Published in final edited form as:

J Frailty Aging. 2019 ; 8(3): 131–137. doi:10.14283/jfa.2018.40.

Serum Vitamin D and Age-related Muscle Loss in Afro-Caribbean Men: The Importance of Age and Diabetic Status

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Abstract

Background: Prospective studies examining the potential association of vitamin D with age-related muscle loss have shown inconsistent results.

Objective: To examine the association between baseline serum 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), and prospective change in lean mass with aging in African ancestry population. We also determined if associations were modulated by age and diabetes mellitus (DM).

Design: Prospective observational cohort study.

Setting: Data were collected from a random sub-sample of 574 men, participants of the Tobago Bone Health Study (TBHS).

Participants: 574 Afro-Caribbean men, aged 43+ years (mean age: 59.1 ± 10.5), who were randomly selected as the participants in both the baseline and the follow-up visits.

Measurements: Baseline fasting serum 25(OH)D was measured using liquid chromatography mass spectrometry (LC-MS/MS), and and $1,25(OH)_2D$ was measured using radioimmunosassay (RIA). Changes in dual-energy X-ray absorptiometry (DXA)-measured appendicular lean mass (ALM), and total body lean mass (TBLM) were measured over an average of 6.0 ± 0.5 years. The associations of 25(OH)D and $1,25(OH)_2D$ with ALM and TBLM were assessed by multiple linear regression model after adjusting for potential confounders.

Results: When stratifying all men into two groups by age, greater baseline 25(OH)D and $1,25(OH)_2D$ levels were associated with smaller losses of ALM and TBLM in older (age 60+ years) but not in younger (age 43 – 59 years) men. When stratifying by DM status, the associations of 25(OH)D and $1,25(OH)_2D$ with declines in ALM and TBLM were statistically significant only in prediabetic, but not among normal glycemic or diabetic men.

Conclusion: Higher endogenous vitamin D concentrations are associated with less lean mass loss with aging among older and prediabetic Afro-Caribbean men independent of potential

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Disclaimers: None of the authors report a conflict of interest related to this study.

confounders. Our findings raise a possibility that maintaining high serum vitamin D level might be important for musculoskeletal health in elderly and prediabetic African ancestry men.

Keywords

lean mass loss; skeletal muscle; aging; diabetes; sarcopenia

1. Introduction

Age-related muscle loss and associated physical function impairment are strongly related to decreased quality of life and increased physical disability, morbidity and mortality in later life (1). Thus, preserving muscle mass in the elderly is of public health importance. In recent years, increasing attention has been drawn to the potential beneficial role of vitamin D on preserving skeletal muscle mass with aging, despite conflicting results have been reported in several prospective studies. In a study by Visser et al., vitamin D deficiency (25(OH)D < 20 ng/mL) in both men and women aged 55–85 years old was associated with increased the risk of sarcopenia more than two times than those who had sufficient serum 25(OH)D levels (2). Similarly, a study by Liu et al. also suggested that lower 25(OH)D was associated with greater appendicular lean mass loss in Chinese aged 50–70 years old (3). Recently, Hirani et al. reported that those who were in the lowest quartile of serum 25(OH)D level (25(OH)D < 40 nmol/L) and $1,25(OH)_2D$ (< 62 pmol/L) had roughly twice the risk of sarcopenia of those with highest quartile during a 5-year follow-up in Australians aged ≥ 70 years old (4). In contrast, Scott et al. reported that baseline 25(OH)D level was not associated with change in appendicular lean mass over an average of 2.6 years in Caucasian aged 50–79 years (5). Chan et al. also found non-significant association over 4 years in Chinese population aged 65 and older (6). The majority of research on this topic has been conducted in Caucasian and Asian individuals, no prospective study was conducted in African ancestry population.

