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ARTICLE

Bone health in patients undergoing surgery for primary hyperparathyroidism at Tygerberg Hospital, Cape Town, South Africa

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Background: Increased bone resorption is a well-described consequence of primary hyperparathyroidism (PHPT). In South Africa, little is known about the impact of PHPT on skeletal health.
Objective: To determine the prevalence of decreased bone mineral density (BMD), vertebral fractures and osteitis fibrosa cystica in patients with PHPT who underwent parathyroidectomy.
Methods: Retrospective study of patients who underwent parathyroidectomy for PHPT at Tygerberg Hospital in Cape Town, from January 2010 to December 2019. Clinical, biochemical and BMD parameters are described.
Results: Final analysis included 56 patients (median age 63.5 years; 80.4% female). Initial calcium, parathyroid hormone (PTH) and 25-hydroxyvitamin D (25[OH]D) levels were 2.93 mmol/l, 19.4 pmol/l and 34.0 nmol/l, respectively. Of the total cohort, 71.4% had decreased BMD. The prevalence of osteoporosis and osteopenia in postmenopausal women and men ≥ 50 years was 50.0% and 39.1% respectively; low bone mass for age in premenopausal women and men < 50 years was 20.0%. Vertebral fractures were seen in 21.2% of patients on radiography. Osteitis fibrosa cystica was present in five patients (9.6%). PTH levels were significantly elevated in patients with osteoporosis compared with those with normal BMD (36.4 vs. 16.1 pmol/l; $p = 0.02$).
Conclusion: Two-thirds of patients who underwent parathyroidectomy for PHPT had decreased BMD, with osteoporosis present in 50% of postmenopausal women and older men. One in five had vertebral fractures. These findings underscore the importance of skeletal assessment in the management of PHPT.

Keywords: calcium, bone mineral density, fracture, osteoporosis, osteitis fibrosa cystica, parathyroid hormone, primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of chronic hypercalcaemia in the outpatient population worldwide.[1,2] It is defined as a raised serum calcium level with a simultaneously elevated or inappropriately unsuppressed parathyroid hormone (PTH) level. PHPT affects bone mineral metabolism and renal calcium handling early in the course of the disease.[3] The adverse skeletal effects can be independent of symptoms,[4] thus the quantification of bone involvement is of paramount importance.[5] The chronic exposure of the skeleton to excess parathyroid hormone in PHPT is characterised by high bone turnover[4] with osteoclastic activity and resultant bone resorption predominating over bone formation.[6] This leads to skeletal pathology ranging from a subclinical decrease in bone mineral density (BMD) to osteoporosis with fragility fractures and osteitis fibrosa cystica (OFC).[6,7] Osteoporosis, irrespective of evidence of fragility, is considered to be an indication for surgical parathyroidectomy.[5]

In well-resourced healthcare environments, the clinical presentation of PHPT has shifted from that of severe skeletal and renal pathology to one of mild or asymptomatic disease,[8] attributable to the increased availability of automated multichannel serum biochemical testing.[8,9] Earlier diagnosis has been slower to occur in the developing world,[10,11] with the majority of patients still presenting with symptomatic disease.[7,10,12] In resource-limited environments, such as the public healthcare sector in South Africa, hypercalcaemia is frequently occult in asymptomatic patients. However, even in asymptomatic PHPT, insidious decline in skeletal health can occur.[13,14] Compromised skeletal strength, as evidenced by decreased BMD and suboptimal bone quality, is associated with increased fracture risk[3,15] and significant morbidity.[16]

Bone mineral density, a robust indicator of skeletal strength, is measured by dual-energy X-ray absorptiometry (DXA). The accelerated bone loss seen in PHPT is linked to the duration and the severity of unopposed PTH excess.[17] Accelerated loss of BMD also occurs during female menopause and in normal ageing, overlapping with the population that develops PHPT. Primary hyperparathyroidism most often affects people older than 50–65 years, with women affected twice more often than men.[18] Fracture risk, however, remains higher in PHPT than matched controls,[19,20] irrespective of BMD category,

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suggestive of an adverse effect of continuous exposure of the skeleton to excess PTH on non-BMD related bone quality.

Despite the protective effects of bisphosphonates and other anti-resorptive agents on bone, the only definitive management of PHPT is surgical removal of the autonomous parathyroid gland(s). Correction of hypercalcemia, improvement in BMD and fracture risk reduction is the norm after parathyroidectomy.[17,21–24]

Very little has been reported on PHPT and its impact on bone health in sub-Saharan Africa. DXA is not readily available in the public health sector, apart from specialist centres, and national disease registries for endocrine disorders do not exist. In this study, we aim to determine the prevalence of osteoporosis, osteopenia and vertebral fractures (VF) in South African patients who had surgery for PHPT.

Methods

Study cohort and data sources

The present study was a retrospective description of patients who underwent parathyroidectomy for PHPT from January 2010 to December 2019 at Tygerberg Hospital (TH), Cape Town, South Africa. Only patients with a confirmed diagnosis of PHPT were selected for inclusion. Patients were excluded if they did not have a DXA scan on record, or if their DXA scan occurred more than three weeks after parathyroidectomy.

Data sources were the OpenText ECM (Enterprise Content Management) system (https://www.opentext.co.uk/products-and-solutions/products/enterprise-content-management) for storage and retrieval of patient clinical records, the National Health Laboratory Services (NHLS) for chemical and anatomical pathology results, and a picture-archiving and communication system (PACS, Phillips, South Africa) for all radiological investigations. Epidemiological information (age, ethnicity, sex, menopausal status and comorbidities), symptoms of PHPT and medication use (specifically corticosteroid use, bisphosphonate administration and preoperative vitamin D supplementation) were recorded.

