

Low Vitamin D and High Parathyroid Hormone Levels as Determinants of Loss of Muscle Strength and Muscle Mass (Sarcopenia): The Longitudinal Aging Study Amsterdam

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The age-related change in hormone concentrations has been hypothesized to play a role in the loss of muscle mass and muscle strength with aging, also called sarcopenia. The aim of this prospective study was to investigate whether low serum 25-hydroxyvitamin D (25-OHD) and high serum PTH concentration were associated with sarcopenia. In men and women aged 65 yr and older, participants of the Longitudinal Aging Study Amsterdam, grip strength (n = 1008) and appendicular skeletal muscle mass (n = 331, using dual-energy x-ray absorptiometry) were measured in 1995–1996 and after a 3-yr follow-up. Sarcopenia was defined as the lowest sex-specific 15th percentile of the cohort, translating into a loss of grip strength greater than 40% or a loss of muscle mass greater than 3%. After adjustment for physical activity level, season of data collection, serum creatinine concentration, chronic dis-

ease, smoking, and body mass index, persons with low (<25 nmol/liter) baseline 25-OHD levels were 2.57 (95% confidence interval 1.40–4.70, based on grip strength) and 2.14 (0.73–6.33, based on muscle mass) times more likely to experience sarcopenia, compared with those with high (>50 nmol/liter) levels. High PTH levels (≥ 4.0 pmol/liter) were associated with an increased risk of sarcopenia, compared with low PTH (<3.0 pmol/liter): odds ratio = 1.71 (1.07–2.73) based on grip strength, odds ratio = 2.35 (1.05–5.28) based on muscle mass. The associations were similar in men and women. The results of this prospective, population-based study show that lower 25-OHD and higher PTH levels increase the risk of sarcopenia in older men and women. (*J Clin Endocrinol Metab* 88: 5766–5772, 2003)

SARCOPIENIA IS DEFINED as the loss of muscle strength and muscle mass with aging (1). It increases the risk for functional limitations and mortality (2, 3). To improve the quality of life in old age, the identification of the determinants of sarcopenia is important. The age-related change in hormone concentrations has been hypothesized to play a role in sarcopenia (1, 4).

Vitamin D deficiency is common in both geriatric patients (30–90%, dependent on the used definition) and independent, community-dwelling older persons (2–60%) (5, 6). This is partly due to a lower sunshine exposure and a reduced capacity of the older skin to synthesize vitamin D₃ under the influence of UV light (7). Several cross-sectional studies have shown that low 1,25-hydroxyvitamin D and low 25-hydroxyvitamin D (25-OHD) are related to lower muscle strength, increased body sway, falls, and disability in older men and women (8–11). Significant associations of vitamin D receptor genotypes with quadriceps strength and grip strength have been observed (12). Furthermore, vitamin D supplementation studies in older persons with vitamin D deficiency have shown improvements in physical function and isometric knee extensor strength *vs.* placebo (13, 14).

Levels of PTH increase with age (15, 16). A low vitamin D

status, renal insufficiency, and a low dietary intake of calcium may result in mild secondary hyperparathyroidism (5, 6, 17). Small clinical studies have shown that patients with hyperparathyroidism have impaired muscle function that can be restored after treatment (18, 19). Higher PTH levels in nursing home patients have been associated with falling, independent of 25-OHD (20).

The studies described above suggest that vitamin D deficiency and hyperparathyroidism may be associated with lower muscle mass and lower muscle strength in patient populations. Although the detrimental effects of low vitamin D and high PTH levels on bone loss in the general population are well known (for review see Ref. 5), no prospective population-based studies have yet examined their role in sarcopenia.

The aim of this prospective study was to investigate whether low serum 25-OHD concentration and high serum PTH concentration were associated with loss of muscle strength and loss of muscle mass during three years of follow-up. We studied 1008 men and women aged 65 yr and older, participants of the Longitudinal Aging Study Amsterdam.