Afro-Caribbeans are known to have lower prevalence of vitamin D deficiency compared to African Americans and Caucasians, possibly due to the difference in geographic location, sunlight exposure, and lifestyles (7,8). Although low vitamin D level has often been associated with increased risk of insulin resistance and diabetes mellitus (9), the Afro-Caribbean populations have, paradoxically, high burden of diabetes mellitus (DM), possibly due, in part, to different characteristics of skeletal muscle, such as different rate of muscular fat infiltration and/or distinct composition of muscle fibers (10–12). Because DM may further exacerbate muscle loss in older adults (13), this population may be at higher risk of age-related muscle loss. However, little is known to what extent their high level of vitamin D and their high burden of DM impact the association of vitamin D with age-related skeletal muscle loss in Afro-Caribbean populations.

In the present study, we investigated the association of the baseline serum levels of 25(OH)D and $1,25(OH)_2D$, a biologically active form of 25(OH)D, with longitudinal changes in lean mass over an average of six years in Afro-Caribbean men aged 43 and older. Further, because advancing age and DM may alter vitamin D levels and are associated with an accelerated loss of lean mass with aging, we also tested if associations depend on age, or the presence of prediabetes or DM.

2. Methods

Study Population

From 1997 to 2003, 3,170 predominantly Afro-Caribbean men aged 40 and older were recruited for population-based Tobago Bone Health Study (TBHS) on the island of Tobago, Trinidad & Tobago. Details of the study design have been previously published (14). Briefly, eligibility criteria included being ambulatory, non-institutionalized and not terminally ill. From 2004 to 2007 (baseline for the current analysis), 2,174 men in the original cohort completed a total body dual energy x-ray absorptiometry (DXA) scan. From 2010 to 2013 (follow-up for the current analysis), 1653 men (76% of participants at baseline visit) who had DXA measured returned for repeat DXA scans. After a follow-up exam was completed, we randomly selected 574 who came both visits to have serum 25-hydroxyvitamin D (25(OH)D) and 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) measured in fasting serum samples obtained at the baseline clinic visit, with average follow-up time of 6.0 years (range: 4.6 – 8.5 years). Men selected for 25(OH)D and $1,25(OH)_2D$ measurement were similar to those not selected in terms of baseline age, height, weight, prevalence of DM and hypertension, and other characteristics. However, selected men had significantly higher rate of physical activity (66.7% vs 42.7%, $P < 0.001$), and lower rate of cancer (5% vs 9.2%, $P = 0.001$). The Institutional Review Boards of the University of Pittsburgh and the Tobago Ministry of Health and Social Services approved this study and all subjects gave written informed consents.

Baseline and Follow-up DXA scans (2004–2007, 2010–2013)

Lean mass was measured at baseline and follow-up exams by Hologic QDR-4500W scanner (Hologic, Bedford, MA, USA) (15) according to the manufacturer's instructions. Scans were analyzed with QDR software version 8.26a. The annual percentage change in ALM and TBLM were calculated for each individual as [(follow-up – baseline)/baseline × 1/follow-up years].

Biochemical Measurements

We were able to measure $1,25(OH)_2D$ levels in addition to 25(OH)D, which only one prospective study has been conducted to investigate it role in musculoskeletal health despite it is a biologically functional form of vitamin D (4). Blood samples were obtained in the morning by venipuncture after a 12-hour fast. Sterile red top (serum) tubes were allowed to stand at room temperature for a maximum of 20 minutes to clot before centrifugation. Serum was aliquoted into cryovials and immediately frozen at −80˚C. All samples remained frozen until assay. 25(OH)D was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) which is considered as a gold standard to measure 25(OH)D (16), and $1,25(OH)_2D$ was measured by radioimmunoassay (RIA) (Diasorin) which is an accurate and validated method (17). The assay involves an extraction and purification step of vitamin D metabolites. The treated sample is assayed using a competitive RIA procedure based on a polyclonal antibody specific for both 25(OH)D and $1,25(OH)_2D$. The intra- and inter- assay coefficients of variation were 7% and 14%, respectively. Measurement of intact parathyroid hormone (iPTH) in serum was performed using a Scantobodies immunoradiometric assay

(Santee, CA) at Columbia University (18). The inter- and intra-assay coefficients of variation were 8.4% and 5.6%, respectively.