Anthropometric data (weight and height) were sourced from the DXA scan reports, performed by a single operator for the study period. Body mass index (BMI) was calculated with the formula $BMI = weight(kg)/height(m)^2$. BMI was categorised according to the World Health Organization (WHO) as underweight, normal, overweight and obese.[25]

Biochemistry

All laboratory analyses were performed on-site at TH NHLS, a South African National Accreditation System (SANAS) accredited medical laboratory service. Preoperative biochemistry included serum total calcium, magnesium and phosphate levels, intact PTH, urea and creatinine as well as serum alkaline phosphatase (ALP) and 25-hydroxyvitamin D (25[OH]D) levels. The highest pre-bisphosphonate (if given), preoperative calcium, concurrent PTH and ALP were recorded as well as the nadir vitamin D level prior to supplementation. Urine calcium excretion was recorded where available. At TH NHLS a Roche Cobas® analyser was used for the measurement of serum total calcium (by spectrophotometric detection), as well as intact PTH and 25(OH)D (both by electrochemiluminescence binding assay). Laboratory reference ranges were as follows: total calcium 2.15–2.50 mmol/l, PTH 1.6–6.9 pmol/l and ALP 42–98 U/l. 25(OH)D levels, expressed in nmol/l, are defined as deficient (< 50 nmol/l), insufficient (52.5–72.5 nmol/l) and sufficient (> 75 nmol/l).[26]

Skeletal assessment, categorisation of BMD and fracture definition

DXA scan reports were reviewed for the presence of one or more VFs by morphometric assessment. Bone mineral density values (g/cm^2), as well as *T*- and Z-scores, were recorded for the spine, proximal femur (femoral neck and total hip region) and the non-dominant, distal-third forearm. Thresholds for diagnosis of a decreased BMD are defined as per the WHO.[27] In postmenopausal women and men $\geq$ 50 years, osteoporosis is defined as a T-score <−2.5 and osteopenia as a T-score of −1.0 to −2.5 at any measured site. In premenopausal women and men under the age of 50 years, low bone mass for age is defined as a Z-score of <−2.0. DXA studies, employing the Hologic Discovery-W, S/N 70215 (software version 13.1; Hologic Canada ULC, Misisissauga, ON, Canada), were all performed in-house at the Division of Endocrinology at TH. All the DXA scans were performed and reported by a single experienced technician.

Plain-film radiographs were retrospectively evaluated by a single specialist radiologist in the Department of Medical Imaging at TH who reported on the presence of one or more VFs as well as any other radiological features in keeping with PHPT. A vertebral fracture was diagnosed if more than 20% reduction in anterior, middle and/or posterior vertebral body height was present.[28] Fractures were regarded as fragility fractures if they occurred in the presence of minimal trauma or due to falling from standing height.[29] The diagnosis of osteoporosis was based on WHO DXA BMD criteria and/or the presence of fragility fracture of the spine on conventional radiology.

Perioperative management

When considering the indication for surgery, participants were coded as 'symptomatic' if review of medical records revealed only symptoms attributable to PHPT without evidence of target organ damage, or they were coded as having renal and/or skeletal indications where these were present. In addition, other surgical indications including 'age younger than 50 years' and 'calcium level over 0.25 mmol/l above the upper limit of normal' were recorded if present.[5]

Ethical considerations

The study was approved by the Human Research Ethics Committee, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital (S20/01/007). Data collection was performed by the principal investigator only, with all information stored on a password-protected computer. Data were de-identified prior to statistical analysis.

Statistical analysis

Data analyses were conducted using SPSS Statistics for Windows, version 26 (IBM Corp, Armonk, NY, USA). Continuous variables were summarised as median and interquartile range (IQR) or mean and standard deviation as appropriate. Categorical variables were summarised as counts and percentages. The Spearman correlation coefficient was used to determine whether there were significant associations between continuous variables. Where appropriate, the Mann–Whitney U-test or the Kruskal–Wallis test was used to assess differences in continuous variables between two or more independent groups. Statistical significance was set at $p < 0.05$.

Table 1: Clinical characteristics and indications for surgery in patients with PHPT ($n = 56$)

Clinical characteristics	
Age (years)[a]	63.5 (53;70)
Gender:	
Female	45 (80.4%)
Premenopausal	8
Postmenopausal	37
Male:	11 (19.6%)
< 50 years of age	2
≥ 50 years of age	9
Ethnicity (self-identified):	
Mixed ancestry	31
White	21
Black	3
Asian	1
Anthropometry:[b]	
Weight (kg)	77.4 ± 18.6
Height (m)	1.62 ± 0.09
BMI (kg/m^2)	29.7 ± 7.3
Underweight (BMI < 18.5)	4 (7.1%)
Normal (BMI 18.5–24.9)	10 (17.9%)
Overweight (BMI 25–29.9)	13 (23.2%)
Obese (BMI > 30)	29 (51.8%)
Other comorbidities and risk factors for osteoporosis:	
Hypertension	39 (69.6%)
Smoking, current	10 (17.9%)
Systemic corticosteroids, current	3 (5.4%)
Rheumatological disease (RA/SLE)	2 (3.6%)
Indications for parathyroidectomy:	
Symptomatic, no target organ damage	12 (21.4%)
Age < 50 years	10 (17.9%)
Calcium > 2.75 mmol/l	53 (94.6%)
Osteoporosis	23 (41.1%)
Renal	17 (30.4%)
Number of indications for parathyroidectomy:	
One	10 (17.9%)
Two	33 (58.9%)
Three	12 (21.4%)
Four	1 (1.8%)

[a]Median and interquartile range are indicated for non-normally distributed data.
[b]Mean ± standard deviation shown for normally distributed data.
Categorical data are expressed as *n* (%).

