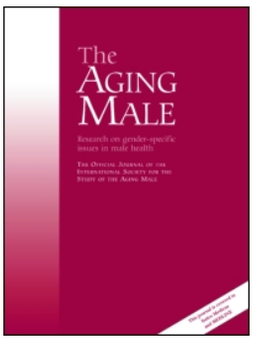

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ORIGINAL ARTICLE

Association of low serum 25-hydroxyvitamin D levels with the frailty syndrome in Mexican community-dwelling elderly

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Abstract

Objective: Since vitamin D is an important regulator of muscle function, the effect of vitamin D deficiency on frailty syndrome has been recently studied. This cross-sectional study aimed to determine the association between 25(OH)-vitamin D levels and frailty status in Mexican community-dwelling elderly.

Methods: Sample of 331 community-dwelling elderly aged 70 or older, a subset of those included in the "Coyoacán cohort" were included. 25(OH)-vitamin D assay and frailty status were measured.

Results: Mean age was 79.3 years and 54.1% were women. Those classified as frail were more likely to have lower Mini-Mental State Examination score ($p = 0.015$), more disability for instrumental activities of daily living ($p < 0.001$) and for activities of daily living ($p < 0.001$). Serum 25(OH)-vitamin D levels were lower in the frail subgroup when compared with the non-frail one ($p < 0.001$). Multivariate logistic regression analyses showed a significant association between intermediate tertile [odds ratios (OR) = 4.13; 95% confidence intervals (CI) 2.00–8.56] or insufficient tertile (OR = 8.95; 95% CI 2.41–33.30) of vitamin D levels and frailty even after adjusting for potential confounders.

Conclusion: These results suggest that older adults with low 25(OH)-vitamin D levels are associated with the probability to being frail compared with those with sufficient vitamin D levels.

Keywords

Frailty syndrome, vitamin D, older people

History

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Introduction

Frailty is a clinical condition, which places the individual on a vulnerable state for adverse health-related outcomes including mortality [1,2]. The prevalence of frailty among independently living adults ranges between 7% in persons >65 years to 40% in those >80 years. Frailty is associated with increased risk of falls, hospitalization, disability and death [3]. Nowadays, special interest has been placed on understanding frailty, since frail persons are frequent users of community and health resources. It is assumed that early interventions for frail persons will improve health-related quality of life and reduce care costs [1]. Although previous studies have focused primarily on the roles of weight loss and sarcopenia on frailty, micronutrient malnutrition is also thought to play an important role [4]. In conceptualizing frailty, Fried et al. postulated that inadequate dietary intake was decisive in promoting the cascade of multiple processes that lead to frailty [5]. Recent findings show that poor nutritional intake is an important factor associated with the frailty syndrome suggesting that nutrition is an important domain in the pathogenesis of frailty [6].

Vitamin D deficiency and/or insufficiency is common among older people as a result of compromised mobility, diminished sun exposure, intrinsic skin response to ultraviolet radiation and low dietary vitamin D intake. The interest on vitamin D (especially among older persons) is growing with the increasing knowledge on the numerous biological effects of vitamin D as a promoter of bone health, physical

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performance and as a possible modulator in age-related clinical conditions [7]. In the elderly, chronic vitamin D deficiency may lead to osteoporosis or gradual bone loss that result in the impaired structural integrity of trabecular bone, thinner and more porous cortical bones, and thereby increased risk of fracture; likewise, components of frailty such as weakness and slowness are potential sequelae of vitamin D deficiency and lower 25(OH)-vitamin D levels in older adults have been inconsistently associated with poorer physical performance and higher risk of falls, fractures and death [8].

Although vitamin D insufficiency and/or deficiency could potentially increase the risk of frailty through multiple pathways involving oxidative stress, inflammation, muscle and bone metabolism, as well as neuromuscular function and immunity [9,10], the relationship between micronutrients and the risk of becoming frail has not been well characterized [9]. Studies examining the relationship between total circulating 25(OH)-vitamin D levels and frailty have yielded mixed results and not all observational studies have confirmed the relationship between 25(OH)-vitamin D and the risk frailty [10]. Furthermore, none of these studies, to our knowledge, were carried out in Latin America. Therefore, the main objective of this study was to investigate the association between 25(OH)-Vitamin D serum levels and frailty syndrome as well as its individual components in a subset of Mexican community-dwelling elderly.

