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ORIGINAL ARTICLE

Serum level vitamin D and parathyroid hormone, and mortality, with or without chronic kidney disease

Chang Kyun Choi[1] · Sun-Seog Kweon[1] · Young-Hoon Lee[2] · Hae-Sung Nam[3] · Kyeong-Soo Park[4] · So-Yeon Ryu[5] · Seong-Woo Choi[5] · Sun A. Kim[1] · Min-Ho Shin[1]

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Abstract

Levels of vitamin D and parathyroid hormone (PTH) are closely associated with renal function. We evaluated the associations among 25-hydroxyvitamin D (25OHD) levels, PTH levels, and mortality, and whether these associations varied by renal function. We used data from the Dong-gu Study, a population-based cohort in Korean adults. We analyzed the associations among intact PTH, 25OHD levels and mortality in 8580 participants. Hazard ratios (HRs) for mortality were calculated using Cox proportional hazards regression after adjusting for age, sex, month of sampling, lifestyle, and comorbidities. We also evaluated the effects of chronic kidney disease (CKD). A total of 860 deaths occurred during the follow-up period of 7.6 years. Compared to the first 25OHD quartile, the HRs of the second, third, and fourth quartiles were 0.96 [95% confidence interval (CI) 0.79–1.16], 0.84 (95% CI 0.68–1.02), and 0.71 (95% CI 0.57–0.89), respectively. The association between intact PTH levels and mortality varied by renal function, and was both nonlinear and significant only in subjects with CKD. Compared to the second intact PTH quartile in such subjects, the HRs for the first, third, and fourth quartiles were 1.61 (95% CI 0.92–2.81), 1.97 (95% CI 1.17–3.31), and 2.19 (95% CI 1.33–3.59), respectively. In conclusion, we demonstrated that low serum levels of 25OHD are associated with an increased risk of mortality. Serum levels of intact PTH are nonlinearly associated with mortality only in subjects with CKD, with the lowest risk for mortality being evident in the second quartile.

Keywords Parathyroid hormone · Vitamin D · Cohort studies · Mortality · Renal insufficiency

Introduction

Vitamin D and parathyroid hormone (PTH) are key components of calcium homeostasis. These materials act on the skeletal system, intestines, and kidneys, maintaining calcium balance [1]. Vitamin D is not only involved in mineral metabolism but also regulates the immune response and has antioxidant effects [2]. Vitamin D deficiency increases the risk of adverse health outcomes such as diabetes and peripheral artery disease [3,4]. However, according to the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV), 63.3% of Koreans are vitamin D deficient, creating future problems because of sedentary lifestyles and insufficient exposure to the sun [5]. Various observational studies have examined associations between vitamin D levels and mortality. Generally, mortality is inversely associated with vitamin D levels [6–11]. However, some studies have reported that vitamin D is not associated with mortality [12, 13] or exhibits a reverse J-shaped association [14, 15]. Two studies that evaluated the associations between vitamin D levels and mortality in Asians reported inconsistent results [6, 12].

PTH regulates calcium and phosphate levels, and is secreted by the parathyroid glands. When calcium levels are low, PTH induces calcium resorption by the kidneys,

✉ Min-Ho Shin
mhshinx@paran.com

1 Department of Preventive Medicine, Chonnam National University Medical School, 264, Seoyang-ro Hwasun-eup, Hwasun 58128, Jeollanam-do, Korea

2 Department of Preventive Medicine & Institute of Wonkwang Medical Science, Wonkwang University College of Medicine, Iksan, Republic of Korea

3 Department of Preventive Medicine, Chungnam National University Medical School, Daejeon, Republic of Korea

4 Cardiocerebrovascular Center, Mokpo Jung-Ang Hospital, Mokpo, Republic of Korea

5 Department of Preventive Medicine, Chosun University Medical School, Gwangju, Republic of Korea

bone, and intestine. Elevated PTH levels are associated with cognitive decline [16] and atherosclerosis [17]. In previous observational studies on general populations, PTH levels were inversely associated with mortality [11, 13, 18].

In observational studies of patients with end-stage renal disease, PTH levels have exhibited a U-shaped association [19, 20] or no association [21] with mortality. The differences in such associations between general populations and end-stage renal disease patients indicate that renal function may act as an effect modifier. However, no studies have explored this possibility. Therefore, we examined the associations among vitamin D, PTH levels, and mortality, and also explored whether chronic kidney disease (CKD) modifies these associations in the general Korean population.

Materials and methods

Study population

This study is based on the Dong-gu Study, a prospective study of risk factors for chronic diseases in Korean adults [22]. The Dong-gu Study included 9260 participants aged ≥ 50 years. Abaseline survey was conducted from May 2007 to July 2010 and we analyzed 8580 individuals with no missing values.

Measurements

The serum 25-hydroxyvitamin D (25OHD) and intact parathyroid hormone (iPTH) concentrations were measured using chemiluminescent microparticle immunoassays (ARCHITECT i2000; Abbott, Lake Bluff, IL, USA). Serum cystatin C was measured using the Gentian Cystatin C Immunoassay (Gentian AS, Moss, Norway). Renal function was assessed using the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin equation adjusted for age, sex, and race [23], and classified as less than 60, and 60 or more. Venous blood samples were collected from subjects following an overnight fast. Serum was separated on-site and stored at −70 °C until analysis.