Other Measurements

We administered questionnaires asking race/ethnicity, demographic characteristics, medical history, physical activity, and lifestyle habits. Moderate alcohol use was defined as having consumed 4 or more drinks per week in the past 12 months. Smoking was defined as self-reported current smoking. We considered that men were physically active if they reported "walking for exercise in the past 7 days", because walking is the major mode of physical activity on the island (19). We measured body weight with lightweight clothing and without shoes in kilograms using a calibrated balance beam scale. Height was measured in centimeters using a wall-mounted height board without participants wearing shoes.

Medical Conditions

DM was defined as fasting serum glucose ≥ 126 mg/dL or currently taking anti-diabetic medication. Prediabetes was defined as a fasting serum glucose level of 100–125 mg/dL measured at baseline without being diagnosed with diabetes or taking antidiabetic medication. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg, or currently taking antihypertensive medication. A history of cancer was identified by self-reported physician's diagnosis. Vitamin D deficiency was defined as serum 25(OH)D < 20 ng/mL, and insufficiency as 20 – 29 ng/mL (20).

Statistical analysis

Descriptive statistics, including mean and standard deviations, were calculated for all variables. Multiple linear regression analyses were performed to assess the relationship of 25(OH)D and $1,25(OH)_2D$ to annualized rates of change in ALM and TBLM. Potential confounders included baseline: age, height, weight, physical activity, smoking, alcohol intake, major comorbidities (diabetes, hypertension, and cancer), and iPTH levels, as well as, change in weight during follow-up. To examine the potential modulating impact of aging on the association, we stratified men into two groups: a younger (age 43 – 59) and older group (age 60+). In secondary analyses, we also examined the potential modulating role of DM on lean mass loss with aging by stratifying subjects into three categories: no diabetes (non-DM), prediabetes (pre-DM) and diabetes (DM). Multicollinearity was assessed by variance influence factor (VIF). For all significant associations, locally weighted scatter smoothing (lowess) plot was used to assess if there was any cut-off point. Statistical significance was defined using an alpha of $P < 0.05$ (two-sided). All analyses were performed by STATA/MP version 14 (StataCorp, College Station, TX).

3. Results

Association of baseline 25(OH)D and $1,25(OH)_2D$ with annual rate of change in lean mass

Table 1 shows the general characteristics for all 574 men and for men stratified by age group (age 43–59 N = 297 versus age 60+ N = 277). Average 25(OH)D and $1,25(OH)_2D$ levels were 33.90 ± 9.12 ng/mL and 104.38 ± 46.21 pg/mL, respectively. The prevalence of vitamin D deficiency and insufficiency were 3.8% and 33.1%, respectively. ALM declined

by −0.81 ± 0.84 %/year, whereas TBLM declined by −0.78 ± 0.70 %/year. There were significant differences in body weight, alcohol consumption, DM, hypertension, serum iPTH level, annual change in ALM and TBLM, and $1,25(OH)_2D$ between middle-aged men (aged 43 – 59) and older men (aged 60+) ($p < 0.05$ for all).

Table 2 shows the results of the multiple linear regression analyses to assess the relationship between each vitamin D and rate of change in lean mass. In all men and the middle-aged group, neither 25(OH)D nor $1,25(OH)_2D$ were significantly associated with ALM or TBLM change during follow-up. However, among older men, 1 standard deviation (SD) greater baseline 25(OH)D was associated with a 10% lower rate of decline in TBLM ($p = 0.010$). Similarly, 1 SD greater baseline $1,25(OH)_2D$ level was associated with a 16% lower rate of decline in ALM ($p = 0.004$) and a 12 % lower decline in TBLM ($p = 0.005$). 25(OH)D was borderline, but not significantly, associated with ALM loss in the older men ($p = 0.068$). Using the lowess regression plot, we did not visually find any cut-off points for both 25(OH)D and $1,25(OH)_2D$ (data not shown).

