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Vitamin D and parathyroid hormone are associated with gait instability and poor balance performance in mid-age to older aged women

Marie-Louise Bird[a,b], Natalie El Haber[c], Frances Batchelor[d], Keith Hill[e], John D. Wark[f,*]

[a] The University of Tasmania, Tasmania, Australia
[b] The University of British Columbia, Canada
[c] The University of Melbourne, Victoria, Australia
[d] National Aging Research Institute, Victoria, Australia
[e] School of Physiotherapy and Exercise Science, Curtin University, Western Australia, Australia
[f] Department of Medicine, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

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ABSTRACT

Context: Vitamin D status and parathyroid hormone (PTH) levels influence the risk of accidental falls in older people, but the mechanisms underlying this effect remain unclear.
Objective: Investigate the relationship between circulating PTH and 25 hydroxyvitamin D (25-OHD) levels and clinical tests of gait stability and balance as physical fall risk factors. We hypothesized that high levels of PTH and low 25-OHD levels would be significantly associated with gait stability and decreased balance performance.
Design: Observational cohort study.
Setting: Australian community.
Participants: 119 healthy, ambulatory female twin adults aged 47–80 years residing in Victoria, Australia.
Outcome measures: Serum PTH and 25-OHD levels with clinical tests of gait stability [double support duration (DSD)] and dynamic balance (Step Test). Associations were investigated by regression analysis and by comparing groups divided by tertiles of PTH (< 3.5, 3.5–4.9, > 4.9 pmol/L) and 25-OHD (< 53, 53–75, > 75 nmol/L) using analysis of variance.
Results: Serum PTH was associated positively with DSD, with an increase of 10.6–15.7% when the mid and highest PTH tertiles were compared to the lowest tertile ($p < 0.025$) when 25-OHD was included in the regression analysis. 25-OHD was significantly associated with DSD (greater by 10.6–11.1% when lowest and mid-tertiles compared with the highest 25-OHD tertile) ($p < 0.025$) and dynamic balance (better performance by 12.6% in the highest compared with the lowest 25OHD tertile) ($p < 0.025$).
Conclusion: These findings reveal an important new relationship between parathyroid hormone and gait stability parameters and add to understanding of the role of 25-OHD in motor control of gait and dynamic balance in community-dwelling women across a wide age span.

1. Introduction

Specific hormones play an important role in musculoskeletal health and in fall and fracture prevention in older adults. Poor vitamin D status (as determined by low serum 25 hydroxyvitamin D (25-OHD) concentration) and high levels of parathyroid hormone (PTH) have been implicated in sarcopenia and loss of muscle strength [1], and may also influence other fall risk factors such as motor control of gait and dynamic balance control. The inter-relationship between PTH, 25-OHD levels and gait parameters is currently unclear [2]. Although supplementation with vitamin D has been shown to improve leg muscle strength [3], postural sway and functional tasks (for example, the Timed Up and Go test), the impact of supplementation on specific balance tasks is less clear [2]. Either in association with low levels of vitamin D or independently, the role of PTH in these fall risks factors remains less clear [4].

Vitamin D levels and accidental falling have been the subject of considerable investigation, largely in frail older people, producing non-linear and conflicting results with differences depending on the functional status of the populations investigated. Current theory supports a relationship which is U-shaped, with both very high and very low levels related to increased rates of falls [5]. Mechanisms for the increased fall rates at both ends of the curve may be different; for higher functioning people, high levels of physical activity and 'risk' associated with some activities may account for this higher fall rate at higher levels of 25-OHD. At the older

* Corresponding author.
E-mail addresses: jdwark@unimelb.edu.au, marie-louise.bird@ubc.ca (J.D. Wark).

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and frailer end of the spectrum, the lower levels of 25-OHD associated with falling [5] may relate to reduced strength and muscle mass [1]. However, the roles of 25-OHD and PTH in neural control are less clear.

There is considerable debate as to the level of 25-OHD that maximally suppresses PTH; it is estimated to vary between 25 and 122 nmol/L [6,7]. More importantly, there is evidence that, in an older cohort, increases in PTH may independently play a role in physiological functioning of muscle and neural tissue, but this area has not been well investigated across the life-course. PTH has been shown to relate to handgrip strength and not balance [8], and more recently the same authors found no relationship between PTH and mobility limitations [9]. While the PTH response to low levels of 25-OHD appears to be a good marker of functional outcomes [10], and a predictor of morbidity and mortality [11], there is increasing evidence that PTH may act independently of vitamin D in adverse health outcomes [12] [13]. For example, PTH predicts mortality independently of vitamin D levels in community-dwelling older adults [14] and in frail older adults [15]. Recently, PTH and not 25-OHD have been found to be associated with gait stability parameters in an older cohort (mean age 81 years) [16].

In relation to falls, serum PTH levels predict time to first fall in a frail population [17]. Higher PTH and lower 25-OHD were reported in long-term care or assisted-living facility residents who had fallen [18]. While PTH was significantly higher in the group who had fallen (mean PTH (SD): fallers = 3.55 ng/L (2.44) vs. non-fallers = 3.32 ng/L (2.05); $p = 0.041$), no association between 25-OHD and fall rates was found once data were adjusted for high PTH levels. This reinforces the importance of PTH, and suggests that low levels of 25-OHD may increase falls risk only when combined with elevated levels of PTH in a frail older population [4].

