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Title page

Title: The interaction of aging with serum 25(OH)D and 1,25(OH)2 D status on muscle strength

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Short title: Muscle strength, vitamin D deficiency and aging

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Authorship

All authors contributed to conception/design of the research; SD, NB and ME contributed to acquisition of data. SD, NB and SSb participated in analysis and interpretation of the data; SD and PG drafted the manuscript; KD, SSb and CC critically revised the manuscript; and SS-b agrees to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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Transparency Declaration: The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The authors affirm that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

The interaction of aging with serum 25(OH)D and 1,25(OH)2 D status on muscle strength

Abstract

Background: To investigate the combination relationship of age with serum 25-hydroxyvitamin D (25(OH) D) and 1,25-(OH)2D3 levels on muscle strength.

Methods: We performed a cross-sectional study on 270 subjects containing 115 men and 155 women. Serum concentration of 25(OH) D and 1,25-(OH)2D3 were assessed. Hand grip strength (HGS) was measured using a digital dynamometer.

Results: There was no significant difference in mean of HGS among tertiles of 25(OH)D (P=0.350) and $1,25(OH)_2$ D (P=0.467) before and after controlling for potential confounding factors. A significant difference in HGS was found between age categories in both crude (P<0.001) and adjusted models (P=0.018), where mean grip strength increased in the three first age categories, but decreased in the last group (48-69 years old). There was also a significant interaction between age and 25(OH) D (P=0.049) and 1,25-(OH)2D3 (P=0.047) on HGS, in which the combination effect increased the mean of muscle strength up to middle age after adjusting for confounders.

Conclusions: Serum 25(OH)D and $1,25(OH)_2$ D, was not related to muscle strength. However, age, and combination of age with both 25(OH)D and $1,25(OH)_2$ D, significantly resulted in improving in muscle strength up to middle age.

Keywords: vitamin D; 25-hydroxyvitamin D; 1,25-(OH)2D3; muscle strength

What is already known about this topic? There are controversial data about the association between vitamin D and muscle strength; interaction of aging with serum 25(OH)D and 1,25(OH)2 D status on muscle strength also is not clear .

What does this article add? Muscle strength was not different among tertiles of 25(OH)D and 1,25(OH)2 D. Muscle strength was decreased significantly across categories of age. Combination of

age with both 25(OH)D and 1,25(OH)2 D, significantly resulted in increasing muscle strength in to middle age.

Introduction

The decline of muscle mass and strength, considered to be one of the most important age-related organic changes, appears to be associated with an increased risk of cardiovascular morbidity, type 2 diabetes, metabolic syndrome, falls, functional limitation, and fractures [1]. An approximately 40 percent decrease in muscle mass occurs between 20 and 80 years of age, and these changes will be become more expedient after the 5th decade of life [2]. Only about 30-40 percent of structural and functional changes in muscle is due to the aging process[3], and other factors, including level of physical activity and nutritional status, particularly vitamin D, are also responsible [4]. Vitamin D plays a key role in bone mineralization and positively effects musculoskeletal health [5]. However, vitamin D deficiency is a prevalent medical condition worldwide [6]. Beyond the negative impacts of

vitamin D insufficiency on non-skeletal disorders, vitamin D deficiency has been related to loss of muscle strength [7], physical function, and quality of life [8].

Advancing age is usually accompanied by decreases in muscle strength [9, 10], additionally, it has been shown that the serum 1,25-(OH)2D3 concentration also decreases with age [11]. Studies linking vitamin D status and physical function have been conducted in older and young adults and revealed a significant relationship between low 25(OH)D concentrations and poor handgrip strength [12, 13]. Given that 1,25-(OH)2D3 3 synthesis occurs in the renal system, it has been suggested that the reduction in 1,25-(OH)2D3 concentrations in older adults could be because of an age-related decrease in renal function[14]. In addition, the sensitivity of VDRs in target tissues to 1,25-(OH)2D3 may decline with advancing age [15]. However, not all evidence is in support the association of vitamin D status with muscle strength [16], for instance, Kenny et al. examined the effect of vitamin D supplementation on physical performance and strength in healthy older men and found no improvement in these outcomes [17]. It is equivocal as to whether changes in strength are related to vitamin D deficiency via the aging process or not; therefore, we sought to, firstly, investigate the relationship between muscle strength and serum vitamin D, and secondly, investigate the interaction of age and serum vitamin D levels, and their influence on muscle strength

Methods

Participants

The study was conducted using 272 males and females, with a mean age of 18-70 years, who volunteered to participate after primary screening and description of all procedures. This study was conducted between May and September 2018 in Tehran. Eligibility criteria included; aged between 18 and 75 years old, not pregnant or lactating, and no difficulties in performing the necessary testing. Individuals with health conditions, including cardiovascular disease (CVD), chronic kidney disease (CKD), parathyroidism disorders, arthritis, disability, atopy, and endocrine disorders affecting muscle metabolism were excluded. People who were previously supplementing with multivitamins or vitamin D were included as long as they had not used these supplements in the preceding three months. All participants gave written informed consent prior to study commencement.