Subjects and Methods

Study participants

Data for this study were collected in the Longitudinal Aging Study Amsterdam (LASA), a prospective study of older persons aged 55–85 yr.

Abbreviations: ASMM, Appendicular skeletal muscle mass; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; LASA, Longitudinal Aging Study Amsterdam; 1,25-(OH)₂D₃, 1,25-dihydroxyvitamin D₃; 25-OHD, 25-hydroxyvitamin D.

The sampling and data collection procedures and nonresponse have been described elsewhere in detail (21). In summary, a random sample stratified by age, sex, and expected 5-yr mortality was drawn from the population registers of 11 municipalities in three geographical areas in the west, northeast, and south of The Netherlands. In total, 3107 subjects were enrolled in the baseline examination (1992–1993) and were representative of the Dutch older population.

The sample for the present study comprised of 1509 participants who participated in the main interview as well as the medical interview of the second follow-up of LASA (1995–1996) and were born in or before 1930 (aged 65 yr and older as of January 1, 1996). The 685 respondents living in the west of The Netherlands were invited to the VU University Medical Center for additional measurements, including the assessment of muscle mass. A total of 535 respondents (77%) participated in this examination and a whole-body dual-energy x-ray absorptiometry (DXA) scan was obtained in 520 respondents.

Three years later, in 1998–1999, 1115 of the 1509 respondents (73.9%) participated again in the medical interview (257 died and 137 were lost to follow-up because of refusal, inability to participate because of cognitive or physical limitations, or no contact established). Of the 520 respondents who had a whole-body DXA scan in 1995–1996, 339 (65%) could be contacted and agreed to a repeated whole-body DXA scan 3 yr later.

For the statistical analyses, complete information on both hormone status and change in grip strength was available for 1008 persons. Complete data on hormone status and change in muscle mass was available for 331 persons. The study was approved by the Medical Ethics Committee of the VU University Medical Center and informed consent was obtained from all respondents.

Sarcopenia

Grip strength. Grip strength was used as an indicator of muscle strength and is known to be positively correlated with both lower-extremity and upper-body strength in older persons, with reported correlation coefficients between 0.47 and 0.63 (22, 23). Moreover, grip strength is a reliable [coefficient of variation 3–6% in elderly persons (24, 25)] and portable muscle strength test that can be administered in a home setting. Grip strength was measured using a grip strength dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd., Tokyo, Japan). The maximum strength (kilograms) of two attempts of each hand was summed up. Relative change in grip strength was calculated as the difference in strength between the baseline and follow-up examination, divided by baseline strength and multiplied by 100. No definition of sarcopenia based on muscle strength data has been published. We defined sarcopenia as a loss of grip strength greater than 40% during follow-up, approximating the lowest 15% of the study sample.

Appendicular skeletal muscle mass. Body composition was assessed using DXA using a Hologic QDR 2000 scanner (Hologic Inc., Waltham, MA) in the enhanced array mode and software version V5.70A. The same DXA apparatus was used at both examinations, and standard quality control procedures were in place to detect potential drift over time. Because sarcopenia is defined as the loss of skeletal muscle mass with aging, we used the fat-free, bone-free mass of the arms and legs as an indicator of appendicular skeletal muscle mass (ASMM). The method has been validated in older persons (26). Relative change in ASMM was calculated as the difference in ASMM between the baseline and follow-up examination, divided by the baseline value and multiplied by 100. No definition of sarcopenia has been published using repeated measurements of muscle mass. We defined sarcopenia as a loss of ASMM greater than 3% during follow-up. The cut point of 3% was based on the reported coefficient of variation for the measurement of ASMM using DXA, which is 2–3% (27, 28). A change larger than 3% is likely not to represent measurement error. In addition, the proportion of the study cohort with a loss of ASMM according to this cut point approximated the lowest 15%, similar to our definition of loss of grip strength.

