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Understanding the Korean Dialysis Cohort for Mineral, Vascular Calcification, and Fracture (ORCHESTRA) Study: Design, Method, and Baseline Characteristics

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Keywords
ORCHESTRA · End-stage renal disease · Cohort · Chronic kidney disease-mineral and bone disorder · Bone mineral densitometry · Cardiovascular outcome · Osteoporosis · Fractures

Abstract
Introduction: End-stage renal disease (ESRD) is a growing disease worldwide, including Korea. This is an important condition that affects patient outcome. To provide optimal management for mineral disturbance, vascular calcification,

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and bone disease in ESRD patients, the Korean dialysis cohort for mineral, vascular calcification, and fracture (ORCHESTRA) study was conducted by enrolling Korean dialysis patients. ***Methods:*** Sixteen university-affiliated hospitals and one Veterans' Health Service Medical Center participated in this study. This prospective cohort study enrolled approximately 900 consecutive patients on dialysis between May 2019 and January 2021. Enrolled subjects were evaluated at baseline for demographic information, laboratory tests, radiologic imaging, and bone mineral densitometry (BMD) scans. After enrollment, regular assessments of the patients were performed, and their biospecimens were collected according to the study protocol. The primary outcomes were the occurrence of major adverse cardiovascular events, invasive treatment for peripheral artery disease, and osteoporotic fractures. The secondary outcomes were hospitalization for cerebrovascular disease or progression of abdominal aortic calcification. Participants will be assessed for up to 3 years to determine whether primary or secondary outcomes occur. ***Results:*** Between May 2019 and January 2021, all participating centers recruited 900 consecutive dialysis patients, including 786 undergoing hemodialysis (HD) and 114 undergoing peritoneal dialysis (PD). The mean age of the subjects was 60.4 ± 12.3 years. Males accounted for 57.7% of the total population. The mean dialysis vintage was 6.1 ± 6.0 years. The HD group was significantly older, had a longer dialysis vintage, and more comorbidities. Overall, the severity of vascular calcification was higher and the level of BMD was lower in the HD group than in the PD group. ***Conclusion:*** This nationwide, multicenter, prospective cohort study focused on chronic kidney disease-mineral and bone disorder and aimed to provide clinical evidence to establish optimal treatment guidelines for Asian dialysis patients.

Introduction

End-stage renal disease (ESRD) is a rapidly growing global disease and an important health problem affecting patient prognosis [1, 2]. ESRD patients have a number of serious complications including anemia, volume overload, mineral disturbance, presence of uremic toxins, altered bone health, and accelerated vascular calcification (VC) [3–6]. Cardiovascular disease (CVD) is a significant complication associated with adverse outcomes related to ESRD. It is a major cause of death and hospitalization in ESRD patients [7, 8].

Mineral bone disorder (MBD) is a well-known clinical consequence of complex interactions between calcium, phosphorus, vitamin D, parathyroid hormone, and fibroblast growth factor 23 (FGF-23) as kidney function declines [9]. This derangement of mineral metabolism causes alterations in bone health and accelerates VC development [10]. In 2017, the Kidney Disease Improving Global Outcome (KDIGO) guidelines recommended monitoring mineral parameters and implementing strategies to manage VC and bone disease in chronic kidney disease (CKD) [11]. The guidelines suggest that instead of using a specific range of parameter values, trends of parameter values should be used to treat patients with ESRD, particularly warning against calcium overloading.

The prevalence of ESRD is increasing in Korea. Cardiac problems are the most common cause of death in Korean patients undergoing dialysis [12]. Therefore, it is important to elucidate the relationship between mineral parameters, VC, and bone abnormalities to improve the outcomes of patients undergoing dialysis. To provide optimal management, a nationwide prospective observational cohort study was conducted by a group of nephrologists in Korea in 2019, called the Korean dialysis cohort for mineral, VC, and fracture (ORCHESTRA) study. In this report, we present the study design, methods, and baseline characteristics of the entire study population enrolled between 2019 and 2021.