Ascertainments of death

Causes and dates of death were obtained by linking with the National Statistical Office data. The date of death was ascertained until December 31, 2016. Events were coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Causes of death were categorized into cardiovascular disease (I20–25 and I60–69), cancer (C00–C96), and others.

Covariates

Data on lifestyle, socioeconomic status, self-rated health, disease history, and intake of calcium or multivitamin supplements were obtained through interviews. Alcohol consumption was coded as nondrinker, less than one standard drink per day, or one standard drink per day or more. Smoking history was coded as never, ex-smoker, or current smoker. Physical activity was coded as walking for 30 min or more at least 5 days per week, or less than that. BMI was calculated in kilograms per meter squared from weight and height measured in a standing position without shoes. Handgrip strength was determined as the maximum handgrip strength of the two sides measured twice. Education level was coded as education for 6 years or less, more than 6 years to less than 12 years, or 12 years or more. Marital status was coded as living with a partner or not. The medical aid program for low-income people was used as an indicator of economic status.

Blood pressure was measured three times using a mercury sphygmomanometer on the upper right arm after the subjects had rested for 5 min. Venous blood samples were collected from subjects. The glycated hemoglobin (HbA1c) level was analyzed by high-performance liquid chromatography (HPLC) using the VARIANT II system (Bio-Rad, Hercules, CA, USA). The calcium, phosphate, high-density lipoprotein (HDL) cholesterol and triglyceride levels were analyzed using an automatic analyzer (Hitachi-7600; Hitachi, Tokyo, Japan).

Statistical analysis

The baseline characteristics of the subjects are expressed as the mean ± standard deviation or n (%). To examine trends in covariates across the 25OHD and iPTH quartiles, linear regression analyzes were performed. The iPTH and triglyceride levels were log transformed because they did not follow normal distributions.

Poisson regression was performed to obtain the age- and sex-adjusted mortality rate according to the quartiles of 25OHD and iPTH. Cox proportional hazards regression was used to evaluate the association of 25OHD and iPTH with mortality. Four models were fitted sequentially. In the first model, adjustments for age, sex, and month of venous sampling were performed. In the second model, adjustments for BMI, lifestyle (physical activity, smoking history, and alcohol history), socioeconomic status (marital status, education years, and health insurance type), and handgrip strength were also performed. In the third model, comorbidities, intake of calcium or multivitamin supplements, and the results of clinical laboratory and other tests

were added. In the fourth model, adjustments for both 25OHD and iPTH were performed. Nonlinear association was analyzed using Cox proportional hazards regression with penalized spline. To avoid distortion of extreme values, the values of 25OHD and iPTH were converted to percentiles and then Cox proportional hazards regression was performed. The nonlinearity was evaluated by comparing the goodness of fit of the penalized spline regression model with the linear regression model. Significance was set at a p value < 0.05. All analyzes were performed using R ver. 3.2.3 (The R Foundation for Statistical Computing).

Results

Tables 1 and 2 present the baseline characteristics of the study population. The average follow-up period was 7.6 ± 1.6 years. During follow-up, 860 (10.0%) participants died, including 292 (3.4%) deaths from cancer, 129 (1.5%) deaths from cardiovascular disease, and 439 (5.1%) deaths from other causes. Table 1 presents the findings according to 25OHD quartiles. Participants in the upper 25OHD quartile were significantly younger, with higher proportion of males, lower BMI, higher rates of smokers, drinkers, and physical activity, greater handgrip strength, more education, a lower rate of living alone, lower frequency of receiving medical aid, lower prevalence of hypertension, diabetes and dyslipidemia, higher rate of taking calcium and multivitamin supplements, and a lower systolic blood pressure, HbA1c, triglycerides, total and HDL cholesterol, iPTH, and phosphate.

Table 2 presents the findings according to iPTH quartiles. Participants in the upper iPTH quartile were significantly older, with lower proportion of males, higher BMI, lower rates of smokers, drinkers and physical activity, lower handgrip strength, less education, higher rate of living alone, higher frequency of receiving medical aid, higher prevalence of hypertension, lower prevalence of diabetes, lower rate of taking multivitamin supplements, higher systolic blood pressure, and lower HbA1c, triglycerides, total cholesterol, 25OHD, eGFR, calcium and phosphate.

Figure 1 shows the age- and sex-adjusted mortality rates per 1000 person-years according to the 25OHD and iPTH quartiles. The mortality rate decreased as the 25OHD quartiles increased. The mortality ratein the first quartile was 123.9 per 1000 person-years [95% confidence interval (CI) 107.1–140.7], while that in the fourth quartile was 77.7 per 1000 person-years (95% CI 66.7–88.8). For iPTH, there was no significant difference in mortality rate from the first to third quartiles, and the mortality rate was highest in the fourth quartile. The mortality rates in the first to fourth quartiles were 93.6 (95% CI 80.6–106.6), 86.4 (95% CI 73.9–98.9), 94.2 (95% CI 81.6–106.8), and 124.2 (95% CI 110.2–138.2) per 1000 person-years, respectively.

