Elevated serum parathyroid hormone predicts impaired survival prognosis in a general aged population

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Abstract

Objective: Short-term studies on selected patients have indicated that elevated serum parathyroid hormone (PTH) is an independent risk factor of death. However, long-term data on unselected populations are lacking, thus far. In order to evaluate the predictive value of elevated serum PTH during the last years of life, random persons of age cohorts of 75, 80 and 85 years were followed for 17 years.

Design: A prospective cohort study.

Methods: Subjects (n = 567) were investigated for calcaemic status including serum intact PTH, serum total calcium (CaT) and ionized calcium (Ca²⁺). Thorough clinical examinations included an assessment of co-morbidity. Mortality data were collected from National Census Records.

Results: Up to 93% of the subjects died within the follow-up. In contrast to Ca²⁺ levels, high serum PTH (≥ 63 ng/L, IV quartile cut point) was associated with significant over-mortality (HR = 1.56, 95% CI: 1.29–1.88) and a 2.3-year reduction of median life expectancy. After controlling for age, gender, co-morbidity and creatinine, the prognostic impact of elevated serum PTH was still significant (HR = 1.24, 95% CI: 1.01–1.53). The tendency for over-mortality was consistent in both genders, in all age groups as well as in subjects with varying co-morbidity, renal function, body mass index categories and Ca²⁺ levels.

Conclusions: Elevated serum PTH level is an independent predictor of impaired long-term survival prognosis in unselected aged population. Serum Ca²⁺ did not emerge as a significant prognostic indicator. The long-term prognostic impact of vitamin D deficiency, the most common cause of elevated PTH levels in the elderly, remains to be investigated.

Introduction

Elevated serum parathyroid hormone (PTH) levels are common in older persons (1–3). The prevalence of primary hyperparathyroidism (PHPT) is ~ 2% in the elderly (4). However, secondary hyperparathyroidism (SHPT) is a far more common cause of elevated PTH levels and the prevalence of which has varied from 20 to 60% in different aged populations (5–8). SHPT is the most common consequence of vitamin D deficiency, which is also associated with multiple poor outcomes in the elderly, such as the increased risk of osteoporosis and fractures as well as muscle weakness and falls (3, 4). SHPT is also a common occurrence in patients with chronic renal failure, in which PTH acts as a uraemic toxin that may lead to long-term consequences including renal osteodystrophy, severe vascular and heart valve calcification, alterations in cardiovascular structure and function, immune dysfunction and renal anaemia (9). Increased mortality risk is a well-known consequence of PHPT (10–14). However, the role of SPTH levels as an independent predictor of mortality has been studied only in selected patient groups, thus far (15–17).

In order to fill this lack of knowledge, we have studied the prognostic significance of serum PTH and calcaemic status in random persons of three age cohorts of 75, 80 and 85 years over the 17-year period. The aim of this study was to determine whether and to what extent serum PTH is an independent predictor of mortality in an unselected aged population during the last years of life.

Subjects and methods

Subjects

Random census record samples of age cohorts of 75, 80 and 85 years including 649 persons were invited by mail to participate in the Helsinki Ageing Study (18). The study protocol was approved by the local ethics committee and all participants provided an informed consent before the start of the trial.
Laboratory analyses

A venous blood sample was drawn after an overnight fast. In addition to all items of calcaemic status and other routine laboratory analyses, serum PTH was measured in 567 persons (87.4% of the invited; Table 1).

An immunoradiometric method (AllegroR Intact PTH kit, Nichols Institute, San Juan Capistrano, CA, USA) was used to determine serum PTH (19). All PTH analyses were performed simultaneously. The sensitivity of the assay was 5 ng/l, the intra-assay coefficient of variation (CV) was 3.6 and 6.1% at 45 and 390 ng/l respectively and the inter-assay CV was 7.9 and 7.7% at 22 and 273 ng/l respectively. The reference range was 10–55 ng/l.