Methods

Organization

The ORCHESTRA study is a cohort study conducted with the participation of 16 university-affiliated hospitals and one Veterans' Health Service Medical Center in South Korea. The hospitals included the Catholic University of Korea Daejeon St. Mary's Hospital, the Catholic University of Korea Eunpyeong St. Mary's Hospital, the Catholic University of Korea Uijeongbu St. Mary's Hospital, CHA Medical School Bundang CHA Medical Center, Chonnam National University Hospital, Gachon University Gil Medical Center, Gangnam Severance Hospital, Hallym University Kangnam Sacred Heart Hospital, Hanyang University Seoul Hospital, Inje University Busan Paik Hospital, Keimyung University Dongsan Medical Center, Korea University Guro Hospital, Kyung Hee University East-West Neo Medical Center, Kyung Hee University Medical Center, Pusan National University Hospital, and Seoul National University Hospital. Of these, five hospitals (CHA Medical School Bundang CHA Medical Center, Kyung Hee University East-West Neo Medical Center, Kyung Hee University Medical Center, Veterans Health Service Medical Center, and Korea University Guro Hospital) have been collecting patient data and blood samples by conducting a prospective cohort observational study for hemodialysis (HD) patients (the K-cohort) since

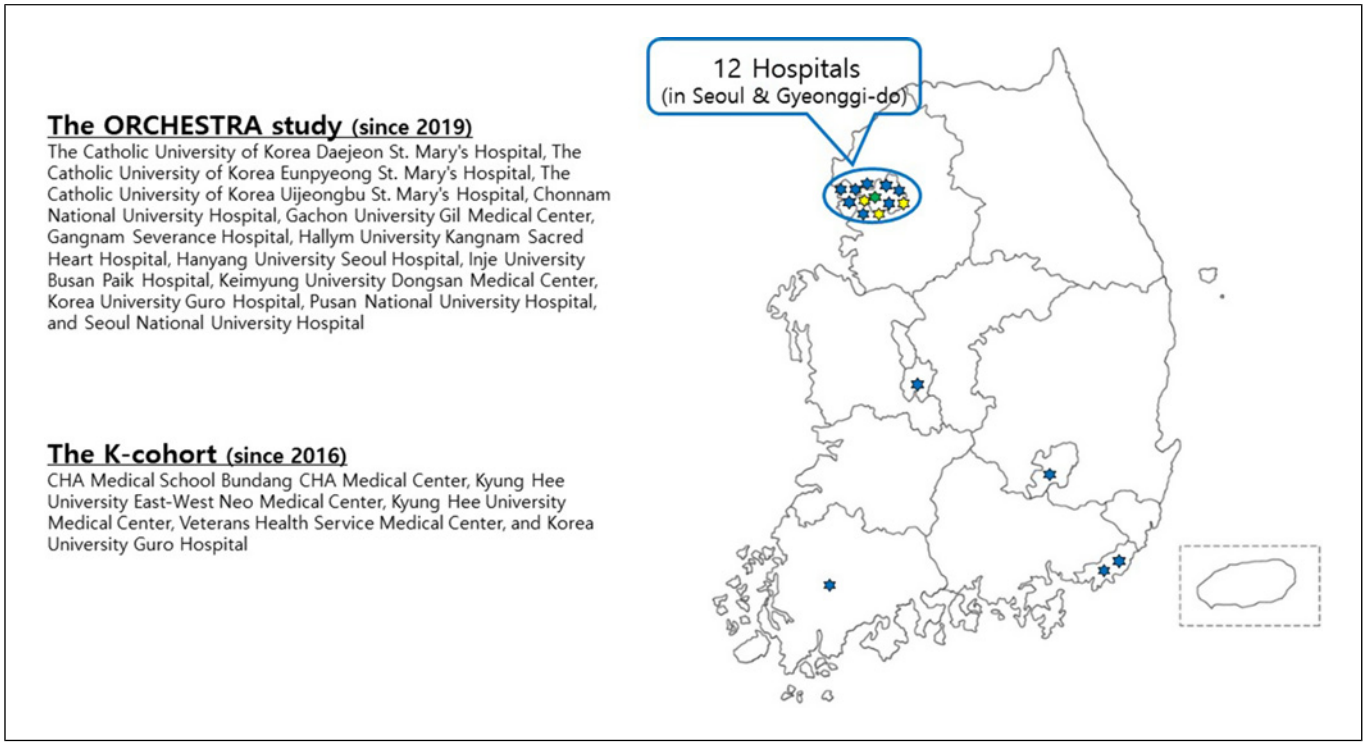

Fig. 1. Distribution of participants for each institution according to cohort study in South Korea.