Materials and methods

Study population

The sample of this cross-sectional study is a subset of participants of the Mexican Study of Nutritional and Psychosocial Markers of Frailty (the ''Coyoacán cohort''), a prospective cohort-study aiming to evaluate the nutritional and psychosocial determinants of frailty among Mexican community-dwelling elderly. A detailed description of the methodology of this study has been reported elsewhere [11]. Briefly, participants were identified through the listing of a government program which includes 95% of community dwelling elderly subjects aged 70 or older living in Mexico City, and which constituted the study's sampling frame. Recruitment was drawn from a random sample procedure, stratified by age and sex and confined to Coyoacán, one of the 16 districts of Mexico City. Among the contacted subjects, the acceptance rate was 86.9% and a total of 1124 participants was finally included in the study. Baseline data were collected in two phases. During the first one, participants were examined at home, and data were collected through a face-to-face interview using a standardized questionnaire. A wide range of information was collected during this phase including socio-demographic factors as well as health issues. In the second phase, an interdisciplinary team constituted by physicians, nurses, nutritionists and dentists evaluated participants. The subjects underwent a comprehensive geriatric assessment including functional status, co-morbidity, pharmacological treatments, physical performance, nutritional state, oral health, arterial tension and anthropometry. Blood samples were drawn from a subset of the total population (84%, $n = 945$) and several determinations were made; about 30% of this subset was randomly selected for the determination of 25(OH)-vitamin D levels. Each participant signed an informed consent and the Ethical Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán approved the study protocol.

Definition of frailty

Frailty was defined as proposed by Fried et al. in the Cardiovascular Health Study [5]. All five components from the original phenotype were retained, but the metrics used to characterize each criterion were slightly different and defined as follows: (1) Weight loss was defined as self-reported unintentional weight loss of 5 kg or more within the past year. (2) Exhaustion or fatigue (low energy) was indicated by self-response of two questions from the Center for Epidemiological Studies-Depression Scale (CES-D): ''I felt that everything I did was an effort'' and ''I could not get going'' [12]. Participants were asked: ''How often, in the last week, did you feel this way?'' Possible answers were 0 = rarely or none of the time; 1 = some or a little of the time; 2 = a moderate amount of the time or 3 = most of the time. Participants answering ''2'' or ''3'' to either of these questions were considered as frail by exhaustion. (3) Low physical activity was defined by the Spanish version of the Physical Activity Scale for the Elderly (PASE) [13]. Participants who scored in the lowest quintile, adjusted by sex, were considered frail for this component. (4) Slowness was considered to be present if subjects gave two positive answers to the questions: ''Does your actual health limit you to climb a single flight of stairs?'' and ''Does your actual health limit you to walk a 100 m block?'' (5) Weakness was defined by a positive answer to the question: ''Because of your current health status, do you have any difficulties lifting a 5 kg weight, such as a heavy grocery bag''. For the purpose of this study, participants were considered to be ''frail'' if they met at least one of the five frailty criteria or ''nonfrail'' if none.

Assessment of 25(OH)-vitamin D

Peripheral blood samples were drawn, processed and stored at −70 °C until analyses. 25(OH)-vitamin D serum levels were measured by a commercially available enzyme-linked immunosorbent assay (ELISA) [25(OH)-vitamin D direct ELISA Kit, Immundiagnostik, AG, Bensheim, Germany] according to the manufacturer's instructions. 25(OH)-vitamin D levels were reported in nmol/L and tertiles were established according to the score distribution. The higher tertile of the distribution was considered as a reference.

Covariates

Socio-demographic variables included in this study were: age (years), sex, educational level (years), blood collection season and self-reported socio-economic status (good, fair and poor). The presence of seven chronic diseases was summed up in a score ranging from 0 to 7, where a higher score indicates more chronic disease (myocardial infarction, stroke, cancer, hypertension, diabetes, dyslipidemia and thyroid disease). Body mass index [BMI = weight (kg)/height $(m)^2$] was

calculated from anthropometrical measurements, and used as a continuous variable. Cognitive function was evaluated through the Mini-Mental State Examination (MMSE), which score ranges from 0 to 30 and where, lower scores indicate poorer cognitive performance [14]. Two domains of disability were investigated, disability for basic (ADL) and instrumental activities of daily living (IADL). For ADL, subjects were asked about their ability to carry out the following tasks without help: bathing, dressing, toileting, transferring, continence and feeding themselves [15]. For IADL, participants reported their ability to perform the following eight activities: using the telephone, shopping, grooming, housekeeping, doing laundry, using transportation, handling medications and handling finances. For each domain of disability, if participants indicated that they were unable to perform at least one of the activities without help, they were considered as having ADL or IADL disability, respectively [16].

