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High parathyroid hormone levels are associated with osteosarcopenia in older individuals with a history of falling

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ABSTRACT

Objectives: The combination of osteopenia/osteoporosis and sarcopenia (osteosarcopenia) defines a diagnostic subset of individuals at higher risk of falls, fractures and institutionalization. In this study we aimed to assess the potential role of high serum levels of parathyroid hormone (PTH) in osteosarcopenia. We hypothesized that a high PTH level is one of the major determinants of this syndrome.

Study design: Cross-sectional study in 400 subjects (mean age = 79, 65% women) assessed between 2009 and 2014 at the Falls and Fractures Clinic, Nepean Hospital (Penrith, Australia).

Main outcome measures: Medical history, physical examination, bone densitometry, body composition, posturography, grip strength, gait parameters, and blood tests for nutrition and secondary causes of sarcopenia and osteoporosis. Patients were assigned to one of four groups: 1) osteopenic/osteoporotic; 2) sarcopenic; 3) osteosarcopenic; or 4) non-sarcopenic/non-osteopenic. Patients with abnormal corrected calcium levels were excluded from analysis. Between-group differences were assessed using one-way analysis of variance and chi-squared tests. Multivariable linear regression was used to evaluate the association between the groups and PTH levels adjusted for age, vitamin D, renal function and albumin.

Results: 24% of the subjects had a high serum PTH level with normal corrected calcium level. These subjects were older, reported more falls per year, and had lower grip strength, limits of stability, BMD, and gait velocity. Subjects with high PTH levels were more likely to be in the osteosarcopenia group than in the non-sarcopenic/non-osteopenic group (OR 6.88; CI: 1.9–9.2).

Conclusions: We reported an independent association between high PTH levels and osteosarcopenia. Our results suggest an important role of PTH in osteosarcopenia that deserves further exploration.

1. Introduction

The simultaneous occurrence of osteopenia/osteoporosis and sarcopenia (osteosarcopenia) in older persons defines a subset of individuals at higher risk of poorer outcomes including falls, fractures, hospitalization, frailty and death [1–4]. The pathophysiology of osteosarcopenia is a subject of major interest [5,6]. Higher levels of fat in bone and muscle are observed in this syndrome [5,7]. Several factors (i.e. myokines, adipokines and osteokines) have been proposed as regulators of the interaction between muscle and bone [8], thus as biological mechanisms in the development of osteosarcopenia.

There is also evidence that several hormones are involved in this interaction [6,8–10], among them, calciotropic hormones (vitamin D and parathyroid hormone [PTH]) may play a role in the pathogenesis of osteosarcopenia. Vitamin D plays a major role in the mineralization of the skeleton at all ages. It also plays a role in the interaction between muscle and bone [11]. There is a significant decline in vitamin D in old age that affects not only calcium and bone metabolism but also muscle mass and function [11–13]. In addition, low levels of vitamin D are a common finding in osteosarcopenic patients [14].

Previous studies have reported an association between hyperparathyroidism (HPTH) and sarcopenia, mostly in association with low

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levels of vitamin D [14,15], but a role of PTH itself in the pathogenesis of sarcopenia and osteosarcopenia remains unknown. We have previously reported that vitamin D deficiency and HPTH were the most frequent metabolic disorders identified in a population of older fallers [17]. Whether these high levels of serum PTH are associated with either sarcopenia or osteosarcopenia remain to be determined.

In this study, we evaluated the role of PTH in a population of older individuals with a history of falls. We hypothesized that high levels of PTH are associated not only with higher prevalence of falls and fractures but also with osteosarcopenia independently of renal function and serum levels of vitamin D and calcium.

2. Methods

2.1. Subjects

This cross sectional observational retrospective study, as part of the Nepean Osteoporosis and Frailty (NOF) study, assessed 400 patients referred to the Falls and Fractures clinic at Nepean Hospital, Sydney, Australia from 2009 −2014. The referrals to this clinic were mainly received from general practitioners, from hospital wards and specialist clinics. The inclusion criteria were: able to mobilize with or without a gait aid and at least one of the following: patients with multiple falls (> 2 in the last year); single faller with established gait and/or balance problem (e.g. by Get Up and Go Test); unexplained fall with apparent complex medical cause(s); history of symptomatic or asymptomatic fragility fracture(s) (last 5 years) and; clinical or radiological (BMD) risk of fractures. The exclusion criteria were, previous history of renal stones, abnormalities in serum calcium and a Mini-Mental State Examination (MMSE) < 17/30. Only those subjects with complete set of assessments relevant for this study were included.

This study was approved by the Nepean Blue Mountains Local Health District Human Research Ethics Committee. Need for previous consent was waived due to the low-risk nature of this study.

