*HPTH and fracture probability V9*

**Primary hyperparathyroidism and fracture probability**

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**Mini abstract**

The incidence of hip and major osteoporotic fracture was increased In patients with primary hyperparathyroidism even in patients not referred for parathyroidectomy. The risk of death was also increased which attenuated an effect on fracture probabilities. The findings argue for widening the indications for parathyroidectomy in mild primary hyperparathyroidism.

**Abstract**

**Introduction** Primary hyperparathyroidism (PHPT) is associated with an increase in the risk of fracture. In FRAX, the increase in risk is assumed to be mediated by low bone mineral density (BMD). However, the risk of death is also increased and its effect on fracture probability is not known.

**Objective** The aim of this study was to determine whether PHPT affects hip fracture and major osteoporotic fracture risk independently of bone mineral density (BMD) and whether this and any increase in mortality affects the assessment of fracture probability.

**Methods** A register-based survey of patients with PHPT and matched controls in Denmark were identified from hospital registers. The incidence of death, hip fracture and major osteoporotic fracture were determined for computing fracture probabilities excluding time after parathyroidectomy. The gradient of risk for fracture for differences in BMD was determined in a subset of patients and in BMD controls. The severity of disease was based on serum calcium and parathyroid hormone levels.

**Results.** We identified 6884 patients with biochemically confirmed PHPT and 68,665 matched population controls. On follow up, excluding time after parathyroidectomy in those undergoing surgery, patients with PHPT had a higher risk of death (+52%), hip fracture (+48%) and major osteoporotic fracture (+ 36%) than population controls. At any given age, average 10-year probabilities of fracture were higher in patients with PHPT than population controls. The gradient of fracture risk with differences in BMD was similar in cases and controls. Results were similar when confined to patients not undergoing parathyroidectomy. Fracture probability decreased with the severity of disease due to an increase in mortality rather than fracture risk.

**Conclusion.**  The risk of hip and other major osteoporotic fracture is increased in PHPT irrespective of the disease severity. Fracture probability was attenuated due to the competing effect of mortality. The increased fracture risk in patients treated conservatively argues for widening the indications for parathyroidectomy in mild PHPT.

**Keywords** · Fracture probability · Hip fracture · Mortality · Primary hyperparathyroidism

**Introduction**

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, particularly in postmenopausal women. It is characterized by elevated serum calcium combined with inappropriate normal or high plasma levels of parathyroid hormone (PTH) [1]. A normocalcaemic variant of PHPT is also described in which the serum total and ionized calcium are consistently normal while the PTH level is elevated. Its clinical presentation has changed markedly in the last 50 years due to the development of automated serum calcium measurement in the early 1970s that enabled the measurement of serum calcium in routine biochemical screening. Thus, the disease typically affects elderly women and is usually characterized by only mild hypercalcemia and few traditional classic (bone and kidney) manifestations. The change in clinical presentation has meant that not all patients with PHPT are referred for surgery particularly "asymptomatic" patients and those with mild hypercalcaemia without renal or skeletal impairment [2, 3, 4, 5. 6].

The most widely used approach to patient stratification for fracture risk is the FRAX® fracture risk assessment tool, which combines clinical factors that independently predict fracture risk as well as (optionally) bone mineral density (BMD) at the femoral neck to predict 10-year probability of major osteoporotic fracture (MOF; a composite of hip, clinical vertebral, forearm and humerus fractures) and 10-year probability of hip fracture [7, 8]. The FRAX tool was initially developed for use in general practice. Since its initial development, it has been included in over 100 clinical practice guidelines and is the most widely used fracture prediction tool worldwide [9]. PHPT is not a direct input to FRAX. An input for secondary osteoporosis (including hyperparathyroidism) is provided in the FRAX algorithm which affects the output when BMD is not available but does not affect the risk calculation when BMD is included. Thus, FRAX assumes, perhaps conservatively, that any increase in fracture risk is mediated by a decrease in BMD. An additional consideration relates to the computation of fracture probability. Many studies including a recent meta-analysis [10] indicate that PHPT is associated with an increase in the risk of fracture which would be expected to increase fracture probability. However, there is also evidence that the risk of death is increased [11, 12, 13, 14]. The question arises how these impact on fracture probability since the increased risk of death acts as a competing hazard for the calculation of fracture probability.

