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Parathyroid Hormone Serum Levels and Mortality among Hemodialysis Patients in the Gulf Cooperation Council Countries: Results from the DOPPS (2012–2018)

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Abstract

Background The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) has collected data since 2012 in all six Gulf Cooperation Council (GCC) countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates). We report the relationship of PTH with mortality in this largest GCC cohort of patients on hemodialysis studied to date.

Methods Data were from randomly selected national samples of hemodialysis facilities in GCC-DOPPS phases 5 and 6 (2012–2018). PTH descriptive findings and case mix–adjusted PTH/mortality Cox regression analyses were based on 1825 and 1422 randomly selected patients on hemodialysis, respectively.

Results Mean patient age was 55 years (median dialysis vintage, 2.1 years). Median PTH ranged from 259 pg/ml (UAE) to 437 pg/ml (Kuwait), with 22% having PTH <150 pg/ml, 24% with PTH of 150–300 pg/ml, 34% with PTH 301–700 pg/ml, and 20% with PTH >700 pg/ml. Patients with PTH >700 pg/ml were younger; on dialysis longer; less likely to be diabetic; have urine >200 ml/d; be prescribed 3.5 mEq/L dialysate calcium; had higher mean serum creatinine and phosphate levels; lower white blood cell counts; and more likely to be prescribed cinacalcet, phosphate binders, or IV vitamin D. A U-shaped PTH/mortality relationship was observed with more than two- and 1.5-fold higher adjusted HR of death at PTH >700 pg/ml and <300 pg/ml, respectively, compared with PTH of 301–450 pg/ml.

Conclusions Secondary hyperparathyroidism is highly prevalent among GCC patients on hemodialysis, with a strong U-shaped PTH/mortality relationship seen at PTH <300 and >450 pg/ml. Future studies are encouraged for further understanding this PTH/mortality pattern in relationship to unique aspects of the GCC hemodialysis population.

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Introduction

Parathyroid hormone (PTH) is a major, systemic, calcium-regulating hormone. Diseases exhibiting elevated PTH levels, such as primary and secondary hyperparathyroidism (sHPT), are associated with increased mortality (1–4). High serum PTH, parathyroid gland hyperplasia, and disturbances in mineral metabolism, such as hyperphosphatemia, are commonly seen in sHPT (5,6). sHPT can be seen in >30% of persons receiving chronic dialysis therapy for ESKD, but the prevalence and severity of sHPT varies considerably across countries and in patients on hemodialysis (HD).

Patients with CKD who are affected by mineral bone disorders (MBD) have higher rates of all-cause mortality (3,7–9), with overall patients on dialysis displaying ten- to 100-fold higher mortality than persons in the general population (9–11). Baseline serum PTH levels and, more recently, changes in serum PTH levels over time, have been associated with mortality in patients on dialysis (9–11). Substantial differences in the levels and control of PTH among patients on HD in Japan, western Europe, and Black versus non-Black patients on HD in the United States have raised questions regarding potential racial differences in PTH control (12).

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Studies examining treatment of MBD in patients on dialysis in developing countries are extremely limited, especially in the Gulf Cooperation Council (GCC) countries. The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international, observational, prospective study with detailed data collection of HD care and outcomes across 21 countries (13). DOPPS provides a unique opportunity for contemporaneous evaluation of MBD control and related outcomes across a diverse set of international health care delivery and financing systems (13).

DOPPS has shed light on numerous different practices and outcomes for various regions around the world. However, an understanding of the relationship between PTH control and outcomes for patients on HD is lacking for the GCC region, which has a patient population, diet, and other pertinent factors that differ considerably from those regions in which the great majority of prior studies have been based. Thus, the role of PTH as a potential predictor of all-cause morbidity and mortality in the GCC HD population warrants investigation to help inform the GCC HD community whether measurement of PTH may provide complementary information for risk stratification of patients, and how best to optimize their care. Hence, this study aims to study the association of serum PTH with all-cause mortality in patients on HD in the GCC population.