2016 [13]. The K-cohort was a multicenter prospective cohort consisting of HD patients in Korea. It was designed to investigate the prognostic factors for cardiovascular complications and death. Patients in the K-cohort and ORCHESTRA studies share similarities in terms of targeted populations, information collection, and specimen samples. Consequently, the K-cohort, which has been ongoing since 2016, has become part of the ORCHESTRA study initiated in 2019 (Fig. 1). Moreover, the Korea University Guro Hospital acted as the main coordinating center for The ORCHESTRA study. It has been a participant in a K-cohort study since 2017. The study population and data collected should be standardized for consistency. Clinical centers across South Korea participated, including nine hospitals in Seoul, three in the satellite areas of Seoul, and five in metropolitan cities (Fig. 1). The study protocol was approved by the Institutional Review Board (IRB) of each participating center. This cohort study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed written consent was obtained from each patient before inclusion.

Study Population

The ORCHESTRA study was designed as a prospective cohort to enroll approximately 900 consecutive patients from May 2019 to January 2021, who had been undergoing HD or peritoneal dialysis (PD) for at least 3 months due to ESRD. Before enrollment, all participants signed consent forms. They were monitored for 3 years. The inclusion and exclusion criteria of the ORCHESTRA study are presented in Table 1. The distribution of participants by sex and dialysis modality for each institution, along with the age range, are presented in online supplementary Table 1 and Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000539030).

Data Collection

All individuals underwent a screening visit during which consent was obtained, and their eligibility was determined based on the inclusion and exclusion criteria (Table 1). The protocols used for data and sample collection for this study are presented in Table 2. At the baseline visit, medical and lifestyle characteristics, current medications, and dialysis information were recorded. Medical history included diabetes, hypertension (HTN), CVD, congestive heart failure (CHF), cerebrovascular disease, thyroid disease, parental fracture history, and ESRD. Lifestyle characteristics included information on alcohol consumption and smoking habits. HTN was defined as a condition involving a history of HTN or the use of antihypertensive medication. Diabetes was characterized by a history of diabetes, the use of oral hypoglycemic agents, or insulin administration. CVD, CHF, and cerebrovascular disease were verified through medical history or obligatory medical record review. CVD, CHF, and cerebrovascular disease were defined as conditions diagnosed through medical assessments, including coronary angiography, echocardiography, cerebral vasculature imaging, or hospitalization, specific to each ailment. Thyroid disorders were defined as a condition with a history of thyroid disorders or current use of the thyroid hormone propylthiouracil (PTU) or methimazole. Parental fracture history was obtained through surveys. The cause of ESRD was ascertained through surveys or mandatory medical record reviews. Height was measured at baseline. Weight and clinical

blood pressure were measured at each follow-up visit. After enrollment, laboratory tests, radiological imaging, and bone mineral densitometry (BMD) scans were performed according to the study protocol. Serum samples were collected using standardized protocols. All data, including demographic information, sociomedical histories, current medications, dialysis details, laboratory results, and outcomes, were systematically validated through chart reviews and data collection via surveys during each patient visit. They were documented on a web-based electronic case reporting form at every visit.

Outcome Measurement

Primary outcomes were the occurrence of major adverse cardiovascular events (MACEs), invasive treatment for peripheral artery disease (PAD), and osteoporotic fractures. MACEs are defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke [14]. Invasive treatment for PAD includes angioplasty or bypass surgery. An osteoporotic fracture is defined as a history or radiologic finding of injury to the hip, vertebrae, upper arm, or wrist [15].

The secondary outcomes were hospitalization for cerebrovascular disease or progression of abdominal aortic calcification (AAC). Hospitalization for cerebro-CVD refers to hospitalization for transient ischemic attack, coronary artery disease (CAD), and HF. AAC progression of AAC is defined as an increase in the abdominal aortic calcification score (AACS). The AACS was assessed at the time of enrollment and subsequently at every 12-month visit, as described in Table 2. Two experienced investigators read all the images according to the established method [16]. During each visit, we assessed the primary and secondary outcomes by conducting surveys and mandatory reviews of medical records.