The aim of this study was to determine the effect of PHPT on fracture probability and whether PHPT affects hip fracture and major osteoporotic fracture risk independently of BMD and thereby also affects the assessment of fracture probability. Where effects were found, an additional aim was to examine fracture probabilities in patients who were managed conservatively.

**Methods**

In Denmark, all citizens are assigned a Civil Personal Registration (CPR) number which allows identification of all individuals assigned a specific hospital discharge diagnosis and linkage between different registers, including data on biochemistry and bone mineral density. Using a retrospective cohort study design, we identified patients diagnosed with PHPT in Denmark between 1997 and June 2015 and compared findings in patients with age, and gender-matched controls. The Danish Data Protection Agency was notified about the database (# 1-16-02-135-15), and the Danish Health and Medicines Authority granted access to retrieve data from hospital charts (# 3-3013-948/1).

*Cases*

Patients with a diagnosis of PHPT were identified using the Danish National Patient Register [15]. The register has a nationwide coverage and includes data on all discharge diagnoses of all hospital admissions and outpatient visits since 1977. Initially, we identified all patients assigned a hospital discharge code of hyperparathyroidism according to the International Classification of Diseases (ICD) between 1977 and June 2015. We searched for ICD codes according to the ICD-8th version (codes: 25200 to 25209) which were used in Denmark from 1971 to 1993 and the 10th version (codes E21.\*) which has been used since 1994. ICD version 9 was never used in Denmark. Initially, we identified 17,025 patients with a diagnosis of hyperparathyroidism

*Biochemistry*

To assure a state of hyperparathyroid hypercalcemia, we also searched for biochemistry data on measurements of plasma PTH, calcium and creatinine levels from major medical laboratories around the country. The search was restricted to those with an ICD code of hyperparathyroidism”. A diagnosis of PHPT was considered as confirmed if blood tests on two separate occasions showed an average PTH level in the upper third- or above the upper limit of the reference interval with concomitant hypercalcemia [16]. We used reference ranges from the local laboratories performing the analyses. The first date being assigned a diagnosis of PHPT was considered as the Index date for the patients.

*Parathyroidectomy*

Using the Danish NPR, we also identified patients who had been assigned a procedural ICD-code of parathyroid surgery (SKS codes before 1994: 080xx-085xx and after 1994: KBBA00-KBBA99). Furthermore, to assure correct classification (parathyroidectomy vs. no surgery) of patients diagnosed with PHPT just prior to end of our initial search in June 2015, we updated our search in November 2017.

*Exclusion criteria*

In addition to excluding patients in whom it was not possible to biochemically verify a diagnosis of PHPT, we excluded patients who (ever) had been assigned a diagnosis of familial hypocalciuric hypercalcemia, multiple endocrine neoplasia or parathyroid cancer. Furthermore, we excluded patients with kidney insufficiency diagnosed more than one year prior to the diagnosis of PHPT based on ICD codes.

*Severity of disease*

The severity of disease was assessed in two ways. The first was based on serum calcium measured close to the date of diagnosis. Mild hypercalcaemia was ascribed where the average of two measurements of plasma ionised calcium lay between 1.33-1.44 mmol/L. Moderate and severe hypercalcaemia were characterised in the same way as an average concentration 1.45-1.64 mmol/L and ≥ 1.65 mmol/L, respectively. If two measurements of ionized calcium were not available, the average of two measurements of total calcium levels (n=793) were taken: upper level of normal to 2.76 mmol/L (mild); 2.77 - 3.02 mmol/L (moderate); ≥ 3.03 mmol/L (severe hypercalcaemia). Patients were additionally graded according to plasma PTH at the time of diagnosis as mild (up to 2-times the upper limit of normal), moderate (2-3 times the upper limit of normal) and severe (> 3 times the upper limit of normal).

*Population controls*

For each case of PHPT, up to ten population controls were assigned matched on sex, age (±2 years) and being alive at index date. The index date for each control was the date when the corresponding patient first received the ICD 10 code for PHPT. Controls were excluded if they had ever been assigned a diagnosis of PHPT.

All individuals were followed from index date to their death, emigration, parathyroidectomy, or 29th November 2017.