Hormonal factors

In 1995–1996, fasting blood samples were collected in the morning, centrifuged, and the serum samples stored at –70 C. Serum concentration of PTH was measured by means of immunoradiometric assay

(Incstar Corp., Stillwater, MN). Serum 25-OHD was determined using a competitive binding protein assay (Nichols Diagnostics, San Juan Capistrano, CA). The analyses were carried out at the Endocrine Laboratory of the VU University Medical Center.

Potential confounders and effect modifiers

The following potential confounders measured in 1995–1996 were included in the statistical analyses: sex, age, body height, body mass index, physical activity level, serum creatinine concentration, season of data collection, chronic disease, and smoking status. These confounders are known to be associated with the concentration of PTH and/or 25-OHD (16, 17, 29, 30) as well as muscle mass and muscle strength (31–33). Body weight was measured without clothes and shoes using a calibrated balance beam scale. Body height was measured using a stadiometer. To limit the biasing effect of height loss with aging (34), we used body height measured at the first LASA examination (1992–1993) in the analyses and to calculate the body mass index (body weight in kilograms divided by height in meters squared). Information on physical activity was obtained using a validated interviewer-administered questionnaire (35). The respondents were asked how often and for how long in the previous 2 wk they had engaged in several activities. A metabolic equivalent value was assigned to each activity and was used to calculate the number of kilocalories per week per kilogram of body weight spent on that activity (36). Only activities with a metabolic equivalent value of 4 or more (moderate to high intensity) were included in the activity score: walking outdoors, bicycling, heavy household activities, and sports activities. For each respondent the scores of these activities were summed up and multiplied by body weight to create an overall physical activity score in kilocalories per week. Information on smoking status was based on self-report and classified as never smoker, former smoker, or current smoker. Because vitamin D status is partly dependent on sunlight exposure, which results in higher serum levels of 25-OHD in spring/summer, compared with fall/winter, the season of blood collection was used to adjust for seasonal effects on PTH and 25-OHD (30). Serum creatinine concentration was used as an indicator of renal function, which is known to influence PTH and 25-OHD levels (17). Participants were asked (yes/no) whether they had or had had any of the following diseases or disease events: chronic obstructive pulmonary disease (asthma, chronic bronchitis, pulmonary emphysema), cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis (rheumatoid arthritis and osteoarthritis), and cancer (37).

Statistical analysis

All analyses were conducted using SAS software (SAS Institute Inc., Cary, NC). The distributions of the PTH and 25-OHD concentration were normalized by transformation into their normal logarithm. PTH and 25-OHD concentration were used as continuous variables as well as categorized variables to examine potentially nonlinear relationships with sarcopenia. PTH was categorized into tertiles and the lowest PTH group (<3.0 pmol/liter) was used as the reference group. Serum 25-OHD was categorized into three groups based on published cut points: less than 25, 25–49.9, and 50+ nmol/liter (reference group) (5). To investigate the potential association between 25-OHD and sarcopenia at higher levels of 25-OHD, we repeated the analyses using four instead of three 25-OHD categories: less than 25, 25–49.9, 50–74.9, and 75+ nmol/liter. Because of limited statistical power, this additional analysis was performed only for sarcopenia based on grip strength. Potential differences between groups in continuous variables were tested using *t* test and in case of percentages with the χ^2 test. *P* values were based on two-sided tests and were considered statistically significant at *P* < 0.05. Multiple logistic regression analysis was used to investigate the association between hormone concentration (independent variable) and sarcopenia (dependent variable). In the first model, adjustment for age and sex was made. In the second model, we additionally adjusted for other potential confounders including smoking status, body mass index, physical activity level, season of data collection, the natural logarithm of serum creatinine concentration, and chronic disease. Change in muscle mass is known to be highly correlated with change in body weight (38). A separate analysis was therefore conducted with relative weight change during follow-up as an additional confounder. Potential sex differences in the relationship between hormone concentration and sar-

copenia were tested by using sex/hormone product terms in additional analyses. Interaction between PTH and 25-OHD concentration was tested using the PTH/25-OHD product term in additional analyses. For testing interaction $P < 0.1$ was considered statistically significant.