Table 2. Baseline biochemistry of total sample ($n = 56$)

Biochemical parameter	Total cohort
Total serum calcium* (normal range 2.15–2.50 mmol/l)	2.93 (2.81; 3.19)
Ca 2.15–2.74 mmol/l	3 (5.4%)
Ca 2.75–2.99 mmol/l	30 (53.6%)
Ca 3.00–3.49 mmol/l	15 (26.8%)
Ca > 3.50 mmol/l	8 (14.3%)
Phosphate** (normal range 0.78–1.24 mmol/l)	0.87 ± 0.24
Phosphate < 0.78 mmol/l	20 (35.7%)
Magnesium** (normal range 0.63–1.05 mmol/l)	0.84 ± 0.17
Magnesium < 0.63 mmol/l	5 (8.9%)
PTH* (normal range 1.6–6.9 pmol/l)	19.4 (14.5; 42.3)
PTH > 6.9 pmol/l	54 (96.4%)
PTH within normal range	2 (3.6%)
PTH 5.1–6.9 pmol/l	1 (1.8%)
PTH < 5.0 pmol/l	1 (1.8%)
ALP* (normal range 42–98 U/l; $n = 45$)	88.0 (74.0; 122.5)
ALP elevated	21 (46.7%)
25(OH)D*[a] (nmol/l; $n = 49$)	34.0 (23.6; 48.0)
Deficient (< 50.0 nmol/l)	39 (79.6%)
Insufficient (52.5–72.5 nmol/l)	8 (16.3%)
Sufficient (> 72.5 nmol/l)	2 (4.1%)
Creatinine* (*F* 49–90 umol/l, *M* 64–104 umol/l)	87.5 (69.3; 121.8)
Creatinine elevated from baseline ($n = 17$)	24 (42.9%)
Urine calcium* (normal range 2.5–7.50 mmol/l; $n = 27$)	2.07 (1.14; 3.25)
24-hour urine calcium*	5.00 (1.80; 7.20)
24-hour urine calcium 7.51–9.99 mmol/24 hour	3 (11.1%)
24-hour urine calcium > 10 mmol/24 hour[b]	3 (11.1%)

Cohort size is $n = 56$ unless otherwise stated. Data expressed as *n* (%) or as indicated by asterisk, as median (IQR)* or mean (± SD)** as appropriate. [a] Recommended classification of 25OHD values as either deficient, insufficient or sufficient according to the Endocrine Society clinical practice guideline[26].
[b]24-hour urine calcium > 10 mmol/l/24 hours indication for surgery per se.

Results

Patient demographics and indication for parathyroidectomy

A total of 163 patients underwent parathyroidectomy during the study period, of which 104 were confirmed to have PHPT. Of the 104 patients with PHPT, 56 had DXA studies prior to their surgery and were included in the final analysis. As shown in Table 1, most patients ($n = 46$; 82.1%) were ≥ 50 years old (median age 63.5 years [53;70]) and female ($n = 45$; 80.4%). Thirty-eight women were postmenopausal)38/45; 84%) and 2/11 men were below the age of 50 years. Most of the patients were either overweight ($n = 13$; 23.2%) or obese ($n = 29$; 51.8%). Ten patients (17.9%) were found to have a normal BMI and four (7.1%) were underweight. Considering modifiable risk factors for excessive bone loss, less than one-third of the cohort ($n = 15$; 26.8%) had a condition other than PHPT associated with decreased BMD. This included: active cigarette smoking (n = 10; 17.9%), any corticosteroid use ($n = 3$; 5.4%) and concomitant rheumatological disease not managed with corticosteroids ($n = 2$; 3.6%).

The indications for parathyroidectomy are listed in Table 1. The majority of patients ($n = 46$, 82.1%) had two or more indications for parathyroidectomy; 94.6% of participants ($n = 53$) had a serum calcium levels in excess of 2.75 mmol/l. Of the patients who qualified for parathyroid surgery, 41.1% ($n = 23$) had osteoporosis.

Baseline biochemistry

Baseline biochemistry is given in Table 2. All but one patient had elevated calcium levels (median: 2.93 mmol/l [2.81; 3.19]) and the vast majority ($n = 53$; 94.6%) displayed a calcium concentration of > 2.75 mmol/l. The single patient with normocalcaemia (calcium level 2.45 mmol/l) had a PTH of 12.9 pmol/l and symptoms attributable to hypercalcaemia (normocalcaemic hyperparathyroidism). Severe hypercalcaemia (> 3.50 mmol/l) was seen in 14.3% of patients. Concomitant decreased phosphate concentrations (mean: 0.87 ± 0.24 mmol/l) were seen in

20 patients (35.7%). Parathyroid hormone levels exceeded the reference interval in all but two patients (54; 96.4%). These two patients had PTH values in the upper half of the normal range (PTH 4.1 and 5.9 pmol/l; reference interval 1.6–6.9 pmol/l), deemed inappropriate given the elevated calcium level.

Increased serum alkaline phosphatase (ALP) without coexistent elevations in gamma-glutamyl transferase (GGT), thus presumed to be mostly from skeletal origin, was present in 21 patients (46.7%). Most patients ($n = 39/49$; 79.6%) were found to have deficient (< 50 nmol/l) 25(OH)D levels, with only two (4.1%) displaying 25(OH)D levels within the 'sufficient' range. Urine calcium excretion was quantified by 24-hour urine collection in 27 patients; three of these patients were found to have a level greater than 10 mmol/24 hours.

Serum calcium levels were positively associated with both PTH ($r = 0.46$; $p < 0.01$) and ALP levels ($r = 0.34$; $p = 0.02$). In addition, ALP levels were positively associated with PTH levels ($r = 0.49$; $p < 0.01$). Inverse associations were evident between 25(OH)D levels and (i) PTH levels ($r = -0.43$; $p < 0.01$) and (ii) calcium levels ($r = -0.33$, $p = 0.02$). The PTH and 25(OH)D levels were similar across the BMI range.

Bone mineral density and the prevalence of osteopenia, osteoporosis and vertebral fractures

BMD at the lumbar spine (LS), femoral neck (FN), total hip region (THR) and distal-third forearm were available for 56, 48, 55 and 18 patients, respectively. Conventional radiographs were available for 52 of the 56 patients within six months of their DXA scan.

In the total study cohort, decreased BMD was observed in 40 patients (71.4%). Based on DXA BMD assessment only, 20 patients in the total cohort of 56 patients had osteoporosis (35.7%); osteopenia was documented in 18 patients (32.1%) and a low bone mass for age based on Z-scores in two patients ($n = 2/56$; 3.6%). Seventeen participants ($n = 17/56$; 30.4%) had a T-score of <−2.5 at more than one skeletal site. The DXA lumbar vertebral fracture assessment (VFA) identified morphometric vertebral abnormalities in eight patients (14.5%), all ≥ 50 years.

Conventional radiology detected significant vertebral compression (> 20% height loss) in 11 (21.2%) patients, including VFs in three patients in the absence of DXA confirmed osteoporosis, thus bringing the total number of participants with osteoporosis in our cohort to 23 (41.1%).