Materials and Methods

Patients and Data Collection

Our findings are based upon data reported for patients on HD, who are ≥18 years old, from the participating GCC countries in DOPPS phase 5 (DOPPS 5; 2012–2015) and DOPPS 6 (2015–2018). As described previously in the GCC-DOPPS study design (14), study patients were selected randomly from a representative sample of randomly selected HD facilities within each country (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates [UAE]). In each country, institutional review boards approved the study, and informed patient consent was obtained in accordance with national and local requirements. Further details of the GCC-DOPPS study design, including number of study sites per GCC country, are provided in Pisoni *et al.* (14).

Our study sample was based on 1346 patients treated at 40 facilities participating in GCC-DOPPS 5, and 928 patients treated at 33 facilities participating in GCC-DOPPS 6. Patients participating in DOPPS 5 were invited to participate in DOPPS 6 if they were still being treated at the same HD unit. These patients were considered separate patients in analyses because key baseline covariates (*e.g.*, age, dialysis vintage, comorbidities) can differ over the several-year time period between the start of these two study phases. Of these 2274 patients enrolled in GCC-DOPPS 5 and 6, (*1*) 423 patients without a PTH measurement in the 4 months before enrollment, and (*2*) 26 patients in facilities where the unit of PTH measurement could not be reliably determined were excluded, yielding a studied population of 1825 patients. In mortality analyses, additional exclusions were applied for eight patients lacking follow-up, and 395 patients with inadequate facility reporting of mortality, resulting in 1422 patients used for mortality analyses. With few exceptions, facilities in the GCC reported using intact PTH assays, with lower and upper limits of normal from 10 to 88 pg/ml.

Statistical Analyses

Our primary outcome of interest was all-cause mortality, and the primary exposure of interest was a patient's PTH level at enrollment into each DOPPS study phase. Cox regression was used to analyze the association between categories of baseline PTH levels and mortality, stratified by region (Saudi Arabia versus non–Saudi Arabia). Analyses were not stratified by individual country due to the small number of HD facilities participating in DOPPS in several of the GCC countries. PTH categories used in mortality models were chosen to provide samples of approximately similar sizes across the spectrum of observed PTH values, while still retaining cut-point values that have been used in some prior guidelines (*e.g.*, 150 and 300 pg/ml in Kidney Disease Outcomes Quality Initiative guidelines). Cox models accounted for facility clustering, using robust sandwich covariance estimators, and adjusted for potential confounders, including age, sex, time (years) on dialysis, body mass index, comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, and other cardiovascular disease [CVD]), serum creatinine, and single-pool Kt/V. Time at risk started at study enrollment and ended at the time of death, or the earliest of the following censoring events: study end; loss to follow-up; or 7 days after leaving the facility due to kidney transplantation, switch to home dialysis, recovery of renal function, withdrawal from HD, or transfer to another HD facility. The median follow-up time was 1.4 years. Standard descriptive statistics were used to characterize the patients included in the study.

Overall, missing values for covariates was low (<10% for the majority of covariates), with the exception of body mass index (17%) and single-pool Kt/V (32%). For missing data, we used the sequential regression multiple imputation method implemented by IVEware to create ten imputed datasets (15,16), and we analyzed them using the MIAnalyze procedure in SAS/STAT version 9.4.

Results

For the initial cross-section of prevalent patients in each country, median PTH ranged from 259 pg/ml in the UAE to 437 pg/ml in Kuwait (Figure 1). Overall, 22% of patients had a PTH <150 pg/ml, 24% had a PTH of 150–300 pg/ml, 34% had a PTH of 301–700 pg/ml, and nearly 20% had a PTH >700 pg/ml. As shown in Figure 1, PTH levels of 600–700 pg/ml occurred in 5% of facilities in Qatar, Saudi Arabia, and UAE; whereas these levels occurred in 6%, 8%, and 1% of facilities in Kuwait, Bahrain, and Oman, respectively. PTH >700 pg/ml occurred in 14%, 17%, 23%, 26%, 27%, and 29% of facilities in Oman, UAE, Qatar, Bahrain, Saudi Arabia, and Kuwait, respectively.