Demographics and blood pressure

Additional covariates, including age, gender, smoking status (non-smokers, smokers), marital status (married, single), education status (high as above the diploma, low as under diploma) medical history (underlying disease such as diabetic, hypertension and dyslipidemia), supplement intake (vitamin D), physical activity level (low, moderate, vigorous), and sedentary time (hour/day) were obtained using questionnaires.

Physical activity

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), which is an interview-administered instrument. Based on the criteria, data were collected regarding walking, moderate, and vigorous activity in the preceding week. Also, time and frequency of activity days were recorded, and finally, a physical activity score was calculated. In the present study, we used the short form of the IPAQ (the "last 7day recall" version of the IPAQ-SF.), which records four intensity levels of activity: 1) vigorous-intensity activity, including, football, aerobics and heavy cycling 2) moderate-intensity activity, including, volleyball, leisure cycling 3) walking, and 4) sitting.

Anthropometric measurements and body composition

Body weight (to the nearest 0.1 kg) and height were assessed according to standardized procedures. Body mass index (kg/m^2) was calculated as; weight (kg) divided by height^2 (m). Waist circumference (WC) was measured between lower rib and iliac crest, at the widest portion, with light clothing, using a tape meter (Seca 201, Germany) without any pressure to the body. Body composition was measured by bioelectrical impedance analysis (Inbody720, Sweden, 2017). The body composition measurements were fat mass, visceral fat area (VFA), lean body mass, and basal metabolic rate (BMR).

Dietary intake

Dietary data were gathered using a validated semi-quantitative food frequency questionnaire to evaluate dietary intake, including amounts of macronutrients, micronutrients, and energy consumption. The food frequency questionnaire, containing 168 items, is a commonly used tool to obtain frequency and portion size data about food and drink consumption over a specified time duration, typically the past year. Finally, grams per day of nutrients were calculated using the USDA dietary composition table not used the Iranian dietary composition table.

Muscle strength

Grip strength is a non-invasive, reliable, and cost-benefit measurement and has been identified to be a reliable indicator of physical performance specially muscle strength [18]. Grip strength was assessed using a digital dynamometer (Saehan, model SH5003; Saehan Corporation, Masan, South Korea). Participants were asked to sit down and place the dynamometer in the dominant and non-dominant hand, sequentially, with the arm flexion to 90° at the elbow and the extended forearm parallel to the ground. The size of the grip handle was adjusted for each participant. The participants were instructed to squeeze, with maximum force, for 3 to 5 s in this position. The assessments were repeated three times in both hands, then the mean of the best result of dominant hand, and best result of both hands was registered.

Biochemical analyses

Fasting blood samples were obtained after 12-hours. Serum samples were stored at 80 ° C until analyses. All samples were analyzed for 25(OH)D and 1,25-(OH)2D3 concentrations by ELISA method using the following kits: 25-(OH) D ELISA kits (Monobind, California, USA) with inter- and intra-assay coefficient variances (CVs) of 10.4 to 11.5%, respectively and 1,25-(OH)2D3 ELISA kits (Crystal Day, Shanghai, China) with inter- and intra-assay coefficient variances (CVs) of 9.8 to 10.3%, respectively. The lower detection limit of 25(OH)D and 1,25-(OH)2D3 were 4 ng/mL and 4.8 pmol/L, respectively. Fasting blood sugar (FBS) was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun, Tehran, Iran). Serum HDL-C was measured using a cholesterol oxidase phenol aminoantipyrine method, and triglyceride (TG) was measured using a glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. All biochemical analyses were performed at the laboratory department of Community Nutrition.