Osteoporosis was thus diagnosed in this cohort with PHPT based on BMD measurements in 20 patients and based on vertebral fracture only in an additional 3 patients. All patients with osteoporosis were either postmenopausal women or men ≥ 50 years, with half of this cohort manifesting with osteoporosis ($n = 23/46$; 50%). Osteoporosis was documented in 32% (10/31), 43% (9/21) and 33% (1/3) of mixed-ancestry, white and black participants. Small numbers limited the ability of this cohort to report on the contribution of ethnicity to the risk of osteoporosis in patients with PHPT.

BMD assessment at the different skeletal sites and the presence of vertebral fractures on conventional radiography for the cohort that comprised postmenopausal women and men ≥ 50 years and for the cohort that included premenopausal women and men < 50 years are displayed in Table 3.

Table 3: Site-specific bone mineral density and vertebral fracture in menopausal and age cohorts.

Cohort: postmenopausal women and men ≥ 50 years ($n = 46$)					
BMD	**LS ($n = 46$)**	**FN ($n = 39$)**	**THR ($n = 45$)**	**DF ($n = 15$)**	**Any ($n = 46$)**
• Absolute value[a]	0.954 ± 0.203	0.672 ± 0.154	0.813 ± 0.182	0.553 ± 0.129	na
• Mean T-score[b]	−1.0 ± 1.7	−1.7 ± 1.4	−1.1 ± 1.5	−2.5 ± 2.2	na
• Osteopenia	14 (30.4%)	15 (38.5%)	13 (28.9%)	2 (13.3%)	18 (39.1%)
• BMD OP[c]	11 (23.9%)	13 (33.3%)	11 (24.4%)	9 (60%)	20 (43.5%)
Radiography	**($n = 42$)**				
• VF	11 (%)				
• VF and BMD OP	8 (%)				
• VF without BMD OP	3 (%)				
BMD + radiography					
• Osteoporosis[d]					23 (50%)
Cohort: premenopausal women and men < 50 years ($n = 10$)					
BMD	**LS ($n = 10$)**	**FN ($n = 9$)**	**THR ($n = 10$)**	**DF ($n = 3$)**	**Any ($n = 10$)**
• Absolute value[a]	0.916 ± 0.99	0.709 ± 0.102	0.824 ± 0.106	0.596 ± 0.129	na
• Mean Z-score[b]	−1.1 ± 0.8	−1.0 ± 0.9	−0.8 ± 0.9	−1.3 ± 2.1	na
• Low bone mass	0 (0%)	1 (11.1%)	1 (10.0%)	1 (33.3%)	2 (20%)
• Osteoporosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Radiography	**($n = 10$)**				
• VF	0 (0%)				

[a]BMD in g/cm^2.
[b]Z- and T-scores are given as mean ± SD, rest of data expressed as *n* (%). Definition of osteopenia, low bone mass and osteoporosis as defined in methods section. Radiography for vertebral fracture performed in 52 of the 56 patients.
[c]BMD OP refers to patients with OP based on BMD measurement in the cohort: postmenopausal women and men ≥ 50 years of age with a T-score lower than −2.5SD.
[d]Osteoporosis refers to patients with BMD OP and/or VF. na = not applicable.
Site-specific BMD as measured by DXA. LS = lumbar spine, FN = femoral neck, THR = total hip region, DF = distal forearm (non-dominant), OP = osteoporosis. 'Any' referring to presence of osteopenia or OP at any site.

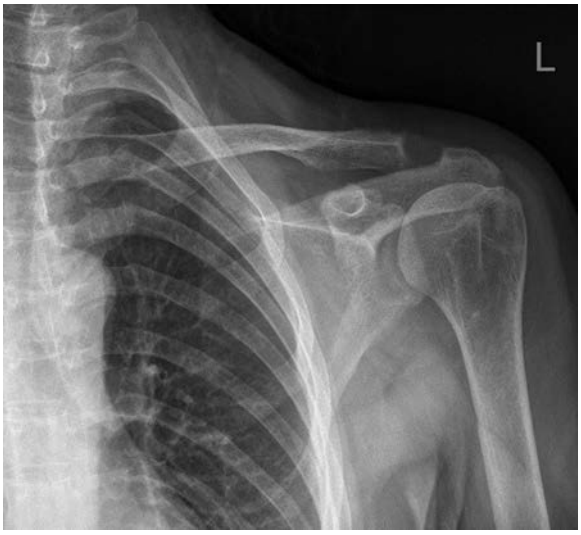

Figure 1: Subperiosteal resorption of the lateral clavicle.

T-scores were calculated only for the cohort that included postmenopausal women and men ≥ 50 years. In this cohort, the mean T-scores, determined for the different skeletal sites, i.e. the LS, FN, THR and distal forearm, were −1.0 ± 1.7, −1.7 ± 1.4, −1.1 ± 1.5 and −2.5 ± 2.2, respectively. The Z-scores were used diagnostically to determine low bone mass in premenopausal women and men < 50 years. Z-scores, similar to the T-scores, were noted to be lowest for the distal forearm in the younger cohort (–1.3 ± 2.1).

Despite few skeletal surveys beingavailable for scrutiny, five patients (9.6%) had evidence of osteitis fibrosa cystica: subperiosteal erosion was seen in the hands, distal clavicles (Figure 1) and/or sacro-iliac joints of three patients; 'salt and pepper skull' was noted in the CT image of one patient; and a brown tumour was seen in the hand radiographs of one patient (Figure 2).

Relationship between bone mineral density and biochemical parameters

The relationship between absolute BMD (g/cm^2) and biochemical parameters was explored, with correction for age and BMI. BMD was positively associated with 25(OH)D levels only at the lumbar spine ($r = 0.66$, $p = 0.04$). BMD was negatively associated with (i) ALP in the distal forearm only ($r = -0.66$, $p = 0.04$) and (ii) PTH in the femoral neck only ($r = -0.63$, $p = 0.05$). No significant association was evident between serum calcium level and absolute BMD at any measured site.