Biospecimen Collection

At the time of enrollment and 24-month visit, whole blood was obtained using serum separation tubes (SSTs) and ethylenediamine tetra-acetic acid tubes. All samples were centrifuged at 3,000 rpm for 10 min at 4°C for serum separation and then stored at −80°C until use.

Follow-Up

From 2019 to 2021, 900 participants were recruited for the ORCHESTRA study. They will undergo a 3-year follow-up observation to assess the occurrence of outcomes. Patients will visit the participating clinical centers based on the study schedule protocol. At every visit, the patients will undergo specific tests according to the study protocol. Investigators will check each patient's recent medical information and occurrence of outcomes. The term "recent medical information" refers to information regarding medications taken at the time of the visit and prescriptions for dialysis. All participants were censored at the time of transplantation, death, failure to follow-up, or end of the study period. Investigators will make efforts, such as telephone calls before the visit schedule, to prevent dropouts.

IRB Approval

The study protocol was approved by the IRB of each participating center in 2019.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Age ≥19 years
Patients receiving HD or PD at least 3 months due to end-stage renal disease
Exclusion criteria
Inpatients
Previous diagnosis of any cancer within 5 years
Previous diagnosis of CVD, cerebrovascular disease, or peripheral vascular disease within 6 months
Previous immunosuppressive treatment within 6 months
Unlikely or unable to participate in required study procedures

Statistical Methods and Plan

The baseline characteristics of the study population were presented using a standard descriptive analysis based on dialysis modalities. Continuous variables are expressed as the mean ± standard deviation. Categorical variables were expressed as percentages with corresponding numbers. Demographic and laboratory findings were compared using Student's t-test for continuous variables and the χ^2 test for categorical variables. To analyze variable outcomes, Kaplan-Meier curves and proportional hazard models were used as important statistical analysis methods. As previously mentioned, the occurrence of study outcomes will be monitored for up to 3 years following study participation. Analyses of the outcomes will be presented in the future when all data are collected. Statistical analyses of baseline data were conducted using the SPSS statistical package for Windows (version 21.0; SPSS, Inc., Chicago, IL, USA). All tests were two-sided. Statistical significance was set at $p < 0.05$.

Results

Baseline Demographic and Clinical Characteristics of Study Participants

Between May 2019 and January 2021, 900 patients were enrolled, including 786 on HD and 114 on PD. The demographic and clinical characteristics of the patients according to dialysis modality are presented in Table 3. The mean age of the study group was 60.4 ± 12.3 years. At the time of study enrollment, 57.7% of the patients were men. HTN and diabetes were present in 799 (88.8%) and 455 (50.6%) patients, respectively. A total of 159 (17.7%), 100 (11.1%), and 138 (15.4%) patients had CAD, CVD, and thyroid disease, respectively. The mean dialysis vintage in the total cohort was 6.1 ± 6.0 years. Diabetes mellitus is the most common cause of ESRD. Antiplatelet agents were prescribed in 543 (60.9%) patients, statins in 460

Table 2. Sequence and schedule for clinic visits and procedures of the ORCHESTRA study

	Screening	Baseline	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
Type of contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit/phone	Visit/phone
Informed consent	∨							
Demographic information	∨							
Medical history	∨	∨						
Social history		∨						
Recent events			∨	∨	∨	∨	∨	∨
Medications		∨		∨		∨		
Dialysis information								
Hemodialysis[1]		∨		∨		∨		
Peritoneal dialysis[2]		∨		∨		∨		
Anthropometry[3]		∨	∨	∨	∨	∨		
Laboratory test								
CBC, chemistry[4], HbA1c[5]		∨	∨	∨	∨	∨		
Ionized Ca		∨	∨	∨	∨	∨		
hs-CRP, Iron panel[6]		∨	∨	∨	∨	∨		
Lipid panel[7], TSH, fT4		∨		∨		∨		
25-VD, intact PTH		∨	∨	∨	∨	∨		
Bone densitometry		∨				∨		
T-L/L-S spine lateral X-ray		∨		∨		∨		

HD, hemodialysis; PD, peritoneal dialysis; CBC, complete blood count; Ca, calcium; Mg, magnesium; hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone; fT4, free thyroxine; 25-VD, 25-hydroxy vitamin D; PTH, parathyroid hormone; T-L, thoracolumbar; L-S, lumbosacral; mo: months. [1]Dry body weight, pre- and post-dialysis vital signs, volume of ultrafiltration, duration, frequency, blood flow rate, vascular access, and dialysis adequacy. [2]Body weight, types of PD solution, dialysis mode, dialysis adequacy, peritoneal equilibrium test (PET), and residual urine volume. [3]Height, body weight, blood pressure. [4]Calcium, phosphorous, glucose, BUN, creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT. [5]For diabetic patients. [6]Iron, TIBC, ferritin. [7]Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.