The relationship between PTH, vitamin D and falls in healthier mid-age to older people remains less investigated than in frail groups, and it is important to also examine relationships between PTH levels specifically among vitamin D replete adults to determine whether independent action of this hormone on fall risk is present. Thus, the purpose of this study was to investigate the relationship between PTH and 25-OHD levels and clinical tests of gait stability and dynamic balance with respect to their role as physical fall risk factors in adults over 45 years old. It was hypothesized that high levels of PTH and low levels of serum 25-OHD would be significantly associated with poorer gait and dynamic balance performance.

2. Participants and methods

2.1. Study participants

Participants who were female twins over the age of 45 years who had previously participated in heritability studies recruited from the Australian Twin Registry (ATR) and Twin Research Program at the Royal Melbourne Hospital (Melbourne, Victoria, Australia) were invited to take part in this study. Those with major musculoskeletal or any neurological disorders or without a good understanding of the English language were excluded. Screening was undertaken to ensure that no neurological balance deficits were present [19], and that people with chronic kidney failure (elevated serum creatinine levels (greater than 100 μmol/l) were excluded. The study was approved by both the Melbourne Health Human Research Ethics Committee and by the ATR. All participants gave informed written consent for participation.

2.2. Procedures

Demographic data were collected by questionnaire, as was history of falls[1] in the previous 12 months [20], exposure to risk factors associated with falling and current activity levels. A brief medical history was taken including information regarding medication use and relevant medical conditions such as arthritis. Physical activity levels were recorded using the Human Activity Profile Questionnaire, reported as both maximal and adjusted activity levels [21].

Clinical tests and venepuncture were performed during a single session of 1.5 h' duration at the National Ageing Research Institute, Melbourne, Victoria, Australia.

2.3. PTH, 25 OHD and calcium measurements

Intact PTH was measured by a two-site chemiluminescence enzyme-labelled immunoassay (IMMULITE 2000) method (Diagnostic Products Corporation CA, USA) in which intact PTH molecules are detected. A normal reference range of 1.3–6.8 pmol/L was used (LeBoff et al. [22] and Sakuma and colleagues [23] also used a value of 6.8 pmol/L as the upper limit of the normal range for intact PTH). The sensitivity of this assay was 0.3 pmol/L, with an intra-assay precision of 5.7% and an inter-assay precision of 6.3%.

Serum 25-OHD was measured using a specific radioimmunoassay (RIA) (DiaSorin, Inc, Stillwater, MN, USA). The assay has a sensitivity of 4 nmol/L with intra-assay precision of 7.6% and an inter-assay precision of 9.0%. The reference range of the assay was 25–108 nmol/L, with deficiency defined as < 25 nmol/L, sub-optimal as 26–54 nmol/L and replete as > 55 nmol/L. A serum 25-OHD level of at least 50 nmol/L is needed to supress PTH levels [24], and therefore a 25-OHD level of 25–50 nmol/L was defined as vitamin D insufficient [25]. Serum calcium was determined using standard methods, was measured by the Arsenazo III method. The reference range for calcium is 2.10–2.60 mmol/L.

2.4. Gait assessment

Gait was assessed using the Clinical Stride Analyser (CSA),[2] a validated and widely-used computerised footswitch system that measures the temporal and spatial characteristics of gait [26]. These characteristics include velocity (m/s) and double support duration (DSD)[3] (% of the gait cycle). Slow gait velocity and increased DSD both reflect poorer performance. Gait was measured over an 8 m walkway with recording occurring across the central 6 m to allow for acceleration and deceleration. Participants were instructed to walk at a comfortable pace.

2.5. Balance assessment

The Step Test was used as a measure of dynamic single limb stance [27], which involved stepping one bare foot as quickly as possible on and off a 7.5 cm-high wooden block in 15 s (one completed step was recorded for stepping on and then off the block). Both legs were tested stepping separately, and the number of completed steps in each trial was recorded and averaged.

2.6. Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS).[4] The Kolmogorov-Smirnov test was used to verify that all variables (including blood parameters) were normally distributed ($p > 0.05$). All p values were two-sided and statistical significance was defined as $p < 0.05$ (unless otherwise stated). Descriptive data were reported for variables of interest. Correlations (Pearson's r) of both PTH and 25-OHD with gait DSD and Step Test were

[1] "event which results in a person coming to rest inadvertently on the ground or other lower level and other than as a consequence of the following: sustaining a violent blow, loss of consciousness, sudden onset of paralysis (as in stroke), or an epileptic seizure".

[2] B & L Engineering, 12309 East Florence Avenue, Santa Fe Springs, CA 90670, USA.

[3] Double support duration is defined as the period of the gait cycle when both feet are in contact with the ground.

[4] SPSS version 22, SPSS for Windows (Chicago, IL; SPSS).