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ORIGINAL REPORT

MUSCLE STRENGTH IS SIGNIFICANTLY ASSOCIATED WITH HIP BONE MINERAL DENSITY IN WOMEN WITH PARKINSON'S DISEASE: A CROSS-SECTIONAL STUDY

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Objective: **To study the influence of physical impairments on hip bone mineral density in women with Parkinson's disease.**
Design: **Cross-sectional study.**
Subjects/patients: **Thirty-four women with Parkinson's disease and 30 age-matched healthy controls.**
Methods: **Patients with Parkinson's disease underwent a hip scan using dual-energy X-ray absorptiometry and total hip bone mineral density values were obtained. Motor Examination III of the Unified Parkinson Disease Rating Scale was used to assess leg tremor, leg agility, leg rigidity and postural stability. In addition, all subjects were evaluated for walking speed, walking endurance, and leg muscle strength.**
Results: **Based on the hip bone mineral density values, 12 patients with Parkinson's disease (35%) had osteopaenia and another 3 patients (9%) had osteoporosis. Patients with Parkinson's disease had significantly lower walking velocity ($p = 0.002$), walking endurance ($p < 0.001$) and leg muscle strength ($p = 0.047$) than controls. Multiple regression revealed that leg muscle strength alone accounted for 8.8–10.6% of the variance in hip bone mineral density among patients with Parkinson's disease, after controlling for body mass index, post-menopausal years, Hoehn and Yahr stage, and postural stability ($p < 0.05$).**
Conclusion: **Hip bone mineral density is independently associated with leg muscle strength in women with Parkinson's disease.**

Key words: bone density, muscle, osteoporosis, Parkinson's disease, rehabilitation.

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INTRODUCTION

People with Parkinson's disease (PD) have a much higher risk of fracture than healthy individuals (1, 2) and the hip is the most common skeletal site of fracture (1). Within 10 years of diagnosis of PD, approximately 27% of individuals suffer a hip fracture compared with only 9% of controls (1). The consequences of hip fractures in people with PD can be devastating, including elevated mortality rate (3), increased length of hospital stay (4, 5), decreased functional status (5), and increased risk of nursing home admission (6). Moreover, the increased medical cost associated with the treatment of fractures would presumably impose a financial burden on the healthcare system.

In addition to the elevated rate of falls (7), another contributing factor to increased fracture risk in individuals with PD may be compromised bone health (2, 7, 8). In a 1-year prospective study, Sato and colleagues (9) identified low bone mineral density (BMD) as a significant predictor of hip fracture in individuals with PD. On average, BMD in patients with PD has been found to be significantly lower than in healthy controls in a number of skeletal sites (7). Previous studies have suggested that low BMD might be associated with certain demographic factors such as advanced Hoehn and Yahr staging (9), and duration of PD (8) and with biochemical factors such as vitamin D deficiency (9, 10), vitamin K deficiency (9), and altered oestrogen or growth hormone levels (11). However, few studies have addressed the association of BMD with the cardinal symptoms (e.g. rigidity, tremor, bradykinesia, postural instability) and other common physical impairments observed in patients with PD (e.g. gait disturbances, muscle weakness) (12).

While the cardinal symptoms of PD have long been known and are well documented, muscle weakness (i.e. decreased ability of the muscle to generate force) in patients with PD has received relatively less attention in the literature, until recently (13). Virtually all major muscle groups in the lower extremity, including the hip flexors, hip extensors, knee flexors, knee extensors, ankle dorsiflexors, and ankle plantarflexors, were found to be weaker in patients with PD than in healthy controls (13, 14), leading some researchers to suggest that muscle weakness is a primary symptom of PD (14). Lower extremity muscle weakness may have a detrimental effect on performance in functional activities such as sit-to-stand (13). In addition, muscle force is a major source of mechanical strain applied to the skeleton. In fact, muscle strength has been strongly associated with bone density in various populations, including young adults (15), older adults (16) and patients with stroke (17). Muscle strength may be an important contributing factor to bone health in patients with PD. However, no study has examined the relationship between muscle strength and hip BMD in patients with PD.

This study aimed to investigate the influence of cardinal symptoms and physical impairments on hip BMD in commu-

nity-dwelling, ambulatory women over 50 years of age with PD for at least one year. We studied this sub-group of patients with PD because the combined effects of female sex and advanced age may put these patients more at risk of fractures (8, 11). In addition, this patient sub-group, who are generally affected by mild to moderate PD, are more prone to recurrent falls compared with healthy controls (relative risk: 13.4) (18). Thus, it would be clinically relevant to study bone health in these individuals.