Sample

For the present study, the sample included 331 subjects. 25(OH)-vitamin D levels were available for 331 individuals, which had complete data for frailty.

Statistical analysis

As previously stated, to overcome the problem of statistical strength, frailty was dichotomized in two groups: frail (at least one criterion) versus nonfrail. Descriptive analyses included tests for categorical variables and *t* test or ANOVA test for continuous variables. Binomial logistic regression models were used to estimate odds ratios (OR) of frailty according 25(OH)-vitamin D tertiles. Models' results are presented without adjustment and with adjustment for numerous potentially confounding factors: age, sex, education level, self-perceived economic situation, season of blood collection, cognitive function, co-morbidities score and BMI. Finally, logistic regression analyses were run to assess the association between 25(OH)-vitamin D with frailty and each of the five components of the phenotype. Statistical significance was established at a p value <0.05 and 95% confidence intervals (CI) were given. All statistical tests were performed with the SAS 9.1 software (SAS Institute, Inc., Cary, NC).

Results

The study sample included 331 participants. Mean age was 79.3 years (SD = 5.8) and 54.1% were women. Table 1 shows the socio-demographic characteristics and health status of participants according to their frailty status. Those classified as frail were more likely to be women ($p = 0.023$), had lower MMSE score ($p = 0.015$) and had more disability for IADL ($p < 0.001$) and ADL ($p < 0.001$) in comparison with nonfrail subjects. There were no differences between the two groups regarding age, educational level, self-reported economic situation, season of blood collection, BMI or co-morbidity score. The mean value of 25(OH)-vitamin D levels was 59.0 nmol/L (SD = 23.3). In comparison with nonfrail subjects, 25(OH)-vitamin D levels were lower in the frail subgroup [67.5 nmol/L (SD = 26.0) versus 54.1 nmol/L (SD = 20.1), $p < 0.001$].

Table 2 shows the association between 25(OH)-vitamin D levels and frailty status. The unadjusted results showed a significant association between 25(OH)-vitamin D levels and frailty. In comparison with the highest tertile, intermediate and insufficient levels of 25(OH)-vitamin D were significantly associated with frail status. Multivariate logistic regression showed that after adjusting for potential confounders the association remained unchanged: the model showed that being intermediate or lower 25(OH)-vitamin D level tertiles were associated with frailty status when compared with the highest tertile (OR = 4.13; 95% CI 2.00–8.56 and OR = 8.95; 95% CI 2.41–33.30, respectively).

Finally, multivariate analysis showed that after adjusting for age, sex, self-perceived economic situation, season of blood collection, co-morbidity score, IADL and ADL disability, cognitive performance, BMI and the other four components of frailty as covariates, 25(OH)-vitamin D levels were independently associated with the weakness component and marginally associated, but not statistically so, with exhaustion (Table 3).

Discussion

In the present cross-sectional study of community dwelling elderly, 25(OH)-vitamin D levels were independently associated with frailty as well as with the weakness component of

Table 1. Characteristics of participants according their frailty status.

		Status of frailty		
Variable	All ($n = 331$)	Nonfrail ($n = 122$)	Frail ($n = 209$)	p
Age, mean (SD)	79.3 (5.8)	79.9 (4.7)	78.9 (6.4)	0.101
Women, %	54.1	45.9	58.9	0.023
Years of education, mean (SD)	6.6 (5.3)	6.6 (5.7)	6.6 (5.0)	0.962
Poor self-perceived economic situation	10.3	6.6	12.4	0.347
Co-morbidity score*, mean (SD)	1.5 (1.3)	1.4 (1.2)	1.6 (1.3)	0.311
MMSE score, mean (SD)	22.3 (3.4)	22.9 (3.1)	21.9 (3.4)	0.015
Disability $\geq$ 1 IADL task, %	49.8	30.3	61.2	<0.001
Disability $\geq$ 1 ADL task, %	33.3	15.7	43.7	<0.001
BMI, kg/m^2, mean (SD)	26.8 (4.3)	26.4 (3.6)	27.1 (4.6)	0.136
Blood collection in winter, %	27.5	25.4	28.7	0.517
25(OH)-vitamin D (nmol/L), mean (SD)	59.0 (23.3)	67.5 (26.0)	54.1 (20.1)	<0.001

MMSE, Mini-Mental State Examination; IADL, instrumental activities of daily living; ADL, activities of daily living; BMI, body mass index. *Co-morbidity score: myocardial infarction, stroke, cancer, hypertension, diabetes, dyslipidemia and thyroid disease.

