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Serum Parathyroid Hormone Levels Predict Falls in Older Diabetic Adults

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Abstract

Objectives—To examine the association between serum parathyroid hormone (PTH) levels and incident falls in older diabetic adults.

Design—Longitudinal analysis of incident falls over 1 year in a sub-study of diabetic participants in the Health, Aging and Body Composition study.

Setting—Pittsburgh, PA, and Memphis, TN.

Participants—Well-functioning, community-dwelling black and white adults aged 70-79 with diabetes (n = 472).

Measurements—Measured baseline serum PTH. Self-report of falls over the subsequent 12 months. Baseline physical performance and self-reported demographic, behavioral, and health status measures including kidney function, chronic conditions and medication use.

Results—30.3% of participants reported falling over one year of follow-up. The mean \pm SD baseline serum PTH was 53.5 ± 30.0 pg/mL in non-fallers and 62.6 ± 46.2 pg/mL in fallers (p = 0.01). For every 1 SD (36 pg/mL) increment in baseline serum PTH, there was approximately a 30% increased likelihood of reporting a fall in the subsequent year after adjusting for age, gender, race, field center, alcohol consumption, BMI, physical activity, and winter/spring season (adjusted

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Author Contributions:

DK Houston conceptualized the idea, analyzed the data, and wrote the first draft of the manuscript. AV Schwartz, JA Cauley, FA Tylavsky, EM Simonsick, TB Harris, N de Rekeneire, and GG Schwartz critically reviewed drafts of the manuscript. SB Kritchevsky contributed to the conceptualization of the idea, interpretation of the data and critical revisions of the manuscript. All authors approved the last version of the manuscript.

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odds ratio (OR) = 1.30, 95% confidence interval (CI) = 1.06-1.59). Further adjustment for kidney function, chronic conditions, medication and supplement use, and physical performance attenuated the association slightly (OR (95% CI): 1.26 (1.01-1.58)). A trend remained after additional adjustment for reported falls in the previous year.

Conclusion—Higher serum PTH was associated with incident falls among older, well-functioning diabetic men and women. Further investigation aimed at understanding the underlying mechanism for the association between serum PTH and falls is needed.

Keywords

PTH; falls; physical performance

INTRODUCTION

Falls affect over one-third of community-dwelling adults aged 65 years and older annually, with approximately one in ten falls resulting in serious injury (1). Fall-related injuries in the elderly are a common cause of pain, functional limitations, disability, placement in long-term care, and death (2;3). As the population ages, the number of fall-related injuries is expected to increase (4). Although most falls do not result in significant physical injury, the psychological effects of a fall often result in fear of falling and restriction of activities leading to a loss of independence (5). Older adults with diabetes are at increased risk of falls (6-8), possibly because of diabetes-related complications including peripheral neuropathy, reduced vision and renal function and their intermediate effects on balance, muscle strength, and gait (9).

Recent evidence suggests that serum parathyroid hormone (PTH) levels, independent of vitamin D levels, may be important for maintaining muscle integrity and physical function and, consequently, preventing falls (10-13). The age-related increase in serum PTH levels is well-recognized and has many causes, including low vitamin D levels, impaired kidney function, low calcium intake or impaired calcium absorption due to malabsorption, and parathyroid gland resistance to suppression of PTH secretion by serum 1,25(OH)₂D₃, the active form of vitamin D (14). PTH may have a direct effect on skeletal muscle. For example, primary hyperparathyroidism is characterized by muscle weakness which improves with parathyroidectomy (15). In animal models, infusion of PTH at high levels increased protein catabolism and decreased the number of type 2 muscle fibers, intracellular energy-rich phosphate compounds, and mitochondrial oxygen uptake (16;17). Several epidemiologic studies have examined the association between serum PTH and muscle strength, physical performance, and falls (10-13;18-21). Among older patients attending a falls clinic, serum PTH was a significant predictor of muscle strength independent of vitamin D levels (11). Furthermore, among older men and women living in assisted living or nursing home facilities, higher serum PTH significantly predicted falls independent of vitamin D levels (10;12). However, among older community-dwelling, vitamin-D replete women, serum PTH was not associated with neuromuscular function or falls over four years of follow-up (21).

The primary objective of this study was to examine the association between serum PTH levels and subsequent falls over one year of follow-up in a retrospective analysis of a sub-study of well-functioning, community-dwelling diabetic men and women aged 70-79 from the Health, Aging and Body Composition (Health ABC) study. The secondary objective was to determine if the association between serum PTH and subsequent falls was mediated, in part, by baseline physical performance.