Association of baseline 25(OH)D and $1,25(OH)_2D$ with annual change in ALM and TBLM by diabetes status

Because DM has been associated with accelerated loss of lean mass with aging (12), we examined the association between baseline vitamin D metabolites levels and lean mass change in strata of DM status (non-DM, pre-DM, and DM; Table 3). Men with DM were significantly older, more obese, but lost more weight over-time than non-diabetic men ($p \leq 0.001$ for all). However, the difference in lean mass change between non-diabetic men and diabetic men lost statistical significance after adjusting for age and body weight (data not shown). The association of greater baseline 25(OH)D and $1,25(OH)_2D$ with lower rate of decline in ALM and TBLM was only significant in the pre-DM group, but not non-DM or DM groups (Table 4). From the lowess regression plot, we did not visually identify any cut-off points for both 25(OH)D and $1,25(OH)_2D$ (data not shown).

4. Discussion

In the present study, we found that higher serum 25(OH)D and $1,25(OH)_2D$ levels are independently associated with lower rate of age-related lean mass loss in older Afro-Caribbean men. Our findings related to endogenous vitamin D and lean masses are in line with some (2–4), but not all (5,6), previous prospective studies on this topic. This discrepancy may be due to the difference in methodology to measure variables and/or population characteristics. Our studied population is entirely African ancestry, which we thus far found no prospective study on the topic conducted in African ancestry population, and found only one cross-sectional study with meaningfully high proportion of non-Caucasian men (21). Although this study reported that no association was found between serum vitamin D and muscle mass, due to the difference in study design, geographic location, and demographic characteristics, this finding may not be comparable to our study.

The men in the TBHS had a much lower prevalence of vitamin D deficiency (3.8%) than studied populations in the most previous prospective studies (9.6 – 53.7%) (2–5). One study investigated Chinese people who had relatively low prevalence of vitamin D deficiency

(5.9%) (6), but unlike the current study, no association was found between appendicular lean mass and baseline 25(OH)D over 4.5 years. In contrast, Liu et al. reported significant association between serum 25(OH)D and appendicular lean mass in older Chinese population with relatively high vitamin D deficiency (53.7%) (3). Based on the two studies conducted in Chinese population, the author suggested that threshold level of 25(OH)D from which 25(OH)D has a preventive effect on muscle mass might exist. However, we did not find any threshold effect for either 25(OH)D or $1,25(OH)_2D$ levels in the associations with a change in lean mass. Whether the difference in race/ethnicity and/or lifestyles affect these inconclusive results is unclear.

In addition, we found that the association between serum vitamin D and lean mass change was dependent on DM status such that the beneficial effect was only significant in those with prediabetes versus normal glycemia or DM. Given that antidiabetic medication has a protective effect on muscle mass (22), we postulate that the treatment effect may be masking the association between serum vitamin D and lean mass loss in the DM group. Although most analyses in the previous studies adjusted for diabetes with other covariates, to our knowledge, no study was conducted in diabetic or prediabetic individuals including cross-sectional studies. Our finding suggests that whereas the relationship between serum vitamin D and lean mass loss is unclear in younger or non-diabetic African ancestry men, it may become linear in those who are old or who have insulin resistance. This may be of clinical importance because individuals with insulin resistance have been shown to be at particularly high risk of age-related muscle mass loss (13).