Statistical analysis

All analyses were carried out with SPSS version 25. Demographic and clinical characteristics, HGS test, and body composition values were reported as mean ± SD across tertiles of 25(OH) D and 1,25-(OH)2D3. We used the chi square test and analysis of variance (ANOVA) to compare qualitative and quantitative values across vitamin D categories, respectively. Pearson correlation coefficients were calculated to assess the relationship between serum level of vitamin D (25(OH) D, 1,25-(OH)2D3), and HGS. Furthermore, analysis of covariance (ANCOVA) and multivariate regression were used to adjust the potential confounders such as age, sex, physical activity level, BMI, lean body mass,

smoking status and medical condition. We performed two-way analysis of variance to investigate the interaction between age and serum level of vitamin D on HGS, across the tertiles of vitamin D and age categories.

HGS was divided to two groups based on the median of HGS (median=27.4 kg). Then, the association between vitamin D and chance of higher HGS was analyzed by logistic regression analysis, in crude and adjusted models for age, sex, BMI, physical activity level, smoking status, underlying disease, and LBM. Statistical significance was accepted, *a priori*, at $P<0.05$.

Results

Demographic and clinical characteristics of participants across tertiles of the serum 25(OH) D and 1,25-(OH)2D3 levels are shown in **Supplemental Table 1**. In this study, 270 cases with 119 men and 151 women participated. More than half of participants were female, married, non-smokers, with high education status, and did not take vitamin D or calcium supplements. The percentage of married subjects (p=0.029) and people with no vitamin D supplementation (p=0.001) was more than 50% of the population, which was statistically significant. Subjects with low education level, moderate physical activity level, and underlying disease (diabetes, hypertension, and dyslipidemia) represented a lower proportion of our study population. The mean age of participants was 36.83±13.18 years, whilst mean serum 25(OH) D and 1,25-(OH)2D3 levels were 20.77±12.50 ng/ml and 59.65±6.51 Pmol/l, respectively. The average maximal hand grip strength was 34.78±12.87 kg. The mean age of subjects in the highest tertile was significantly higher than the other two tertiles. There were significant differences across 25(OH) D tertiles in some variables, including height (p=0.04), BMI (p=0.007), body fat percentage (p=0.04), body fat mass (p=0.039), visceral fat area (VFA) (p=0.03) and abdominal fat (p=0.05). No significant differences were observed among 25(OH) D tertiles in the other physical and clinical parameters. There were no significant differences between the serum 1,25-(OH)2D3 category in any demographic or clinical characteristics. Grip strength for the dominant hand or both hands in the highest tertile of vitamin D (25(OH)D and 1,25-(OH)2D3) was non significantly different between tertiles.

Supplemental Table 2 presents the Pearson correlation coefficients for the association of anthropometric measures, body composition, dietary intakes, clinical characteristics and hand grip strength with serum 25(OH) D and 1,25-(OH)2D3 levels. Significant correlations were only observed

between age (P<0.001), height (P=0.003), body fat percentage (P=0.023) and bone mineral content (P=0.040) with serum 25(OH) D levels. None of measurements had a significant correlation with serum 1,25-(OH)2D3 levels.

Linear regression analysis was performed with and without adjusting for age, sex, body mass index, physical activity level, WC, LBM, underlying disease and smoking status in different models, as demonstrated in **Table 1.** There were no significant associations between hand grip strength and 25(OH) D or 1,25-(OH)2D3.

Table 2 shows the mean of HGS according to tertiles of 25(OH) D and 1,25-(OH)2D3. No significant relationship was observed between serum 25(OH)D or 1,25-(OH)2D3 levels and HGS, even after adjusting for all confounders. However, HGS was significantly different across age categories in both crude (P<0.001) and adjusted models (P=0.008). As age increased, HGS increased significantly across age quartiles, except the highest quartile (**Supplemental Table 3**).

Table 3 shows the interaction of age and serum 25(OH) D and 1,25-(OH)2D3 levels before and after adjustment for confounders. There was a significant interaction between serum level of 25(OH) D and age on HGS in crude (p=0.038) and adjusted models (p= 0.049). There was a significant interaction between age and serum levels of 1,25-(OH)2D3 on HGS (p= 0.199), but only after controlling for all confounders (p=0.047). Hand grip strength increased in the three first age categories, but decreased in the last age group (48-69 years old).

Logistic regression analysis was applied to show the association between vitamin D or age categories with HGS (**Table 4**). The odds of a higher HGS did not differ across tertiles of 25(OH)D and 1,25-(OH)2D3, with and without controlling for confounders. The odds ratio of a higher HGS was significantly different across quartiles of age in crude and adjusted models (p=0.031), in which chance of higher HGS in the last quartile of age, as compared with the first quartile was 89% lower.