Table 3 shows the hazard ratios (HRs) according to the 25OHD quartiles. HRs for 25OHD were calculated using the first quartile as a reference. The HRs of the second to fourth quartiles were attenuated as additional variables were added. In model 4, the mediation effect of iPTH was additionally adjusted. When comparing the HRs in model 4 with the HRs in model 3, the HR of the second quartile changed from 0.91 (95% CI 0.75–1.10) to 0.93 (95% CI 0.77–1.13), the HR of the third quartile changed from 0.77 (95% CI 0.63–0.94) to 0.81 (95% CI 0.66–0.99), and the HR of the fourth quartile changed from 0.66 (95% CI 0.53–0.82) to 0.71 (95% CI 0.57–0.88). When stratified according to the renal function, the HRs did not show any significant difference from the stratification analysis (P value for interaction test = 0.054). In subgroups with eGFR less than 60 mL/min/1.73 m^2, the HR was 0.92 (95% CI 0.61–1.37) in the second quartile, 0.75 (95% CI 0.48–1.17) in the third quartile, and 0.71 (95% CI 0.44–1.12) in the fourth quartile. In subgroups with eGFR greater than 60, the HR was 0.89 (95% CI 0.71–1.11) in the second quartile, 0.81 (95% CI 0.64–1.02) in the third quartile, and 0.67 (95% CI 0.52–0.87) in the fourth quartile.

Table 4 shows the HRs according to the iPTH quartiles. HRs were calculated using the second quartile as a reference. There was no significant difference from the first to third quartiles, and only the HR of the fourth quartile was significantly higher. When the mediation effect of 25OHD was adjusted in model 4, the HRs were attenuated, but still significant. The HR of the fourth quartile in model 4 was attenuated from 1.41 (95% CI 1.16–1.71) to 1.34 (95% CI 1.10–1.63) when compared to the HR of model 3. When stratified according to the renal function, the association between iPTH and mortality varied according to the subgroup (P value for interaction test = 0.006). When the eGFR was lower, the association between iPTH and mortality was stronger, and the risk increased not only in the quartiles with higher iPTH but also in the lower quartile. The HR of the first quartile was 1.59 (95% CI 0.91–2.80), the HR of the third quartile was 1.88 (95% CI 1.12–3.17), and the HR of the fourth quartile was 1.97 (95% CI 1.19–3.27). When the eGFR was above 60, the risk increased only in the fourth quartile, similar to the previous stratification analysis, but was less associated with iPTH. In model 4, the HR of the first quartile was 1.06 (95% CI 0.85–1.33), the HR of the third quartile was 1.02 (95% CI 0.82–1.29), and the HR of the fourth quartile was 1.20 (95% CI 0.96–1.49).

Figure 2 shows the HRs for 25OHD and iPTH. The median was used as a reference. 25OHD was linearly associated with mortality regardless of renal function. On the other hand, the association between iPTH and mortality was nonlinear (P value for nonlinearity < 0.001). The risk of PTH did not increase until the 71.5th percentile (48.6 pg/mL), and then subsequently increased with increasing iPTH. In the subgroup with low eGFR, there was a U-shaped association

Table 1 Baseline characteristics of study population according to serum 25-hydroxyvitamin D (ng/mL) quartiles

	< 12.6 (*N* = 2187)	12.6–15.7 (*N* = 2131)	15.7–19.8 (*N* = 2134)	≧ 19.8 (*N* = 2128)	*p* value for trend
Death	235 (10.7)	215 (10.1)	208 (9.7)	202 (9.5)	0.155
Follow-up duration (years)	7.5 ± 1.7	7.7 ± 1.5	7.6 ± 1.6	7.7 ± 1.5	< 0.001
Month of sampling					< 0.001
April	623 (28.5)	421 (19.8)	353 (16.5)	255 (12.0)	
May	826 (37.8)	745 (35.0)	642 (30.1)	569 (26.7)	
June	523 (23.9)	586 (27.5)	718 (33.6)	764 (35.9)	
July	215 (9.8)	379 (17.8)	421 (19.7)	540 (25.4)	
Age (years)	65.8 ± 8.4	64.8 ± 8.1	64.8 ± 8.1	65.0 ± 7.9	0.004
Male	390 (17.8)	608 (28.5)	989 (46.3)	1403 (65.9)	< 0.001
BMI (kg/m^2)	24.4 ± 3.1	24.5 ± 3.0	24.4 ± 2.9	24.1 ± 2.7	0.002
Smoking history					< 0.001
Never	1822 (83.3)	1609 (75.5)	1360 (63.7)	1102 (51.8)	
Ex-smoker	206 (9.4)	320 (15.0)	527 (24.7)	716 (33.6)	
Current smoker	159 (7.3)	202 (9.5)	247 (11.6)	310 (14.6)	
Alcohol intake					< 0.001
Nondrinker	1343 (61.4)	1060 (49.7)	823 (38.6)	657 (30.9)	
< 1 standard drink/day	169 (7.7)	171 (8.0)	203 (9.5)	214 (10.1)	
≥ 1 standard drink/day	675 (30.9)	900 (42.2)	1108 (51.9)	1257 (59.1)	
Physical activity[a]	1273 (58.2)	1334 (62.6)	1388 (65.0)	1458 (68.5)	< 0.001
Handgrip strength (N)	23.5 ± 6.8	25.3 ± 7.6	27.9 ± 8.5	30.6 ± 8.5	< 0.001
Education years					< 0.001
≤ 6 years	1067 (48.8)	967 (45.4)	807 (37.8)	750 (35.2)	
6–12 years	908 (41.5)	891 (41.8)	967 (45.3)	948 (44.5)	
> 12 years	212 (9.7)	273 (12.8)	360 (16.9)	430 (20.2)	
Living alone	615 (28.1)	545 (25.6)	410 (19.2)	286 (13.4)	< 0.001
Medical aid	194 (8.9)	169 (7.9)	120 (5.6)	137 (6.4)	< 0.001
Hypertension	800 (36.6)	733 (34.4)	784 (36.7)	719 (33.8)	< 0.001
Diabetes	300 (13.7)	299 (14.0)	269 (12.6)	240 (11.3)	< 0.001
Dyslipidemia	210 (9.6)	178 (8.4)	189 (8.9)	143 (6.7)	0.002
Calcium supplement	377 (17.2)	416 (19.5)	389 (18.2)	445 (20.9)	0.010
Multivitamin supplement	427 (19.5)	491 (23.0)	485 (22.7)	597 (28.1)	< 0.001
SBP (mmHg)	124.4 ± 17.1	123.3 ± 17.1	123.2 ± 16.9	122.1 ± 16.3	< 0.001
HbA1c (%)	5.9 ± 1.1	5.8 ± 0.9	5.8 ± 0.9	5.8 ± 0.9	< 0.001
Triglyceride (mg/dL)	151.3 ± 120.3	144.3 ± 96.2	138.4 ± 89.4	136.5 ± 94.8	< 0.001
Total cholesterol (mg/dL)	211.1 ± 41.7	204.5 ± 38.3	196.4 ± 37.8	191.4 ± 37.6	< 0.001
HDL cholesterol (mg/dL)	52.8 ± 12.1	51.8 ± 12.1	50.9 ± 11.7	50.5 ± 11.9	< 0.001
iPTH (pg/mL)	49.7 ± 30.1	44.2 ± 19.0	40.9 ± 17.6	38.1 ± 15.2	< 0.001
eGFR < 60mL/min/1.73m^2	184 (8.4)	153 (7.2)	132 (6.2)	146 (6.9)	< 0.001
eGFR (mL/min/1.73m^2)	91.9 ± 24.6	92.0 ± 23.5	92.3 ± 22.9	91.6 ± 22.7	0.814
Calcium (mg/dL)	9.2 ± 0.5	9.2 ± 0.4	9.2 ± 0.5	9.2 ± 0.4	0.901
Phosphate (mg/dL)	3.9 ± 0.5	3.8 ± 0.6	3.7 ± 0.5	3.6 ± 0.5	< 0.001
Death by cancer	67 (3.1)	62 (2.9)	78 (3.7)	85 (4.0)	0.044
Death by CVD	33 (1.5)	49 (2.3)	21 (1.0)	26 (1.2)	0.066
Death by other cause	135 (6.2)	104 (4.9)	109 (5.1)	91 (4.3)	0.010