METHODS

Subjects

Community-dwelling women with PD were recruited on a volunteer basis from the Hong Kong Parkinson's Disease Association. A total of 62 women with PD volunteered to participate in the study and were screened through a telephone interview. The inclusion criteria were: a history of PD for a duration of one year or more as diagnosed by a neurologist, using the UK Parkinson's Disease Society Brain Bank Criteria (19); female sex; living in the community (i.e. not institutionalized); aged 50 years or more; able to walk without physical assistance from others for at least 10 m; and able to communicate and follow verbal commands. The exclusion criteria were: significant orthopaedic problems (e.g. rheumatoid arthritis); other neurological diseases (e.g. stroke) in addition to the diagnosis of PD; metal implants in the scanned area; and previous fracture in the scanned lower extremity. Twenty-eight patients did not fulfil the criteria and were thus excluded from the study. A total of 34 patients with PD enrolled in the study (Table I).

In addition, age- and sex-matched healthy controls were recruited to participate in the study. They had to fulfil the criteria as stated above, except that they did not have any history of PD. Forty-one healthy individuals volunteered to participate in the study but 11 of them did not meet the eligibility criteria. Thus, a total of 30 control subjects were included in the study (Table I). Ethics approval was obtained from the Hong Kong Polytechnic University. Eligible subjects gave informed, written consent before they participated in the study. All procedures were performed in accordance with the Declaration of Helsinki.

Medical history, medications and other relevant information (e.g. history of factures) were obtained by interview. Fallers were identified by asking the subject whether they had had any falls within the past 12 months. A fall is defined as "an event during which a subject comes to rest on the ground or at some lower level, not as the result of a major intrinsic event e.g. syncope, stroke and seizure, or overwhelming hazard" (20). Physical activity level was measured by the modified version of the Minnesota Leisure-Time Physical Activity (MNLTPA) questionnaire (21). Subjects were classified into 3 separate categories according to the types of habitual physical activities that they most frequently participated in during the past year (Level I: light intensity (< 4 metabolic equivalents (METs)), Level II: moderate intensity (4–5.5 METs), Level III: heavy intensity (> 5.5METs)). Modified Hoehn and Yahr (MHY) staging was used to indicate the severity of PD (22). It consisted of 8 stages ranging from stage 0 to stage 5, with a higher value indicating more advanced PD. For standardization of testing procedures across subjects, patients with PD completed all tests within 1 h during their "ON" phase of the medication cycle.

Primary outcomes

Patients with PD underwent a hip scan on the non-dominant side with dual-energy X-ray absorptiometry (DXA; Hologic Inc., Bedford, MA, USA). The primary outcome was total hip BMD (g/cm^2). The values

Table I. *Subject characteristics. Means (standard deviations) are presented unless indicated otherwise*

Variable	Patients with PD (n = 34)	Healthy controls (n = 30)	p-value
Demographics			
Age, years	64.2 (7.8)	65.5 (6.7)	0.472
Body mass index, kg/m^2	23.0 (3.2)	23.6 (2.4)	0.396
Physical activity level (Level I/II/III), *n*	22/8/4	20/3/7	0.229
Had at least one fall in the past year, *n*	15	3	0.006*
Post-menopausal, *n*	30	30	0.155
Post-menopausal, years	14.7 (8.0)	14.1 (10.5)	0.806
Duration of Parkinson's disease, years	7.1 (3.7)	–	–
Medications/supplements for osteoporosis, n			
Bisphosphonates	4	3	1.000
Calcium	6	9	0.244
Vitamin D	4	4	1.000
Primary outcomes: bone health			
Total hip bone mineral density, g/cm^2	0.779 (0.113)	–	–
T-score	–1.0 (1.1)	–	< 0.001†
Z-score	0.2 (1.0)	–	0.258
Normal/osteopaenia/osteoporosis	19/12/3	–	–
Secondary outcomes			
Walking speed, m/sec	1.01 (0.18)	1.15 (0.17)	0.002*
Six-minute walk distance, m	319.5 (82.8)	388.6 (52.9)	< 0.001*
Leg muscle strength, kg	29.9 (6.7)	33.2 (6.3)	0.047*
Leg tremor score (out of 8), median (IQR)	0.0 (0.0)	–	–
Leg rigidity score (out of 8), median (IQR)	2.0 (3.0)	–	–
Leg agility score (out of 8), median (IQR)	2.0 (1.3)	–	–
Postural stability (out of 8), median (IQR)	2.0 (1.0)	–	–
UPDRS total motor score (max = 108), median (IQR)	21.5 (13.5)	–	–
Hoehn and Yahr staging, median (IQR)	3.0 (0.5)	–	–

*Significant difference between PD group and control group ($p < 0.05$).

