult to perform or inconclusive for CKD stage 5D population [78]. As *De Vriese and Schmidt* pointed out in their reviews, the exercise tolerance test can only be performed in 23–53% of patients because of the restricted exercise capacity. Furthermore, a dialysis session with a blood flow rate over 300 mL/min can be regarded as a reliable exercise test for dialysis patients. As for the other noninvasive methods, myocardial perfusion scintigraphy has a low sensitivity level (30–80%, depending on the stress agent used) and computer tomography examinations are expensive, involving contrast medium without offering a therapeutic solution, as angiography does [78, 79]. Consequently, revascularization is underperformed in ESRD patients [80]. The indications to perform coronary angiography are limited, and the presence of ancillary criteria added to clinical criteria (e.g., angina) may be helpful. Risk assessment in these circumstances requires an optimal plan of investigation in order to improve the prognosis and quality of life. Although angiography is the gold standard in highlighting headquarters and severity of vascular lesions, its currently screening indication stays only for dialysis

patients who are evaluated for kidney transplant [81, 82]. We decided, as a secondary objective for the study, to use the obtained *MBD-coronary risk score* for extending the indications for coronary angiography in asymptomatic high-risk patients.

Many agreed that the management of the acute coronary events should be guided based on the evaluation of individual risk. The *GRACE risk score*, assembled based on an 8-year study involving over 55.000 patients with acute coronary events, assessed the risk of death in all the patients admitted with this type of pathology in 123 hospitals from 14 countries [81]. In the same study, Hitinder et al. conducted a separate investigation regarding patients receiving dialysis prior the coronary event. They pointed out that *GRACE risk score* underestimated the risk of major events after acute coronary accidents in this group of patients (12 versus 7.8% predicted) and the prevalence for in-hospital mortality rates, complication rates and rehospitalization were greater in patients receiving dialysis comparing with non-dialysis patients [83].

In our study, the validation of the *MBD-coronary risk score* pointed out a prevalence of 19.20% high-risk patients in the asymptomatic control group. In the majority (77.77%) of the patients who accepted the invasive investigation the presence of CAD was demonstrated and 71.4% of them revealed severe coronary obstructions. Considering that no incidents had been reported and a number of four patients received curative treatment (PTCA), it is an encouraging start for further researches.

Strength and limitations of the study

Our investigation is the *first pilot study* that elaborates an algorithm between biochemical and imagistic parameters of MBD and the presence of significant coronary obstructions as a noninvasive screening method for the asymptomatic CAD in non-diabetic HD patients. By adding this score to the monitoring program for the patients on maintenance dialysis and applying it yearly, we can perform targeted coronary angiography and contribute to the early diagnosis and treatment of asymptomatic coronary obstructions in this high-risk class of patients.

Coronary arteriography is an invasive technique that allows direct visualization of an artery and its branches. Despite the use of an iodinated contrast agent, it remains an accurate and safe method of diagnosing subclinical atherosclerosis, mostly in dialysis patients in which the concern about the renal toxicity is not a particularly important objective [74, 84, 85]. Coronary computed tomography angiography is much more expensive and high-dose radiation, while stress cardiac scintigraphy is not so effective in detecting coronary obstruction, showing mostly the effect

of myocardial ischemia [78, 86]. It seems that the investigation that better distinguishes between the two natures of CAD in CKD patients—medial and intimal calcifications—is optical coherence tomography (OCT) [87, 88]. This is, however, a very expensive analysis and not easy to perform. Therefore, we agreed to deal with CAD, including both types of coronary obstructions detected in our patients. Although intimal lesions and medial calcifications coexist in hemodialysis patients, many studies failed to establish a direct relation between them; therefore, coronary artery intimal calcifications are not a reliable marker for CAD in this group of patients [89–91].

In the last 3 years, there were 2042 coronary angiographies performed in our hospital, and 68 (3.38%) of them in chronic dialysis patients. By using iso-osmolar contrast media in patients receiving adequate dialysis we registered only two minor events (minimal bleedings at the injection site) and no variations in residual diuresis. The limitations and the risks for this procedure are minimal for dialysis patients, and the advantages can be considerable: early detection of significant occult coronary obstructions and their concomitant treatment. On the other hand, biochemical parameters which we found to be involved in coronary risk are within reach, being monthly assessed as required by the guidelines for the monitoring of maintenance dialysis patients [92].