All values are given as *n* (%) or mean ± standard deviation

BMI body mass index, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *iPTH* intact parathyroid hormone, *CVD* cardiovascular diseases

[a]Walking for more than or equal to 30 min at least 5 days per week

Table 2 Baseline characteristics of study population according to serum intact parathyroid hormone (pg/mL) quartiles

	< 30.6 (*N* = 2150)	30.6–39.4 (*N* = 2151)	39.4–50.8 (*N* = 2152)	≧ 50.8 (*N* = 2127)	*p* value for trend
Death	194 (9.0)	174 (8.1)	207 (9.6)	285 (13.4)	< 0.001
Follow-up duration (years)	7.7 ± 1.6	7.7 ± 1.5	7.6 ± 1.5	7.4 ± 1.7	< 0.001
Month of sampling					<0.001
April	415 (19.3)	416 (19.3)	400 (18.6)	421 (19.8)	
May	640 (29.8)	649 (30.2)	728 (33.8)	765 (36.0)	
June	643 (29.9)	676 (31.4)	641 (29.8)	631 (29.7)	
July	452 (21.0)	410 (19.1)	383 (17.8)	310 (14.6)	
Age (years)	64.1 ± 8.1	64.4 ± 7.9	65.3 ± 8.0	66.7 ± 8.3	< 0.001
Male	974 (45.3)	870 (40.4)	836 (38.8)	710 (33.4)	< 0.001
BMI (kg/m^2)	24.2 ± 2.8	24.2 ± 3.0	24.4 ± 2.9	24.5 ± 3.1	0.006
Smoking history					< 0.001
Never	1390 (64.7)	1493 (69.4)	1501 (69.7)	1509 (70.9)	
Ex-smoker	492 (22.9)	443 (20.6)	433 (20.1)	401 (18.9)	
Current smoker	268 (12.5)	215 (10.0)	218 (10.1)	217 (10.2)	
Alcohol intake					< 0.001
Nondrinker	850 (39.5)	950 (44.2)	985 (45.8)	1098 (51.6)	
< 1 standard drink/day	221 (10.3)	175 (8.1)	159 (7.4)	202 (9.5)	
≥ 1 standard drink/day	1079 (50.2)	1026 (47.7)	1008 (46.8)	827 (38.9)	
Physical activity[a]	1427 (66.4)	1382 (64.2)	1367 (63.5)	1277 (60.0)	< 0.001
Handgrip strength (N)	27.7 ± 8.2	27.3 ± 8.5	26.8 ± 8.4	25.4 ± 7.9	< 0.001
Education years					< 0.001
≤ 6 years	844 (39.3)	883 (41.1)	907 (42.1)	957 (45.0)	
6–12 years	936 (43.5)	954 (44.4)	936 (43.5)	888 (41.7)	
>12 years	370 (17.2)	314 (14.6)	309 (14.4)	282 (13.3)	
Living alone	380 (17.7)	410 (19.1)	483 (22.4)	583 (27.4)	< 0.001
Medical aid	145 (6.7)	150 (7.0)	152 (7.1)	173 (8.1)	< 0.001
Hypertension	694 (32.3)	690(32.1)	767 (35.6)	885 (41.6)	< 0.001
Diabetes	407 (18.9)	261 (12.1)	230 (10.7)	210 (9.9)	< 0.001
Dyslipidemia	192 (8.9)	173 (8.0)	172 (8.0)	183 (8.6)	0.726
Calcium supplement	413 (19.2)	410 (19.1)	411 (19.1)	393 (18.5)	0.530
Multivitamin supplement	530 (24.7)	531 (24.7)	467 (21.7)	472 (22.2)	0.010
SBP (mmHg)	121.8 ± 16.7	122.0 ± 16.0	123.6 ± 17.0	125.6 ± 17.4	< 0.001
HbA1c (%)	6.0 ± 1.1	5.8 ± 1.0	5.8 ± 0.8	5.8 ± 0.8	< 0.001
Triglyceride (mg/dL)	149.1 ± 104.7	140.3 ± 107.7	140.6 ± 93.7	140.7 ± 97.7	0.010
Total cholesterol (mg/dL)	202.3 ± 41.1	201.2 ± 38.6	200.7 ± 39.3	199.5 ± 39.5	0.020
HDL cholesterol (mg/dL)	51.0 ± 11.6	51.7 ± 11.8	51.8 ± 12.5	51.6 ± 12.0	0.118
25OHD (ng/mL)	18.2 ± 6.2	17.2 ± 5.9	16.5 ± 5.5	14.9 ± 5.0	< 0.001
eGFR <60 mL/min/1.73 m^2	116 (5.4)	95 (4.4)	129 (6.0)	275 (12.9)	0.118
eGFR (mL/min/1.73 m^2)	93.1 ± 21.9	94.2 ± 22.0	93.1 ± 23.0	87.5 ± 26.0	< 0.001
Calcium (mg/dL)	9.3 ± 0.4	9.2 ± 0.4	9.2 ± 0.4	9.2 ± 0.5	< 0.001
Phosphate (mg/dL)	3.9 ± 0.6	3.8 ± 0.5	3.7 ± 0.5	3.6 ± 0.6	< 0.001
Death by cancer	78 (3.6)	72 (3.3)	74 (3.4)	68 (3.2)	0.494
Death by CVD	20 (0.9)	28 (1.3)	39 (1.8)	42 (2.0)	0.002
Death by other cause	96 (4.5)	74 (1.2)	94 (4.4)	175 (8.2)	< 0.001