Results

Among the 1008 LASA participants with complete follow-up data, the mean change in grip strength during 3 yr of follow-up was -7.7 kg (SD 12.8) or -13.2% (SD 23.9%). Using these prospective data, sarcopenia was defined as a loss of grip strength greater than 40% and was experienced by 136 respondents (13.5%). The mean 3-yr change in ASMM ($n = 331$) was $+0.3$ kg (SD 0.9) or $+1.9\%$ (SD 5.4%). A decline in ASMM was experienced by 37.5% of the respondents, and 52 respondents (15.7%) met our definition of sarcopenia (ASMM loss $> 3\%$).

Vitamin D deficiency, using the proposed definition of a serum concentration less than 25 nmol/liter (5), was observed for 9.6% of the study sample, and severe vitamin D deficiency (<12.5 nmol/liter) was observed for 1.3% of the study sample. Hyperparathyroidism (>7 pmol/liter) was detected in 3.8% of the study sample.

The baseline characteristics (1995–1996) for participants with and without sarcopenia are shown in Table 1. Participants who lost grip strength were older, weighed less, had a poorer health status (higher prevalence of stroke and arthritis), had a lower initial grip strength, and were more likely to be female and never smoker. No differences in baseline characteristics were observed between those with and without ASMM loss.

An association was observed between the 25-OHD categories and sarcopenia (Fig. 1). Those with lower 25-OHD levels were more likely to experience loss of grip strength ($P = 0.001$) and tended to experience a loss of ASMM ($P =$

0.09). In addition, those with higher PTH concentrations were more likely to experience loss of grip strength ($P = 0.02$) and tended to lose more ASMM ($P = 0.1$) (Fig. 2).

Higher PTH concentration was associated with an increased risk of sarcopenia. Per unit increase in $\ln(\text{PTH})$, the risk of sarcopenia was 1.52 [95% confidence interval (CI) 0.97–2.39] based on grip strength and 3.52 (95% CI 1.43–8.67) based on ASMM after adjustment for all potential confounders. Higher 25-OHD concentration was protective of sarcopenia. Per unit increase in $\ln(25\text{-OHD})$, the risk of sarcopenia was 0.55 (95% CI 0.36–0.83) based on grip strength and 0.59 (95% CI 0.29–1.20) based on ASMM after adjustment

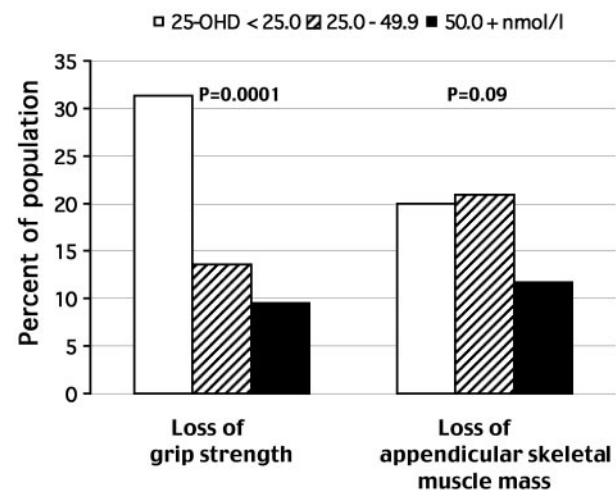


FIG. 1. Prevalence of grip strength loss (defined as loss $>40\%$, study sample $n = 1,008$) and appendicular muscle mass loss (defined as loss $>3\%$, study sample $n = 331$) during 3-yr follow-up according to categories of baseline serum 25-OHD concentration. P value of χ^2 test.