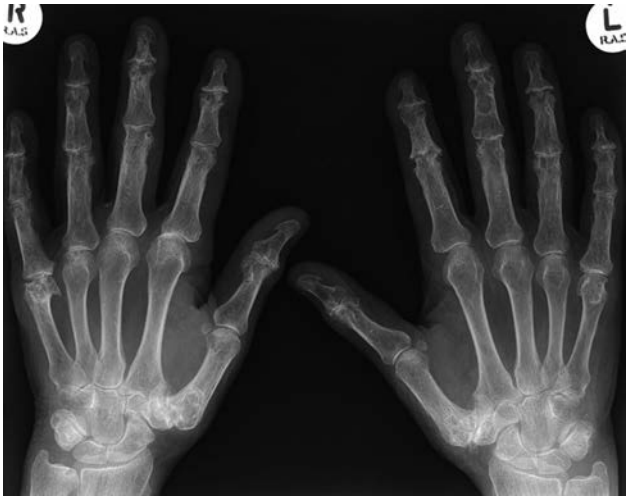

Figure 2: Subperiosteal resorption of medial phalanges and brown tumour of left third, middle phalanx.

Biochemical parameters within the different BMD subgroups are presented in Table 4. In the total cohort, a significantly higher PTH level was seen in those with decreased BMD (osteoporosis, osteopenia and low bone mass for age) compared with those with normal BMD (mean PTH 20.6 vs. 16.7 pmol/l respectively, $p = 0.04$). No significant differences were evident between the two groups in terms of calcium, ALP or 25(OH)D levels. When exploring the same variables in the subgroup of patients ≥ 50 years, PTH levels in the osteoporosis group tended to be higher compared with both the osteopenia and normal BMD groups ($p = 0.07$), reaching statistical significance only in a direct comparison between those with normal BMD versus those with osteoporosis ($p = 0.02$).

There was no association between vertebral fracture (assessed by VFA or conventional radiology) and PTH or 25(OH)D.

Discussion

In this study, we present a detailed report on the skeletal health and biochemical characteristics of a cohort of mostly overweight patients with symptomatic moderate to severe PHPT, who underwent surgical parathyroidectomy. More than two-thirds (71.4%) of the patients had decreased BMD and half (50%) of the cohort that comprised postmenopausal women and men ≥ 50 years had osteoporosis. One in five patients had morphometric vertebral fractures at diagnosis.

In the developing world, in contrast to well-resourced healthcare settings, the prevalence of PHPT has not been determined. Underdiagnosis, underreporting and lack of national health registries in lesser-resourced countries probably contribute to this. It is therefore not surprising that only three studies have been published on the nature of PHPT and its impact on skeletal health in South African patients.[23,30,31] In patients with PHPT in the developed world, the prevalence of osteoporosis ranges from 24% to 62.9%[32,33] and vertebral fractures from 21% to 47%.[33–35] These varied results are likely due to different study populations, different methods for diagnosis and change in presentation of the disease over time. In the current study, the prevalence of osteoporosis and vertebral fractures in South African patients with PHPT falls within these ranges.

The reduction in bone density that occurs in PHPT follows a specific pattern: demineralisation of cortical bone, mainly the radius, tibia and femur, with relative preservation of trabecular or cancellous bone (vertebrae, pelvis, ribs).[17,36] Concordant with this, the skeletal site most severely affected in our study was the distal-third forearm. The mean T-score at this site was lower compared with the other measured sites (−2.5 ± 2.2) and 60% ($n = 9/15$) of measured patients had osteoporosis range BMD. The proximal femoral region has both cortical and cancellous bone[36] and shows intermediate changes in bone density.[37] The total hip site contains more cortical bone compared with the femoral neck region and it is thus surprising in our cohort that more bone loss occurred in the femoral neck region (mean T-score of −1.7 ± 1.4 versus mean T-score of −1.1 ± 1.5 for the total hip region). BMD at the lumbar spine, an area rich in trabecular bone, was relatively preserved, with a mean

Table 4: Biochemical parameters within BMD subgroups.

Total cohort ($n = 56$)				
	Total cohort	**Normal BMD**	**Decreased BMD**	***p*-value***
Calcium (mmol/l)	2.93 (2.81, 3.19)	2.93 (2.84, 3.12)	2.95 (2.81, 3.27)	0.74
Phosphate (mmol/l)	0.87 (0.71, 1.00)	0.80 (0.67, 0.94)	0.89 (0.73, 1.02)	0.40
PTH (pmol/l)	19.40 (14.65, 42.0)	16.7 (14.1, 20.8)	20.6 (16.0, 52.6)	0.04*
ALP (U/l)	88.0 (75.0, 122.0)	82.0 (73.0, 106.0)	89.0 (77.0, 133.5)	0.28
25(OH)D (nmol/l)	34.0 (24.30, 47.2)	32.0 (21.0, 51.8)	35.90 (28.6, 47.0)	0.54
Cohort: postmenopausal women and men ≥ 50 years ($n = 46$)				
	Normal BMD	**Osteopenia**	**Osteoporosis**	***p*-value****
Calcium (mmol/l)	2.91 (2.79, 3.02)	2.91 (2.80, 3.17)	3.05 (2.81, 3.42)	0.42
Phosphate (mmol/l)	0.91 (0.74, 1.05)	0.94 (0.80, 1.03)	0.89 (0.71, 1.00)	0.65
PTH (pmol/l)	16.1 (11.9, 19.5)	18.7 (13.7, 45.7)	36.4 (17.3, 80.4)	0.07***
ALP (U/l)	105.5 (82.0, 119.0)	79.0 (69.0, 90.0)	108.0 (85.0, 151.0)	0.13
25(OH)D (nmol/l)	33.7 (26.5, 53.3)	39.0 (29.7, 55.9)	31.1 (19.4, 42.8)	0.18

*p-value comparing normal BMD with decreased BMD.
**p-value comparing the three categories of normal, osteopenia and osteoporosis in postmenopausal women and men ≥ 50 years.
***In a direct comparison of PTH in normal BMD vs. osteoporosis $p = 0.02$.
Values given are median (IQR). Decreased BMD referring to either low bone mass in patients < 50 years and osteopenia or osteoporosis in patients ≥ 50 years.