All values are given as *n* (%) or mean ± standard deviation

BMI body mass index, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *iPTH* intact parathyroid hormone, *CVD* cardiovascular diseases

[a]Walking for more than or equal to 30 min at least 5 days per week

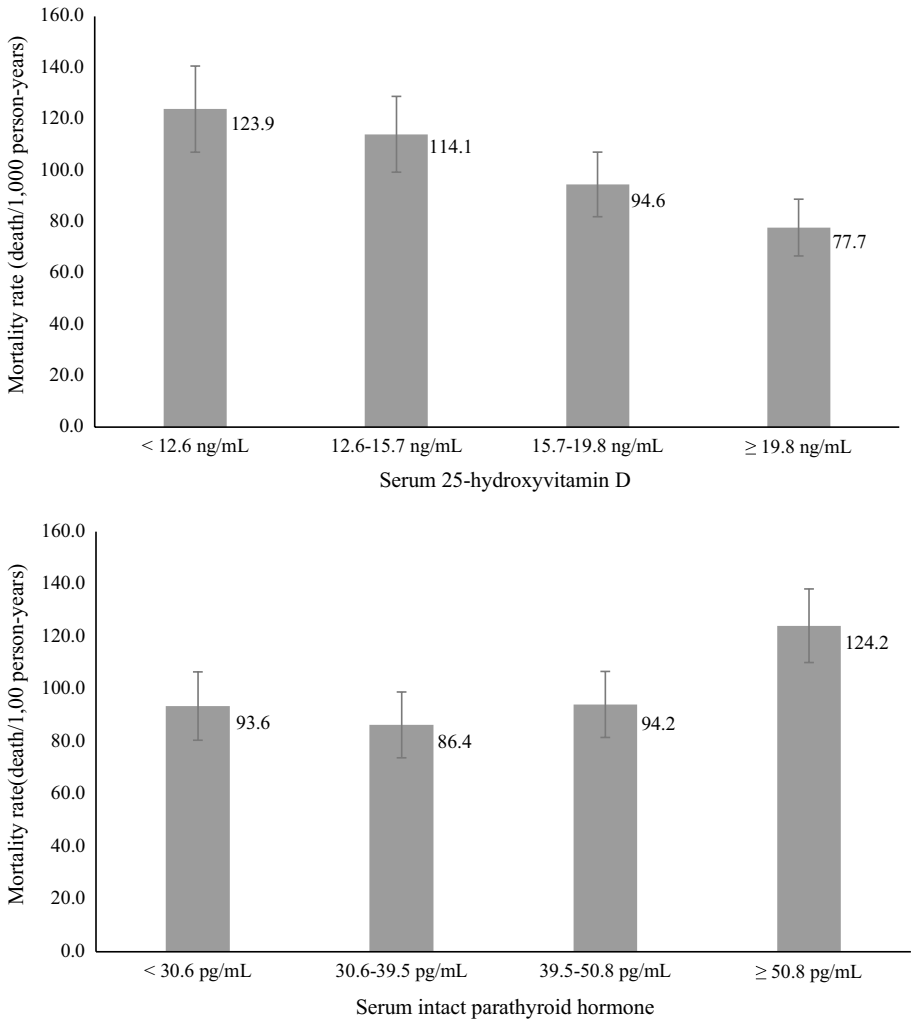

Fig. 1 Age- and sex-adjusted mortality rate according to serum 25-hydroxyvitamin D quartiles and intact parathyroid hormone (death per 1000 person-year). Vertical bar represents 95% confidence interval

(*P* value for nonlinearity =0.024) with the lowest risk at 22.8th percentile (29.8 pg/mL). In the subgroups with high eGFR, the nonlinearity was not significant (P value for nonlinearity = 0.104).