TABLE 1. Baseline characteristics according to 3-yr change in grip strength and appendicular skeletal muscle mass

	Grip strength ($n = 1008$)			Appendicular skeletal muscle mass ($n = 331$)		
	Stable/gain ($n = 872$) Mean (SD)	Loss $> 40\%$ ($n = 136$) Mean (SD)	P	Stable/gain ($n = 279$) Mean (SD)	Loss $> 3\%$ ($n = 52$) Mean (SD)	P
Age (yr)	74.2 (6.1)	76.9 (6.5)	0.0001	73.7 (5.9)	74.9 (6.4)	0.2
Body weight (kg)	75.3 (12.4)	71.8 (12.1)	0.002	75.1 (11.9)	74.8 (13.4)	0.9
BMI (kg/m^2)	26.8 (4.0)	26.8 (4.3)	0.9	26.7 (4.0)	26.2 (3.7)	0.4
Physical activity (kcal/wk)	175 (198)	144 (204)	0.09	193 (209)	208 (191)	0.6
Serum creatinine ($\mu\text{mol}/\text{liter}$)	89 (79–102) ^a	85 (78–99) ^a	0.2	90 (80–100) ^a	92 (75–102) ^a	0.8
Chronic diseases (no.)	1.1 (1.0)	1.5 (1.3)	0.002	1.1 (1.0)	1.0 (1.0)	0.4
Grip strength (kg)	59.0 (20.0)	49.0 (21.7)	0.0001			
Muscle mass (kg)				17.9 (4.3)	18.9 (4.3)	0.12
Follow-up weight change (%)	+0.6 (5.6)	-1.8 (6.7)	0.0001	-0.5 (5.1)	-1.9 (4.6)	0.06
Female (%)	50.2	68.4	0.001	53.8	42.3	0.13
Data collection in summer/spring (%)	41.6	37.5	0.4	42.7	40.4	0.8
Smoking (%)						
Never	34.9	44.1		30.1	34.6	
Former	48.5	35.3		52.7	46.2	
Current	16.6	20.6	0.02	17.2	19.2	0.7
Pulmonary disease (%)	13.8	11.8	0.5	11.1	11.5	0.9
Cardiac disease (%)	24.4	27.9	0.4	21.9	15.4	0.3
Peripheral atherosclerosis (%)	11.5	16.9	0.07	12.5	13.5	0.9
Diabetes mellitus (%)	5.9	8.8	0.2	6.1	5.8	0.9
Stroke (%)	6.2	11.0	0.04	5.4	5.8	0.9
Arthritis (%)	45.9	62.5	0.001	50.5	40.4	0.2
Cancer (%)	10.9	13.2	0.4	9.7	15.4	0.2

^a Median (interquartile range).

for all potential confounders. An interaction was observed between PTH and 25-OHD concentration for loss of ASMM ($P = 0.06$). No interaction was observed between PTH and 25-OHD concentration for loss of grip strength ($P = 0.4$).

After adjustment for age and sex, participants with 25-OHD levels less than 25 nmol/liter were more likely to experience loss of grip strength, compared with those with levels 50+ nmol/liter (Table 2). The odds ratio did not markedly change (from 2.67 to 2.57) after adjustment for all potential confounders. To investigate whether the association between 25-OHD and sarcopenia was still present at higher levels of 25-OHD, we repeated the analyses using four instead of three 25-OHD categories: less than 25, 25–49.9, 50–74.9, and 75+ nmol/liter. The odds ratios for sarcopenia based on grip strength were 4.41 (1.93–10.08), 1.99 (0.97–4.07), 2.05 (1.01–4.16), and 1.0, respectively, indicating that persons with 25-OHD levels between 50 and 74.9 nmol/liter still had an increased risk of sarcopenia. High PTH status was also associated with loss of grip strength. After adjustment for all potential confounders, participants in the highest tertile of PTH (4.0+ pmol/liter) were 1.71 times more likely to

experience a loss of grip strength (95% CI 1.07–2.73), compared with those in the lowest tertile (<3.0 pmol/liter).