(51.7%) patients, calcium-based phosphate binders (P binders) in 313 (35.1%) patients, and non-calcium-based P binders in 510 (57.4%) patients. The HD group had significantly older age (61.2 ± 12.3 years vs. 54.6 ± 10.9 years, $p < 0.001$), longer dialysis vintage (6.3 ± 6.2 vs. 4.6 ± 3.7 years, $p < 0.001$), and more comorbidities such as diabetes, CAD, and CVD than the PD group.

The baseline laboratory findings are shown in Table 4. Mean levels of hemoglobin, albumin, alkaline phosphatase, corrected calcium, phosphorous (P), ionized calcium (i-Ca), and magnesium (Mg) were 10.7 ± 1.2 g/dL, 3.9 ± 0.3 g/dL, 115 ± 107 U/L, 8.8 ± 0.7 mg/dL, 5.0 ± 1.4 mg/dL, 0.87 ± 0.36 mmol/L, and 2.5 ± 0.2 mg/dL, respectively. There were significant differences in the serum potassium, chloride, total CO_2, corrected calcium, P, i-Ca, total cholesterol, and LDL cholesterol (LDL C) levels between the HD and PD groups.

AAC Status of the Study Population at the Time of Enrollment

A total of 841 (93.4%) patients underwent plain radiography of the lateral spine at enrollment. The baseline mean AACS was 5.2 ± 5.7. HD patients had significantly more severe calcification than PD patients (HD vs. PD of AACS: 5.5 ± 5.8 vs. 3.6 ± 5.0, $p < 0.001$). The proportion of patients with severe calcification was significantly higher in the HD group and the proportion of patients without calcification was significantly higher in the PD group (Table 5).

Baseline Bone Mineral Density of the Study Group

Bone mineral density (BMD) of the hip and spine was evaluated in 735 (81.7%) patients at enrollment using dual-energy X-ray absorptiometry (DXA). We collected the T-scores, Z-scores, and BMD. Study participants who underwent DXA were classified by sex, with male participants divided into those over 50 years

Table 3. Demographic and clinical characteristics of participants at baseline

	Total	HD	PD	*p* value
Patients, *n*	900	786 (87.3%)	114 (12.7%)	
Age, years	60.4±12.3	61.2±12.3	54.6±10.9	<0.001
Gender				0.448
Male	57.7 (519/900)	58.1 (457/786)	54.4 (62/114)	
Female	42.3 (381/900)	41.9 (329/786)	45.6 (52/114)	
Comorbidities, % (*n*)				
Diabetes	50.6 (455/900)	52.3 (411/786)	38.6 (44/114)	0.006
HTN	88.8 (799/900)	88.0 (692/786)	93.9 (107/114)	0.066
Coronary artery disease (CAD)	17.7 (159/900)	18.7 (147/786)	10.5 (12/114)	0.032
Congestive heart failure (CHF)	6.6 (59/900)	6.7 (53/786)	5.3 (6/114)	0.551
Cerebrovascular disease (CVD)	11.1 (100/898)	12.0 (94/784)	5.3 (6/114)	0.033
Thyroid disease	15.4 (138/897)	14.9 (117/783)	18.4 (21/114)	0.336
Parent's fracture history	7.5 (44/586)	7.2 (34/472)	8.8 (10/114)	0.568
Dialysis vintages, years	6.1±6.0	6.3±6.2	4.6±3.7	<0.001
Causes of ESRD				<0.001
Diabetes	40.9 (363/888)	42.2 (327/774)	31.6 (36/114)	
HTN	18.8 (167/888)	19.5 (151/774)	14.0 (16/114)	
Chronic glomerulonephritis	19.6 (174/888)	17.8 (138/774)	31.6 (36/114)	
Smoking history				0.093
Never smoker	68.8 (404/587)	70.4 (333/473)	62.3 (71/114)	
Current or former smoker	31.2 (183/587)	29.6 (140/473)	37.7 (43/114)	
Charlson comorbidity score	3.7±1.6	3.7±1.5	3.3±1.4	0.001
Antihypertensive drugs	77.2 (661/856)	76.7 (572/746)	80.9 (89/110)	0.323
Glucose-lowering agents	37.7 (339)	38.2 (300)	34.2 (39)	0.415
Antiplatelet agents	60.9 (543/892)	66.6 (518/778)	21.9 (25/114)	<0.001
Anticoagulants	9.4 (84/892)	9.3 (72/778)	10.5 (12/114)	0.664
Statin	51.7 (460/889)	52.1 (404/775)	49.1 (56/114)	0.549
Calcium-based P binder	35.1 (313/892)	35.5 (276/778)	32.5 (37/114)	0.528
Non-calcium-based P binder	57.4 (510/889)	56.3 (436/775)	64.9 (74/114)	0.081
Vitamin D and vitamin D analogue	53.9 (485)	53.4 (420)	57.0 (65)	0.473
Calcimimetics	20.7 (182/878)	20.5 (157/765)	22.1 (25/113)	0.695
Iron (oral or intravenous)	67.3 (599/890)	66.2 (514/776)	74.6 (85/114)	0.077
ESA	82.0 (727/887)	81.9 (634/774)	82.3 (93/113)	0.920
Mg supplements	1.6 (11/670)	1.6 (9/559)	1.8 (2/111)	0.885
Proton pump inhibitors (PPI)	24.3 (167/688)	27.4 (158/576)	8.0 (9/112)	<0.001