†Significant different between PD group and age-and sex matched control in Lynn et al. (23) ($p < 0.05$).

PD: Parkinson's disease; UDPRS: Unified Parkinson Disease Rating Scale; IQR: interquartile range.

obtained were compared with the young reference values based on a large normative study in Hong Kong and associated T-scores were computed (23). The T-score indicated whether the BMD value was desirable for a particular patient and was used for diagnosis of osteopaenia and osteoporosis (24). For example, a T-score of –1 indicated that the obtained BMD value was 1 standard deviation below the mean of the young reference population. A T-score between –1 and –2.5 was defined as osteopaenia and a score less than –2.5 was defined as osteoporosis according to the guidelines set by the World Health Organization (24). In addition, the BMD values were compared with the age- and sex-matched mean reference value from the same normative study and a Z-score was computed (23). The Z-score was not used for diagnosis but only helped to determine whether the obtained BMD value was similar to that expected for an individual with the same age and sex. For example, a Z-score of –1 indicated that the obtained BMD value was 1 standard deviation below the mean of the age- and sex-matched reference population (23). The bone scanning was performed by the same certified technician, who had many years of relevant experience. Regarding the reliability of our DXA scanner, the coefficient of variation was 0.78% for measuring total hip BMD.

Secondary outcomes

Patients with PD and control subjects underwent an evaluation of physical function, which was conducted by a well-trained research technician. The walking speed of each subject was assessed using the GAITRite system (CIR Systems, Inc., Havertown, PA, USA). This system is a 4.2 m portable carpet with embedded force sensors. Each subject was instructed to walk along this carpet at a self-selected speed, using walking aid if needed. The walking speed (metres/second) was calculated by the specialized software of the GAITRite system (CIR Systems, Inc.). A total of 3 trials were performed and the mean value was used for further analysis. Our data showed that the instrument had excellent test-retest reliability in measuring walking speed (intraclass correlation coefficient [(ICC(3,1)] = 0.93).

Walking endurance was assessed by the 6-minute walk test. The test was conducted in a 15-m unobstructed corridor (25). Subjects were instructed to walk as far as they could in 6 min. The total distance walked (metres) was recorded. The 6-min walk test has been shown to be a reliable assessment when used in individuals with PD (ICC > 0.90) (26).

Isometric hip flexion and knee extension strength on the non-dominant side were measured using hand-held dynamometry (Nicholas MMT; Lafayette Instruments; Lafayette, IN, USA). These muscles were selected as they have been shown to demonstrate significant weakness among patients with PD in previous studies and are related to the ability to perform important functional tasks such as standing up from a chair (13). The subjects were instructed to sit on a chair with back support. The height of the chair was adjustable and the hip was positioned at 90° flexion. To test hip flexion strength, the lower trunk was stabilized by a strap and the subjects performed a maximal isometric contraction of hip flexion. To test knee extension strength, the thigh was stabilized by a strap and the knee was placed in 90° flexion. Subjects performed a maximal isometric contraction of knee extension. Three trials were performed with a brief rest between trials. The force data (kg) for each muscle were averaged to obtain the mean muscle strength. The mean hip flexion and knee extension strength was then summed to yield the leg muscle strength score. Our data showed that our isometric muscle strength assessment had good to excellent test-retest reliability [ICC(3,1)] = 0.87–0.90.

The Motor Examination III of the Unified Parkinson Disease Rating Scale (UPDRS) (27) was used to assess the cardinal symptoms of PD. This 27-item scale is a common assessment tool used to measure the longitudinal course of PD and has demonstrated good content validity and internal consistency (27). The subscores on leg tremor, rigidity, and degree of bradykinesia (agility) on each side were summed. The postural stability score as well as the total score were also reported. Each item scored from 0 to 4, with 0 indicating no disability and 4 denoting maximum disablement. Hence, a higher UPDRS score indicates more severe deficits (27).

Statistical analysis

First, we were interested in determining whether patients with PD had different characteristics when compared with healthy controls. Independent *t*-tests, Mann-Whitney *U* tests, and χ^2 tests were used to compare between the 2 groups in continuous, ordinal, and nominal variables, respectively. One-sample *t*-tests were used to determine whether the mean T-score and Z-score were significantly different from the local reference population (i.e. mean = 0) in Lynn et al. (23).