Patients with PTH levels >700 pg/ml were younger; had been on dialysis substantially longer; and were less likely to be diabetic, have urine >200 ml/d, or be treated with 3.5 mEq/L calcium dialysate (Table 1). Patients with PTH levels >700 pg/ml also had higher mean serum phosphate and serum creatinine levels; lower white blood cell counts; and were much more likely to be prescribed cinacalcet,

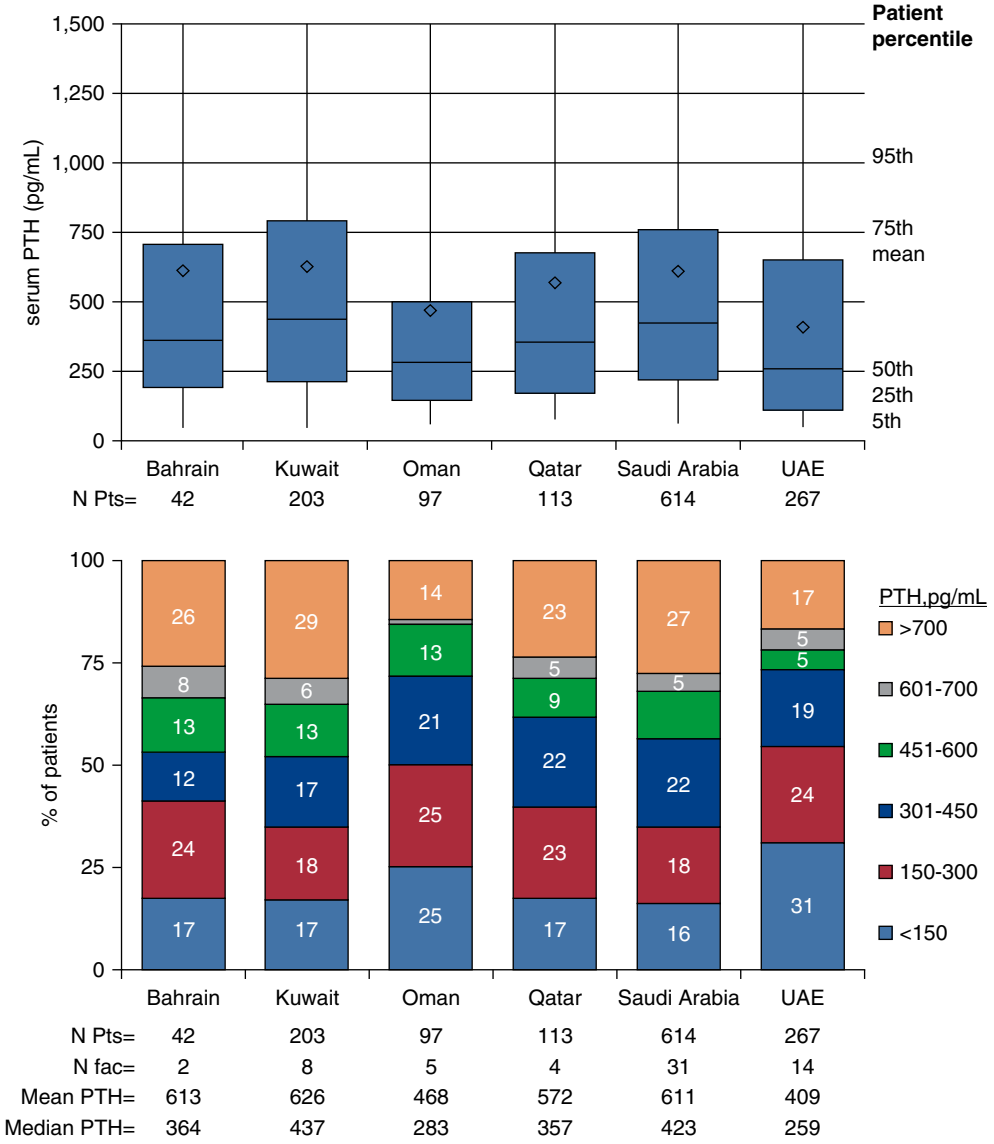

Figure 1. | **Many patients in the GCC-DOPPS countries have elevated PTH levels (2015–2018).** Estimates weighted by sampling fraction in each facility. Data based on initial cross-sections in DOPPS phase 5 (2012–2015) and DOPPS phase 6 (2016–2018) in each country. DOPPS, Dialysis Outcomes and Practice Patterns Study; Fac, facility; GCC, Gulf Cooperation Council; PTH, parathyroid hormone; Pts, patients; UAE, United Arab Emirates.

phosphate binders, and intravenous (IV) vitamin D. A history of parathyroidectomy before study enrollment was indicated for 3%–4% of patients who had either low PTH (<150 pg/ml) or high PTH levels (>700 pg/ml), whereas 0%–2% of patients with a PTH of 150–700 pg/ml had a prior parathyroidectomy.