A strong association was observed between the 25-OHD categories and loss of ASMM (Table 2). The adjusted odds ratio for loss of ASMM was 2.14 (95%CI 0.73–6.33) for participants with 25-OHD levels less than 25 nmol/liter and 2.25 (1.11–4.56) for participants with 25-OHD between 25 and 50 nmol/liter. Furthermore, persons with PTH levels 4.0 pmol/liter or greater were 2.35 times (95% CI 1.05–5.28) more likely to experience loss of ASMM. The associations of PTH and 25-OHD with sarcopenia were similar in men and women (for interaction $P > 0.12$).

We also investigated whether the observed association of PTH and 25-OHD with sarcopenia could be explained by differences in body weight change. Indeed, participants who lost ASMM experienced a larger weight change [–1.9% (SD 4.6%)] during follow-up, compared with those without ASMM loss [–0.5% (SD 5.1%), $P = 0.06$]. However, when we additionally adjusted for relative weight change in the logistic regression models, the odds ratios were only slightly attenuated. For example, the odds ratio for 25-OHD levels less than 25 nmol/liter changed from 2.14 (0.73–6.33) to 2.24 (95%CI 0.76–6.66). Adjustment for relative weight change also did not change the relationship of PTH and 25-OHD with loss of grip strength.

We also investigated the risk of sarcopenia using combined categories of PTH and 25-OHD. Participants with a high PTH concentration (4.0+ pmol/liter) as well as a 25-OHD concentration less than 25 nmol/liter were 2.51 (95% CI 1.12–5.62) times more likely to experience loss of grip strength and 2.38 (95% CI 0.56–10.18) times more likely to experience loss of ASMM, compared with persons with a low PTH and a high 25-OHD concentration.

Discussion

The results of our study suggest that a lower 25-OHD concentration and a higher PTH concentration increase the risk of sarcopenia (loss of grip strength and loss of appendicular muscle mass) in old age. These relationships were present after careful adjustment for health factors and lifestyle factors, including physical activity. The results are even more striking when considering that we used a large, population-based cohort of older men and women that included

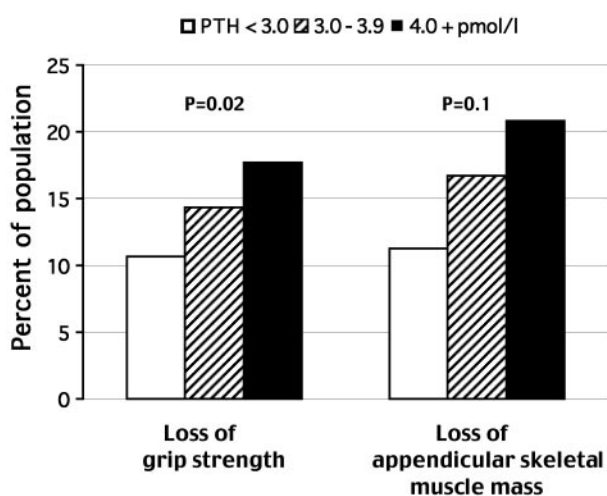


FIG. 2. Prevalence of grip strength loss (defined as loss >40%, study sample n = 1,008) and appendicular muscle mass loss (defined as loss >3%, study sample n = 331) during 3-yr follow-up according to tertiles of baseline serum PTH concentration. P value of χ^2 test.