METHODS

Study Population

Data for this analysis are from the Health ABC study, a prospective cohort study investigating the associations between body composition, weight-related health conditions, and incident functional limitations in older adults. The Health ABC study enrolled 3,075 community-dwelling black and white men and women aged 70-79 years between April 1997 and June 1998. Participants were recruited from a random sample of white and all of black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. Participants were eligible if they reported no difficulty walking one-fourth of a mile, climbing up 10 steps, or performing basic activities of daily living, and were free of life-threatening illness, planned to remain in the geographic area for at least three years, and were not enrolled in life-style intervention trials. All participants provided written informed consent and all protocols were approved by the institutional review boards at both study sites. As part of a sub-study of bone health in diabetic older adults, PTH was assessed in those participants with diabetes at study baseline (n = 519). Diabetes was ascertained based on reported use of a hypoglycemic medication or an elevated fasting glucose. At the one year follow-up, 31 participants were missing information on falls; of these, 8 were deceased and 12 were lost to follow-up. An additional 16 participants were missing information on pertinent covariates. The final sample for this retrospective analysis was 472 (91%) participants.

Assessment of Falls

At study baseline and the one-year follow-up visit, participants were asked: "In the past 12 months, have you fallen and landed on the floor or ground?" Those answering yes were asked how many times they fell and the number of falls categorized as: one, two or three, four or five, or six or more.

Physical Performance

A short physical performance battery (SPPB) modified from the lower-extremity performance tests used in the Established Populations for the Epidemiologic Studies of the Elderly (EPESE) (22) was used to summarize lower extremity physical performance. The Health ABC SPPB consisted of 5 repeated chair stands, standing balance (semi- and full-tandem stands and a single leg stand for 30 seconds), a 6 meter walk to assess usual gait speed, and a narrow 6 meter walk test of balance (walking at usual pace within lines of tape spaced 20 cm apart). The scoring system for the Health ABC SPPB was developed to minimize ceiling effects and has previously been described (23). The Health ABC SPPB scores are continuous and range from 0 to 4, with higher scores indicating better performance.

Serum PTH

Fasting blood samples were collected in the morning after a 12-hour fast, centrifuged, and stored at -80° C. Serum intact PTH was measured at baseline using a two site immunoassay (ELECSYS, Roche Diagnostics) by Synarc, Inc. (Lyon, France). The intra-assay and inter-assay coefficients of variation for PTH were <5% and <7%, respectively.

Potential Confounders

Demographic characteristics (age, gender, race, education, and field center), smoking status, alcohol use, and physical activity were ascertained by an interviewer-administered questionnaire at study baseline. The time and intensity of physical activity performed in the past 7 days, including walking for exercise, other walking, climbing stairs, aerobic dance,

weight training, and other high and medium intensity activities, was summed (kcal/week). Body mass index (BMI; kg/m²) was calculated from measured weight and height. The season in which the blood sample was obtained (winter/spring vs. summer/fall) was included to account for seasonal effects on PTH levels. Participants were asked to rate their eyesight (with glasses or contact lenses if they wore them). Participants who reported their eyesight as poor, very poor, or completely blind were classified as having poor eyesight. The Modified Mini-Mental State Examination (3MS), with a minimum score of zero and maximum score of 100 (best), was used as an indicator of general cognitive status (24). Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) (25). The prevalence of chronic conditions was determined using algorithms based on self-report and medication use at baseline and participants with definitive health conditions were coded as 'yes'. Knee pain, as an indicator of knee osteoarthritis, was assessed by self-report. Participants who reported unintentionally leaking urine once per week or more in the past 12 months were classified as having urinary incontinence. Specific medications including antihypertensive agents, hypotensive agents, insulin, oral hypoglycemic agents, benzodiazepines, and selective serotonin reuptake inhibitors and dietary supplements including calcium and vitamin D were identified. Hemoglobin A_{1c} (HbA_{1c}) was measured as an indicator of glucose control (Bio-Rad, Hercules, CA). Because impaired kidney function can lead to hyperphosphatemia and reduced calcium reabsorption, both of which increase PTH levels (26), we included a measure of kidney function. Cystatin C is a relatively new marker of kidney function that is correlated with serum creatinine but whose levels are unconfounded by age, gender, or lean body mass (27;28). Cystatin C was measured by a BNII nephelometer (Dade Behring Inc, Deerfield, Ill) using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring Inc) (29).