Switching patients with higher PTH from oral vitamin D to IV vitamin D appeared to be a common practice, as suggested by the pattern of decline in oral vitamin D–only prescription and rise in IV vitamin D prescription in patients with higher PTH (Table 1). Prescription of calcium-containing phosphate binders without coprescription of sevelamer was substantially lower among patients with higher PTH levels. In contrast, prescription of the noncalcium-containing phosphate binder, sevelamer, or sevelamer in combination with a calcium-containing phosphate binder, was markedly higher among patients with higher PTH levels.

Figure 2 shows PTH categories and mortality among GCC-DOPPS patients on HD during the 2012–2018 time period. There were 222 deaths from among 1422 participants, resulting in an observed crude mortality rate of 11.4 deaths per 100 patient-years. A U-shaped relationship was observed between PTH levels and mortality, with a higher adjusted hazard ratio (HR) of death seen at PTH levels of <300 pg/ml and >450 pg/ml, compared with PTH values of 301–450 pg/ml (reference group). Compared with this reference group, mortality was more than two-fold higher for patients with PTH >700 pg/ml (HR, 2.04; 95% CI, 1.42 to 2.92). Interestingly, mortality was also elevated for patients with PTH of 150–300 pg/ml (HR, 1.51; 95% CI, 1.07 to 2.13). Similar results were obtained when additionally adjusting

Table 1. Patient characteristics and treatments, by PTH category in the GCC-DOPPS (2012–2018)