HD, hemodialysis; PD, peritoneal dialysis; ESRD, end-stage renal disease; ESA, erythropoietin-stimulating agent.

of age and those younger than 50 years. Female participants were classified according to menopausal status. We assessed individuals under 50 years of age, men, and premenopausal women using z-scores, and we assessed individuals over 50 years of age, men, and postmenopausal women using T-scores, in accordance with clinical guidelines [17]. Overall, the proportion of low BMD estimated by the T-score was higher in the HD group than in the PD group, especially among men (Tables 6, 7).

Table 4. Laboratory findings of participants at baseline

	Total	HD	PD	*p* value
Patients, *n*	900	786	114	
Hemoglobin, g/dL	10.7±1.2	10.7±1.1	10.6±1.4	0.322
WBC, $\times10^3$/μL	5.8±1.9	5.7±1.9	6.5±2.0	<0.001
Platelet, $\times10^3$/μL	182±66	178±65	210±61	<0.001
Total protein, g/dL	6.7±0.5	6.8±0.5	6.6±0.6	0.001
Albumin, g/dL	3.9±0.3	3.9±0.3	3.9±0.4	0.076
Alkaline phosphatase, U/L	115±107	117±113	106±47	0.076
Sodium, mmol/L	137±3.2	137±3.2	137±3.5	0.395
Potassium, mmol/L	4.8±0.7	4.8±0.7	4.6±0.7	0.003
Chloride, mmol/L	99±4.1	99±3.8	96±5.0	<0.001
Total CO_2, mmol/L	23.6±3.1	23.2±2.9	26.0±3.3	<0.001
Uric acid, mg/dL	6.0±1.6	5.9±1.6	6.1±1.6	0.381
Corrected calcium, mg/dL	8.8±0.7	8.8±0.7	9.0±0.7	0.016
i-Ca, mmol/L	0.87±0.36	0.89±0.34	0.72±0.45	<0.001
Phosphorous, mg/dL	5.0±1.4	4.9±1.4	5.5±1.3	<0.001
Mg, mg/dL	2.5±0.2	2.5±0.5	2.5±0.6	0.892
Transferrin saturation, %	31.8±14.1	31.2±13.8	35.8±15.4	0.004
Ferritin, ng/mL	285.4±278.1	282.6±273.8	304.5±306.8	0.432
HbA1c, %	6.1±1.3	6.2±1.4	5.8±1.1	0.004
Intact PTH, pg/mL	356.0±410.7	361.4±431.5	318.4±215.6	0.299
Total cholesterol, mg/dL	136±35	133±34	156±37	<0.001
HDL cholesterol, mg/dL	47±15	46±15	48±16	0.158
LDL cholesterol, mg/dL	70±27	68±26	83±29	<0.001
hs-CRP, mg/dL	2.6±7.3	2.6±7.5	2.4±6.0	0.790

HD, hemodialysis; PD, peritoneal dialysis; WBC, white blood cell; CO_2, carbon dioxide; PTH, parathyroid hormone; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.