Serum total calcium (CaT) was determined by the Gindler (20) method in an automatic analyser (Hitachi model 705, Naka Woeks, Hitachi Ltd, Katsuta, Japan). The inter-assay CV was 1.4% (long-term serum control) and the intra-assay CV was 0.7 and 1.1% in a subject serum sample with 1.27 mmol/l and 3.15 mmol/l CaT. The reference range was 2.20–2.60 mmol/l.

Ionized calcium was measured with an ion-selective electrode (radiometer ICA1) at pH 7.40 (21). The inter-assay CV was 1.7 and 0.8% at 0.75 and 1.75 mmol/l (long-term aqueous controls) Ca2⁺ levels respectively. The intra-assay CV was 0.5% in a subject serum sample of 0.70 and 1.74 mmol/l Ca2⁺ levels. The reference range was 1.17–1.29 mmol/l.

Clinical assessments

After collecting all subject records, subjects were examined clinically and assessed for co-morbidity. Subjects were identified as healthy (no co-morbidity) if their subjective and objective (according to the examining physicians) health was good or moderate; they had no hypertension, diabetes, dementia or symptoms of cardiovascular, cerebrovascular or pulmonary diseases, cancer or other disabling diseases and had a normal exercise tolerance by history (18). Estimated glomerular filtration rate (eGFR) was calculated by Cockcroft–Gault equation (22). Body mass index (BMI) was determined as well.

End points

The date of death for each diseased subject was collected from National Census Records in July 2007. Five subjects were excluded from the survival analyses, because the mortality data were not obtained due to an incomplete social security number (ID).

Statistical analysis

The data were analysed using Windows SPSS, release 15.0.1 (SPSS Inc., Chicago, IL, USA). The statistical differences in characteristics of subjects between age cohorts were determined by one-way ANOVA procedure (continuous variables) and \(\chi^2\) test (dichotomous variables). Natural logarithmic transformation of PTH (lnPTH) was used in the calculation of the Pearson’s correlation coefficients and their level of significance. Mean survival times for the quartiles of serum PTH were determined by Kaplan–Meier analysis. A series of multivariate Cox regression models were created to calculate the adjusted hazard ratios, 95% confidence intervals and their level of significance for the association between serum PTH and mortality. Covariates with predictive values were entered one by one to the models.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of subjects by age.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>75 years</td>
</tr>
<tr>
<td>Number</td>
<td>205</td>
</tr>
<tr>
<td>Women (%)</td>
<td>70.7</td>
</tr>
<tr>
<td>Co-morbidity (%)</td>
<td>64.1</td>
</tr>
<tr>
<td>Normal parathyroid status (%)(a)</td>
<td>68.8</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism (%)(b)</td>
<td>16.1</td>
</tr>
<tr>
<td>Primary hyperparathyroidism (%)(c)</td>
<td>3.9</td>
</tr>
<tr>
<td>Idiopathic hypercalcaemia (%)(c)</td>
<td>10.7</td>
</tr>
<tr>
<td>Parathyroid hormone (ng/l)</td>
<td>45 (5–230)</td>
</tr>
<tr>
<td>Ionized calcium (mmol/l)</td>
<td>1.26 (1.18–1.65)</td>
</tr>
<tr>
<td>Total calcium (mmol/l)</td>
<td>2.41 (2.15–2.91)</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.01 (0.64–1.71)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>37.9 (28.6–45.3)</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>94 (60–160)</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)(d)</td>
<td>54 (28–85)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3 (15.6–41.8)</td>
</tr>
</tbody>
</table>

\(a\)Normal parathyroid hormone (10 ng/l \(\leq\) PTH \(\leq\) 55 ng/l) and no hypercalcaemia (Ca²⁺ \(\leq\) 1.29 mmol/l).
\(b\)Elevated parathyroid hormone (>55 ng/l) and no hypercalcaemia (Ca²⁺ \(\leq\) 1.29 mmol/l).
\(c\)Elevated parathyroid hormone (>55 ng/l) and hypercalcaemia (Ca²⁺ > 1.29 mmol/l).
\(d\)Normal parathyroid hormone (10 ng/l \(\leq\) PTH \(\leq\) 55 ng/l) and hypercalcaemia (Ca²⁺ > 1.29 mmol/l).
\(e\)Glomerular filtration rate estimated by Cockcroft–Gault equation.
Results