We found that $1,25(OH)_2D$, a hormonally active form of 25(OH)D, was associated with age-related changes in lean mass to a similar extent as 25(OH)D. It has been suggested that these metabolites may have distinct effects on the muscle, with $1,25(OH)_2D$ being correlated with muscle strength, versus 25(OH)D linked to muscle efficiency and muscle-specific gene expression (23). With regards to muscle mass, only two previous studies investigated the effect of $1,25(OH)_2D$. While Hirani et al. suggested that the effect of $1,25(OH)_2D$ was similar with 25(OH)D with regards to the risk of sarcopenia (4), a cross-sectional study conducted by Marantes et al. reported a significant association of $1,25(OH)_2D$ with muscle mass and power, but not for 25(OH)D (24). However, in our study, the effects of 25(OH)D and $1,25(OH)_2D$ on lean mass were largely similar. Thus, potential differences in the effects of vitamin D metabolites on muscle mass and function should be clarified in future studies.

Several potential mechanisms have been proposed to explain the beneficial effects of vitamin D on age-related skeletal muscle loss. Vitamin D may regulate insulin sensitivity in skeletal muscle (25), possibly by upregulating insulin receptors expression (26), and enhancing the insulin signaling pathway (27). Vitamin D may alter the serum levels of muscle growth factors and atrophy markers as reported in an animal study (28). Furthermore, it has been suggested that vitamin D may directly contribute to myoblast proliferation and differentiation in animal (29), and human cells (30) by regulating gene transcription via vitamin D receptor (VDR) signaling pathway.

Our study has potential several limitations. First, although our study was longitudinal, our observational study design does not enable us to definitely confirm a causal relationship

between serum vitamin D and lean mass changes. Second, our sample included only Afro-Caribbean men; thus, our findings may not be applicable to women or other racial/ethnic groups. A previous study reported that although the effect modification by sex was not detected in the association between serum vitamin D and muscle mass change, the degree of muscle mass loss was greater in men than women in Chinese population, suggesting the difference in sex-specific hormonal status between men and women may play a role in the association (3). Thus, the potential effect of sex, as well as, of sex-specific hormones in the association should be clarified in future studies. Third, we were not able to examine the potential modulating effect of nutritional status and sunlight exposure due to limited data in the TBHS. Fourth, the random selection of men to have vitamin D measured was performed after the follow-up visits were completed. Although we tested for baseline differences between the men selected versus those not selected for vitamin D measurement, and found them to be largely similar, we detected significant differences in the prevalence of cancer and the level of physical activity. Thus, it is possible that a survival bias remained at play in the observed associations. Finally, our data collection completed by 2013, which can be considered to be old. However, we believe that the trend we observed among Tobagonian Afro-Caribbean men would remain to date, unless a considerable change in their nutrition, lifestyle or weather on the island occurred. Despite our study limitations, the current study has a number of unique strengths ands add to the current literature on vitamin D and lean mass loss with aging. First, our study is the first longitudinal study that we are aware of that focuses on serum vitamin D and lean mass changes with aging in African ancestry individuals. Additionally, we were able to examine the individual relationships between 25(OH)D and its hormonally active form, $1,25(OH)_2D$, with age-related changes in lean mass. Finally, our relatively large sample size enabled us to have enough statistical power to stratify total sample to subgroups to assess potential modulating effect of both age and DM status.

In conclusion, we found that greater serum 25(OH)D and $1,25(OH)_2D$ levels were independently associated with lower age-related loss of lean muscle mass in older and prediabetic Afro-Caribbean men. Our findings suggest that maintaining high serum vitamin D level may be important in musculoskeletal health, particularly in the elderly and those who have insulin resistance. Further studies are needed to better understand the association between vitamin D and skeletal muscle aging.

Acknowledgments

Funding

This research was supported, in part, by funding or in-kind services from the Division of Health and Social Services and Tobago House of Assembly, and by grants R01-AR049747 and R01-DK097084 from the National Institute of Health (NIH).

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Table 1.