Secondly, we were interested in identifying whether leg muscle strength was independently associated with hip BMD in patients with PD. We first examined the bivariate correlations between hip BMD values and other variables (e.g. age, MHY, leg rigidity, etc.) in patients with PD by using Pearson's correlation coefficients (for continuous variables) and Spearman's rho (for ordinal variables). A hierarchical multiple regression model was then constructed, with hip BMD as the dependent variable. The selection of independent variables for the regression model was based on both biological relevance and results from the bivariate correlation analysis. On the basis of biological relevance, body mass index (BMI) and post-menopausal years were selected as they were highly associated with bone health in older women (28, 29). To account for the influence of other relevant factors on hip BMD, any variables with a weak, but not necessarily statistically significant correlation with hip BMD, were also entered into the regression model (threshold $p < 0.3$). The rationale behind this was that the small sample size in this study would make it relatively difficult to detect statistically significant correlations. Thus, a less stringent standard was used for selection of independent variables. To avoid multi-colinearity, the degree of association among the potential independent variables was also checked. The above statistical analyses were performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). A significance level of 0.05 was set for all statistical tests (2-tailed).

Additionally, considering the relatively small sample size, it was helpful to determine whether our study was underpowered to detect significant differences/associations for some of our analyses. Therefore, *post-hoc* power analyses were performed to examine the statistical power for the comparisons of walking speed, walking endurance, and leg muscle strength between the PD and control groups as well as for the bivariate correlation and multiple regression analyses. The *post-hoc* power analyses were performed using the G*Power computer program (Faul & Erdfelder, Bonn University, Germany).

RESULTS

Primary outcomes

The mean total hip BMD value in patients with PD was 0.779 (0.113 g/cm^2). Three women with PD (9%) fulfilled the definition of osteoporosis (T-score < 2.5). Another 12 patients (35%) had osteopaenia (–2.5 < T-score < –1.0). The T-score was significantly different from zero ($p = 0.001$), indicating that the mean hip BMD obtained was well below the desired value. The Z-score, on the other hand, was not significantly different from zero, showing that the mean hip BMD obtained was quite similar to that expected for an individual with matched age and sex (Table I).

Secondary outcomes

Overall, the patients were mildly and moderately impaired by PD, as indicated by the MHY stage (median stage = 3.0, interquartile range (IQR) = 0.5) and the UPDRS motor score (median = 21.5, IQR = 13.5). The relative contribution of hip flexion and knee extension strength to the composite leg muscle strength score was 48.5% (5.2%) and 51.5% (5.2%), respectively, for the patients with PD. The corresponding

values in healthy controls were 43.2% (8.5%) and 56.8% (8.5%), respectively. None of the patients with PD or controls was undergoing hormone replacement therapy or had any history of fragility fractures. None of the patients with PD demonstrated any freezing episode during the walking tests. Table II outlines the anti-Parkinsonian medications taken by the patients with PD.

Comparison between patients with Parkinson's disease and controls

There was a significant difference between patients with PD and controls in walking speed ($p = 0.002$), 6-min walk distance ($p < 0.001$), and leg muscle strength ($p = 0.047$). The proportion of individuals who had at least one fall in the past year was also significantly higher in the PD group than controls ($p = 0.006$). There was no significant difference in any other variables between the 2 groups listed in Table I, including age, BMI, physical activity level, post-menopausal years, and medications ($p > 0.100$).

Correlations with hip bone density in patients with Parkinson's disease

Table III shows the correlations between hip BMD and other variables of interest in patients with PD. There were significant associations of hip BMD with BMI ($\rho = 0.380$, $p = 0.027$), MHY stage ($\rho = -0.412$, $p = 0.016$), postural stability score ($\rho = -0.399$, $p = 0.019$), and leg muscle strength ($\rho = 0.553$, $p = 0.001$) (Fig. 1). In addition, hip BMD had a weak but insignificant relationship with age ($\rho = -0.223$, $p = 0.205$), and post-menopausal years ($\rho = -0.314$, $p = 0.071$). None of the other demographic variables (i.e. disease duration) or other cardinal symptoms (leg rigidity, agility and tremor) or physical measures (i.e. walking speed, 6-min walk distance) had significant correlations with hip BMD and the associated *p*-values were all greater than 0.3.