A notable strength of our study was the significant percent of positive coronary angiography in patients with high *MBD-coronary risk score* (despite the low number of patients). The absence of diabetic patients and the limited prescription for expensive MBD-specific treatment (VDRD and calcimimetics) could be interpreted as strength (uniform cohort) but also as a limitation of our trial; the study results can be a plea for proper investment in CKD-MBD treatment.

There are several limitations of our study. First, the number of patients willing to perform coronary angiography is reduced, leading to a low number of subjects for the validation of *MBD-coronary risk score*. The anxiety of performing an invasive investigation and the high number of medical procedures they were forced to attend in CKD evolution, determined the chronic dialyzed patients to refuse coronary angiography in the absence of disabling symptoms. A second limitation is the exclusion of other noninvasive screening methods from our study procedures; we explained in the manuscript their limitations and the doubt that they can considerably improve the CAD diagnosis in hemodialysis patients. The isolation of MBD factors from other important traditional and non-traditional risk factors for CAD can be regarded more as strength than as a limitation of the study; this score can be integrated in the complex scene including all the factors involved in the coronary impairment in chronic dialysis patient.

Conclusion

Chronic dialysis patients with documented MBD have to be considered a very high-risk population for developing major coronary events. The serious lethal potential of these events and the high probability of subclinical coronary lesions justify a much active attitude in diagnosing and treating coronary obstructions in ESRD patients. Highly significant positive correlation between CAD and elevated serum phosphate, serum calcium, PTH on the one hand, values of PWV and the presence of vascular/valve calcifications on the other hand, suggests that non-diabetic chronic dialysis patients with high risk of CAD follow a specific clinical and biological pattern. Our work is the first pilot prospective study carried out in a homogenous population of non-diabetic HD patients that emphasize the negative influence of MBD parameters on the risk of CAD development. A *coronary risk score for MBD in dialysis patients*, based on non-invasive parameters, should be used as a tool for extending the indication for coronary angiography and helping early diagnosis and treatment in this life-threatening pathology.

References

1. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, Lewis J, Rocco M, Toto R, Windus D, Ornt D, Levey AS, HEMO Study Group (2004) Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int 65(6):2380–2389

2. US Renal Data System (2011) USRDS 2011 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD

3. Herzog CA, Passman R (2016) Evaluation of sudden cardiac arrest and sudden cardiac death in dialysis patients. UpToDate http://www.uptodate.com/contents/evaluation-of-sudden-cardiac-arrest-and-sudden-cardiac-death-in-dialysis-patients.com. Accessed March 2016

4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351(13):1296–1305

5. Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32(5 Suppl 3):S112–S119

6. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, Kasiske B, Kutner N, Liu J, Stpeter W, Guo H, Gustafson S, Heubner B, Lamb K, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L (2012) United States Renal Data System 2011 Annual Data Report: atlas of chronic kidney disease end-stage renal disease in the United States. Am J Kidney Dis 59(1 Suppl 1):A7, e1–e420

7. Herzog CA, Ma JZ, Collins AJ (1998) Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 339(12):799–805

8. Nakai S, Masakane I, Akiba T, Iseki K, Watanabe Y, Itami N, Kimata N, Shigematsu T, Shinoda T, Syoji T, Syoji T, Suzuki K, Tsuchida K, Nakamoto H, Hamano T, Marubayashi S, Morita O, Morozumi K, Yamagata K, Yamashita A, Wakai K, Wada A, Tsubakihara Y (2007) Overview of regular dialysis treatment in Japan (as of 31 December 2005). Ther Apher Dial 11(6):411–441

9. Takeda K, Harada A, Okuda S, Fujimi S, Oh Y, Hattori F, Motomura K, Hirakata H, Fujishima M (1997) Sudden death in chronic dialysis patients. Nephrol Dial Transplant 12(5):952–955

10. Vázquez E, Sánchez-Perales C, García-García F, García-Cortés MJ, Torres J, Borrego F, Salas D, Liébana A, Fernandez-Guerrero JC (2014) Sudden death in incident dialysis patients. Am J Nephrol 39(4):331–336