Characteristic	Baseline PTH				
	<150 pg/ml	150–300 pg/ml	301–450 pg/ml	451–700 pg/ml	>700 pg/ml[a]
Demographics					
Sample patients, *N* (row %)	407 (22)	431 (24)	339 (19)	290 (16)	358 (20)
Age in years, mean (SD)	56.7 (15.7)	57.9 (15.8)	56.1 (15.6)	52.0 (15.7)	50.6 (16.8)
Male, %	56	57	61	57	58
Years on dialysis, median (IQR)	1.7 (0.7–4.3)	1.5 (0.5–4.1)	1.9 (0.5–4.4)	2.2 (0.5–4.9)	3.5 (1.3–6.7)
Urine output >200 ml/d, %	29	30	35	30	24
Current smoker, %	7	7	5	10	6
Body mass index in kg/m^2, mean (SD)	25.9 (6.1)	26.9 (6.8)	26.7 (6.5)	27.5 (7.5)	26.6 (6.7)
Dialysis treatment					
Catheter use, %	44	42	41	43	35
SBP in mm Hg, mean (SD)	144 (22)	147 (22)	146 (21)	147 (21)	146 (21)
Treatment time in minutes, mean (SD)	217 (26)	223 (24)	224 (24)	224 (26)	220 (25)
Blood flow rate in ml/min, mean (SD)	285 (45)	295 (47)	297 (45)	302 (55)	300 (48)
Single-pool Kt/V, mean (SD)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)
Dialysate calcium, %					
<2.5 mEq/L	1	0	1	0	0
2.5 mEq/L	13	21	25	28	26
3.0 mEq/L	54	48	50	47	56
3.5 mEq/L	32	30	25	25	18
Comorbidities, %					
Coronary artery disease	31	31	35	27	30
Other cardiovascular disease	18	16	15	14	14
Cerebrovascular disease	11	9	10	10	7
Congestive heart failure	23	19	19	19	22
Diabetes	67	63	63	62	46
Hypertension	92	95	94	93	87
Lung disease	7	6	6	5	4
Neurologic disorder	9	8	5	5	9
Psychologic disorder	11	8	9	8	12
Peripheral vascular disease	17	17	19	20	15
Recurrent cellulitis	9	7	10	8	9
Cancer	2	2	1	2	1
Gastrointestinal bleed in last year	6	4	3	2	3
Parathyroidectomy[b]	4	2	0	1	3
Laboratory test results					
Total calcium in mg/dl, mean (SD)	8.9 (0.9)	8.7 (0.8)	8.7 (0.9)	8.7 (0.9)	8.7 (0.9)
Phosphate in mg/dl, mean (SD)	4.7 (1.9)	5.0 (1.8)	5.2 (1.9)	5.2 (1.9)	5.7 (1.9)
Creatinine in mg/dl, mean (SD)	8.4 (3.2)	8.9 (2.9)	9.1 (3.2)	9.4 (3.3)	10.1 (3.0)
Albumin in g/dl, mean (SD)	3.4 (0.6)	3.5 (0.5)	3.6 (0.5)	3.5 (0.6)	3.5 (0.5)
Hemoglobin in g/dl, mean (SD)	10.8 (1.5)	10.9 (1.5)	10.9 (1.5)	10.8 (1.6)	10.9 (1.4)
Serum magnesium in mg/dl, mean (SD)	2.2 (0.5)	2.2 (0.5)	2.2 (0.6)	2.2 (0.4)	2.3 (0.8)
WBC count, mean (SD)	7.1 (2.6)	6.9 (2.2)	6.9 (2.3)	6.7 (2.2)	6.4 (2.1)
Serum bicarbonate in mEq/L, mean (SD)	22.0 (3.6)	21.3 (3.4)	21.8 (3.3)	22.0 (3.7)	21.4 (3.2)
PTH in pg/ml, mean (SD)	82.9 (39.4)	220 (41)	376 (44)	563 (72)	1293 (620)
PTH in pg/ml, median (IQR)	84.6 (50.4–115.0)	223 (184–252)	373 (336–416)	560 (504–621)	1067 (842–1560)
Percent HbA1c, mean (SD)[c]	6.7 (1.8)	7.2 (1.6)	7.1 (1.6)	6.9 (1.6)	7.3 (2.6)
Medications prescribed, %[d]					
Cinacalcet	12	10	17	29	51
Phosphate binder	75	75	74	76	80
IV vitamin D	14	19	28	37	40
Oral vitamin D	37	43	41	31	25
IV or oral vitamin D	50	59	67	65	62
Statin	48	47	57	52	43
ACE inhibitor or ARB	24	19	21	21	23
Medications details, %[e]					
Vitamin D route					
Oral vitamin D only	72	68	59	43	37
IV vitamin D only	26	29	39	53	60
IV and oral vitamin D	2	3	2	4	3
Vitamin D (IV or oral) type					
Alfacalcidol only	87	84	88	74	74
Calcitriol only	10	13	9	18	8
Paricalcitol only	1	2	2	5	17

Table 1. (Continued)

Characteristic	Baseline PTH				
	<150 pg/ml	150–300 pg/ml	301–450 pg/ml	451–700 pg/ml	>700 pg/ml[a]
Other vitamin D or combination	2	2	1	3	1
Phosphate binder type					
Calcium-based only	70	60	54	47	41
Sevelamer only	13	14	22	23	28
Calcium and sevelamer only	14	24	20	29	29
Other binder or combination	3	2	3	2	2

Values are shown as prevalence (%), mean (SD), or median (IQR). PTH, parathyroid hormone; GCC, Gulf Cooperation Council; DOPPS, Dialysis Outcomes and Practice Patterns Study; IQR, interquartile range; SBP, systolic BP; WBC, white blood cell; HbA1c, hemoglobin A1c; IV, intravenous; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a]25% of patients had PTH >600 pg/ml.
[b]Parathyroid surgery or percutaneous ethanol injection therapy into the parathyroid gland.
[c]Restricted to patients with diabetes.
[d]Prescription at DOPPS enrollment or in the month before DOPPS enrollment; vitamin D restricted to active vitamin D (calcitriol or one of its synthetic analogues).
[e]Restricted to patients prescribed the drug class of interest.

for serum albumin, serum calcium, serum phosphate, and residual kidney function (Supplemental Table 1), or excluding the small number of patients (n=26) who had a prior parathyroidectomy. Similar results were also observed when treating cardiovascular mortality as the outcome (Supplemental Table 2).