Interaction by age, sex, or multivitamin supplementation was not significant and was not described. The cause-specific mortality was also analyzed, but it was not presented due to lack of power.

Discussion

In this population-based cohort study, we found that low serum levels of 25OHD were associated with an increased risk of mortality. Intact PTH levels were nonlinearly associated with mortality only in subjects with CKD, with the lowest risk for mortality evident in the second quartile. To the best of our knowledge, this is the first study to define a nonlinear association between intact PTH levels and mortality, by renal function, in a general population.

As in previous observational cohort studies [6–11], we showed that the lower 25OHD level was associated with higher mortality, consistent with a report that genetically low 25OHD levels increase mortality risk [24]. However, other studies have found a reverse J-shaped association [14, 15]. A high level of mortality in those with high 25OHD levels may reflect vitamin D supplementation in patients who are ill [25]. However, we found no significant differences in the association between vitamin D level and mortality by multivitamin supplementation status. Some studies have found that 25OHD levels are not associated with mortality, probably because of a small sample size [13] or too few assessments during follow-up [12].

The association between low vitamin D levels and mortality might be explained in several ways. First, vitamin D is involved in both immune system homeostasis and macrophage maturation, improving innate immunity [26]. Randomized controlled trials have consistently shown that 1,25-dihydroxyvitamin D_3 supplementation reduces infection [27]. Second, low levels of 25OHD are associated with

Table 3 Hazard ratios according to serum 25-hydroxyvitamin D

	First quartile (< 12.6)	Second quartile (12.6–15.7)	Third quartile (15.7–19.8)	Fourth quartile (≧ 19.8)
25OHD (ng/mL)				
Death/person-year	235/16,372.66	215/16,309.27	208/16,299.44	202/16,327.34
Model 1[a]	1 (referent)	0.91 (0.76–1.10)	0.75 (0.62–0.92)	0.62 (0.50–0.76)
Model 2[b]	1 (referent)	0.93 (0.77–1.12)	0.80 (0.65–0.97)	0.67 (0.54–0.82)
Model 3[c]	1 (referent)	0.91 (0.75–1.10)	0.77 (0.63–0.94)	0.66 (0.53–0.82)
Model 4[d]	1 (referent)	0.93 (0.77–1.13)	0.81 (0.66–0.99)	0.71 (0.57–0.88)
eGFR ≤ 60 mL/min/1.73 m^2				
Death/person-year	64/1181.82	55/1027.92	41/878.72	46/953.22
Model 1[a]	1 (referent)	0.87 (0.60–1.26)	0.66 (0.44–1.00)	0.63 (0.42–0.94)
Model 2[b]	1 (referent)	0.93 (0.64–1.36)	0.75 (0.49–1.13)	0.69 (0.46–1.04)
Model 3[c]	1 (referent)	0.89 (0.60–1.32)	0.71 (0.46–1.09)	0.65 (0.42–1.01)
Model 4[d]	1 (referent)	0.92 (0.61–1.37)	0.75 (0.48–1.17)	0.71 (0.44–1.12)
eGFR ≥ 60 mL/min/1.73 m^2				
Death/person-year	171/15,190.84	160/15,281.35	167/15,420.72	156/15,374.12
Model 1[a]	1 (referent)	0.91 (0.73–1.13)	0.79 (0.63–0.99)	0.62 (0.49–0.79)
Model 2[b]	1 (referent)	0.91 (0.73–1.14)	0.82 (0.66–1.03)	0.66 (0.52–0.84)
Model 3[c]	1 (referent)	0.88 (0.70–1.09)	0.79 (0.63–0.99)	0.65 (0.51–0.83)
Model 4[d]	1 (referent)	0.89 (0.71–1.11)	0.81(0.64–1.02)	0.67 (0.52–0.87)

eGFR estimated glomerular filtration rate, *25OHD* 25-hydroxyvitamin D, *iPTH* intact parathyroid hormone, *BMI* body mass index

[a]Adjusted for age, sex, and month of sampling

[b]Additionally adjusted for physical activity, BMI, smoking history, alcohol history, handgrip strength and socioeconomic status (education level, marital status, and health insurance type)

[c]Additionally adjusted for comorbidities (hypertension, diabetes, and dyslipidemia), calcium and multivitamin supplementation, and clinical laboratory and other tests (systolic blood pressure, glycated hemoglobin, serum triglycerides, total and high-density lipid cholesterol, calcium, phosphate, and eGFR)

[d]Additionally adjusted for log-transformed serum iPTH

the development of cardiovascular disease via activation of the renin–angiotensin–aldosterone system. 1,25-Dihydroxyvitamin D_3 inhibits this system independent of calcium metabolism status, reducing hypertension and cardiac hypertrophy [28]. However, we found that the association between vitamin D and mortality remained significant even after adjusting for cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia.