TABLE 2. Adjusted odds ratios (95% confidence interval) for loss of grip strength and loss of appendicular skeletal muscle mass according to categories of baseline concentration of 25-OHD and PTH

	Loss of grip strength (n = 1008)		Loss of appendicular skeletal muscle mass (n = 331)	
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
25-OHD (nmol/liter)				
<25.0	2.67 (1.52–4.71) ^a	2.57 (1.40–4.70) ^a	1.96 (0.70–5.45)	2.14 (0.73–6.33)
25.0–49.9	1.12 (0.72–1.74)	1.17 (0.74–1.83)	2.05 (1.06–3.95) ^a	2.25 (1.11–4.56) ^a
50.0+	1.0	1.0	1.0	1.0
PTH (pmol/liter)				
<3.0	1.0	1.0	1.0	1.0
3.0–3.9	1.31 (0.83–2.07)	1.39 (0.87–2.23)	1.51 (0.71–3.20)	1.59 (0.74–3.44)
4.0+	1.56 (1.00–2.42) ^a	1.71 (1.07–2.73) ^a	1.81 (0.85–3.87)	2.35 (1.05–5.28) ^a

Model 1, Adjusted for age and sex; Model 2, additionally adjusted for smoking, in serum creatinine concentration, chronic disease, body mass index, season of data collection, and physical activity level.

^a $P < 0.05$ vs. reference category.

very few persons who had 25-OHD levels less than 12.5 nmol/liter (1.3%) or had hyperparathyroidism (3.8%).

A cross-sectional relationship between low vitamin D concentration and poor muscle function has been suggested in some (9, 11, 39–41) but not all (33, 42) studies. The present study is the first population-based study investigating the prognostic value of serum 25-OHD concentration for sarcopenia in older persons using a longitudinal design. Our results are supported by the results of intervention studies that show an improvement of muscle strength and functional performance after vitamin D supplementation in vitamin D-deficient older persons (13, 14, 43). However, oral vitamin D supplementation during 6 months in 98 men and women aged 69+ yr did not improve quadriceps isokinetic strength *vs.* placebo (44). In contrast to our findings, a recent study by Verrault *et al.* (45) showed no association between low vitamin D status and 3-year change in grip strength, knee extensor strength and hip flexor strength among 628 disabled older women. The study by Verrault *et al.* (45) included only women with moderate to severe disability and most participants may already have been below a threshold of strength where vitamin D might not have any additional impact.

It has been suggested that the association between poor vitamin D status and muscle function can be explained by mild secondary hyperparathyroidism (46). However, when we included the natural logarithm of 25-OHD and PTH into a single model, higher levels of 25-OHD remained protective of sarcopenia after adjustment for potential confounders (*e.g.* odds ratio 0.59, 95% CI 0.38–0.92 for grip strength).

Our study also showed that an elevated PTH concentration is a risk factor for sarcopenia in older men and women. A recent prospective study also observed a trend between higher PTH levels and loss of hip flexor and knee extensor strength (45). Our findings are also in line with previous reports of impaired muscle function in patients with primary hyperparathyroidism, which can be restored after treatment (18, 19). In addition, higher PTH levels in nursing home patients have been associated with falling, independent of 25-OHD (20).

Vitamin D metabolites can influence muscle cell metabolism in three ways: by mediating gene transcription, through rapid pathways not involving DNA synthesis, and by the allelic variant of the vitamin D receptor (see Ref. 47 for review). *In vitro* studies show that skeletal muscle cells are a target for 1,25-dihydroxyvitamin D₃ [1,25-(OH)₂D₃] (48). In muscle biopsies taken from middle-aged and elderly orthopedic patients, the presence of nuclear 1,25-(OH)₂D₃ receptor was also demonstrated (41). Myofibrillar protein degradation is increased in rats with vitamin D deficiency, and vitamin D deficiency may affect muscle protein turnover by inducing hypocalcemia and decreasing insulin secretion (49). Furthermore, vitamin D depletion induces negative changes in muscle contraction kinetics in animals (50, 51). A direct effect of vitamin D on human muscle was also demonstrated by an increase in the relative number and cross-sectional area of fast-twitch fibers after a 3- to 6-month treatment with a vitamin D analog (52).