Statistical Analyses

Cross-sectional analyses of baseline data by tertiles of serum PTH were conducted using SAS statistical software (v. 9.1; SAS Institute, Cary, NC). Differences in the frequencies and means of covariates by tertiles of PTH were examined using chi-square and analysis of variance (ANOVA). Spearman partial correlations were used to examine the association between baseline serum PTH and physical performance adjusted for age and gender. Participants were categorized into those who did and did not report falling one or more times during one year of follow-up. Two-way interactions between race and serum PTH and gender and serum PTH were tested but were not significant ($p > 0.20$). Thus, all analyses are presented in the total population. Multiple logistic regression was used to examine the association between baseline serum PTH and falls over the subsequent year. Models were adjusted for potential confounding variables including baseline demographic characteristics (age, gender, race, education, field center), health behaviors (BMI, physical activity, smoking, alcohol consumption), season of year, vision, cognition, depression, prevalent chronic conditions, falls in the previous year, selected medications and dietary supplements, HbA_{1c}, and cystatin C if they were associated with serum PTH at $p < 0.20$ in univariate analyses. Additional analyses adjusted for measures of physical function to determine if the association between baseline serum PTH and falls was mediated by baseline physical performance.

RESULTS

The mean age of the study population was 73.6 years. Participants in the sub-study who were excluded ($n = 47$) were more likely to be black (78.3% vs. 21.7%, $p = 0.002$) and tended to have a higher serum PTH (66.1 vs. 56.2 pg/mL, $p = 0.08$). Of those included in the analyses, 143 participants (30.3%) reported falling in the subsequent year, with 82 (57.3%)

reporting falling once, 47 (32.9%) reporting falling two or three times, and 14 (9.8%) reporting falling 4 or more times. The prevalence of reporting a fall in the subsequent year was similar across gender (28.1% in women and 31.9% in men) and race (33.2% in whites and 27.9% in blacks). As expected, blacks had higher mean serum PTH than whites (63.4 pg/mL vs. 47.6 pg/mL, $p < 0.001$). The mean \pm SD baseline serum PTH was 53.5 ± 30.0 pg/mL in non-fallers and 62.6 ± 46.2 pg/mL in fallers ($p = 0.01$). The prevalence of elevated PTH levels (the upper quintile for PTH, >69 pg/mL) was 25.9% in fallers and 17.3% in non-fallers ($p = 0.03$). Table 1 shows the baseline participant characteristics by tertiles of serum PTH. Participants in the upper tertile of serum PTH were more likely to be black, sedentary, have a higher BMI, have prevalent cardiovascular disease, take insulin, and have lower physical performance scores, but less likely to be a current drinker or take vitamin D supplements. There was evidence of a seasonal effect on serum PTH; participants in the upper tertile of serum PTH were more likely to have had their PTH measured in the winter or spring months. Cystatin C, a marker of kidney function, was also higher among those in the upper tertile of serum PTH.

Table 2 shows the Spearman partial correlations of serum PTH with physical performance after adjusting for age and gender. Participants with higher serum PTH levels had lower Health ABC SPPB summary scores ($r = -0.10$; $p = 0.03$). Of the three components of the SPPB, 6 meter gait speed was negatively correlated with serum PTH ($p = 0.006$).

The association between serum PTH and reporting one or more falls in the subsequent year is shown in Table 3. For each standard deviation increment in serum PTH (36 pg/mL), the odds of falling one or more times over the subsequent year increased 30% after adjustment for demographic characteristics and health behaviors. Further adjustment for kidney function, prevalent cardiovascular disease, medication use, and calcium and vitamin D supplement use attenuated the association; however, a trend remained. The association between serum PTH and reported falls remained after further adjustment for the Health ABC SPPB summary score. Additional adjustment for reported falls in the previous year attenuated the association slightly; however, a trend remained. Similar associations were observed when participants were stratified by race (data not shown).

We also examined the association between elevated serum PTH (>69 pg/mL) and falls. Participants with elevated serum PTH had 71% higher odds of falling in the subsequent year after adjustment for demographic characteristics and health behaviors (OR (95% CI): 1.71 (1.04-2.80)). Further adjustment for kidney function, prevalent cardiovascular disease, medication use, calcium and vitamin D supplement use, physical performance, and reported falls in the previous year attenuated the association; however, a trend remained (OR (95% CI): 1.61 (0.91-2.86)).

DISCUSSION

Among well-functioning, community-dwelling, diabetic older adults, higher serum PTH levels appear to identify persons at increased risk of falling in the subsequent year independent of other risk factors for falls. Among participants who reported falling in the subsequent year, the mean baseline serum PTH level was approximately 18% higher compared to those who did not report falling. For every one standard deviation increment in baseline serum PTH, there was approximately a 30% increase in the likelihood of reporting falls in the subsequent year after adjusting for demographic characteristics, health behaviors, kidney function, health conditions, and medication and dietary supplement use. Even though serum PTH was associated with lower extremity physical performance at baseline, physical performance did not appear to mediate the association between serum PTH and incident

falls. A trend also remained between serum PTH and incident falls after further adjustment for reported falls in the previous year, a major risk factor for subsequent falls.