Determinants of hip bone density in patients with Parkinson's disease

Multiple regression analysis was then performed to identify the determinants of hip BMD. Post-menopausal years and BMI were first entered into the regression model based on

Table II. Anti-Parkinsonian medications taken by patients with Parkinson's disease ($n = 34$)

Anti-Parkinsonian medications	Subjects, *n*
Not taking anti-Parkinsonian medications	1
Levodopa	9
Levodopa + entacapone	1
Levodopa + selegiline	2
Levodopa + dopamine agonist	7
Levodopa + dopamine agonist + amantadine	2
Levodopa + dopamine agonist + entacapone	2
Levodopa + dopamine agonist + selegiline	3
Levodopa + dopamine agonist + selegiline + entacapone	1
Dopamine agonist	2
Dopamine agonist + amantadine	2
Dopamine agonist + selegiline	2

Table III. *Correlation matrix in patients with Parkinson's disease (PD)*

	Hip BMD	Age	BMI	PA	PM years	MHY	PD duration	Gait speed	6MWT	Leg muscle strength	Leg tremor	Leg agility	Leg rigidity	Postural stability	UPDRS total
Hip BMD	–	–0.223	0.380	–0.055	–0.314	–0.412	–0.148	0.013	–0.006	0.553*	–0.044	0.110	–0.026	–0.399*	–0.083
Age	–0.223	–	0.221	–0.016	0.837*	0.173	–0.148	–0.610	–0.355*	–0.334	0.005	0.109	–0.014	0.145	0.168
BMI	0.380*	0.221	–	–0.403*	0.124	0.031	–0.316	–0.303	–0.455*	0.247	0.012	0.283	0.218	0.036	0.302
PA	–0.055	–0.016	–0.403*	–	–0.058	–0.198	0.224	0.280	0.300	–0.107	0.007	–0.138	–0.085	–0.192	0.000
PM years	–0.314	0.837*	0.124	–0.058	–	0.292	–0.052	–0.598*	–0.303	–0.348*	0.001	0.209	0.001	0.272	0.207
MHY stage	–0.412*	0.173	0.031	–0.198	0.292	–	0.135	–0.222	–0.328	–0.414*	0.222	0.151	0.328	0.994*	0.401*
PD duration	–0.148	–0.148	–0.316	0.224	–0.052	0.135	–	–0.041	–0.076	–0.507*	0.019	0.275	0.182	0.164	0.271
Gait speed	0.013	–0.610*	–0.303	0.280	–0.598*	–0.222	–0.041	–	0.773*	0.405*	0.172	–0.463*	–0.327	–0.202	–0.514*
6MWT	–0.006	–0.355*	–0.455*	0.300	–0.303	–0.328	–0.076	0.773*	–	0.367*	–0.055	–0.474*	–0.467*	–0.320	–0.510*
Leg muscle strength	0.553*	–0.344	0.247	–0.107	–0.348*	–0.414*	–0.507*	0.405*	0.367*	–	–0.196	–0.258	–0.249	–0.418*	–0.376*
Leg tremor	–0.044	0.005	0.012	0.007	0.001	0.222	0.019	–0.172	–0.055	–0.196	–	–0.067	–0.153	0.219	0.304
Leg agility	0.110	0.109	0.283	–0.138	0.209	0.151	0.275	–0.463*	–0.474*	–0.258	–0.067	–	0.499*	0.124	0.675*
Leg rigidity	–0.026	–0.014	0.218	–0.085	0.001	0.328	0.182	–0.327	–0.467*	–0.249	–0.153	0.499*	–	0.332	0.605*
Postural stability	–0.399*	0.145	0.036	–0.192	0.272	0.994*	0.164	–0.202	–0.320	–0.418*	0.219	0.124	0.332	–	0.394*
UPDRS total	–0.083	0.168	0.302	0.000	0.207	0.401*	0.271	–0.514*	–0.510*	–0.376*	0.304	0.675*	0.605*	0.394*	–

*$p < 0.05$.

BMD: bone mineral density; BMI: body mass index; MHY: modified Hoehn and Yahr stage; PA: physical activity; PM: post-menopausal; 6MWT: 6-minute walk test: UDPRS: Unified Parkinson Disease Rating Scale.

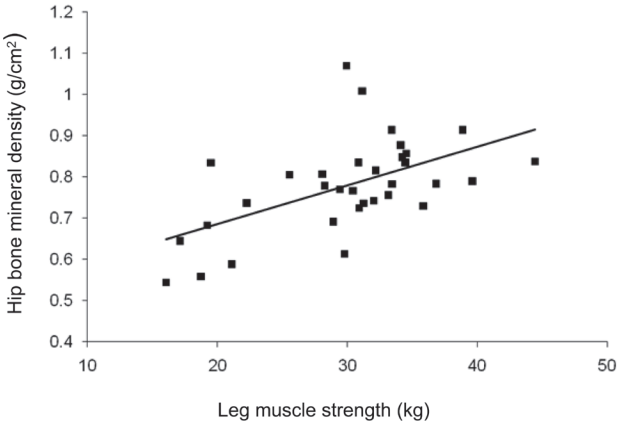

Fig. 1. Correlation between leg muscle strength and hip bone mineral density (BMD). A moderate, positive relationship between leg muscle strength and hip BMD was identified. Each square represents the data from a single subject. The solid line represents the trend line.

their biological relevance to bone health. Although the correlation hip BMD with age had an associated p-value < 0.3, age was not entered into the model, because it was highly correlated with post-menopausal years ($\rho = 0.837$, $p < 0.001$). In addition, using post-menopausal years in the regression analysis would allow for the estimation of the effects of both age and menopause.