*Bone mineral density*

Dual-energy x-ray absorptiometry (DXA) scans of the femoral neck in patients with PHPT were extracted from clinical databases available at medical departments or departments of clinical physiology/nuclear medicine at hospitals treating PHPT patients. If a patient had several scans, we selected the scan performed closest to the index date. In the case of patients undergoing parathyroidectomy, we only included BMD measurements performed prior to surgery. Using the same clinical DXA databases, we also identified DXA scans from approximately three controls per PHPT patient matched on gender and age (± 2 years). We only included scans performed using Hologic machines. It should be noted that the BMD controls were not population based but drawn from referral populations for skeletal assessment.

*Baseline measurements*

Registers of cases and population controls were examined for 5 years prior to the index date to determine a history of prior fracture, a diagnosis of osteoporosis or renal urolithiasis from ICD codes.

*Outcome measurements*

Hip fractures were identified based on relevant ICD codes (ICD8: 8200 or ICD 10: S720, S721, or S722) combined with a relevant code for a procedure (SKS code) related to hip fracture (KNFB—or KNFJ4x to 9x).

Incident MOF was defined as a fracture of the hip, vertebrae, proximal humerus or distal radius. In addition to hip fracture, additional MOF included ICD 8: 8050-8055, 8058-8059, 8060-8065, 8068-8069, 8120-8123, 8134-8135 and ICD 10: S120-S122, S220-S221, S320, S422-S423, S525-526, T08. The method would miss subclinical morphometric fractures.

 Kidney stones were identified by ICD codes (9DN20, 5920, 5929, 5939 or 5921) in the 5 years before the index date. Osteoporosis was identified by ICD codes in the 5 years before the index date (ICD codes 73309, 73319, DM80, DM800, DM801, DM802, DM803, DM804, DM805, DM808, DM809, DM809A, DM809B, DM809C, DM809D, DM81, DM810, DM811, DM812, DM813, DM814, DM815, DM816, DM818, DM818A or DM819).

Outcomes of interest for the subset of patients and controls with BMD assessment was the fracture risk associated with a given femoral neck BMD. Additionally, the gradient of risk (GR: increase in fracture risk/SD decrement in BMD) was determined for the outcome of hip fracture and MOF.

Probabilities for fracture were calculated from the hazard functions of death, hip fracture and MOF without hip fracture in 1-year intervals from the age of 50 years in men and women for the calendar year 2005 [7, 17]. Ten-year probabilities of hip fracture, other major osteoporotic fracture, and major osteoporotic fracture were determined in patients that did not undergo parathyroidectomy.

*Statistical methods*

Comparisons between groups were performed with Fisher’s permutation test or Fisher’s exact test. To estimate the instantaneous hazard function (HF) for death and fracture risk an extension of Poisson regression model was used [18, 19] to study the relationship between the risk of death or fracture on one hand and current time since index date, current age, current calendar year, sex, PHPT diagnosis and BMD on the other hand. Models were also additionally adjusted for previous fractures. Models were also developed for those with PHPT with adjustments for levels of PTH and hypercalcaemia. For all deaths and fracture, the exact date of death and fracture was included in the calculations. The observation period of each participant was divided into intervals of one month. The first of any endpoint per individual was used. The time at risk was censored at the time of parathyroidectomy (PTX), death, emigration, or end of follow up. In a sensitivity analysis we censored time of follow up to one year for both cases and controls to explore the effect of unequal follow up in cases and controls.

From the hazard functions described above for fracture and death, the 10-year probability of hip fracture and MOF was calculated [20]. It is important to note that the probability models used were based on purpose-built models similar to, but not identical to FRAX. Indeed, many of the traditional FRAX risk factors were unavailable.

**Results**

*Baseline and follow up characteristics*

We identified 6884 patients with biochemically confirmed PHPT and 68,665 matched population controls. The baseline characteristics are shown in table 1. More than three quarters of cases and controls were female with a mean age of 65 years in men and women combined. Patients with PHPT had a significantly higher prevalence of prior fracture, diagnosis of osteoporosis and renal stones in the previous 5 years than their age and sex matched controls.

**[Table 1** **near here]**

As might be expected, patients that underwent PTX differed in baseline characteristics from those treated conservatively (see Table 1). Cases that underwent PTX were younger than those managed conservatively (61 vs. 72 years). Additionally, they had a higher prevalence of kidney stones (8.6% vs. 3.2%) and severe hypercalcaemia at baseline but a lower prevalence of osteoporosis.