Table 2. Logistic regression analyses of frailty according 25(OH)-vitamin D levels.

	Frail versus nonfrail							
	Non-adjusted				Adjusted*			
Variables	OR	95% CI	*p*	*P* Global	OR*	95% CI	*p*	*p* Global
25(OH)-vitamin D								
High	1	–	–	<0.001	1	–	–	<0.001
Intermediate	4.49	2.51–8.02	<0.001		4.13	2.00–8.56	<0.001	
Insufficient	10.50	3.21–34.35	0.001		8.95	2.41–33.30	<0.001	

25(OH)-Vitamin D intermediate = ≥30 to <75 nmol/L; 25 (OH)-Vitamin D insufficient = <30 nmol/L. CI, confidence intervals.
*Adjusted by age, sex, years of education, self-perceived economic situation, season of blood collection, co-morbidity score (myocardial infarction, stroke, cancer, hypertension, diabetes, dyslipidemia and thyroid disease), instrumental and basic activities of daily living, Mini-Mental Status Examination score, body mass index.

Table 3. Logistic regression analyses of each component of frailty and 25(OH)-vitamin D levels.

Frail component	25 (OH)-vitamin D levels	OR*	95% CI	*p*	*p* Global
Slowness	High	1	–	–	0.641
	Intermediate	1.44	0.40–5.2	0.580	
	Insufficient	2.18	0.43–11.01	0.348	
Weight loss	High	1	–	–	0.342
	Intermediate	1.54	0.68–4.68	0.442	
	Insufficient	3.02	0.68–13.39	0.146	
Low physical activity level	High	1	–		0.462
	Intermediate	1.87	0.56–6.19	0.309	
	Insufficient	1.04	0.19–5.72	0.967	
Exhaustion	High	1	–	–	0.068
	Intermediate	2.48	1.12–5.49	0.026	
	Insufficient	2.84	0.89–9.06	0.077	
Weakness	High	1	–	–	0.040
	Intermediate	18.56	1.88–183.36	0.012	
	Insufficient	20.50	1.72–243.41	0.017	

CI, confidence intervals.
*Adjusted by age, sex, self-perceived economic situation, season of blood collection, co-morbidity score (myocardial infarction, stroke, cancer, hypertension, diabetes, dyslipidemia and thyroid disease), instrumental and basic activities of daily living, Mini-Mental Status Examination score, body mass index, and each other components of frailty. 25 (OH)-vitamin D intermediate = ≥30 to < 75 nmol/L; 25(OH)-vitamin D insufficient = <30 nmol/L.

the frailty syndrome. Recently, an etiological role of vitamin D insufficiency/deficiency on the development of frailty syndrome has been proposed [17], since a relationship between 25(OH)-vitamin D levels and muscle weakness, functional performance (important components of the frailty syndrome), and frailty itself has been reported [18–20].

Our results are consistent with those of previous studies. In the Longitudinal Aging Study Amsterdam (LASA), Puts et al. reported that elderly individuals that were frail at baseline had lower concentrations of 25(OH)-vitamin D. Furthermore, the same study found that low 25(OH)-vitamin D serum levels were associated with incident frailty a 3-year follow-up (OR of the 2.04) [21]. In addition, in a cohort of 1606 community-dwelling men aged 65 or older enrolled in the Osteoporotic Fractures in Men Study (MrOS), low levels of 25(OH)-vitamin D were independently associated with greater evidence of frailty at baseline but did not predict greater evidence of frailty status at the 4.6 years follow-up [22].