A limited number of studies have examined the association between serum PTH and muscle strength or physical performance with inconsistent results (11;18-21). Among older ambulatory women, serum PTH was significantly correlated with gait speed and balance but not with knee extension or knee flexion strength (19). However, among older patients attending a falls clinic, serum PTH was a significant predictor of isometric quadriceps strength independent of vitamin D levels (11). Older community-dwelling adults with high serum PTH levels were significantly more likely to experience loss of grip strength and appendicular skeletal muscle mass over three years of follow-up (18). However, among moderately to severely disabled older women, serum PTH was not associated with muscle strength or physical performance over three years of follow-up (20). Furthermore, serum PTH was not associated with baseline or four-year change in quadriceps strength, chair stand pace, gait speed, or tandem walk time in older, community-dwelling, vitamin-D replete women (21). In contrast, this study found significant correlations between serum PTH and physical performance, particularly for standing balance and gait speed, among older, well-functioning diabetic men and women.

There are only a few studies that have examined the association between serum PTH and falls (10;12;13;21). Among older men and women living in assisted living or nursing home facilities, median serum PTH levels were approximately 30% higher among those who reported falling (10). In longitudinal analyses, higher serum PTH levels were a significant predictor of time to first fall among older adults residing in assisted living or nursing home facilities independent of vitamin D levels (12). However, among older community-dwelling, vitamin-D replete women, serum PTH was not associated with falls over four years of follow-up (21). In this study, serum PTH was associated with greater odds of falling over one year of follow-up among older, well-functioning diabetic men and women.

The prevalence of falls over one year of follow-up was similar in blacks and whites. Previous studies have also found similar rates of falling in blacks and whites (30;31). Consistent with other studies (32-34), the current study found that blacks had higher mean serum PTH levels than whites. Higher PTH levels in blacks are primarily the result of increased skin pigmentation and the concomitant reduction in vitamin D production in the skin along with low intakes of vitamin D (35;36). Although blacks had higher serum PTH levels on average, we did not find an interaction between race and serum PTH and the likelihood of reporting falls associated with a one standard deviation increment in serum PTH did not appear to be higher among blacks compared to whites. Previously, studies have suggested that blacks may have a skeletal resistance to PTH-stimulated bone resorption (33;37). Resistance to the effects of elevated PTH in blacks may extend to muscle function and falls.

There are important characteristics of this Health ABC sub-study of bone health that limit the generalization of these findings. Health ABC participants were well-functioning and free of lower-extremity functional limitations at baseline. It is possible that the associations between serum PTH and muscle strength, physical performance, and falls may have been stronger had participants of all stages of functional ability been included. Only participants with diabetes were included in this sub-study. Participants were asked to recall falls over the previous 12 months. It is possible that some participants may not have recalled falling; however, in a meta-analysis, falls recalled over the previous year compared favorably to more resource intensive strategies (e.g., fall diaries, weekly or monthly fall postcards) (38). Furthermore, elevated serum PTH could be a marker for low vitamin D levels which have previously been associated with increased risk of falls (12;21;39;40). A major limitation of

this study is that vitamin D levels were not measured as part of this sub-study; thus, we could not distinguish between falls due to vitamin D deficiency versus falls due to elevated PTH levels. It is possible that the association between PTH and falls was driven by low vitamin D status. However, previous studies have shown an association between PTH and falls independent of vitamin D status (10;12;13). Finally, the observational design of our study does not allow us to evaluate a causal association between serum PTH and falls. However, the association is biologically plausible as PTH may play a role in falls through several different biological mechanisms. In animal models, infusion of PTH has been shown to increase protein catabolism and decrease the number of type 2 muscle fibers, intracellular energy-rich phosphate compounds, and mitochondrial oxygen uptake (16;17;41).