Baseline characteristics

Serum PTH levels varied widely from 3 to 1394 ng/l, the cut points for the quartiles of PTH being 33, 45 and 63 ng/l respectively. Elevated PTH (> 55 ng/l, laboratory reference value) was found in 32.6% of the persons. Serum PTH increased with advancing age (Table 1), but CaT and Ca$^{2+}$ levels were similar among the age cohorts. Up to 80.7% of the patients had eGFR levels below 60 ml/min, the median eGFR level being 46 ml/min. The lnPTH correlated with measures of renal function (eGFR: $r = -0.205$, $P < 0.001$; creatinine: $r = 0.248$, $P < 0.001$; inverse of creatinine: $r = 0.160$, $P < 0.001$) and calcaemic status (CaT: $r = 0.141$, $P < 0.001$; Ca$^{2+}$: $r = 0.381$, $P < 0.001$).

Predictive value of calcium and PTH

Up to 93.1% of the subjects died within the 17-year follow-up, the mortality rate being 86.1, 97.8 and 98.9% in the age cohorts of 75, 80 and 85 years ($P < 0.001$) respectively. Elevated serum calcium levels (CaT or Ca$^{2+}$) did not emerge as significant predictors of mortality (data not shown). However, elevated serum PTH levels were significantly associated with impaired survival prognosis (Figure 1). PTH levels above 63 ng/l (IV quartile) predicted a 1.51-fold (95% CI: 1.25–1.86) over-mortality compared with the subjects with PTH levels below 63 ng/l. The excess mortality of subjects with elevated PTH increased over time for approximately 7 years, the median survival time being 2.3 years shorter compared with persons with lower PTH levels.

The predictive value of elevated PTH remained significant after adjusting for age and gender (HR = 1.27, 95% CI: 1.04–1.56). Apart from age and gender, the presence of co-morbidity (HR = 1.56, 95% CI: 1.29–1.88) and renal function (eGFR: HR = 0.99, 95% CI: 0.98–1.00; creatinine: HR = 1.01, 95% CI: 1.00–1.01; inverse of creatinine: HR = 0.58 95% CI: 0.52–1.44) emerged as significant independent predictors of death. After controlling for co-morbidity, the prognostic impact of elevated PTH still remained significant (HR = 1.26, 95% CI: 1.03–1.55). Neither additional controlling for creatinine (HR = 1.24, 95% CI: 1.01–1.53) nor for inverse of creatinine (HR = 1.26, 95% CI: 1.02–1.55) abolished this significance.

Consistency of the observation

The subgroup analyses revealed that over-mortality appeared to be quite consistent in both genders, in all age groups and in persons with and without major co-morbidity or alterations in renal function (Figure 2). Elevated PTH also emerged as a consistent predictor of impaired survival when the persons were stratified by median Ca$^{2+}$(1.25 mmol/l) and BMI (25.3 kg/m$^2$).

Discussion

This longitudinal study shows that elevated serum PTH (≥63 ng/l) is associated with impaired long-term survival prognosis resulting in a 2.3-year reduction of life expectancy in the oldest age. This observation was independent of general health and was not explained by...
Ca\(^{2+}\) levels, BMI or alterations in renal function. The results accord well with the few earlier studies on selected patients groups (15-16). Sambrook et al. followed frail elderly (n=842, mean age 85.3 years) living in residential care facilities in Sydney for 31 months and found that elevated serum PTH associated with increased mortality independently of vitamin D status, bone mass and renal function (16). In a relatively small mixed emergency department population (n=140) high PTH was shown to be common and also related to the severity of diseases and increased mortality (15). To the best of our knowledge, however, the present study is the first one to address the long-term prognostic impact of serum PTH in unselected aged population during the last years of life.