On follow up, including follow up after parathyroidectomy, patients with PHPT had a higher risk of death (HR=1.28; 95% CI=1.22, 1.34) and a higher risk of both hip fractures (HR=1.20; 95% CI=1.07, 1.35) and other major osteoporotic fractures (HR=1.20; 95% CI=1.09, 1.30). On follow up, excluding follow up after parathyroidectomy, patients with PHPT had a higher risk of death and major osteoporotic fracture than population controls (Table 2). The risks of both hip fractures and other major osteoporotic fractures were increased. Adjustment for length of follow up decreased the hazard ratio but for all outcomes was significantly higher than unity (Table 2). The risk of hip fracture was increased by 48% and that for MOF by 36%.

**Table 2:** Clinical outcomes for all cases and population controls.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Controls** | **Cases** | **p-value** |
|   | N=68,665 | N=6884 |  |
|  |  |  |  |
| Time at risk, years, median (IQR) | 6.4 (4.0-10.7) | 1.1 (0.4-4.3) |  |
|  |  |  |  |
| **Death** |  |  |  |
| Events, n (%) | 18221 (26.5%) | 1356 (19.7%) |  |
| per 1000 person years (95% CI) | 34.1 (33.6-34.6) | 66.8 (63.3-70.4) |  |
| HR (95%CI) | reference | 1.96 (1.85-2.07) | <0.001 |
| Adjusted HR (95%CI) \* | reference | 1.52 (1.44-1.60) | <0.001 |
|  |  |  |  |
| **Major osteoporotic fracture** |  |  |  |
| Events, n (%) | 6776 (9.9%) | 455 (6.6%) |  |
| per 1000 person years (95% CI) | 13.4 (13.0-13.7) | 24.0 (21.8-26.3) |  |
| HR (95%CI) | reference | 1.79 (1.63-1.97) | <0.001 |
| Adjusted HR (95%CI) \* | reference | 1.36 (1.24-1.50) | <0.001 |
|  |  |  |  |
| **Hip fracture** |  |  |  |
| Events, n (%) | 2846 (4.1%) | 228 (3.3%)  |  |
| per 1000 person years (95% CI) | 5.4 (5.2-5.6) | 11.6 (10.1-13.2) |  |
| HR (95%CI) | reference | 2.14 (1.87-2.45) | <0.001 |
| Adjusted HR (95%CI) \* | reference | 1.48 (1.29-1.69) | <0.001 |
|  |  |  |  |
| **Other major osteoporotic fracture** |  |  |  |
| Events, n (%) | 4520 (6.6%) | 267 (3.9%) |  |
| per 1000 person years (95% CI) | 8.8 (8.5-9.0) | 13.7 (12.1-15.4) |  |
| HR (95%CI) | reference | 1.56 (1.38-1.76) | <0.001 |
| Adjusted HR (95%CI) \* | reference | 1.26 (1.11-1.42) | <0.001 |
|  |  |  |  |
| \*Adjusted for sex, current age, current time since index date and calendar year. |
| HR: Hazard ratio |

When patients who subsequently underwent parathyroidectomy were excluded, the risk of death was significantly higher than in matched population controls (HR=1.63; 95%CI=1.54-1.73; p<0.001), as was the risk of hip fracture (HR=1.45; 95%CI=1.26-1.68; p<0.001) and other major osteoporotic fractures (HR=1.29; 95%CI=1.12-1.47; p<0.001) (Table 3). There was no significant difference in fracture risk between those who did or did not undergo parathyroidectomy. There was no significant interaction between men and women and PHPT for the outcome of fracture, i.e., the HR for the outcome of fracture (hip fracture and major osteoporotic fracture) was not significantly different between men and women. In contrast, there was a significant interaction between sex for the outcome of death (p=0.0059). For example, the HR for women, at age 70 years was 1.58 (95% CI: 1.25-1.99). For men the corresponding HR at the same age and calendar year was 1.30 (1.05-1.61).