Discussion

CVD is the leading cause of death in patients on dialysis, with approximately 50% of deaths due to cardiovascular causes (17–19). Traditional risk factors for CVD, such as advanced age, hypertension, and smoking, do not fully explain the much higher rate of mortality in patients on dialysis versus the nondialysis population (17). Thus, nontraditional cardiovascular risk factors, such as mineral metabolism disorders (in which serum calcium, phosphate, and PTH levels are elevated), have been shown to be associated with increased cardiovascular mortality and all-cause mortality (20).

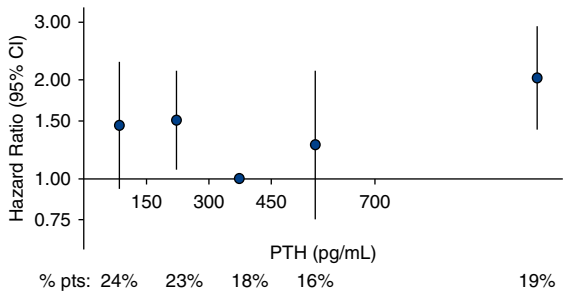

Figure 2. | Low and high PTH are associated elevated mortality in the GCC-DOPPS (2012–2018). N=1422 patients and n=222 deaths; adjusted for age, sex, vintage, body mass index, comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, other cardiovascular disease), serum creatinine, and single-pool Kt/V; stratified by GCC region and phase; placement of estimates along the *x* axis determined by median PTH in each group (<150, 150–300, 301–450, 451–700, >700 pg/ml). Categories chosen to yield approximate similar sample sizes across categories. The PTH of 301–450 pg/ml category served as the reference group, and the median PTH among the >700 pg/ml category was 1090 pg/ml.

sHPT leading to elevated PTH levels is common among patients with advanced CKD. This excess PTH can play an important role in the development of left-ventricular hypertrophy (21–22), low left-ventricular ejection fraction (23), and increased risk of vascular calcification (24–27) in increasing cardiovascular morbidity and mortality risk. However, even with contemporary management approaches, a large percentage of our patients have inadequately controlled PTH, serum phosphate, and/or calcium levels (12,28,29). Among the GCC-DOPPS HD population, the prevalence of high PTH levels is one of the highest reported among the 21 countries participating in the international DOPPS 5 (12,28,29,30). This is especially true for younger patients, a common observation across countries.

In this study, a U-shaped relationship was seen between PTH and mortality, with mortality risk lowest at PTH levels between 301 and 450 pg/ml, and then rising substantially both at PTH levels ≤300 pg/ml and >450 pg/ml. Overall, 25% and 20% of study participants had a PTH >600 and >700 pg/ml, respectively, whereas 46% had PTH ≤300 pg/ml, and 22% had PTH <150 pg/ml. The mortality HR was nearly two-fold higher for patients with PTH >700 pg/ml, and approximately 60% higher for patients with PTH ≤300 pg/ml versus PTH of 301–450 pg/ml. Tentori *et al.*'s (7,11) report from earlier phases of DOPPS observed the highest mortality risk at serum PTH levels of >600 pg/ml, although significantly higher risk was also seen at PTH levels as low as 301–450 pg/ml (compared with PTH of 150–300 pg/ml). Furthermore, Kalantar-Zadeh *et al.* (31) found time-updated serum PTH values of ≥300 pg/ml to be strongly correlated with higher mortality risk. Moreover, Floege *et al.* (32,33) recently showed baseline serum PTH concentrations of >600 pg/ml to be associated with greater mortality risk (adjusted HR, 2.10; 95% CI, 1.62 to 2.73) versus PTH of 150–300 pg/ml. We also found the highest mortality risk at high PTH levels of >700 pg/ml (two-fold higher HR of death versus reference PTH of 301–450 pg/ml) for GCC patients on HD. However, our results suggest modest mortality risks at PTH levels between 450 and 700 pg/ml.