Discussion

According to our findings, no significant relationship was found between serum 25(OH)D and 1,25-(OH)2D3 levels and HGS with or without adjustment for confounders. However, mean HGS was different by age quartiles, where HGS increased to about 50 years old, and thereafter, HGS decreased. It was also shown that there was a significant interaction of age and serum 25(OH)D and 1,25-(OH)2D3 levels on muscle strength and mean HGS increased up to middle age.

The molecular pathways by which vitamin D may influence muscle cells have been partly determined. Vitamin D plays a role in muscle contractility and plasticity by interacting with calcium [19]. Further, serum 25(OH) D levels have also been linked to ATP synthesis by recovery muscular creatine phosphate stores after exercise [20], whilst vitamin D may contribute to muscle strength development via vitamin D receptors (VDR). VDR for 1,25-dihydroxy vitamin D have been identified in muscle cell; indeed, reduced VDR expression can lead to decreases in the muscle cell response, including synthesis of myogenic transcription factors to 1,25-(OH)2D3 or calcitriol[21]. Recent studies have reported inconsistent results regarding the association between vitamin D status and muscle strength or disability in the elderly population. The findings of Von Hurst et al showed that there is a positive and significant relationship between 25(OH)D and hand grip strength [22]; however, a cross-sectional study asserted a negative relationship between vitamin D status and muscle strength [23]. In contrast, the present study did not show a significant relationship between serum vitamin D level and hand grip strength. Correspondent with our finding, Verreault et al.[16], advocated that vitamin D deficiency is not related to decreased muscle strength, functional mobility, or disability in older women. In addition, Boonen et al.[24], also observed no relationship between 1,25-(OH)2D3 and knee extensor strength in healthy women aged 70 years and older.

Several clinical trials have also investigated the effect of vitamin D on muscular strength [25, 26] and disability in the elderly [27]. In most of these studies, supplementation yielded no beneficial effect on muscle function, including mobility, lower extremity muscle strength, or hand grip strength. However, it should be noted that most of these studies were short term trials (less than 6 months) in participants with normal vitamin D levels, and only two clinical trials have reported beneficial effects on grip strength [27, 28]. Frequency of the VDR allele and the imbalance of linkage between the markers and the disease alleles, which is largely dependent on ethnicity, may be responsible for our finding [29]. Geusens et al.[30], reported that grip strength was directly related to the VDR *Bsm*I polymorphism in Belgian elderly women. Wu et al. [31] also demonstrated that the *Apa*I polymorphism was associated with poor HGS in elderly Chinese subjects, but corresponding results were not confirmed by Ike et al., in Japanese women. Consequently, the mechanism for the contradictory relationship between serum 25-hydroxy vitamin D concentration and HGS is unclear;

although tut the ethnic differences in expression of VDR may be, at least in part, responsible for these inconsistencies.

Prior studies to have reported positive associations between vitamin D and muscle function have included subjects aged 65 years and over, in contrast, studies in populations with different age ranges of older and young women do not avow such findings. Age is another factor affecting muscle strength, where muscle strength increases from childhood to adulthood, reaching its peak in mid-adulthood, and then gradually decreases. Many studies have reported that muscle strength reduces with advancing age, and this gradual decline begins at around 50 years of age [32, 33]. A study in China noted that measures to preserve muscle health and strength should be performed at the same time [34]. In the current study, HGS changes were similar to previous observations with ageing, and the loss of muscle strength was evident from the age of 48. Age-related loss of muscle is inevitable, and probably the most important contributing component to diminished muscle strength. In an attempt to elucidate the main cause of age-associated atrophy, a large number of studies have evaluated muscle morphology, and a consensual conclusion indicates a decrease in the average type II and type I fibers size with increasing age. The reduction in muscle fiber size is shown to be less than the decrease in muscle volume, so a decline in the number of muscle fibers has also been suggested, and empirical evidence highlights that a reduction in the motor unit number in the lower and upper limbs occurs concurrently with age. The present study confirmed the loss of muscle mass in the aging process, and consequently age-related reduction in muscle strength, which is concordant with findings of previous studies [35, 36].

In addition to loss of muscle mass and strength with aging, other age-related factors affect vitamin D metabolism; for instance, 1,25-(OH)2D3, the active metabolite of 25(OH)D, can mediate the impact of 25(OH)D on grip strength. Numerous studies have found serum levels of 1,25-(OH)2D3 decline with advancing age. Since 1,25-dihydroxy vitamin D is synthesized in the kidney, it has been suggested that this age-related decline in the elderly may be due to decreased renal function. Moreover, the expression of VDR in skeletal muscles reduces with ageing [37], which can also diminish the muscles functional response to calcitriol [37]. Furthermore, 1,25-dihydroxy vitamin D purportedly regulates the synthesis of calcium transporter proteins and muscle contraction [38].