**Table 3.** Clinical outcomes for all cases and population controls (excluding follow up after parathyroidectomy). Cases are divided into those undergoing parathroidectomy (N=4186) and those managed conservatively (N=2698). Hazard ratios are adjusted for sex, current age, current time since index date and calendar year. There was no significant difference in fracture risk between those who did or did not undergo parathyroidectomy (PTX).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Controls** | **Cases no PTX** | **p-value1** | **Cases with PTX** | **p-value2** |
|  |  | HR | 95%CI |  | HR | 95%CI |  |
| Death | 1.0 | 1.63 | 1.54-1.73 | <0.001 | NA |  |  |
| Major osteoporotic fracture | 1.0 | 1.37 | 1.24-1.52 | <0.001 | 1.24 | 0.96-1.61 | 0.104 |
| Hip fracture | 1.0 | 1.45 | 1.26-1.68 | <0.001 | 1.61 | 1.04-2.48 | 0.033 |
| Other major osteoporotic fracture | 1.0 | 1.29 | 1.12-1.47 | <0.001 | 1.09 | 0.79-1.50 | >0.30 |
| NA – not applicable; 1 Controls vs. Cases not undergoing PTX; 2 Controls vs. Cases undergoing PTX |

*Probability*

As expected, the 10-year probability of fracture increased progressively with age and was higher in women than in men (Figure 1). At any given age, average probabilities were higher in patients with PHPT than those of population controls. The increment was higher for hip fracture probability (9-44%, depending on age) than for the probability of MOF (5-28%), and similar in men and women. The differences in fracture probability were very similar when cases and controls did not have a prior fracture (data not shown).



**Fig. 1** 10-year probability of hip fracture (HF) and major osteoporotic fracture (MOF) in men and women with PHPT and marched population-based controls. Cases exclude patients that underwent parathyroidectomy.

*Severity of hyperparathyroidism*

Three thousand eight hundred patients were categorised as having mild hypercalcaemia. In these patients, mean total serum calcium at the first measurement of plasma total calcium levels was 2.59 mmol/l adjusted for serum albumin. For 2103 patients with moderate hypercalcemia, mean total serum calcium at first measurement was 2.74 mmol/l. Mean total serum calcium for 457 patients with severe hypercalcaemia was 3.11 mmol/l. The numbers of patients with mild, moderate and severe levels of plasma PTH were 4309, 1226 and 825 with mean total serum calcium at first measurement of 2.62, 2.72 and 2.89 mmol/l, respectively.

In patients treated conservatively, there was no significant relationship between fracture risk and the degree of hypercalcaemia or the degree of hyperparathyroidism (p>0.3). In contrast, there was a significant increase in death risk for each step in the degree of hypercalcaemia (HR=1.31; 95% CI = 1.20-1.45) and for each step in the degree of hyperparathyroidism (HR=1.27; 95% CI = 1.17-1.37). Thus, fracture probability decreased with the severity of disease (Fig. 2).



**Fig. 2** 10-year probability of hip fracture (HF) and major osteoporotic fracture (MOF) in women with PHPT at the age of 60 years according to the degree ofhypercalcaemia and hyperparathyroidism. Calcium 1, 2 and 3 denote mild, moderate and severe hypercalcaemia as defined in the methods. PTH 1, 2 and 3 denote mild, moderate and severe hyperparathyroidism as judged by serum PTH as defined in the methods.

*Cases with BMD and BMD controls*

BMD tests were available in 2858 of the 6884 patients with hyperparathyroidism. Those tested with BMD were younger (64.0 vs. 65.2 years; p<0.001) with a less frequent history of prior fracture and of renal stones (4.7% vs. 7.7%) than those in whom BMD was not available (p<0.001). The prevalence of severe hypercalcemia and high levels of PTH was lower in those with available BMD compared to those without BMD (4.2% vs. 9.7%; p<0.001). A history of prior fracture was similar in both groups (11.0% vs. 11.7%; p>0.3). Perhaps unsurprisingly, a history of osteoporosis was higher in the BMD cohort than those without BMD tests.

**** When the subset of PHPT cases who had undergone BMD measurement or all PHPT cases, regardless of whether BMD measurement had been obtained, were compared with their relevant matched population controls, the BMD cohort was associated with a significantly (p<0.001) lower hazard ratio for death than the whole cohort (HR 1.13; 95%CI 1.01-1.26; p=0.036 vs. 1.52; 95%CI 1.44-1.60; p<0.001). The risks of hip fracture and major osteoporotic fracture were, however, comparable (p>0.3) (Figure 3).