General Characteristics of Afro-Caribbean Men

Characteristics	All subjects N = 574	Age < 60 N = 297	Age ≥ 60 N = 277	P-value
Age (years)	59.1 ± 10.5	50.3 ± 4.2	68.6 ± 6.2	<0.001
Height (cm)	174.6 ± 6.7	176.1 ± 6.6	172.9 ± 6.4	0.640
Weight (kg)	83.4 ± 14.7	86.1 ± 15.3	80.6 ± 13.6	<0.001
Weight change (kg)	−0.4 ± 7.1	−0.2 ± 7.5	−0.7 ± 6.6	0.414
Annual change in ALM (%/year)	−0.81 ± 0.84	−0.66 ± 0.75	−0.97 ± 0.90	<0.001
Annual change in TBLM (%/year)	−0.78 ± 0.70	−0.65 ± 0.63	−0.93 ± 0.74	<0.001
Physical activity	384 (66.9)	196 (66.0)	188 (67.9)	0.634
Current smokers (%)	44 (7.7)	28 (9.4)	16 (5.8)	0.101
Alcohol consumption (%)	50 (8.7)	33 (11.1)	17 (6.1)	0.035
Diabetes Mellitus (%)	121 (21.1)	49 (16.5)	72 (26.0)	0.005
Hypertension (%)	309 (53.8)	123 (41.4)	186 (67.2)	<0.001
Cancer (%)	28 (4.9)	10 (3.4)	18 (6.5)	0.082
iPTH (pg/mL)	50.34 ± 19.70	48.66 ± 20.83	52.14 ± 18.28	0.035
25(OH)D (ng/mL)	33.90 ± 9.12	33.93 ± 9.74	33.87 ± 8.42	0.937
$1,25(OH)_2D$ (pg/mL)	104.38 ± 46.21	112.86 ± 50.85	95.30 ± 38.73	<0.001
Vitamin D deficiency (%)	22 (3.8)	14 (4.7)	8 (2.9)	0.255
Vitamin D Insufficiency (%)	190 (33.1)	101 (34.0)	89 (32.1)	0.520

• Abbreviations: iPTH, Intact parathyroid hormone, ALM, Appendicular lean mass, TBLM, Total body lean mass, 25(OH)D, 25 hydroxyvitamin D_3, $1,25(OH)_2D$, 1,25 dihydroxyvitamin D_3

• Continuous variables are presented as mean value ± SD, and categorical variables are presented as frequency (percentage)

Table 2.

Associations of Baseline 25(OH)D and 1,25$(OH)_2$D with Annual Percentage Change in ALM and TBLM by Age Category

		All subjects (N = 574)	**Age < 60 (N = 297)**	**Age ≥ 60 (N = 277)**
ALM(%/years)	25(OH)D	0.01 (−0.05, 0.07) p = 0.664	−0.05 (−0.12, 0.03) p = 0.195	0.09 (−0.01, 0.19) p = 0.068
	1,25$(OH)_2$D	0.04 (−0.02, 0.10) p = 0.250	−0.04 (−0.11, 0.03) p = 0.233	0.16 (0.05, 0.26) p = 0.004
TBLM(%/years)	25(OH)D	0.01 (−0.03, 0.06) p = 0.545	−0.05 (−0.11, 0.01) p = 0.092	0.10 (0.02, 0.18) p = 0.010
	1,25$(OH)_2$D	0.03 (−0.02, 0.08) p = 0.247	−0.03 (−0.09, 0.03) p = 0.276	0.12 (0.04, 0.21) p = 0.005

• Abbreviations: ALM, Appendicular lean mass, TBLM, Total body lean mass

• Data presented are β coefficient (95% CI) for annual lean mass change per 1 SD difference in vitamin D (95% CI)

• All models were adjusted for covariates: age, height, weight, physical activity, smoking, alcohol intake, major comorbidities (diabetes, hypertension, and cancer), and iPTH levels, as well as, change in weight during follow-up

Table 3.