Many of the earlier population-based studies on hyperparathyroidism have focused on PHPT and have shown an increased mortality, particularly in patients with hypercalcaemia, (10, 11, 14). In the present study, the prevalence of PHPT (concurrent hyperparathyroidism and hypercalcaemia) was slightly higher than in earlier population-based reports (23) and varied from 3.4 to 4.4% among the three age cohorts. Interestingly, baseline calcaemic status (CaT or Ca\(^{2+}\)) had no prognostic value in the present study, probably due to the low number of subjects with PHPT. The tight regulation of Ca\(^{2+}\) by PTH and vitamin D may also explain the lacking prognostic significance of Ca\(^{2+}\) levels in this population.

The results of the present study raise a question, as to what extent the differences in the survival prognosis are based on harmful effects of elevated serum PTH or possible beneficial effects of low serum PTH. Interestingly, the absence of SHPT in the presence of vitamin D deficiency has been found to associate with lower mortality in a 2-year follow-up study of frail elderly (n=1280, age=86±7.5) living in residential care facilities (17). However, the data supporting the beneficial effects of low PTH are scarce, to date. It should also be noted that the number of persons with truly low PTH (<10 ng/l) was very low (n=4) in our study.

In contrast to low PTH, elevation of PTH levels has been connected to several adverse effects. SHPT due to vitamin D deficiency or chronic renal failure may affect cardiac muscle contractility, promote atherosclerosis and vascular calcification, have permissive role for cardiac fibrosis and be associated with elevated blood pressure resulting in increased prevalence of cardiovascular disease and subsequent mortality (24, 25). However, the present study, in which PTH and calcaemic status was determined only once at entry, does not allow any conclusions to be drawn about the mechanisms leading to the excess mortality of persons with elevated PTH.

The lack of data on vitamin D is the major weakness of our study, because in light of the increasing evidence on pleiotropic effects of vitamin D (26) and according to a recent meta-analysis, vitamin D supplementation may postpone death (27). Thus, vitamin D deficiency, the most common cause of SHPT in the elderly, could possibly offer an explanation for over-mortality of subjects with elevated PTH. Interestingly, according to our previous systemic review of 52 clinical trials (n=6290) on vitamin D supplementation, a rather linear relationship exists between serum PTH and 25-hydroxyvitamin D (25-OHD) levels: 25-OHD (nmol/l) = −1.032PTH (ng/l) + 107.192 (28). The respective calculated 25-OHD values for each cut point of PTH quartiles would be 73, 61 and 42 nmol/l, the calculated 25-OHD values of the highest PTH quartile clearly indicating insufficient vitamin D status (2, 3). Sample size is also a relative weakness of this population study, because the power calculations were originally made at the beginning of the study in order to evaluate the prognostic significance of common clinical findings in the elderly over a 5-year period. The major interest was laid on echocardiography observations. Power calculations were not made for the prognostic significance of PTH. The clear positive result attests to the sufficient power of the present study.

This study has numerous strengths e.g. the exceptionally long follow-up at the end of life – the vast majority of the subjects were followed until death – the complete data of end points from the daily updated National Census Records, the exact determination of calcaemic status by Ca\(^{2+}\), the strict age limits of the three cohorts and the large number of baseline data including the thorough clinical examinations at entry, enabling the successful registration of co-morbidity as also shown by its independent prognostic significance.

It can also be discussed whether and to what extent the observed predictive value of the elevated PTH is resulted by the high prevalence of renal failure in the study population. In fact, even mild impairment in renal function (GFR <60 ml/min) has been shown to be associated with significant mortality in several selected patient groups (29) as well as in elderly men (30). However, despite the strong negative correlation found between PTH and eGFR levels in the present study, the tendency for over-mortality was consistent even if patients were stratified by median eGFR level. Furthermore, the results were also controlled for creatinine levels in addition to age, sex and co-morbidity. Thus, it is not likely that the observed predictive value of the elevated PTH levels would be explained by alterations in renal function.

In conclusion, elevated serum PTH (≥63 ng/l) levels are associated with impaired long-term survival prognosis resulting in a 2.3-year reduction of median life expectancy at old age. This observation was independent of general health and was not explained by Ca\(^{2+}\) levels, BMI or alterations in renal function. The long-term prognostic impact of vitamin D deficiency, the most common cause of elevated PTH levels in the elderly, remains to be investigated.
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