11. Nakano T, Ninomiya T, Sumiyoshi S, Fujii H, Doi Y, Hirakata H, Tsuruya K, Iida M, Kiyohara Y, Sueishi K (2010) Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. Am J Kidney Dis 55(1):21–30

12. McCullough PA, Soman S (2004) Cardiovascular calcification in patients with chronic renal failure. Are we on target with this risk factor? Kidney Int Suppl 90:S18–S24

13. Fox CS, Larson MG, Keyers MJ, Clouse ME, Culleton B, O'Donnell CJ (2004) Kidney function is inversely associated with coronary artery calcification in men and women free of cardiovascular disease: the Framingham Heart Study. Kidney Int 66(5):2017–2021

14. Koukoulaki M, Papachristou E, Kalogeropoulou C, Papathanasiou M, Zampakis P, Vardoulaki M, Alexopoulos D, Goumenos DS (2012) Increased prevalence and severity of coronary artery calcification in patients with chronic kidney disease stage III and IV. Nephron Extra 2(1):192–204

15. Baber U, de Lemos JA, Khera A, McGuire DK, Omland T, Toto RD, Hedayati SS (2008) Non-traditional risk factors predict coronary calcification in chronic kidney disease in a population-based cohort. Kidney Int 73(5):615–621

16. Checherita IA, Manda G, Hinescu ME, Peride I, Niculae A, Bilha S, Gramaticu A, Voroneanu L, Covic A (2016) New molecular insights in diabetic nephropathy. Int Urol Nephrol 48(3):373–387

17. Nakamura S, Ishibashi-Ueda H, Niizuma S, Yoshihara F, Horio T, Kawano Y (2009) Coronary calcification in patients with chronic kidney disease and coronary artery disease. Clin J Am Soc Nephrol 4(12):1892–1900

18. McCullough PA, Sandberg KR, Dumler F, Yanez JE (2004) Determinants of coronary vascular calcification in patients with chronic kidney disease and end-stage renal disease: a systemic review. J Nephrol 17(2):205–215

19. McCullough PA, Agrawal V, Danielewicz E, Abela GS (2008) Accelerated atherosclerotic calcification and Monckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. Clin J Am SocNephrol 3(6):1585–1598

20. Amann K (2008) Media calcification and intima calcification are distinct entities in chronic kidney disease. Clin J Am SocNephrol 3(6):1599–1605

21. Kumar S, Bogle R, Banerjee D (2014) Why do young people with chronic kidney disease die early? World J Nephrol 3(4):143–155

22. Cheung AK, Henrich WL (2016) Risk factors and epidemiology of coronary heart disease in end-stage renal disease (dialysis). UpToDate http://www.uptodate.com/contents/risk-factors-and-epidemiology-of-coronary-heart-disease-in-end-stage-renal-disease-dialysis.com. Accessed February 2016

23. Fraker TD Jr, Fihn SD, Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Williams SV, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of Cardiology, American Heart Association, American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group (2007) 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. Circulation 116(23):2762–2772

24. Onan B, Onan IS, Bakir I (2012) Left anterior descending coronary artery muscular bridge: lengthy and complete. Tex Heart Inst J 39(4):598–600

25. Afazali B, Goldsmith DJA (2014) Vascular calcification in chronic kidney disease. UpToDate http://www.uptodate.com/contents/vascular-calcification-in-chronic-kidney-disease.com. Accessed March 2016

26. Román-García P, Rodríguez-García M, Cabezas-Rodríguez I, López-Ongil S, Díaz-López B, Cannata-Andía JB (2011) Vascular calcification in patients with chronic kidney disease: types, clinical impact and pathogenesis. Med Princ Pract 20(3):203–212

27. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM (2011) Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res 109(6):697–711

28. Checherita IA, Smarandache D, David C, Ciocalteu A, Ion DA, Lascar I (2012) Vascular calcifications in chronic kidney disease - clinical management. Rom J Morphol Embryol 53(1):7–13

29. Lu KC, Wu CC, Yen JF, Liu WC (2014) Vascular calcification and renal bone disorders. ScientificWorldJournal 2014:637065