In this GCC study, it appears that the U-shaped PTH/mortality curve may possibly be uniquely shifted slightly to the right, with the nadir for mortality risk observed at higher PTH levels than seen previously in similarly conducted studies in western Europe, Japan, and the United States (2,32,34). However, GCC patients are on average approximately 10 years younger (mean age, 55 years) than those in western Europe (67 years), Japan (66 years), and North America (63 years), with GCC patients on HD also having a shorter median dialysis vintage (2.2 years) than that of patients on HD in Japan (6.6 years), western Europe (3.2 years), and North America (2.8 years) (30). Prior studies have shown younger age and longer dialysis vintage to be strongly correlated with higher PTH levels in patients on HD (9,12,35). Furthermore, despite being substantially younger with shorter dialysis vintage, GCC patients on HD also have the highest diabetes prevalence, and generally a lower cardiovascular comorbidity burden (30). It is conceivable that these substantial differences in demographics, dialysis vintage, and comorbidity burden for GCC patients on HD versus those in western Europe, the United States, and Japan may affect how elevated PTH levels influence the survival of such patients in the GCC versus elsewhere. What is not unique to the GCC is that a U-shaped PTH/mortality relationship has been consistently seen across cohort studies in Latin America and Europe (32,33,36), the United States (37,38), and internationally in DOPPS (11,39,40). However, the inflection point at which higher PTH has been significantly associated with increased all-cause mortality varies across studies, ranging from PTH levels of between 300 and 600 pg/ml (9,11,29,31,37,41–44) and >600 pg/ml (7,11); but some of these associations may also reflect a study's sample size and PTH reference range.

In addition to the elevated mortality risk for GCC patients on HD with high PTH levels, the approximately 1.5-fold higher risk seen at PTH levels of <300 pg/ml (versus PTH of 301–450 pg/ml) indicates a need for additional research to understand the mechanisms underlying this elevated risk at lower PTH levels. Patients with PTH <300 pg/ml at study entry represented 46% of all GCC patients on HD in this study sample. Prior studies have also shown elevated mortality risks at lower PTH, but typically at substantially lower PTH levels (*e.g.*, <50, <100, or <150 pg/ml, depending upon the study [7,9,35,45]). The 22% of GCC patients on HD with PTH <150 pg/ml had lower serum phosphate and serum albumin levels compared with patients in all other PTH categories. However, adjusting for serum phosphate and albumin levels had little effect on the PTH/mortality associations seen in our current analyses.

Low PTH (<150 pg/dl) has also been shown to be associated with greater use of a higher dialysate calcium bath concentration and inversely associated with Black race and vitamin D therapy (9,46). GCC countries use a high dialysate calcium bath to primarily control PTH levels. In this study, a dialysate calcium bath of ≥3 mEq/L was used in 86% of patients with PTH <150 pg/ml, compared with 72%–74% of patients with PTH >300 pg/ml. This practice pattern of high calcium dialysate bath, given the potential for excessive treatment contributing to the development of adynamic bone disease, needs to be investigated further. A change in this practice pattern may help PTH levels return toward the recommended target ranges for some patients who currently have PTH levels of ≤150 pg/ml and may avoid adynamic bone disease.

Treatment of patients on HD with PTH-controlling medications appeared to be as high or higher in the GCC when compared with other DOPPS international regions of Europe, Japan, and North America (30). Percent of cinacalcet use (almost 60% among those with PTH >700 pg/ml) was higher in the GCC than in any of these three international regions, and use of active vitamin D (60%) was higher than in Europe but slightly lower than that reported for North America and Japan (30). Some previous studies have found that vitamin D receptor activators are associated with greater survival in patients on maintenance HD (31,47,48–50), but with no meaningful association when using an instrumental variable approach (7,39). PTH levels were strongly and positively associated with IV vitamin D and cinacalcet use in this study, suggesting general appropriateness in prescribing vitamin D therapy and calcimimetics in response to a patient's PTH level (9), and suggest possibly allowing higher PTH levels before initiating HD.

There are several limitations of this study. Our observational study design limits causal inference due to possible residual confounding despite the factors accounted for in our analyses. Furthermore, analyses were based on a single-baseline PTH value, which has been applied in numerous prior research studies internationally but may inherently not represent long-term PTH control for a given patient. Relatedly, our study design could not inform how different approaches to sHPT management affect mortality outcomes for GCC patients on HD. Despite these limitations, our study has strong points including (*1*) being the largest GCC cohort of patients on HD studied to date, regarding PTH control and mortality; and (*2*) the study is based on randomly selected patients and dialysis centers within each GCC country.