**Fig. 3** The hazard ratio (HR) for the risk of death, major osteoporotic fracture (MOF) and hip fracture in the whole cohort of PHPT cases and the subset with BMD. The HRs are derived from comparison with the relevant matched population controls.

The characteristics of patients with a BMD test and their BMD controls are shown in table 4. Compared to the BMD controls, patients with PHPT had a higher body mass index but lower femoral neck BMD than the matched BMD controls (Table 4). PHPT cases had a slightly but statistically significantly lower prevalence of prior fracture and osteoporosis diagnosis but had a higher prevalence of kidney stones.

**Table 4**. Baseline and outcome data of cases with an available BMD test and their BMD controls.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Cases | BMD controls | p |
| n |  | 2858 | 8212 |  |
| Female (%) | n (%) | 2276 (80) | 6555 (80) | >0.30 |
| Age at index date (years) | Mean (SD) | 63.9 (12.9) | 63.8 (13.1) | >0.30 |
| BMI (kg/m2) | Mean (SD) | 27.5 (5.5) (n=2746) | 26.0 (5.0) (n=7938) | <0.001 |
| BMD femoral neck (g/cm2) | Mean (SD) | 0.67 (0.13) | 0.69 (0.14) | <0.001 |
| BMD femoral neck t-score  | Mean (SD) | -1.57 (1.12) | -1.43 (1.14) | <0.001 |
| Prior fracture\* | n (%) | 315 (11.0) | 1064 (13.0) | 0.0077 |
| Diagnosis of osteoporosis\* | n (%) | 471 (16.5) | 1584 (19.3) | <0.001 |
| Kidney stones\* | n (%) | 135 (4.7) | 56 (0.7) | <0.001 |
| Incidence hip fracture\*\* | /1000 p.y(95% CI) | 8.8 (6.9-11.1) | 6.4 (5.7-7.0) | >0.30\*\* |
| Incidence other MOF\*\* | /1000 p.y(95% CI) | 14.9 (12.3-17.8) | 14.3 (13.3-15.3) | >0.30\*\* |
| Incidence MOF\*\* | /1000 p.y(95% CI) | 22.2 (19.0-25.7) | 19.9 (18.7-21.1) | >0.30\*\* |
| GR Hip fracture for femoral neck BMD\*\*  | Mean (95% CI) | 1.77 (1.39-2.25)  | 1.86 (1.65-2.09) | >0.30 |
| GR Other MOF for femoral neck BMD) \*\* | Mean (95% CI) | 1.44 (1.18-1.76)  | 1.45 (1.34-1.57) | >0.30 |
| GR MOF for femoral neck BMD\*\*  | Mean (95% CI) | 1.57 (1.34-1.84)  | 1.55 (1.45-1.66) | >0.30 |
| \* N=2855 and n=8203 |
| \*\* Adjusted for sex, current age, current time since index and calendar year |
| BMI; Body mass index |
| GR; HR for fracture per 1 SD decrease in femoral neck BMD |

*Relationship between femoral neck BMD and fracture risk*

The incidences of hip fracture, other MOF or all MOF were not significantly different between the patients with PHPT with BMD and the BMD controls (see Table 4). Although mean femoral neck BMD was significantly lower in hyperparathyroid patients than in BMD controls, the absolute difference was modest (0.02 g/cm2; Table 3) and additional adjustment for BMD showed no effect of PHPT on fracture risk. For hip fracture, the hazard ratio was 0.96 (0.74-1.23) and for MOF was 0.89 (0.76-1.05). For MOF without hip fracture, the hazard ratio was 0.89 (0.74-1.09).

In terms of the relationship between BMD and fracture incidence, for hip fracture the gradient of risk (GR: fracture risk/SD decrement in BMD) was marginally but not significantly lower in hyperparathyroid patients (1.77; 1.39-2.25) compared with BMD controls (1.86;1.65, 2.09; p>0.30). For other MOFs or all MOFs, the gradient of risk was almost identical to that seen in the BMD referral cohort (see Table 4).