PTH may also have a direct effect on skeletal muscle because administration of PTH has been shown to impair energy production, transfer and utilization in skeletal muscle of

rats (53) and influences skeletal muscle protein and amino acid metabolism in rats (54). PTH is also known to increase free intracellular calcium concentrations in muscle tissue (55), which may disrupt muscle structure or function (46). An indirect effect can also be hypothesized. PTH is known to induce the production of IL-6 and IL-6sR in rat liver and increases circulating levels of these cytokines *in vivo* (56). Elevated IL-6 levels in older persons have recently been associated with lower muscle mass and lower muscle strength (57) and are hypothesized to influence sarcopenia (58).

No generally accepted, sharp diagnostic criteria for vitamin D deficiency are currently available. In our study we used the proposed threshold less than 25 nmol/liter to indicate vitamin D deficiency and 25–50 nmol/liter to indicate mild vitamin D deficiency (5). However, results from other studies suggest that the threshold for vitamin D deficiency should be 50 nmol/liter (59, 60) or as high as 76–90 nmol/liter (61, 62). Of interest is our observation that study participants with 25-OHD levels between 50 and 74.9 nmol/liter were 2 times more likely to experience loss of grip strength, compared with those with 25-OHD levels of 75+ nmol/liter. This suggests that 25-OHD concentrations should be as high as 75 nmol/liter to avoid loss of grip strength. Future research is needed to define optimal vitamin D levels that may contribute to the prevention of sarcopenia, falls, and disability in older persons.

Vitamin D deficiency is common in geriatric patients (30–90% based on the used definition) and independent, community-dwelling older persons (2–60%) (5, 6). In addition, hypovitaminosis D is also prevalent in young persons, especially African Americans, with uncertain consequences (63). This high prevalence and the results of our study suggest that poor vitamin D status and secondary hyperparathyroidism may have a large impact on the loss of muscle mass and muscle strength with aging in the general population. It is known that vitamin D supplementation increases 25-OHD and 1,25-(OH)₂D₃ and decreases PTH (5, 64). Spending more time outdoors will also increase vitamin D status (65). The last option seems preferable for older persons when combined with physical activity because physical activity will increase muscle strength and will lower the risk for decline in functional performance and disability with aging (39, 66, 67).

Some of the weaknesses of the present study should be discussed. Persons who were lost during the 3-yr follow-up are likely to have had a poorer health status and a greater loss of muscle mass and strength. However, this selection will likely have resulted in an underestimation of the associations under study. Second, no repeated measurements of hormone status were made during follow-up, and no other hormones were assessed in the study. We therefore could not account for changes in hormone status over time or for other potentially important hormones such as sex hormones. Third, no accepted definition of sarcopenia based on repeated measurements of muscle mass or muscle strength is available. We rather arbitrarily based our definition on the 15th percentile of the study sample with the greatest loss of muscle mass or muscle strength. However, in a sensitivity analysis, we repeated the statistical analyses using the 10th or 20th percen-

tile of the study sample to define sarcopenia, and very similar results were obtained. Fourth, we used grip strength as an indicator of overall body strength. Future studies should include isometric and isokinetic measures of upper and lower extremity strength to better reflect body strength. Fifth, the current study was conducted in three regions in The Netherlands, and its results should not be generalized to other geographical regions. Lastly, we had no information on the nutritional status of the participants. We therefore cannot exclude whether poor nutritional status associated with lower vitamin D status may partly explain our results. However, adjustment for baseline body mass index and relative weight change during follow-up did not markedly change the results of our study.

In conclusion, the results of this prospective, population-based study show that lower 25-OHD levels and higher PTH levels increase the risk of sarcopenia in older men and women.

Acknowledgments

Received April 8, 2003. Accepted September 2, 2003.

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This work was supported by a fellowship of the Royal Netherlands Academy of Arts and Sciences. The Longitudinal Aging Study Amsterdam study is financially supported by the Dutch Ministry of Public Health, Welfare, and Sports.

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