30. Checherita IA, Smarandache D, Radulescu D, Peride I, Bratu O, Ciocalteu A, Sebe I, Lascar I (2013) Calcific uremic arteriolopathy in hemodialyzed patients. Chirurgia (Bucur) 108(5):736–740

31. Johnson RC, Leopold JA, Loscalzo J (2006) Vascular calcification: pathobiological mechanisms and clinical implications. Circ Res 99(10):1044–1059

32. Mizobuchi M, Towler D, Slatopolsky E (2009) Vascular calcification: the killer of patients with chronic kidney disease. J Am Soc Nephrol 20(7):1453–1464

33. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15(8):2208–2218

34. Chang JF, Feng YF, Peng YS, Hsu SP, Pai MF, Chen HY, Wu HY, Yang JY (2014) Combined alkaline phosphatase and phosphorus levels as a predictor of mortality in maintenance hemodialysis patients. Medicine (Baltimore) 93(18):e106

35. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB (2000) Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 342(20):1478–1483

36. Garland JS, Holden RM, Groome PA, Lam M, Nolan RL, Morton AR, Pickett W (2008) Prevalence and associations of coronary artery calcification in patients with stages 3 to 5 CKD without cardiovascular disease. Am J Kidney Dis 52(5):849–858

37. Palit S, Kendrick J (2014) Vascular calcification in chronic kidney disease: role of disordered mineral metabolism. Curr Pharm Des 20(37):5829–5833

38. Ewence AE, Bootman M, Roderick HL, Skepper JN, McCarthy G, Epple M, Neumann M, Shanahan CM, Proudfoot D (2008) Calcium phosphate crystals induce cell death in human vascular smooth muscle cells: a potential mechanism in atherosclerotic plaque destabilization. Circ Res 103:e28–e34

39. Larsson TE, Olauson H, Hagström E, Ingelsson E, Arnlöv J, Lind L, Sundström J (2010) Conjoint effects of serum calcium and phosphate on risk of total, cardiovascular, and noncardiovascular mortality in the community. Arterioscler Thromb Vasc Biol 30(2):333–339

40. Yamada K, Fujimoto S, Nishiura R, Komatsu H, Tatsumoto M, Sato Y, Hara S, Hisanaga S, Ochiai H, Nakao H, Eto T (2007) Risk factors of the progression of abdominal aortic calcification in patients on chronic haemodialysis. Nephrol Dial Transplant 22(7):2032–2037

41. West SL, Swan VJ, Jamal SA (2010) Effects of calcium on cardiovascular events in patients with kidney disease and in a healthy population. Clin J Am Soc Nephrol 5(Suppl 1):S41–S47

42. Bălăceanu A, Diaconu C, David C, Niculae A, Peride A, Aron G (2014) Vascular calcifications, major risk factor for cardiovascular events in chronic kidney disease: an update on the pathophysiological process. Mod Med 21(2):116–119

43. Shroff RC, McNair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, Rees L, Shanahan CM (2010) Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. J Am Soc Nephrol 21(1):103–112

44. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM (2004) Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol 15(11):2857–2867

45. Proudfoot D, Skepper JN, Hegyi L, Bennett MR, Shanahan CM, Weissberg PL (2000) Apoptosis regulates human vascular calcification in vitro: evidence for initiation of vascular calcification by apoptotic bodies. Circ Res 87(11):1055–1062

46. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD (2006) Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int 70(4):771–780

47. Kalantar-Zadeh K, Shah A, Duong U (2010) Kidney bone disease and mortality in CKD: revisiting the role of vitamin D, calcimimetics, alkaline phosphatase, and minerals. Kidney Int Suppl 117:S10–S21

48. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A, Goldsmith D (2009) Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. Nephrol Dial Transplant 24(5):1506–1523

49. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA (2004) The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. Am J Kidney Dis 44(5 Suppl 2):7–15

50. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, Young EW, Akizawa T, Akiba T, Pisoni RL, Robinson BM, Port FK (2008) Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 52(3):519–530

51. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, Akizawa T, Kurokawa K, Bommer J, Piera L, Port FK (2005) Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns study. Kidney Int 67(3):1179–1187

52. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Members Task Force (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31(7):1281–1357

53. Jadhav UM, Kadam NN (2005) Non-invasive assessment of arterial stiffness by pulse-wave velocity correlates with endothelial dysfunction. Indian Heart J 57(3):226–232