The relationship between femoral neck BMD and fracture risk is shown in Figure 4. Given that the gradient of risk was very similar in patients and controls, differences were largely due to the differences, albeit not significant, in the incidence of fracture. For MOF, patients with PHPT had a slightly higher fracture risk for any given BMD that varied by 8-16% according to BMD. In the case of hip fracture, the risk was 46-86% higher for a given BMD.



**Fig 4.** Schematic diagram illustrating the relation between hip fracture (HF), MOF risk and BMD in patients with PHPT (and population controls. For the empirical data on BMD, fracture risk and gradient of risk see Table 4.

*Sensitivity analysis*

Censoring by time diminished the number of events. Notwithstanding, the fracture and death risk remained significantly increased, as shown in table 5.

**Table 5.** The effect of censoring follow up to one year in cases and controls on the hazard ratio (HR) and 95% confidence interval (CI) for death, hip fracture and major osteoporotic fracture.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Principal analysis |  | Censoring at 1 year |
| Outcome | HR (95% CI) | p |  | HR (95% CI) | p |
| Death | 1.52 (1.44-1.60) | <0.001 |  | 1.60 (1.40-1.83) | <0.001 |
| Major osteoporotic fracture | 1.36 (1.24-1.50) | <0.001 |  | 1.68 (1.41, 2.00) | <0.001 |
| Hip fracture | 1.48 (1.29-1.69) | <0.001 |  | 2.27 (1.77, 2.90) | <0.001 |

**Discussion**

The present study identifies several characteristics of PHPT that are relevant for the calculation of fracture probability. The risk of both hip fracture and other major osteoporotic fractures was increased in line with the published experience [10, 21, 22, 23, 24, 25]. It is notable that hazard ratios were less than those reported in early studies [10] but consistent with a recent study [21] reflecting the increasing presentation of milder cases of PHPT. The present study also confirms that the risk of death is increased in PHPT, particularly in patients with the more severe hypercalcaemia [3, 14, 21, 26,]. The increased risk of death acts as a competing hazard for the calculation of fracture probability but in the present study, fracture probabilities were still higher in patients with PHPT than in population-based controls. However, cases had a higher recent history of fracture than controls (11.4 vs. 8.3 %, respectively) and a prior fracture has a well-established independent effect on fracture probability [7, 27]. When probabilities from cases and controls were compared setting a recent history of fracture to ‘no’, the differences in fracture probability were similar. Had we been able to adjust for other clinical risk factors, it is possible that differences in fracture probability would have been less.

The presentation of fracture probabilities in the present study differs from FRAX in that full account cannot be made of additional risk factors that contribute to fracture probability in FRAX models. We could, however, characterise the effect of BMD. The relationship between differences in femoral neck BMD and differences in fracture incidence, termed the gradient of risk, was very similar in PHPT to that of the BMD controls. Notwithstanding, for any given BMD, the fracture risk was higher than that seen in the BMD controls in keeping with a view that the quality of bone in PHPT is impaired in comparison with the controls [28, 29, 30]. It should be recalled that the BMD controls were not drawn from the general population but a BMD referral population predominately for the assessment of osteoporosis. It is possible, therefore, that differences in BMD-independent risk factors for fracture might also account for the greater fracture risk for any given BMD. The prevalence of one such factor, namely a prior fracture, was however lower among cases than BMD controls and barely affected our results.

It is of interest that the severity of the disease as judged by baseline serum calcium or PTH had no effect on fracture risk. In contrast, the more severe the disease, the higher the mortality and thus, the lower the fracture probability. Thus, a modest effect of PHPT on fracture probability due to the higher death hazard masks the fact that fracture risk is markedly increased. This has implications for the management of PHPT in that conservative treatment in mild PHPT appears to be associated with the same fracture risk as in severe cases that would preferentially be referred for parathyroidectomy [2, 5, 6, 10]. An increased fracture risk was also evident in the present study when we excluded patients who underwent parathyroidectomy. These findings suggest, contrary to most guidelines [2, 3, 5, 6], that parathyroidectomy should be considered irrespective of the degree of hypercalcaemia. The argument would be considerably strengthened if fracture risk was decreased in such patients after parathyroidectomy. It is of interest that a recently published prospective controlled trial showed no apparent effect of parathyroidectomy in mild PHPT on fracture and survival benefit [31] but the study was much underpowered.