T-score near normal (−1.0 ± 1.7). Interpretation of lumbar spine BMD, especially in older people, must be done cautiously. Falsely elevated BMD in the lumbar spine can occur with osteoarthritic spondylosis, acquired scoliosis, vertebral fractures and aortic calcifications.[38–40] Given the age and extent of hypercalcemia in our patients, extra-skeletal calcifications may also have accounted for a falsely elevated lumbar spine BMD. In all three last-mentioned sites the percentage of patients with osteoporosis range BMD was, however, similar (LS 23.9%; FN 33.3% and TH 24.4%).

Despite the apparent preserved axial BMD, epidemiological studies describing fracture risk in PHPT report similar fracture risk in both vertebral and non-vertebral sites.[15] VFs are known to occur more commonly in PHPT than matched controls[19,20] and these fractures appear to occur at a higher BMD than in patients without PHPT,[33,34] suggesting that factors other than reduced BMD play a role.

PHPT represents a state of high bone resorption with increased bone turnover, a well-documented BMD-independent risk factor for decreased bone quality and fragility.[41] An association between the degree of PTH elevation and the severity of skeletal involvement has previously been reported[42] and was reaffirmed in our study. The mean PTH level was significantly higher in the patients with decreased BMD when compared with those who had normal BMD in the total cohort (mean PTH 16.7 vs. 20.6 pmol/l respectively, $p = 0.04$). A significantly higher mean PTH was also noted in a direct comparison of patients with osteoporosis and those with normal BMD (mean PTH 36.2 vs 16.7 pmol/l, $p = 0.02$). An elevated ALP level was noted in 21 of 45 patients tested (46.7%), indicative of decreased skeletal mineralisation. This may be a consequence of accelerated bone turnover in PHPT and may impact negatively on bone strength and bone quality irrespective of BMD. A significant correlation between ALP and PHPT bone disease could be expected,[4] but was not proven to be significant in this study. Research using high-resolution peripheral quantitative computed tomography (HRpQCT) has confirmed microarchitectural deterioration and decreased volumetric density at both cortical and trabecular sites,[43,44] findings in keeping with a high bone turnover state with a consequent adverse impact on bone quality.

No significant differences in serum calcium or 25(OH)D were found between patients with normal and decreased BMD. The impact of vitamin D deficiency on skeletal health in PHPT remains to be fully defined. First, it appears that vitamin D deficiency is more common in patients with PHPT than in matched controls[45,46] and, second, that vitamin D deficient patients with PHPT have more severe skeletal manifestations of the disease.[11,47] What is unclear, however, is the causality of the relationship:[48] does pre-existing vitamin D deficiency worsen the clinical picture of PHPT, or does PHPT cause vitamin D deficiency, particularly if severe? There is ongoing active research in this area. Vitamin D deficiency is common in South Africa; deficient levels have been found in 38% to 55%[49,50] of patients. In our study, deficiency was seen in 39 patients (79.6%) with PHPT, exceeding the deficiency rates seen in other South African cohorts and supporting the evidence that vitamin D deficiency is more common in PHPT. While we were able to show an inverse correlation between 25(OH)D and PTH ($r = -0.43$, $p < 0.01$), this did not translate to a significant relationship with osteoporosis, a finding that has been reported in other studies.[51] It is noteworthy that normal 25(OH)D was only documented in 2 of the 49 patients who underwent testing and the almost universal lowered 25(OH)D levels in the study cohort may be the reason why a significant correlation with adverse BMD outcome was not demonstrated. The true existence of a correlation between 25(OH)D deficiency and severity of bone disease in PHPT has not been consistently forthcoming in the literature to date; some studies have found a significant relationship,[42] while others, like ours, have not.[52]

The once common and pathognomonic mode of presentation of PHPT, osteitis fibrosa cystica, is considered a rarity in high-income nations today.[1,6,53] Developing countries such as Brazil, India and Thailand, however, still report rates of OFC between 6.7% and 47%.[10] In South Africa, a 1976 study[30] reported three cases of PHPT with gross bone disease, which the authors ascribed to a severe variant as opposed to delayed presentation and management. Paruk et al. reported a 47.6% ($n = 10/21$) prevalence of hyperparathyroidism-related bone disease on plain radiographs (a combined value given for subperiosteal resorption, bone cysts, loss of skull lamina dura, bone sclerosis and brown tumours).[23] Despite very few

dedicated skeletal surveys in our study, OFC was seen in five patients (9.6%). These were likely patients who were suspected of having more severe PHPT or were symptomatic from skeletal disease. This figure may well have been higher had all patients undergone screening radiographs.

Limitations of this study include its retrospective nature and small sample size; it does, however, represent the largest study to date of bone health in South African patients with PHPT. By selecting a cohort of patients with PHPT requiring surgery, bias towards more severe PHPT is introduced and may overestimate the severity of skeletal disease in a broader PHPT population. Of a total of 104 patients who underwent parathyroidectomy for PHPT, only 56 (53.8%) had a DXA study on record, highlighting deficient evaluation of skeletal health in many patients with PHPT. Studies have shown that, even in asymptomatic patients, VFs and osteoporosis will be detected in 34.7% and 65.8% of cases if radiographic imaging and DXA is performed.[33]

Conclusion

In the South African public sector, the majority of patients diagnosed with PHPT have skeletal disease. Insufficient vitamin D is almost universal. This emphasises the importance of skeletal and biochemical assessment and calls for a multidisciplinary approach to managing patients with PHPT.