MHY stage, postural stability, and leg muscle strength were also used as independent variables because they were significantly correlated with hip BMD, as shown in the bivariate correlation analyses ($p < 0.05$). As MHY stage and postural stability were also highly correlated with each other ($p = 0.994$, $p < 0.001$) (Table III), separate regression models were used to predict hip BMD to avoid multi-colinearity. In the first model, we used post-menopausal years, BMI, MHY stage, and leg muscle strength to predict hip BMD. Post-menopausal years and BMI combined to account for 27.7% of the variance in hip BMD ($F_{2,31} = 5.931$, $p = 0.007$). Addition of MHY stage did not significantly improve the prediction model (F score change $_{1,30} = 1.280$, $p = 0.267$). Finally, adding leg muscle strength accounted for another 10.6% of the variance in hip BMD, and significantly improved the prediction model (F score change $_{1,29} = 5.225$, $p = 0.030$) (Table IV, model 1). This regression model accounted for a total of 41.2% of the variance in hip BMD. The importance of leg muscle strength in determining hip BMD was also reflected by the magnitude of the standardized regression coefficient (beta weight = 0.379), which was the greatest among all the predictors.

In the second regression model, we used post-menopausal years, BMI, postural stability score, and leg muscle strength to predict hip BMD (Table IV, model 2). After controlling for post-menopausal years and BMI, addition of postural stability did not significantly improve the regression model (F score change $_{1,30} = 2.500$, $p = 0.124$). Addition of leg muscle strength, however, significantly improved the prediction model (F score change $_{1,29} = 4.397$, $p = 0.045$) and accounted for an additional 8.8% of the variance in hip BMD. This regression model accounted for 42.0% of the variance in hip BMD. Similar to regression model 1, leg muscle strength was the most important predictor of hip BMD (beta weight = 0.355).

Post-hoc power analysis

For the comparison between patients with PD and controls (Table I), the statistical power for the analysis of walking speed, 6-minute walk distance, and leg muscle strength were 0.87, 0.97, and 0.58, respectively. For the bivariate correlation analysis, the association of hip BMD with age, post-menopausal years, and disease duration had modest statistical power, at 0.36, 0.60, and 0.21, respectively. This may explain why these variables failed to show a significant correlation with hip BMD. On the other hand, the association of hip BMD with leg muscle strength, MHY stage, and postural stability had much higher statistical power, at 0.98, 0.83, and 0.80, respectively. For the multiple regression analyses, both models had a statistical power of 0.97.

DISCUSSION

The most important finding of this study is that leg muscle strength, but not the cardinal symptoms of PD, is independently associated with hip BMD in women with PD.

Table IV. *Multiple regression analysis for determining hip bone mineral density in patients with Parkinson's disease*

Independent variable	R^2	R^2 change	*B* (95% CI)	β	*p*
Model 1	0.412				
Post-menopausal years		0.277	–0.002 (0–0.006, 0.001)	–0.203	0.205
Body mass index			0.011 (0.000, 0.022)	0.311	0.049*
Modified Hoehn and Yahr stage		0.030	–0.020 (–0.096, 0.055)	–0.083	0.585
Leg muscle strength		0.106	0.006 (0.001, 0.012)	0.379	0.030*
Model 2	0.420				
Post-menopausal years		0.277	–0.002 (–0.006, 0.001)	–0.204	0.198
Body mass index			0.042 (0.000, 0.022)	0.321	0.042*
Postural stability		0.056	–0.024 (–0.082, 0.034)	–0.130	0.406
Leg muscle strength		0.088	0.006 (0.000, 0.012)	0.355	0.045*

*$p < 0.05$.
B (95% CI): unstandardized regression coefficient (95% confidence interval); β: standardized regression coefficient (beta weight).

Leg muscle strength is independently associated with hip bone mineral density

Our study showed that a substantial proportion of ambulatory women with PD had low BMD, with 9% of the subjects fulfilling the criteria for osteoporosis and another 35% having osteopaenia. Hip BMD has been identified as a significant predictor of hip fracture in patients with PD (9), it is thus important to identify the key modifiable factors related to bone health in PD.