We found that mortality was higher in those with higher PTH levels, as in previous studies [11, 13, 18]. However, in the Copenhagen Study on clinical outpatients [15], both high and low levels of intact PTH were associated with mortality. As outpatients were studied, comorbidities such as endocrine dysfunctions may have been more common in the study than in the general population. We found that intact PTH levels were nonlinearly associated with mortality in subjects with CKD, with those in the second quartile being at the lowest risk. A study that used data from the Taiwan Renal Registry Data System [21] found no association between intact PTH levels and mortality. Rhee et al. reported a *J* shaped association between PTH levels and mortality in patients on peritoneal dialysis [19] and Folege et al. found a similar association in hemodialysis patients [20]. In the Multi-Ethnic Study of Atherosclerosis (MESA), the association between hypertension and intact PTH levels was *U* shaped [29]; however, no interaction between PTH level and renal function was evident.

In the CKD subgroup, mortality increased in those with both low and high PTH levels, which can be explained in part by the mineral and bone disorders associated with CKD. Such disorders are divided into high-turnover bone diseases, mixed osteodystrophy, and low-turnover bone diseases. Low PTH levels are associated with low-turnover bone diseases. In adynamic bone disease (a low-turnover disease), the bone PTH receptor is downregulated, and PTH synthesis and secretion are lower [30]. Reduced bone turnover compromises the repair of bone microdamage and increases fracture risk [31]. A reduction in PTH activity also triggers changes in calcium kinetics, including reduced plasma calcium excretion and bone calcium accumulation, often triggering hypercalcemia [32]. Elevated levels of calcium accelerate vascular calcification via complexation with pyrophosphates [33], in turn triggering aldosterone secretion and fluid retention [34]. On the other hand, hyperparathyroidism causes high-turnover bone diseases. Bone reabsorbed because of turnover is replaced

Table 4 Hazard ratios according to intact parathyroid hormone

	First quartile (< 30.6)	Second quartile (30.6–39.5)	Third quartile (39.5–50.8)	Fourth quartile (≧ 50.8)
iPTH (pg/mL)				
Death/person-year	194/16,524.71	174/16,512.57	207/16,455.09	285/15,816.34
Model 1[a]	1.08 (0.88–1.33)	1 (referent)	1.09 (0.89–1.34)	1.46 (1.21–1.76)
Model 2[b]	1.12 (0.91–1.38)	1 (referent)	1.14 (0.93–1.39)	1.50 (1.24–1.82)
Model 3[c]	1.08 (0.88–1.33)	1 (referent)	1.15 (0.94–1.41)	1.41 (1.16–1.71)
Model 4[d]	1.09 (0.89–1.34)	1 (referent)	1.13 (0.92–1.38)	1.34 (1.10–1.63)
eGFR < 60 mL/min/1.73m^2				
Death/person-year	32/780.70	24/662.34	47/857.74	103/1740.90
Model 1[a]	1.38 (0.81–2.35)	1 (referent)	1.62 (0.99–2.65)	1.97 (1.26–3.10)
Model 2[b]	1.60 (0.93–2.75)	1 (referent)	1.84 (1.11–3.04)	2.10 (1.33–3.32)
Model 3[c]	1.63 (0.93–2.86)	1 (referent)	1.95 (1.16–3.27)	2.12 (1.31–3.43)
Model 4[d]	1.59 (0.91–2.80)	1 (referent)	1.88 (1.12–3.17)	1.97 (1.19–3.27)
eGFR ≥ 60 mL/min/1.73m^2				
Death/person-year	162/15,744.01	150/15,850.23	160/15,597.35	182/14,075.44
Model 1[a]	1.04 (0.84–1.30)	1 (referent)	1.01 (0.80–1.26)	1.22 (0.98–1.51)
Model 2[b]	1.06 (0.85–1.33)	1 (referent)	1.03 (0.82–1.29)	1.26 (1.01–1.56)
Model 3[c]	1.04(0.83–1.30)	1 (referent)	1.04 (0.83–1.31)	1.25 (1.01–1.56)
Model 4[d]	1.06 (0.85–1.33)	1 (referent)	1.02 (0.82–1.29)	1.20 (0.96–1.49)

eGFR estimated glomerular filtration rate, *25OHD* 25-hydroxyvitamin D, *iPTH* intact parathyroid hormone, *BMI* body mass index

[a]Adjusted for age, sex, and month of sampling

[b]Additionally adjusted for physical activity, BMI, smoking history, alcohol history, handgrip strength and socioeconomic status (education level, marital status, and health insurance type)

[c]Additionally adjusted for comorbidities (hypertension, diabetes, and dyslipidemia), calcium and multivitamin supplementation, and clinical laboratory and other tests (systolic blood pressure, glycated hemoglobin, serum triglycerides, total and high-density lipid cholesterol, calcium, phosphate, and eGFR)

[d]Additionally adjusted for serum 25OHD

with incompletely mineralized material and cortical bone becomes thinner, resulting in bone loss [31].

Our study had several limitations. First, vitamin D supplementation can affect the associations among vitamin D, PTH levels, and mortality. However, the questionnaire did not assess the use of vitamin D supplements, rather only multivitamin supplements. Second, the statistical power was inadequate to allow us to assess the association between PTH levels and mortality of CKD patients. Thus, although nonlinearity was evident when PTH levels were treated as a continuous variable, the HR of the lowest quartile was of borderline significance.