In the present study, we showed that age and serum level of vitamin D interacted with muscle strength. However, considering the trend observed in different age groups and serum levels of vitamin D, it seems that the effect of age on muscle strength is more prominent. In this regard, a previous study was conducted to evaluate the association between vitamin D and HGS at age 50 and over, divided by age (before and after age 50) and gender, and no relationship was found in any age and sex group, except men over the age of 50 years.

Apart from age as main contributor of vitamin D deficiency and muscle strength, it should be noted that there is a gender difference in both vitamin D deficiency and muscle strength. Although we adjusted all analyses for sex, noteworthy that there is a qualitative difference in muscle tissue ad strength between men and women[39], despite no significant differences in muscle fibers number[40]. It has been reported that women were more commonly to be vitamin D deficient than men and a significant sex differences in the associations between vitamin D deficiency and musculoskeletal health has been found[41]. However, in another study no association was found between skeletal muscle mass and muscle index in any age or sex specific group[42]. It was suggested that serum levels of vitamin D may not be an appropriate biomarker or therapeutic targets for skeletal muscle mass when considering muscle health[43]. Also, variation in body fat mass and body size may be another reason for variation in vitamin D deficiency by sex[44], due to sequestration of vitamin D in adipose tissue after cutaneous synthesis or dietary intake[45]. In a study by Halliday et al., no difference in vitamin D status depending on sex in athletes has been found which may be related to the reduced body fat range of the athlete population[46].

A major strength of this study was recruitment of participants with a wide age range in both sexes. In addition, most previous studies have investigated the association of grip strength with age or vitamin D separately, however, the present study evaluated the interaction of between serum vitamin D level and age on hand grip strength, which is novel in the literature. Moreover, the current study included information regarding nutritional status, serum levels of both 25-hydroxyvitamin D and 1 and 25-dihydroxyvitamin D, and a sufficient sample size. However, the cross-sectional design of the study is one of its limitations because no causal inferences are able to be made, and therefore, cohort studies and randomized controlled trials are required to investigate this association. Other limitations of this study include that no evaluation of Ca and PTH was conducted, whilst self-reported IPAQ was

utilized to assess physical activity level, although validity and reliability of IPAQ has been systematically approved. Finally, our findings cannot be generalized to a large population of elderly people because the number of elderly subjects was limited.

Conclusion

Overall, there is no relationship between serum vitamin D and muscle strength in the present study. However, grip strength increased in to middle age. Combination of age with both 25(OH)D and $1,25(OH)_2$ D levels increased muscle strength in to middle age.

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Table 1. The relationship between hand grip strength (HGS) and serum levels of 25(OH) D and 1, 25(OH) D

	ß	**SE**	**P value**
25(OH)D (ng/ml)			
Crude	-0.114	0.65	0.62
Model 1	-0.001	0.42	0.984
Model 2	-0.125	0.41	0.973
Model 3	0.002	0.036	0.959
$1,25(OH)_2D$ (pmol/l)			

Crude	0.006	0.122	0.928
Model 1	-0.027	0.76	0.487
Model 2	-0.027	0.75	0.482
Model 3	-0.043	0.65	0.198

Model 1 adjusted for age and sex, Model 2 adjusted for age, sex, BMI and physical activity level, Model 3 adjusted for age, sex, BMI, physical activity level, lean body mass, smoking status and some underlying disease (diabetic, hypertension and dyslipidemia)

Table 2. Analysis of covariance for hand grip strength (HGS) across tertiles (T) of 25(OH) D and 1, 25(OH) D

	25(OH)D (ng/ml)						
	T1	T2	T3	P*	P1	P2	P3
Dominant hand GS (kg)	34.44 ± 12.77	36.70 ± 13.83	33.16 ± 11.79	0.174	0.552	0.542	0.350
Two hands GS (kg)	33.06 ± 12.29	35.22 ± 13.06	32.04 v 11.66	0.213	0.354	0.371	0.292
	$1,25(OH)_2D$ (pmol/l)						

Dominant hand GS (kg)	34.94 ± 13.45	35.09 ± 12.57	34.60 ± 12.74	0.968	0.942	0.649	0.467
Two hands GS (kg)	33.74 ± 13.44	33.91 ± 12.07	33.01 ± 11.71	0.878	0.977	0.814	0.672