Table 5. AAC status of patients at enrollment

	Total	HD	PD	*p* value
Patients, *n*	841	727 (86.4%)	114 (13.6%)	
AACS	5.2±5.7	5.5±5.8	3.6±5.0	0.001
AAC severity				<0.001
No calcification (AACS = 0)	28.9 (260)	27.0 (212)	42.1 (48)	
Mild to moderate calcification (1 ≤AACS ≤6)	24.8 (313)	34.5 (271)	36.8 (42)	
Severe calcification (AACS ≥7)	36.3 (327)	38.5 (303)	21.1 (24)	

AACS, Abdominal aortic calcification score [16]; HD, hemodialysis; PD, peritoneal dialysis; AAC, abdominal aortic calcification.

Discussion

The ORCHESTRA study was a nationwide, multicenter, prospective cohort study focusing on patients with ESRD in South Korea. We enrolled ethnic Korean patients because of racial and ethnic differences in clinical complications and outcomes of ESRD [18, 19]. Over a 2-year period, all participating centers recruited 900 consecutive patients and collected their clinical information, laboratory findings, and radiologic images.

Cardiovascular problems are a major factor determining the outcomes of patients with ESRD. This is closely related to

Table 6. Baseline BMD findings of male subjects in cohort

	HD, *n* (%)	PD, *n* (%)	*p* value
Age <50 years	64	20	0.647
Within expected range ($Z \geq -2.0$)	84.4 (54)	80.0 (16)	
Below expected range ($Z < -2.0$)	15.6 (10)	20.0 (4)	
Age ≥50 years	290	42	0.046
$T \geq -1.0$	13.8 (40)	28.6 (12)	
$-2.5 < T < -1.0$	42.8 (124)	33.3 (14)	
$T \leq -2.5$	43.4 (126)	38.1 (16)	

HD, hemodialysis; PD, peritoneal dialysis.

Table 7. Baseline BMD findings of female subjects in cohort

	HD	PD	*p* value
Pre-menopause	63	11	0.852
Within expected range ($Z \geq -2.0$)	79.4 (50)	81.8 (9)	
Below expected range ($Z < -2.0$)	20.6 (13)	18.2 (2)	
Post-menopause	206	41	0.354
$T \geq -1.0$	5.4 (11)	9.8 (4)	
$-2.5 < T < -1.0$	32.8 (67)	39.0 (16)	
$T \leq -2.5$	61.8 (128)	51.2 (21)	

HD, hemodialysis; PD, peritoneal dialysis.

VC caused by mineral disturbances [20]. Therefore, it is important to manage the mineral metabolism to prevent VC [10]. Recent studies have reported that Mg plays an important role in VC pathogenesis and VC [21]. Hence, we focused on Mg, i-Ca, and VC levels in our cohort. Our study collected serum Mg data to provide clinical evidence for establishing strategies for Mg management.

Since the publication of the 2017 KDIGO guidelines, physicians have been wary of calcium overload in patients on dialysis. When dialysis patients with metabolic acidosis show asymptomatic hypocalcemia, their i-Ca levels may remain within the normal range. Therefore, the clinical implications of i-Ca and total Ca levels have emerged in patients undergoing dialysis [22]. Because it is difficult to measure i-Ca in clinical practice, various formulas for estimating i-Ca based on total Ca have been proposed. However, their clinical usefulness has not yet been established [23]. Based on this background, we developed a new equation for estimating i-Ca, which would be more suitable. We gathered serum total Ca, i-Ca, and other parameters simultaneously to explore the accurate Ca status of ESRD patients and develop a new equation for estimating i-Ca that would be more suitable.