In this study, we found that the patients with PD sustained multiple physical impairments, with significantly lower walking speed, walking endurance and leg muscle strength than controls. However, among the various physical impairments, leg muscle strength is the only significant determinant of hip BMD. A recent study has attempted to examine the relationship between leg muscle strength and bone health in individuals with PD (12). In their study, a significant relationship was identified between isometric quadriceps strength and bone quality of the right calcaneus (12). However, their study had several limitations. First, the sample size was extremely small (14 patients). Secondly, both men and women were included in their sample. Thirdly, the skeletal site used in their study (i.e. calcaneus) is not the most common site of fracture in patients with PD. Finally, BMD was not directly measured in their study. Rather, the speed of sound (SOS) value of the calcaneus, as measured by a qualitative ultrasound device, was used to indicate bone health. However, it was previously shown that the ultrasound measurements at the calcaneus only had modest correlation with hip BMD measured by DXA ($\rho < 0.5$) (30). Our study is the first to investigate the relationship between hip BMD and muscle strength in patients with PD.

Our results showed that leg muscle strength alone accounted for approximately 10% of the variance in hip BMD. Is this clinically important? It is difficult to compare our R^2 value obtained with other studies due to difference in subject characteristics, the combination of variables entered into the regression models, and the strategies used (enter strategy vs stepwise strategy) (9). However, it is well known that bone density is typically influenced by a multitude of factors, such as sex, race, family history, nutrition, and others. In patients with PD, the picture is even more complex, as many PD-related factors may potentially exert important influence on bone health. Therefore, the fact that leg muscle strength itself could explain about 10% of the variance in hip BMD even after adjusting for relevant factors (i.e. BMI, post-menopausal years, MHY, postural stability) is impressive. Although mounting evidence has demonstrated reduced muscle strength among patients with PD (13, 14), the issue of muscle weakness in patients with PD tends to be overlooked in clinical practice, as reflected by the limited number of intervention studies in this area (13). Our finding suggests that muscle weakness merits more attention and should trigger further diagnostic and therapeutic efforts.

Possible mechanisms underlying muscle-bone relationship

The basis of the association between BMD and muscle strength has not been well elucidated. The possible factors involved are illustrated in Fig. 2. The first factor underlying the muscle-bone relationship may be the direct impact of muscle force on bone structure. It is well known that bone tissue is sensitive to mechanical forces, including those generated from muscle contractions (31). Numerous studies have demonstrated positive associations of muscle strength with BMD measured at sites local to the action of the muscle (15, 16). For example, quadriceps muscle strength was significantly correlated with hip BMD in healthy older women (16) and individuals with stroke (17). Grip and forearm muscle strength was also highly related to radial BMD in healthy subjects (15).

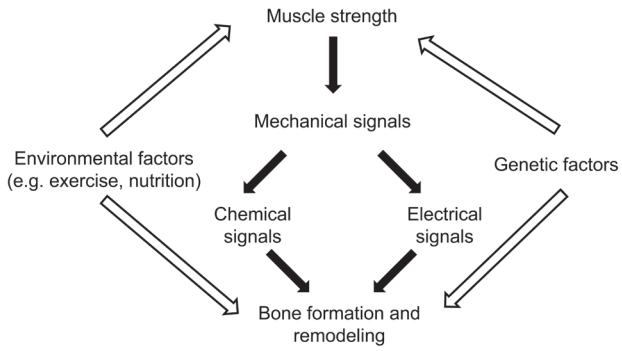

Fig. 2. The possible factors underlying the relationship between bone health and muscle strength. Bone formation and remodelling may be affected by local mechanical signals generated by muscle contractions. The mechanical loads may be mediated through chemical and/or electrical signals within bone tissue. Genetic and environmental factors may act on both bone mineral density and muscle strength.

The physiological mechanisms by which muscle forces influence bone tissue are not certain. The cellular network within the bone tissue is characterized by extensive interconnections among osteocytes by way of cytoplasmic processes and gap junctions, allowing for molecular transport deep within bone tissue as well as electrical coupling (31). Some have suggested that this cellular network senses the mechanical loads, which in turn induces a cascade of chemical signals involved in bone formation or remodelling (31). Others have proposed that electrical signals in form of piezoelectric currents are produced in response to mechanical deformation, and new bone may be formed in reaction to the electrical fields (31).

Several studies have shown significant associations of muscle strength and BMD at distant skeletal sites (15, 32). For example, grip strength was identified as the best predictor of lumbar spine BMD in young adults (15). Therefore, the muscle-bone relationship is not simply attributable to local biomechanical factors, but to factors involved in determining general muscle strength (32, 33).