Characteristics of Afro-Caribbean Men at Baseline by Diabetes Status

Basal characteristics	Non-diabetic N = 335	Prediabetic N = 118	Diabetic N = 121	P-value
Age (years)	57.6 ± 10.6	60.8 ± 10.8	61.3 ± 9.7	<0.001
Height (cm)	174.9 ± 6.5	174.4 ± 6.6	174.1 ± 7.3	0.251
Weight (kg)	81.7 ± 13.1	85.6 ± 14.7	86.1 ± 18.2	0.001
Weight change (kg)	0.4 ± 5.7	−0.9 ± 5.9	−2.3 ± 10.5	<0.001
Annual change in ALM (%/year)	−0.72 ± 0.79	−0.90 ± 0.85	−0.98 ± 0.92	0.001
Annual change in TBLM (%/year)	−0.68 ± 0.67	−0.90 ± 0.70	−0.95 ± 0.92	<0.001
Smoking (%)	27 (8.1)	9 (7.6)	8 (6.6)	0.616
Alcohol consumption (%)	30 (9.0)	12 (10.2)	8 (6.6)	0.540
Hypertension (%)	155 (46.3)	69 (58.5)	85 (70.3)	<0.001
Cancer (%)	20 (6.0)	5 (4.2)	3 (2.5)	0.117
iPTH (pg/mL)	55.18 ± 17.77	53.55 ± 19.17	45.50 ± 20.98	<0.001
25(OH)D (ng/mL)	34.29 ± 9.78	33.39 ± 8.03	33.33 ± 8.20	0.262
$1,25(OH)_2D$ (pg/mL)	108.26 ± 49.84	103.37 ± 40.54	94.65 ± 39.27	0.006
Vitamin D deficiency (%)	11 (3.3)	4 (3.4)	7 (5.8)	0.452
Vitamin D insufficiency (%)	115 (34.3)	40 (33.9)	35 (28.9)	0.545

• Abbreviations: iPTH, Intact parathyroid hormone, ALM, Appendicular lean mass, TBLM, Total body lean mass, 25(OH)D, 25 hydroxyvitamin D_3, $1,25(OH)_2D$, 1,25 dihydroxyvitamin D_3.

• Continuous variables are presented as mean value ± SD, and categorical variables are presented as frequency and percentage

• P-values were determined using tests for linear trend across the groups

Table 4.

Associations of Baseline 25(OH)D and 1,25$(OH)_2$D with Annual Percentage Change in ALM and TBLM by DM Status

		Non-DM (N = 335)	Pre-DM (N = 118)	DM (N = 121)
ALM(%/years)	25(OH)D	−0.04 (−0.10, 0.03) p = 0.254	0.15 (0.01, 0.29) p = 0.039	0.09 (−0.10, 0.27) p = 0.338
	1,25$(OH)_2$D	−0.03 (−0.09, 0.04) p = 0.426	0.19 (0.05, 0.32) p = 0.007	0.10 (−0.09, 0.30) p = 0.301
TBLM(%/years)	25(OH)D	−0.03 (−0.08, 0.02) p = 0.220	0.13 (0.02, 0.25) p = 0.022	0.12 (−0.02, 0.26) p = 0.094
	1,25$(OH)_2$D	−0.03 (−0.08, 0.03) p = 0.320	0.18 (0.07, 0.29) p = 0.002	0.12 (−0.03, 0.27) p = 0.124

• Abbreviations: Non-DM, Non-diabetes mellitus, Pre-DM. Pre-diabetes mellitus, DM, Diabetes mellitus, ALM, Appendicular lean mass, TBLM, Total body lean mass; 25(OH)D, 25 hydroxyvitamin D_3, 1,25$(OH)_2$D, 1,25 dihydroxyvitamin D_3

• Data presented are β coefficient (95% CI) for annual lean mass change per 1 SD difference in vitamin D

• All models were adjusted for covariates: age, height, weight, physical activity, smoking, alcohol intake, major comorbidities (hypertension, and cancer), and iPTH levels, as well as, change in weight during follow-up