In summary, serum PTH was associated with incident falls among older, well-functioning diabetic men and women. An association between serum PTH and incident falls remained after adjusting for physical performance suggesting that the association between PTH and falls was not mediated by physical performance. Further investigation aimed at understanding the underlying mechanism for the association between serum PTH on muscle strength, physical performance, and falls is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Selected Baseline Participant Characteristics by PTH Tertiles in Older Diabetic Adults*

Median PTH, pg/mL (interquartile range)	1 st Tertile	2 nd Tertile	3 rd Tertile	P-value
	31.0 (26.7-36.4)	48.1 (44.2-52.4)	72.8 (65.0-95.2)	
Age (yrs)	73.3 ± 2.8	73.5 ± 2.9	74.0 ± 2.8	0.10
Female (%)	36.3	41.1	49.0	0.07
Black race (%)	40.1	55.7	68.2	<0.001
Pittsburgh field center (%)	51.0	51.9	46.5	0.59
< High school education (%)	35.0	35.4	35.0	0.99
Current smoker (%)	10.8	8.2	10.2	0.72
Current drinker (%)	35.7	45.6	26.1	0.002
<500 kcal/wk walking or exercise (%)	56.0	55.7	67.5	0.05
BMI (kg/m ²)	28.5 ± 4.6	29.2 ± 4.6	30.5 ± 5.0	<0.001
Winter/spring season (%)	49.7	55.1	67.5	0.005
Poor eyesight (%)	3.2	5.7	7.6	0.22
Cognition (3MS score)	88.6 ± 10.2	88.2 ± 8.6	87.4 ± 8.6	0.49
Depressive symptoms (CES-D score)	5.3 ± 6.5	4.6 ± 5.2	4.5 ± 5.7	0.40
Fell in the previous 12 months (%)	17.8	26.6	19.8	0.14
Chronic conditions				
Cardiovascular disease (%)	23.6	33.5	35.7	0.05
Osteoporosis (%)	7.0	6.3	8.3	0.79
Knee pain (%)	14.0	15.8	19.8	0.38
Urinary incontinence (%)	15.9	19.0	17.8	0.77
Medications				
Anti-hypertensive agents (%)	63.1	66.5	73.2	0.14
Hypotensive agents (%)	7.6	5.7	8.9	0.55
Insulin (%)	16.6	17.1	32.5	<0.001
Oral hypoglycemics (%)	55.4	49.4	47.1	0.32
Benzodiazepines (%)	6.4	2.5	1.9	0.07
SSRIs (%)	2.6	0.6	1.3	0.36
Total # of medications	4.2 ± 2.5	4.1 ± 3.2	4.8 ± 2.9	0.08
Multivitamin use (%)	30.1	30.3	20.6	0.09
Calcium supplement use (%)	13.4	7.6	7.0	0.10
Vitamin D supplement use (%)	8.3	3.2	0.6	0.002
Cystatin C (mg/dL)	1.05 ± 0.31	1.03 ± 0.21	1.18 ± 0.38	<0.001
Hemoglobin A1c	7.98 ± 1.33	8.02 ± 1.56	8.16 ± 1.65	0.54
Health ABC SPPB summary score	2.08 ± 0.58	2.01 ± 0.59	1.91 ± 0.61	0.04

* Means ± SD or frequencies with chi-square or ANOVA to evaluate the distribution. PTH: parathyroid hormone; BMI: body mass index; 3MS: Modified Mini-Mental State Examination; CES-D: Center for Epidemiologic Studies Depression Scale; SSRI: selective serotonin reuptake inhibitors; SPPB: Short Physical Performance Battery.

Table 2
Spearman Partial Correlations between Baseline PTH and Physical Performance in Older Diabetic Adults*

Physical Performance Measure	Coefficient	P-value
Health ABC SPPB summary score	-0.10	0.03
Chair stands (#/sec)	-0.03	0.51
Standing balance (sec)	-0.08	0.06
6 meter gait speed (m/sec)	-0.13	0.006

* Corrected for age and gender. PTH: parathyroid hormone; SPPB: Short Physical Performance Battery.

Table 3
Baseline PTH and Odds (95% CI) of Falling Over 1 Year of Follow-up in Older Diabetic Adults.*

	OR (95% CI) per 1 SD of PTH [†]	P-value
Model 1	1.30 (1.06-1.59)	0.01
Model 2	1.23 (0.99-1.52)	0.07
Model 3	1.26 (1.01-1.58)	0.04
Model 4	1.26 (0.99-1.61)	0.06

* Model 1 adjusted for age, gender, race, field center, alcohol consumption, BMI, physical activity, and winter/spring season. Model 2 adjusted for variables in model 1 plus cystatin C, prevalent cardiovascular disease, anti-hypertensive agents, benzodiazepine, insulin, multivitamins, calcium and vitamin D supplement use, and total number of medications. Model 3 adjusted for variables in model 2 plus Health ABC Short Physical Performance Battery summary score. Model 4 adjusted for variables in model 3 plus reported falls in the previous year. PTH: parathyroid hormone; OR: odds ratio; CI: confidence interval.

[†] 1 SD of PTH = 36 pg/mL.