Likewise, Shardell et al. in the InCHIANTI study of older Italian men and women reported that lower 25(OH)-vitamin D levels were associated with frailty in men and weakly so in women. The authors also showed that low vitamin D levels were associated with two individual components of frailty: low activity level (low energy expenditure) in both sexes and slowness in men [23]. Associations between low vitamin D levels and frailty have also been found between North American [3], Taiwanese [24] as well as in a population-based study of older European adults [17].

Nevertheless, others studies have shown inconsistent results; Semba et al., in the Women's Health and Aging Study I, reported that the OR for becoming frail (versus nonfrail) did not differ between women in the lowest quartile of 25(OH)-vitamin D levels versus women in the upper three quartiles [9]. Likewise, Michelon et al. reported that the age-adjusted odds of being classified as frail (versus nonfrail) was 1.7 times as high in women with 25(OH)-vitamin D levels in the lowest quartile in comparison with women with levels in the upper three quartiles, but the association failed to reach statistical significance after further adjustment [4]. However, Ensrud et al. also observed independent associations between lower 25(OH)-vitamin D levels and the presence of each of five individual frailty dimensions (weakness, shrinking, exhaustion, slowness, low activity level) [25].

The small inconsistences mentioned above may be explained in part by differences in the study populations, sample sizes, methods to measure vitamin D levels, cut-off points used to define vitamin D status, frailty definitions, adequacy of adjustment for potential confounders, as well as

by gender differences in vitamin D metabolism [23]. It should be appreciated that vitamin D levels are simply an integrated measure of exposure to dietary vitamin D and sunlight that can vary over time; both dietary intake and sunlight exposure are frequently compromised in older adults [21,26]. However, our study was not designed to identify if the association between vitamin D and frailty is mediated by differences in sun exposure and diet amongst frail and not-frail older adults.

The biological mechanisms by which the association between low vitamin D levels and the frailty syndrome exists have not been completely elucidated. Nevertheless, there are several plausible biologic pathways (bone and muscle metabolism as well as inflammatory phenomena) that may explain the association. Previous work suggests that low vitamin D levels are related with greater risk of incident mobility limitation and disability [27], given vitamin D's influence on muscle cell metabolism including calcium transport, inorganic phosphate uptake for the energy-rich phosphate compounds production and protein synthesis [28]. Furthermore, vitamin D receptors (VDRs) are located in skeletal muscle cells, and low 25(OH)-vitamin D may result in decreased muscle strength from both decreased muscle synthesis and altered contractile properties of muscle [29].

Also, the VDR has been identified on most immune system cells. Vitamin's D active metabolite, 1,25-$(OH)_2$D, inhibits the secretion of interleukin-12 (IL-12) by antigen-presenting cells. Since IL-12 stimulates the development of CD4+ helper T cells subtype 1 (Th1), 1,25-$(OH)_2$D actions result in a shift away from a pro-inflammatory Th1 like profile and toward an anti-inflammatory Th2 profile. Low vitamin D has been associated with increased risk of Th1 cytokine-mediated autoimmune diseases including inflammatory bowel disease, rheumatoid arthritis and type 1 diabetes mellitus [23]. Moreover, evidence suggests that inflammation plays a major role in the pathophysiology of frailty through an abnormal, low-grade chronic inflammatory response [30,31]. Several studies have also shown a heightened inflammatory state in frail older adults, marked by high serum levels of inflammatory mediators, such as cytokines and acute phase proteins, supporting the existence of a dysregulated immune system in frailty [2]. It is believed that a dysregulation of immune and inflammatory responses that occur as we age substantially contributes to morbidity and mortality in humans [32].

Several limits must be acknowledged, the cross-sectional nature of the study being probably the most relevant. The methodological design prevents us from establishing the direction of the association described above. Also, vitamin D levels were only available for a subset of subjects in this cohort. However, the present study was carried out in a scarcely studied population, Latin American older adults, where ethnicity and sun exposure may differently characterize the association between vitamin D levels and frailty. In conclusion, our results suggest that older adults with low 25(OH)-vitamin D levels have higher risk of frailty than those with adequate vitamin D levels.

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Declaration of interest

The authors declared no conflict of interest. The National Council for Science and Technology of Mexico (CONACyT) funded this project (SALUD-2006-C01- 45075). In addition, the study has received funding from the National Institute of Geriatrics (Instituto Nacional de Geriatría, México, D.F.) under Grant agreement No.DI-PI-003/2012 for Nora Magdalena Torres-Carrillo.

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