P*= unadjusted, P1= adjusted for age and sex, p2= adjusted for age, sex, BMI and physical activity level, p3= adjusted for age, sex, BMI, physical activity level, lean body mass, smoking status and some underlying disease (diabetic, hypertension and dyslipidemia)

Table 3. Interaction of age and vitamin D on HGS in adults and the elderlies

		Age (year)							
		Q1 (18-25)	Q2 (26-33)	Q3 (34-47)	Q4 (48-69)	P*	P1	P2	P3
25(0H)D (ng/ml)	T1	33.01 ± 12.73	31.01 ± 11.37	40.07 ± 12.99	36.30 ± 13.64	0.038	0.257	0.10	0.049
	T2	29.94 ±	41.46	41.27 ±	232.29 ±				

		10.41	±14.28	15.70	10.61				
	T3	28.36 ± 10.15	38.59 ± 11.62	36.97 ± 11.24	29.22 ± 11.16				
1,25(OH)$_2$D (Pmol/l)	T1	27.85 ± 9.01	37.25 ± 15.43	37.34 ± 13.74	35.57 ± 11.03	0.222	0.139	0.096	0.047
	T2	32.37 ± 9.94	37.13 ± 12.81	41.90 ± 13.62	27.91 ± 9.10				
	T3	32.64 ± 15.02	36.66 ± 12.83	38.11 ± 12.26	30.66 ± 13.79				
Total		30.83 ± 11.39	36.82 ± 13.29	39.28 ± 13.22	31.68 ± 11.63				

P*= unadjusted, P1= adjusted for age and sex, p2= adjusted for age, sex, BMI and physical activity level, p3= adjusted for age, sex, BMI, physical activity level, lean body mass, smoking status and some underlying disease (diabetic, hypertension and dyslipidemia)

Table 4. Odds ratios and confidence interval for different levels of vitamin D and age

HGS (kg)		**Crude**		**Model 1**		**Model 2**		**Model 3**	
		OR (CI)	P value	OR (CI)	P value	OR(CI)	P value	OR(CI)	P value
25(OH)D (ng/ml) *$_1$	T1	Ref	0.477	Ref	0.151	Ref	0.193	Ref	0.391
	T2	0.89 (0.49,1.61)	0.710	2.26 (0.81, 6.26)	0.117	2.11 (0.74, 6.04)	0.161	1.71 (0.56, 5.18)	0.338
	T3	0.70 (0.39, 1.25)	0.234	2.61 (0.89, 7.67)	0.080	2.52 (0.85, 7.51)	0.095	2.08 (0.68, 6.29)	0.193
1,25(OH)$_2$D (Pmol/l) *$_1$	T1	Ref	0.50	Ref	0.343	Ref	0.357	Ref	0.447
	T2	1.02 (0.56, 1.84)	0.938	0.83 (0.29, 2.35)	0.735	0.82 (0.29, 2.32)	0.71	0.70 (0.24, 2.05)	0.519
	T3	0.74 (0.41, 1.34)	0.333	0.48 (0.17, 1.34)	0.168	0.48 (0.17, 1.36)	0.168	0.48 (0.15, 1.48)	0.205
Age (year) *$_2$	Q1	Ref	0.015	Ref	0.010	Ref	0.006	Ref	0.061
	Q2	1.13 (0.56, 2.30)	0.722	0.28 (0.6, 1.30)	0.106	0.22 (0.04, 1.09)	0.065	0.35 (0.06, 1.88)	0.221
	Q3	0.59 (0.30, 1,15)	0.128	0.12 (0.02, 0.51)	0.004	0.09 (0.02, 0.47)	0.004	0.15 (0.03, 0.84)	0.031
	Q4	0.40 (0.19, 0.81)	0.011	0.09 (0.02, 0.40)	0.002	0.06 (0.01, 0.32)	0.001	0.11 (0.02, 0.63)	0.013

*$_1$: Model 1 adjusted for age and sex, Model 2 adjusted for age, sex, BMI and physical activity level, Model 3 adjusted for age, sex, BMI, physical activity level, lean body mass, smoking status and some underlying disease (diabetic, hypertension and dyslipidemia)

*$_2$: Model 1 adjusted for sex, Model 2 adjusted for sex, BMI and physical activity level, Model 3 adjusted for sex, BMI, physical activity level, lean body mass, smoking status and some underlying disease (diabetic, hypertension and dyslipidemia)