2.2. Definition of falls

Falls were defined as “unexpected event in which the participants come to rest on the ground, floor, or lower level” as per prevention of Falls Network Europe (ProFaNE) collaborative project recommendations. [18]. A detailed falls assessment was conducted which included history of falls and the number of falls during the six-month period prior to the clinic visit.

2.3. Clinical assessment

A nutritional assessment was performed using Body Mass index (BMI) and Mini-Nutritional Assessment tool (MNA). The Geriatric Depression Scale (GDS) was used to assess depression. The detailed medical assessment included comorbidities, family history, fracture history, osteoporosis risk assessment (smoking, alcohol hormone replacement therapy, age at menopause), and falls risk (altered elimination, impaired mobility, hearing & visual deficit), and assessment for orthostatic hypotension.

2.4. Bone mineral density and body composition by dual-energy X-ray absorptiometry (DXA)

Bone mineral density (BMD) and body composition (fat and lean mass) were assessed using a Hologic DPX-IQ Discovery DXA machine (GE Healthcare, Pollards Wood, UK). Osteopenia/osteoporosis (OP) was defined using the WHO standard criteria of T-score less than −1.0 SD.

2.5. Grip strength

The Gronigen Elderly Test using a Smedley Hand Dynamometer was used to measure the grip strength [19]. The best effort on grip strength from three attempts from both hands (with 30 s rest between the attempts) was recorded as the grip strength.

2.6. Gait assessment

We recorded the spatiotemporal gait data using an instrumented walkway, GAIT Rite® (CIR Systems Inc, Havertown, PA) (810 cm × 89 cm × 0.625 cm, sample rate = 80 Hz)

2.7. Sarcopenia

Sarcopenia was determined by fulfillment of at least two of the following accepted criteria [20]: gait velocity < 0.8 m/s, grip strength < 20 kg for females and < 30 kg for males and height adjusted appendicular lean mass (ALM/ht2) < 5.5 kg/m2 (female) and < 7.26 kg/m2 (male). Patients were then assigned to four pre-specified subgroups: 1) Osteopenia/Osteoporosis (BMD < −1.0 SD); 2) Sarcopenia 3) Osteosarcopenia and; 4) non-osteoporotic/non-sarcopenic.

2.8. Serum measurements

Venous blood samples were collected from resting subjects at baseline prior to their first visit to the clinic. The blood collections and measurements were performed at the pathology networks affiliated with the Nepean Hospital, Penrith, Australia.

Serum vitamin D concentration was measured by chemiluminescence using the Elecsys 25(OH)D3 assay (Roche; normal range: 10–132nmol/l). The intra- and interassay precisions were respectively 7.5% and 10.6% respectively. Intact PTH was measured by immunochemoluminometric assay (Immulite 2000; normal range: 3.9–77.2 pmol/L). The intra- and inter-assay precisions were 7% and 5% respectively. Serum calcium, albumin and creatinine were determined using automated standard laboratory methods. As there is a high prevalence of hypoalbuminemia in older adults, the serum concentration of albumin and calcium were used to correct the calcium value (calcium corrected value = Ca + 0.8 [40-albumin]). The corrected calcium value (normal range = 2.15-2.55 mmol/L) was used in the subsequent analysis. Creatinine clearance was calculated from the Cockcroft formula ([(140-age in years) x weight (Kg)/72 x creatinine mmol/l]).

2.9. Statistical analysis

We used Chi-squared X^2 tests for comparison of categorical variables and two-tailed independent *t*-tests for comparison of continuous variables. Factors showing univariate association with the outcome at issue were extracted as candidate variables to be used in the multivariate regression analysis and were adjusted for age, serum vitamin D and albumin/creatinine ratio. In all the data analyses $p \leq 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS version 21.0 statistical package (SPSS Inc., Chicago, Ill., USA).

3. Results

The baseline characteristics of the study group are given in Table 1.

Of the 400 subjects (mean age 79, 65% female) 160 were osteosarcopenic (40%), 51 osteoporotic (12.75%), 114 sarcopenic (28.5%) and 75 non-osteoporotic/non-sarcopenic (18.75%). The subjects of osteosarcopenia group were mostly females (82.5%) and older (81 ± 7, $p < 0.01$). Osteosarcopenic subjects had lower grip strength (15.6 ± 4.9 kg, $p < 0.001$), limits of stability (113 ± 57, $p < 0.001$), BMD (-2.49 ± 0.6, $p < 0.001$), and gait velocity (65 ± 14.2 cm/sec, $p < 0.01$). In addition, the osteosarcopenic group had a significantly higher proportion of self-reported fractures in the