54. Safar ME, Henry O, Meaume S (2002) Aortic pulse wave velocity: an independent marker of cardiovascular risk. Am J Geriatr Cardiol 11(5):295–298

55. Blacher J, Asmar R, Djane S, London GM, Safar ME (1999) Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 33(5):1111–1117

56. Nichols WW, O'Rourke MF (1990) Properties of the arterial wall. In: Nichols WW, O'Rourke MF, McDonald DA (eds) McDonald's blood flow in arteries: theoretical, experimental and clinical principles, 3rd edn. Edward Arnold, London, pp 77–114

57. Lehmann ED, Gosling RG, Sönksen PH (1992) Arterial wall compliance in diabetes. Diabet Med 9(2):114–119

58. Wada T, Kodaira K, Fujishiro K, Maie K, Tsukiyama E, Fukumoto T, Uchida T, Yamazaki S (1994) Correlation of ultrasound-measured common carotid artery stiffness with pathological findings. Arterioscler Thromb Vasc Biol 14(3):479–482

59. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K, London AM (1990) Aortic and large artery compliance in end-stage renal failure. Kidney Int 37(1):137–142

60. Shantouf R, Kovesdy CP, Kim Y, Ahmadi N, Luna A, Luna C, Rambod M, Nissenson AR, Budoff MJ, Kalantar-Zadeh K (2009) Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients. Clin J Am Soc Nephrol 4(6):1106–1114

61. Kaysen GA (2000) Malnutrition and the acute-phase reaction in dialysis patients - how to measure and how to distinguish. Nephrol Dial Transplant 15(10):1521–1524

62. Yamada S, Tokumoto M, Tatsumoto N, Tsuruya K, Kitazono T, Ooboshi H (2016) Very low protein diet enhances inflammation, malnutrition, and vascular calcification in uremic rats. Life Sci 146:117–123

63. Yamada S, Tokumoto M, Tatsumoto N, Taniguchi M, Noguchi H, Nakano T, Masutani K, Ooboshi H, Tsuruya K, Kitazono T

(2014) Phosphate overload directly induces systemic inflammation and malnutrition as well as vascular calcification in uremia. Am J Physiol Renal Physiol 306(12):F1418–F1428

64. Nam HS, Lee SM, Jeong EG, Lee DY, Son YK, Kim SE, Chung SH, Cho YR, Park JS, Lee SW, Noh MH, An WS (2015) Vascular calcification on plain radiographs is related with the severity of lesions detected by coronary angiography in dialysis patients. Tohoku J Exp Med 235(2):135–144

65. Adragão T, Pires A, Birne R, Curto JD, Lucas C, Gonçalves M, Negrão AP (2009) A plain X-ray vascular calcification score is associated with arterial stiffness and mortality in dialysis patients. Nephrol Dial Transplant 24(3):997–1002

66. Moe SM, Chertow GM (2006) The case against calcium-based phosphate binders. Clin J Am Soc Nephrol 1(4):697–703

67. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, TerWee P, Teta D, Wang AY, Wanner C, International Society of Renal Nutrition and Metabolism (2013) Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int 84(6):1096–1107

68. K/DOQI National Kidney Foundation (2000) Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis 35(6 Suppl 2):S1–S140

69. Bommer J, Locatelli F, Satayathum S, Keen ML, Goodkin DA, Saito A, Akiba T, Port FK, Young EW (2004) Association of pre-dialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 44(4):661–671

70. Yonova D (2009) Vascular calcification and metabolic acidosis in end stage renal disease. Hippokratia 13(3):139–140

71. Mendoza FJ, Lopez I, Montes de Oca A, Perez J, Rodriguez M, Aguilera-Tejero E (2008) Metabolic acidosis inhibits soft tissue calcification in uremic rats. Kidney Int 73(4):407–414

72. Arnett T (2003) Regulation of bone cell function by acid-base balance. Proc Nutr Soc 62:511–520

73. Charytan D, Kuntz RE, Mauri L, DeFilippi C (2007) Distribution of coronary artery disease and relation to mortality in asymptomatic hemodialysis patients. Am J Kidney Dis 49(3):409–416

74. Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, Saito S (2005) High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: an angiographic examination. J Am Soc Nephrol 16(4):1141–1148

75. Hakeem A, Bhatti S, Chang SM (2014) Screening and risk stratification of coronary artery disease in end-stage renal disease. JACC Cardiovasc Imaging 7(7):715–728

76. Sosnov J, Lessard D, Goldberg RJ, Yarzebski J, Gore JM (2006) Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. Am J Kidney Dis 47(3):378–384

77. Cai Q, Mukku VK, Ahmad M (2013) Coronary artery disease in patients with chronic kidney disease: a clinical update. Curr Cardiol Rev 9(4):331–339

78. De Vriese AS, Vandecasteele SJ, Van den Bergh B, De Geeter FW (2012) Should we screen for coronary artery disease in asymptomatic chronic dialysis patients? Kidney Int 81(2):143–151

79. Schmidt A, Stefenelli T, Schuster E, Mayer G (2001) Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. Am J Kidney Dis 37(1):56–63

80. Sedlis SP, Jurkovitz CT, Hartigan PM, Goldfarb DS, Lorin JD, Dada M, Maron DJ, Spertus JA, Mancini GB, Teo KK, O'Rourke RA, Boden WE, Weintraub WS, COURAGE Study Investigators (2009) Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease. Am J Cardiol 104(12):1647–1653

81. Avezum A, Makdisse M, Spencer FA, Gore JM, Fox KA, Montalescot G, Eagle KA, White K, Mehta RH, Knobel E, Collet JP, Investigators GRACE (2005) Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 149(1):67–73

82. Pidgeon GB, Lynn KL, Bailey RR, Robson RA, Ikram H (1995) Coronary angiography prior to renal transplantation. Nephrology 1(1):59–64

83. Gurm HS, Gore JM, Anderson FA Jr, Wyman A, Fox KAA, Steg PG, Eagle KA (2012) Comparison of acute coronary syndrome in patients receiving versus not receiving chronic dialysis (from the Global Registry of Acute Coronary Events [GRACE] Registry). Am J Cardiol 109(1):19–25

84. Erbel R, Budoff M (2012) Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. Eur Heart J 33(10):1201–1213

85. Gowdak LHW, de Lima JJG (2011) Coronary angiography in patients with chronic kidney disease. In Kiraç SF (ed) Advances in the diagnosis of coronary atherosclerosis. InTech, http://www.intechopen.com/books/advances-in-the-diagnosis-of-coronary-atherosclerosis/coronary-angiography-in-patients-with-chronic-kidney-disease. Accessed March 2016

86. Marwick TH, Steinmuller DR, Underwood DA, Hobbs RE, Go RT, Swift C, Braun WE (1990) Ineffectiveness of dipyridamole SPECT thallium imaging as a screening technique for coronary artery disease in patients with end-stage renal failure. Transplantation 49(1):100–103

87. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PW, Expert's OCT Review Document (2010) Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J 31(4):401–415

88. Voiculeţ C, David C, Dragomirescu RF, Zară OD, Tiron AT, Bălăceanu A, Aron G (2015) Tomografia prin coerenţă optică, metodă inovatoare de evaluare a microarhitecturii plăcilor de aterom la pacienţii dializaţi cronic. Med Intern 6:65–70

89. Patsalas S, Eleftheriadis T, Spaia S, Theodoroglou H, Panou E, Liakopoulos V, Antoniadi G, Passadakis P, Vayonas G, Kanakis E, Vargemezis V (2005) The value of computed tomography-derived coronary artery calcification score in coronary artery disease detection in asymptomatic hemodialysis patients. Ren Fail 27(6):683–688

90. Patsalas S, Eleftheriadis T, Spaia S, Theodoroglou H, Antoniadi G, Liakopoulos V, Passadakis P, Vayonas G, Vargemezis V (2007) Thirty-month follow-up of coronary artery calcification in hemodialysis patients: different roles for inflammation and abnormal calcium-phosphorous metabolism? Ren Fail 29(5):623–629

91. Drüeke TB (2008) Arterial intima and media calcification: distinct entities with different pathogenesis or all the same? Clin J Am Soc Nephrol 3(6):1583–1584

92. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009) KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 113:S1–S130