The common factors that act on both BMD and muscle strength could be environmental or genetic. Environmental influence may include factors such as physical activity and nutrition. For example, exercise is beneficial for increasing both muscle strength and BMD (34). Vitamin D deficiency is also related to both bone health and muscle function (35). Genetics may also partly explain the muscle-bone relationship. In twin studies, it was found that BMD, lean mass and muscle strength all had a major genetic component (32, 33).

For example, the estimated heritability of femoral neck BMD and leg extensor strength was estimated to be 76% and 46%, respectively (32, 33). Approximately 7%–17% of genetic variance of BMD at various skeletal sites can be explained by genetic variance of muscle parameters (32). However, it is important to point out that over 50% of leg muscle strength was explained by environmental factors, indicating the potential of clinical intervention on improving muscle strength and, ultimately, BMD (32).

Clinical implications and future research directions

Based on the strong relationship between muscle strength and hip BMD in women with PD, it is possible that muscle strength assessment may be useful in screening patients with PD for osteoporosis. Future research should explore different muscle strength assessment techniques (i.e. hand-held dynamometry vs isokinetic dynamometers), different types of muscle contraction (i.e. isometric, concentric, eccentric), and different muscle groups, in order to identify the muscle strength parameter that has the strongest relationship with hip BMD. Further study is also required to determine the optimal cut-off leg muscle strength score for screening osteoporosis in patients with PD.

Given the significant relationship between leg muscle strength and hip BMD, would strength training be beneficial in enhancing bone health and reducing fracture rate in patients with PD? Muscle strengthening exercises have been shown to produce positive effects on bone health in the elderly (34). In patients with PD, resistance training has been shown to improve muscle strength (13, 36, 37). Hirsch et al. (37) showed that a 10-week combined balance and resistance training (knee extensors and flexors, ankle plantarflexors) programme resulted in substantially more gain in muscle strength than balance training alone among patients with idiopathic PD. However, no study has examined the effect of muscle strengthening on BMD and fracture rate in patients with PD. Research is much needed in this area.

Limitations

The results should be interpreted with caution as the study has several limitations. First, the sample size is small. The decreased statistical power may explain some of our insignificant results. For example, the magnitude of the hip BMD-age correlation was low ($\rho = -0.223$), with a power of 0.36. A sample size of 120 patients would have been required for detecting a significant correlation between these 2 variables at a power of 0.8.

Secondly, the patients are all community-dwelling and ambulatory individuals recruited from the Hong Kong Parkinson's Disease Association on a volunteer basis. These subjects attended regular meetings of the Association and may therefore be more motivated and active than their counterparts (i.e. self-selection bias). This may partly explain why the hip BMD values are not significantly different from the age- and sex-matched population (Z-score not significantly different from zero). For the same reason, the results cannot be generalized to those who are institutionalized or wheelchair-bound.

Thirdly, over half of the variance in hip BMD remains unexplained. As mentioned previously, bone health is determined by a multitude of factors (i.e. genetics, environment). Some of the potentially important determinants were not measured (e.g. sunlight exposure, dietary habits, etc.). We also did not examine the relationship between hip BMD and anti-Parkinsonian medications. A couple of studies have shown an association of fractures and use of anti-Parkinsonian medications (38, 39). For example, Vestergaard et al. (39) demonstrated that levodopa use was associated with an increased hip fracture risk that was dose-dependent. The authors suggested that the association could be due to the fact that higher degree of drug use was related to more severe PD, and that the drugs failed to completely normalize the locomotor function, thereby leading to falls and fractures (39). Although levodopa does not interact with standard medications for treating osteoporosis (40), whether anti-Parkinsonian medications have any impact on BMD will require further investigation.

Fourthly, contrary to our expectations, age and disease duration are not significantly related to hip BMD. As mentioned, the reduced statistical power may partly explain the insignificant results. The limited range of age (50–80 years) and disease duration (1–14 years) among our patients may also be a factor. Alternatively, our findings may indicate that severity of disease and muscle weakness may take precedence over the influence of these demographic factors in determining hip BMD. It is also intriguing that better bone health is not related to better walking performance (walking speed, 6-minute-walk distance) in our sample. One of the explanations may be that these tests are all objective measures of behavioural performance in a laboratory setting. A satisfactory performance in these walking tests does not necessarily mean that the subject habitually participates in loading activities.

Finally, this is a cross-sectional study. We could not establish a causal relationship between bone loss and muscle weakness. Further research should address the temporal relationship between muscle strength changes and bone loss, as well as the effect of muscle strengthening on BMD.

In conclusion, this is the first study to show that hip BMD is independently associated with leg muscle strength in ambulatory women with PD. Further research should address the potential use of muscle strength assessment in screening osteoporosis, and the effects of muscle strengthening exercise on bone health in the PD population.

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