sHPT is highly prevalent among patients on HD in the GCC and is associated with increased all-cause mortality. This high prevalence of high PTH levels in GCC patients on HD is seen despite ample treatment with PTH-controlling medications and patients having a relatively short dialysis vintage overall, raising questions regarding how well PTH is managed before dialysis in the GCC. Our findings indicate that patients on HD who achieved PTH levels of 301–450 pg/ml had a lower subsequent mortality risk compared with patients who had PTH ≤300 pg/ml or >450 pg/ml. This nadir for mortality risk is, uniquely, at somewhat higher PTH levels than those seen previously in similarly conducted studies in western Europe, Japan, and the United States, and may be influenced by the differences in patient characteristics of patients on HD in the GCC versus other international regions. Altogether, these findings should be considered within the contexts of overall MBD control, benefits-to-life prognosis, maintenance of daily living activities, and quality of life from a patient-centered care perspective. Randomized controlled trials are needed to demonstrate whether treatments aimed at achieving specific PTH levels affect patient survival.

Disclosures

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Author Contributions

M. Al Rukhaimi, A. Al Sahow, I. Al Salmi, R. Pisoni, and B. Robinson conceptualized the study; I. Al Salmi, B. Bieber, R. Pisoni, and B. Robinson wrote the original draft; B. Bieber and R. Pisoni were responsible for formal analysis; R. Pisoni and B. Robinson were responsible for investigation and methodology; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000772020/-/DCSupplemental.

Supplemental Table 1. PTH categories and mortality: effect of progressive adjustment, GCC DOPPS (2012–2018).

Supplemental Table 2. PTH categories and cardiovascular mortality in the GCC DOPPS (2012–2018).

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Supplemental Materials Table of Contents

Supplemental Table 1: PTH categories and mortality: effect of progressive adjustment, GCC DOPPS (2012-2018)

	Hazard Ratio (95% CI) for Mortality					
PTH category	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
< 150	1.56(1.01-2.41)	1.56(1.00-2.43)	1.52(0.98-2.36)	1.46(0.93-2.28)	1.46(0.93-2.31)	1.36(0.87-2.14)
150-300	1.44(1.02-2.03)	1.46(1.03-2.07)	1.48(1.05-2.07)	1.51(1.07-2.13)	1.51(1.06-2.15)	1.45(1.02-2.05)
301-450	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
451-700	1.26(0.73-2.15)	1.31(0.77-2.24)	1.23(0.73-2.08)	1.27(0.75-2.15)	1.28(0.75-2.18)	1.26(0.72-2.20)
> 700	1.73(1.18-2.53)	1.76(1.20-2.59)	1.89(1.30-2.73)	2.04(1.42-2.92)	2.00(1.39-2.86)	1.95(1.36-2.79)

N=1,422 patients and n=222 deaths;

Model 1: stratified by GCC region and adjusted for age

Model 2: model 1 adjustments + sex, years on dialysis, body mass index

Model 3: model 2 adjustments + comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, other cardiovascular disease)

Model 4: model 3 adjustments + serum creatinine, single pool Kt/V (model for figure 1)

Model 5: model 4 adjustments + serum albumin (<3.2, 3.2-4.0, >4.0 g/dL)

Model 6: model 5 adjustments + serum calcium, serum phosphate (< 3.5, 3.5-5.5, >5.5 mg/dL), and urine output > 1 cup per day

Supplemental Table 2: PTH categories and cardiovascular mortality in the GCC DOPPS (2012-2018)

	HR for mortality (95% CI)	
	All-cause	**CV mortality**
PTH, pg/mL	(1,422 pts, 222 deaths)	(1,352 pts*, 107 CV deaths)
< 150	1.46(0.93-2.28)	1.38(0.81-2.35)
150-300	1.51(1.07-2.13)	1.47(0.90-2.40)
301-450	1 (ref)	1 (ref)
451-700	1.27(0.75-2.15)	1.14(0.55-2.36)
> 700	2.04(1.42-2.92)	1.85(1.06-3.23)

Adjusted for age, sex, vintage, body mass index, comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, other cardiovascular disease), serum creatinine, and single pool Kt/V; stratified by GCC region and phase (same adjustments as Figure 2)

* Excludes 70 deaths patients with missing cause; other causes of mortality treated as censoring events