We checked DXA in our cohort for characteristics, fracture risk, and relationship to VC. The 2017 KDIGO suggests that DXA for BMD should be performed in patients with a high fracture risk. Mineral disturbances in CKD can cause alterations in the bone metabolism. Patients with ESRD not only have bone quantity problems, but also have bone quality problems that can lead to fragility fractures. Bone disease in ESRD is characterized by impaired bone volume, turnover, and mineralization [24]. The prevalence of low BMD and fractures in patients with ESRD is remarkably higher than that in the general population [25, 26]. In particular, a systemic review showed that the incidence of hip fracture in HD patients was consistently higher than that reported in PD or KT patients [26]. In our cohort, we observed significantly higher proportions of low BMD in the HD group than in the PD group, particularly in men.

Over the past few years, experimental and clinical evidence has shown a close relationship between bone disease and VC in CKD patients. The concept of a bone-vascular axis implies that bone disease may influence VC and consequently lead to poor cardiovascular outcomes [27]. We confirmed that vertebral fractures were associated with myocardial infarction in patients undergoing HD [28].

The ORCHESTRA study has the following goals: (1) to conduct a prospective, nationwide cohort representing Korea by analyzing MACE and PAD to establish clinical evidence for optimal management of CKD-MBD; (2) to elucidate the clinical implications of Mg and i-Ca in CKD-MBD and provide strategies for management; (3) to develop a new equation for estimating i-Ca; (4) to explore the prevalence of low BMD and VC in ESRD patients and investigate causal relationships between fractures, VC, and cardiovascular outcomes; and (5) to identify the most useful biomarkers using serum samples.

Conclusion

The ORCHESTRA study focused specifically on CKD-MBD. This study aimed to provide clinical evidence to establish optimal treatment guidelines for Asian dialysis patients, ultimately improving patient survival.

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Statement of Ethics

The study protocol was approved by the Ethics Committee of each participating center, including the Institutional Review Board of each center. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each patient before inclusion in the study. The IRB approval number for each participating center is as follows: Korea University Guro Hospital: 2019GR0029/2019GR0060, Kyung Hee University Medical Center: KHUH 2016-04-201, Keimyung University Dongsan Medical Center: 2019-04-016/2019-04-021, Kyung Hee University East-West Neo Medical Center: 2016-04-039, CHA Medical School Bundang CHA Medical Center: 2016-03-053, Gachon University Gil Medical Center: GCIRB2019-176/GCIRB2019-177, Seoul National University Hospital: 1907-149-1050/1907-148-1050, Hallym University Kangnam Sacred Heart Hospital: HKS 2019-06-005-027/HKS 2019-06-006-022, Hanyang University Seoul Hospital: 2019-07-005, Chonnam National University Hospital: CNUH-2019-230/CNUN-2019-236, Inje University Busan Paik Hospital: 2019-01-169, Veterans Health Service Medical Center: 2016-03-013, the Catholic University of Korea Daejeon St. Mary's Hospital: DC19ECDI0067, Gangnam Severance Hospital: 3-2019-0090/3-2019-0091, the Catholic University of Korea Uijeongbu St. Mary's Hospital: UC19OCDI0101, the Catholic University of Korea Eunpyeong St. Mary's Hospital: PC19OEDI0085, and Pusan National University Hospital: 1908-009-081.

Conflict of Interest Statement

The authors have no conflicts of interest relevant to this study to disclose.

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Author Contributions

Shin Young Ahn, Gang Jee Ko, Hyeon Seok Hwang, Kyung Hwan Jeong, Kyubok Jin, Yang Gyun Kim, Ju-Young Moon, Sang Ho Lee, So-Young Lee, Dong-Ho Yang, Ji Yong Jung, Kook-Hwan Oh, Young-Ki Lee, Gheun-Ho Kim, Soo Wan Kim, Yeong Hoon Kim, Dong-Young Lee, Yu Ah Hong, Hyeong Cheon Park, Sun Ae Yoon, Bum Soon Choi, Tae Hyun Ban, Hyo Jin Kim, and Young Joo Kwon recruited participants and collected clinical data and biospecimens. Young Joo Kwon, Shin Young Ahn, and Gang Jee Ko designed the study. Shin Young Ahn and Young Joo Kwon participated in the writing of this manuscript. Shin Young Ahn, Young Joo Kwon, and Gang Jee Ko participated in the data analysis and interpretation. All authors read and approved the final manuscript.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available in the ORCHESTRA study repository [https://www.mytrial.co.kr/service/Login]. Please contact the respective author for further inquiries.

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