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References

1. Zanocco KA, Yeh MW. Primary hyperparathyroidism. Endocrinol Metab Clin North Am. 2017 Mar;46(1):87–104. https://doi.org/10.1016/j.ecl.2016.09.012
2. Shepard MM, Smith JW. Hypercalcemia. Am J Med Sci. 2007 Nov;334(5):381–385. https://doi.org/10.1097/MAJ.0b013e31812f4947
3. Silverberg SJ, Shane E, de la Cruz L, Dempster DW, Feldman F, Seldin D, et al. Skeletal disease in primary hyperparathyroidism. J Bone Miner Res. 1989;4(3):283–291. https://doi.org/10.1002/jbmr.5650040302
4. Mosekilde L. Primary hyperparathyroidism and the skeleton. Clin Endocrinol (Oxf). 2008 Jul;69(1):1–19. https://doi.org/10.1111/j.1365-2265.2007.03162.x
5. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the fourth international workshop. J Clin Endocrinol Metab. 2014 Oct;99(10):3561–3569. https://doi.org/10.1210/jc.2014-1413
6. Makras P, Anastasilakis AD. Bone disease in primary hyperparathyroidism. Metab Clin Exp. 2018 Mar;80:57–65. https://doi.org/10.1016/j.metabol.2017.10.003
7. Bandeira F, Cassibba S. Hyperparathyroidism and bone health. Curr Rheumatol Rep. 2015 Jul 24;17(7):48. https://doi.org/10.1007/s11926-015-0523-2
8. Mundy G, Cove D, Fisken R. Primary hyperparathyroidism: changes in the pattern of clinical presentation. Lancet. 1980 Jun;315(8182):1317–1320. https://doi.org/10.1016/S0140-6736(80)91783-3
9. Heath H, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. N Engl J Med. 1980 Jan 24;302(4):189–193. https://doi.org/10.1056/NEJM198001243020402
10. Silverberg SJ, Clarke BL, Peacock M, Bandeira F, Boutroy S, Cusano NE, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. J Clin Endocrinol Metab. 2014 Oct;99(10):3580–3594. https://doi.org/10.1210/jc.2014-1415
11. Bilezikian JP, Meng X, Shi Y, Silverberg SJ. Primary hyperparathyroidism in women: a tale of two cities–New York and Beijing. Int J Fertil Womens Med. 2000;45(2):158–165.
12. Bandeira F, Correia A. Clinical presentation of primary hyperparathyroidism. In: The Parathyroids. Elsevier; 2015. p. 309–15. https://doi.org/10.1016/B978-0-12-397166-1.00020-5
13. Bilezikian JP, Silverberg SJ, Shane E, Parisien M, Dempster DW. Characterization and evaluation of asymptomatic primary hyperparathyroidism. J Bone Miner Res. 2009 Dec 3;6(S2):S85–S89. https://doi.org/10.1002/jbmr.5650061419
14. Adami S, Braga V, Squaranti R, Rossini M, Gatti D, Zamberlan N. Bone measurements in asymptomatic primary hyperparathyroidism. Bone. 1998 May;22(5):565–570. https://doi.org/10.1016/S8756-3282(98)00042-8
15. Khosla S, Melton J. Fracture risk in primary hyperparathyroidism. J Bone Miner Res. 2002 Nov;17(Suppl 2):N103–N107.
16. Yu N, Donnan PT, Flynn RW, Murphy JM, Smith D, Rudman A, et al. Increased mortality and morbidity in mild primary hyperparathyroid patients. Clin Endocrinol. 2010 Jul;73(1):30–34. https://doi.org/10.1111/j.1365-2265.2009.03766.x
17. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008 Sep;93(9):3462–3470. https://doi.org/10.1210/jc.2007-1215
18. Yeh MW, Ituarte PHG, Zhou HC, Nishimoto S, Amy Liu I-L, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab. 2013 Mar 1;98(3):1122–1129. https://doi.org/10.1210/jc.2012-4022
19. Kenny A, Macgillivray D, Pilbeam C, Crombie H, Raisz L. Fracture incidence in postmenopausal women with primary hyperparathyroidism. Surgery. 1995 Jul;118(1):109–114. https://doi.org/10.1016/S0039-6060(05)80017-0
20. Vignali E, Viccica G, Diacinti D, Cetani F, Cianferotti L, Ambrogini E, et al. Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2009 Jul;94(7):2306–2312. https://doi.org/10.1210/jc.2008-2006
21. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med. 1999 Oct 21;341(17):1249–1255. https://doi.org/10.1056/NEJM199910213411701
22. Vestergaard P. Cohort study of risk of fracture before and after surgery for primary hyperparathyroidism. Br Med J. 2000 Sep 9;321(7261):598–602. https://doi.org/10.1136/bmj.321.7261.598
23. Paruk IM, Esterhuizen TM, Maharaj S, Pirie FJ, Motala AA. Characteristics, management and outcome of primary hyperparathyroidism in South Africa: a single-centre experience. Postgrad Med J. 2013 Nov;89(1057):626–631. https://doi.org/10.1136/postgradmedj-2012-131707
24. Yeh MW, Zhou H, Adams AL, Ituarte PHG, Li N, Liu I-LA, et al. The relationship of parathyroidectomy and bisphosphonates with fracture risk in primary hyperparathyroidism. Ann Intern Med. 2016 Jun 7;164(11):715. https://doi.org/10.7326/M15-1232
25. World Health Organization (WHO) [Cited 2020 Jan 22] Available from: https://apps.who.int/bmi/index.jsp
26. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911–1930. https://doi.org/10.1210/jc.2011-0385
27. Alexeeva L, Burkhardt P, Christiansen C, Cooper C, Delmas P, Johnell O, et al. Reviews and notes: assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Ann Intern Med. 1995 Apr 1;122(7):558. https://doi.org/10.7326/0003-4819-122-7-199504010-00024

28. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 2009 Dec 3;8(9):1137–1148. https://doi.org/10.1002/jbmr.5650080915
29. Brown JP, Josse RG. Scientific advisory council of the osteoporosis society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ. 2002 Nov 12;167(10 Suppl):S1–34.
30. Angorn IB, Seedat YK. Primary hyperparathyroidism in black South Africans. South African Med J. 1976 Jul 24;50(32):1246–1248.
31. Diamond TH, Botha JR, Kalk WJ, Shires R. Primary hyperparathyroidism. A study of 100 patients in Johannesburg. S Afr Med J. 1986 Jan 18;69(2):94–97.
32. Assadipour Y, Zhou H, Kuo EJ, Haigh PI, Adams AL, Yeh MW. End-organ effects of primary hyperparathyroidism: a population-based study. Surgery. 2019 Jan;165(1):99–104. https://doi.org/10.1016/j.surg.2018.04.088
33. Cipriani C, Biamonte F, Costa AG, Zhang C, Biondi P, Diacinti D, et al. Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. J Clin Endocrinol Metab. 2015 Apr;100(4):1309–1315. https://doi.org/10.1210/jc.2014-3708
34. Ejlsmark-Svensson H, Bislev LS, Lajlev S, Harsløf T, Rolighed L, Sikjaer T, et al. Prevalence and risk of vertebral fractures in primary hyperparathyroidism: a nested case-control study. J Bone Miner Res. 2018 Sep;33(9):1657–1664. https://doi.org/10.1002/jbmr.3461
35. De Geronimo S, Romagnoli E, Diacinti D, D'Erasmo E, Minisola S. The risk of fractures in postmenopausal women with primary hyperparathyroidism. Eur J Endocrinol. 2006 Sep;155(3):415–420. https://doi.org/10.1530/eje.1.02225
36. Bilezikian Jp, Brandi Ml, Rubin M, Silverberg Sj. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med. 2005 Jan;257(1):6–17. https://doi.org/10.1111/j.1365-2796.2004.01422.x
37. Eller-Vainicher C, Falchetti A, Gennari L, Cairoli E, Bertoldo F, Vescini F, et al. Diagnosis of endocrine disease: evaluation of bone fragility in endocrine disorders. Eur J Endocrinol. 2019 Jun;180(6):R213–R232. https://doi.org/10.1530/EJE-18-0991
38. Rand T, Seidl G, Kainberger F, Resch A, Hittmair K, Schneider B, et al. Impact of spinal degenerative changes on the evaluation of bone mineral density with dual energy X-ray absorptiometry (DXA). Calcif Tissue Int. 1997 May 11;60(5):430–433. https://doi.org/10.1007/s002239900258
39. Schneider DL, Bettencourt R, Barrett-Connor E. Clinical utility of spine bone density in elderly women. J Clin Densitom. 2006 Jul;9(3):255–260. https://doi.org/10.1016/j.jocd.2006.04.116
40. Pappou IP, Girardi FP, Sandhu HS, Parvataneni HK, Cammisa FP, Schneider R, et al. Discordantly high spinal bone mineral density values in patients with adult lumbar scoliosis. Spine (Phila Pa 1976). 2006 Jun;31(14):1614–1620. https://doi.org/10.1097/01.brs.0000222030.32171.5f
41. Melton LJ, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. J Bone Miner Res. 1997 Jul 1;12(7):1083–1091. https://doi.org/10.1359/jbmr.1997.12.7.1083
42. Moosgaard B, Christensen SE, Vestergaard P, Heickendorff L, Christiansen P, Mosekilde L. Vitamin D metabolites and skeletal consequences in primary hyperparathyroidism. Clin Endocrinol (Oxf). 2008 May;68(5):707–715. https://doi.org/10.1111/j.1365-2265.2007.03109.x
43. Vu TDT, Wang XF, Wang Q, Cusano NE, Irani D, Silva BC, et al. New insights into the effects of primary hyperparathyroidism on the cortical and trabecular compartments of bone. Bone. 2013 Jul;55(1):57–63. https://doi.org/10.1016/j.bone.2013.03.009
44. Cusano NE, Rubin MR, Silva BC, Tay Y-KD, Williams JM, Agarwal S, et al. Skeletal microstructure and estimated bone strength improve following parathyroidectomy in primary hyperparathyroidism. J Clin Endocrinol Metab. 2018 Jan 1;103(1):196–205. https://doi.org/10.1210/jc.2017-01932
45. Moosgaard B, Vestergaard P, Heickendorff L, Melsen F, Christiansen P, Mosekilde L. Vitamin D status, seasonal variations, parathyroid adenoma weight and bone mineral density in primary hyperparathyroidism. Clin Endocrinol (Oxf). 2005 Nov;63(5):506–513. https://doi.org/10.1111/j.1365-2265.2005.02371.x
46. Boudou P, Ibrahim F, Cormier C, Sarfati E, Souberbielle JC. A very high incidence of low 25 hydroxy-vitamin D serum concentration in a French population of patients with primary hyperparathyroidism. J Endocrinol Invest. 2006 Jun 11;29(6):511–515. https://doi.org/10.1007/BF03344140
47. Bandeira F, Caldas G, Griz L, Bandeira C, Bandeira C, Bandeira C, et al. Relationship between serum vitamin D status and clinical manifestations of primary hyperparathyroidism. Endocr Pract. 2002 Jul;8(4):266–270. https://doi.org/10.4158/EP.8.4.266
48. Silverberg SJ. Vitamin D deficiency and primary hyperparathyroidism. J Bone Miner Res. 2007 Dec 1;22(S2):V100–V104. https://doi.org/10.1359/jbmr.07s202
49. Baatjes KJ, Kotze M, McCaul M, Conradie M. Baseline bone health status in multi-ethnic South African postmenopausal breast cancer patients at initiation of aromatase inhibitor therapy: a descriptive study. PLoS ONE. 2019;14(4):e0214153. https://doi.org/10.1371/journal.pone.0214153
50. Chutterpaul P, Paruk F, Cassim B. Prevalence of vitamin D deficiency in older South Africans with and without hip fractures and the effects of age, body weight, ethnicity and functional status. J Endocrinol Metab Diabetes South Africa. 2019 Jan 2;24(1):10–15. https://doi.org/10.1080/16089677.2018.1534360
51. Walker MD, Cong E, Lee JA, Kepley A, Zhang C, McMahon DJ, et al. Vitamin D in primary hyperparathyroidism: effects on clinical, biochemical, and densitometric presentation. J Clin Endocrinol Metab. 2015 Sep 1;100(9):3443–3451. https://doi.org/10.1210/jc.2015-2022
52. Yamashita H, Noguchi S, Uchino S, Watanabe S, Koike E, Murakami T, et al. Vitamin D status in Japanese patients with hyperparathyroidism: seasonal changes and effect on clinical presentation. World J Surg. 2002 Aug 1;26(8):937–941. https://doi.org/10.1007/s00268-002-6622-z
53. Bandeira L, Bilezikian J. Primary hyperparathyroidism. F1000Res. 2016 Jan 4;5:1. https://doi.org/10.12688/f1000research.7039.1

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