Compared to previous studies, the strengths of our work are as follows. The cystatin C test was used to calculate the eGFR; this test is more accurate than the creatinine test [35]. Only one prior study has used the cystatin C test [29].

In conclusion, vitamin D levels exhibited an inverse linear association with mortality, and PTH levels showed a nonlinear association modified by renal function. These

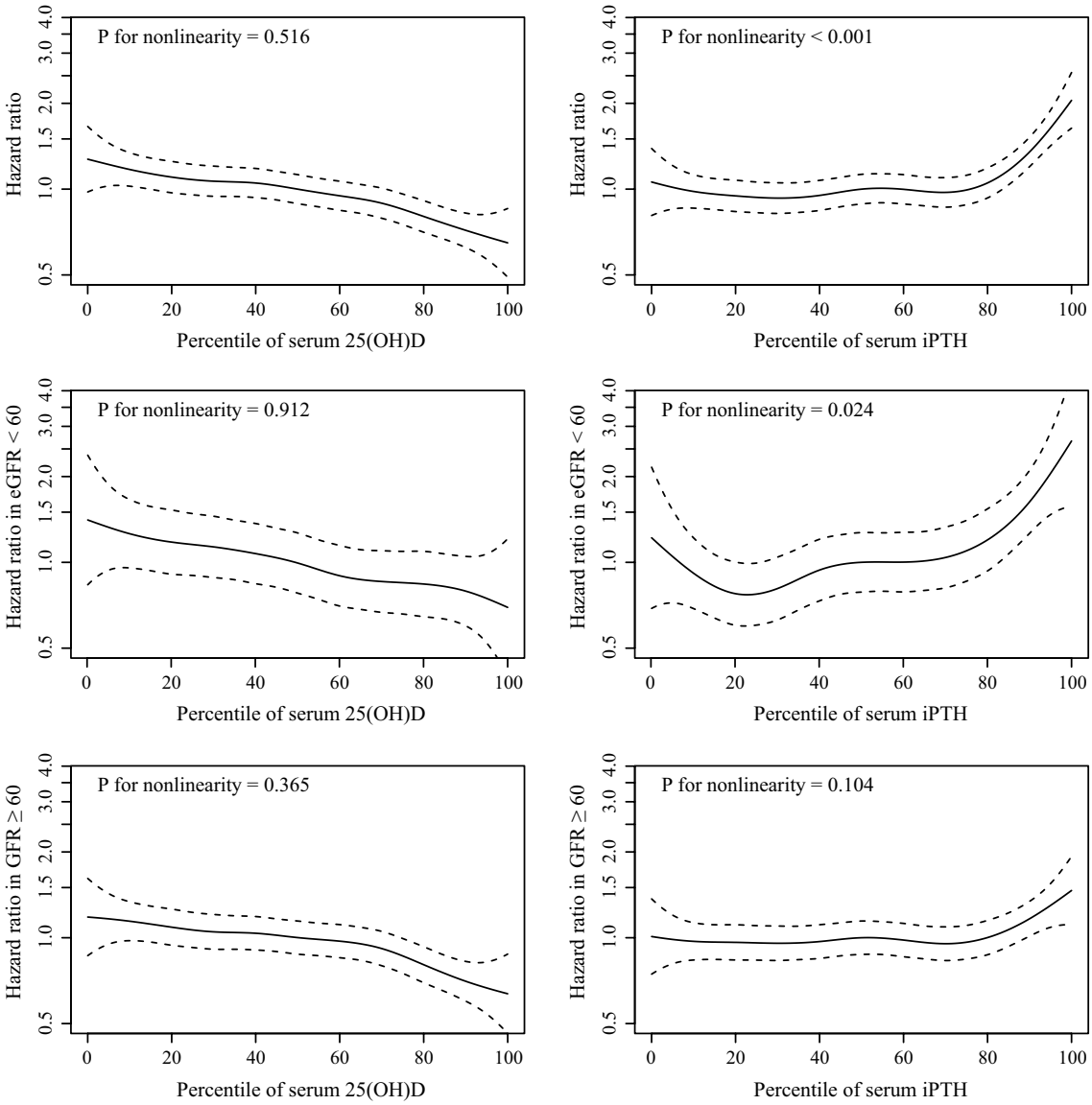

Fig. 2 Risk according to percentiles of serum 25-hydroxyvitamin D and intact parathyroid hormone. Solid line represents hazard ratios and dashed line represents the confidence interval. Months of sampling, age, gender, and BMI were adjusted

associations were independent of lifestyle, socioeconomic status, and comorbidities.

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Author's contributions Study design: CKC and MHS. Study conduct: CKC and MHS. Data collection: SSK, YHL, HSN, KSP, SYR, SWC, SAK, and MHS. Data interpretation: CKC, SSK, YHL, HSN, KSP, SYR, SWC, SAK, and MHS. Drafting manuscript: CKC, and MHS. Approving final version of manuscript: CKC, SSK, YHL, HSN, KSP, SYR, SWC, SAK, and MHS. MHS takes responsibility for the integrity of the data analysis.

Compliance with ethical standards

Conflict of interest Chang Kyun Choi, Sun-Seog Kweon, Young-Hoon Lee, Hae-Sung Nam, Kyeong-Soo Park, So-Yeon Ryu, Seong-Woo Choi, Sun A Kim, and Min-Ho Shin declare that they have no conflict of interest.

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