A strength of the present study is the large number of patients available for assessment and follow up. We were able to capture all cases, both inpatient and outpatient that came to hospital attention. Additionally, data on serum calcium and PTH were available, permitting an assessment of the severity of PHPT. The present study has several limitations. We studied predominantly a white population, and our findings may not pertain to other ethnicities. We did not register the use of drugs such as lithium or thiazides among participants. The granularity of the data available did not permit a detailed analysis of all clinical risk factors that contribute to fracture probability. This applies to the cases, population-based controls and the BMD controls. It is notable that cases referred for parathyroidectomy had a shorter follow up than cases managed conservatively. Comparisons with an unequal length of follow up would have been problematic with Cox regression. However, with Poisson model as used in the present study, the current age and current time since baseline are used and adjusted for in the model. Moreover, censoring data to one year of follow up in cases and controls, strengthened rather than weakened the effect of PHPT on the risk of death and fracture.

In conclusion, the risk of hip and other major osteoporotic fracture is increased in PHPT irrespective of the disease severity and BMD. Fracture probability is less affected due to the competing effect of mortality. The increase in mortality and fracture risk in patients treated conservatively argue against conservative management of apparently asymptomatic patients with PHPT.

**Competing interests**

JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases. EV McCloskey, WD Leslie, M Lorentzon, NC Harvey, E Liu, L Vandenput and H Johansson are members of the FRAX team. JA Kanis reports no additional competing interests.

NC Harvey has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Consilient Healthcare and Internis Pharma.

M Lorentzon has received lecture fees from Amgen, Lilly, Meda, Renapharma and UCB Pharma and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma and Consilient Health, all outside the presented work.

EV McCloskey has received consultancy/lecture fees/grant funding/honoraria from AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, Gilead, GSK, Hologic, Internis, Lilly, Merck, Novartis, Pfizer, Radius Health, Redx Oncology, Roche, Sanofi Aventis, UCB, ViiV, Warner Chilcott and I3 Innovus.

E Liu, L Vandenput and H Johansson declare no competing interests in relation to this work.

R Bouillon has received lecture fees from FAES Farma (Spain) and Abiogen (Italy)

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L Rejnmark has received consultancy/lecture fees/grant funding/honoraria from Takeda Pharma, Ascendis Pharma and Kyowa-Kirin International.

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**Table 1**. Baseline data of cases and population controls.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | All cases | Population controls | P1 | Conservative management | PTX | P2 |
| n |  | 6884 | 68665 |  | 2698 | 4186 |  |
| Female (%) | n (%) | 79 | 79 | >0.30 | 81 | 78 | 0.0031 |
| Age at index date (years) | Mean (SD) | 65.2 (14.0) | 65.2 (14.0) | >0.30 | 72.3 (12.6) | 60.6 (12.9) | <0.001 |
| Prior fracture  | n (%) | 784 (11.4) | 5676 (8.3) | <0.001 | 393 (14.6) | 391 (9.3) | <0.001 |
| Diagnosis of osteoporosis | n (%) | 876 (12.7) | 2018 (2.9) | <0.001 | 430 (16.0) | 446 (10.7) | <0.001 |
| Kidney stones | n (%) | 446 (6.5) | 285 (0.4) | <0.001 | 87 (3.2) | 359 (8.6) | <0.001 |
| Degree of hypercalcaemia Mild Moderate Severe | n (%)n (%)n (%) | 4047 (58.8)2331 (33.9)506 (7.4) |  |  | 2042 (75.7)571 (21.2)85 (3.2) | 2005 (47.9)1760 (42.0)421 (10.1) | <0.001 |
| Degree of hyperparathyroidism Mild Moderate  Severe | n (%)n (%)n (%) | 4604 (66.9)1345 (19.5)935 (13.6) |  |  | 2014 (74.6)414 (15.3)270 (10.0) | 2590 (61.9)931 (22.2)665 (15.9) | <0.001 |
| Parathyroidectomy | n (%) | 4186 (60.8) |  |  | 0 (0.0) | 4186 (100.0) |  |
| Time to parathyroidectomy (years) | Mean (SD) | 1.1 (1.7) |  |  | - | 1.1 (1.7) |  |
| P1, All cases vs. population controls; P2, Conservative management vs. Parathyroidectomy (PTX) |