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Trabajo Original

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Serum vitamin D levels and mortality in Mexicans: results from the Mexican Health and Aging Study

Niveles séricos de vitamina D y mortalidad en mexicanos: resultados del Estudio Nacional de Envejecimiento en México

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Abstract

Background: the population in Latin America is aging and elders face several obstacles for good health, including an elevated frequency of vitamin D deficiency. Thus, identification of patients at high risk to develop its negative consequences should be a priority**.**

Objective: the objective of this analysis was to determine if levels of vitamin D lower than 15 ng/ml are associated with high mortality in Mexican elderly population, from the database of the Mexican Health and Aging Study (MHAS).

Methods: prospective, population study in Mexico, that included Subjects of 50 years and older who were evaluated for Serum vitamin D levels during the year 2012 (third wave of the study). Serum 25(OH)D levels were categorized into four groups, based on cutoff points used in previous studies on vitamin D and frailty: < 15, 15-< 20, 20-< 30 and ≥ 30 ng/ml. Mortality was evaluated during 2015 (fourth wave of the study). Hazard ratio was calculated (for mortality) through Cox Regression Model, adjusted for covariates.

Results: we included 1626 participants, and those with lower levels of vitamin D were older, more often women, required more aid for activities of daily living, reported higher number of chronic diseases, and lower scores on cognition. The relative risk of death was 5.421 (95 % CI 2.465-11.92, $p < 0.001$) for the participants with vitamin D levels < 15, which after adjusting for covariates, remained statistically significant.

Conclusions: levels of vitamin D lower of 15, are associated with an increase in the rate of mortality in community-dwelling senior Mexicans.

Keywords:

Vitamin D. Mortality. Mexico. Elderly.

Resumen

Introducción: la población en América Latina está envejeciendo y los adultos mayores enfrentan varios obstáculos para gozar de buena salud, incluida una frecuencia elevada de deficiencia de vitamina D. Por lo tanto, la identificación de pacientes con alto riesgo de desarrollar sus consecuencias negativas debe ser una prioridad.

Objetivo: el objetivo de este análisis fue determinar si los niveles de vitamina D inferiores a 15 ng/ml están asociados con una alta mortalidad en la población adulta mayor mexicana, a partir de la base de datos del Estudio de Salud y Envejecimiento en México.

Métodos: estudio poblacional prospectivo en México, que incluyó Sujetos de 50 años y mayores que fueron evaluados para los niveles de vitamina D en suero durante el año 2012 (tercera ola del estudio). Los niveles séricos de 25(OH)D se clasificaron en cuatro grupos, según los puntos de corte utilizados en estudios previos sobre vitamina D y fragilidad: < 15, 15-< 20, 20-< 30 y ≥ 30 ng/ml. La mortalidad se evaluó durante 2015 (cuarta ola del estudio). Se calculó la razón de riesgo (para la mortalidad) a través del modelo de regresión de Cox, ajustado por covariables.

Resultados: incluimos 1626 participantes, y aquellos con niveles más bajos de vitamina D eran mayores, más a menudo mujeres, requerían más ayuda para las actividades de la vida diaria, informaron un mayor número de enfermedades crónicas y puntuaciones más bajas en cognición. El riesgo relativo de muerte fue de 5,421 (IC 95 % 2,465-11,92, $p < 0,001$) para los participantes con niveles de vitamina D < 15, que después de ajustar por covariables, se mantuvo estadísticamente significativo.

Conclusiones: niveles de vitamina D inferiores a 15, se asocian con un aumento en la tasa de mortalidad en adultos mayores mexicanos residentes en la comunidad.

Palabras clave:

Vitamina D. Mortalidad. México. Ancianos.

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INTRODUCTION

Vitamin D status has been studied in all continents and most countries over the world, and there is a global high prevalence of deficiency (1), ranging from 30 to 70 %, constituting a public health problem (2). The aging population in Latin America is characterized by an elevated poverty rate, a high burden of comorbidity, and sub-optimal social conditions contributing to a poor health status, where social and health services are limited (3), which may also contribute to increase the prevalence of vitamin D deficiency (4). Mexico is living the demographic and epidemiological transitions associated with the increase in life expectancy, and a growing number of elders (5), and a high prevalence of vitamin D deficiency (6,7), despite being a country with adequate exposure to sun and ultraviolet B rays (UVB) during the year (8).

Low levels of vitamin D are frequently found in the elderly as a result of changes associated with aging on vitamin D and calcium and metabolism such as decreased calcium absorption, intestinal resistance of calcium absorption to circulating $1,25(OH)_2D$, decreased vitamin D receptor, decreased renal production of $1,25(OH)_2D$ by the aging kidney, decreased skin production of vitamin D, and substrate deficiency of vitamin D (9).

Low vitamin D levels are associated with several geriatric syndromes, including frailty (10-12), sarcopenia (13), falls, fractures, cognitive impairment, depression, cardiovascular disease, colorectal cancer, diabetes (14), and mortality in general (15-20), and in distinct clinical scenarios, such as institutionalized elderly people (21). Although, the evidence shows that low serum levels of vitamin D are associated with mortality, currently there is no consensus on optimal 25(OH)D concentrations (14,22,23). While there are many recommendations regarding optimal levels of vitamin D (24), a putative threshold in which of vitamin D is associated with higher mortality in Mexican population has not been defined. Our hypothesis is that vitamin D levels below 15 are associated with a higher mortality in Mexican population. Therefore, the objective of this analysis was to determine the association between low levels of vitamin D and mortality in Mexican population, from the database of the Mexican Health and Aging Study (MHAS) (25), a prospective study in Mexicans, as well as their couples, who through a survey on the processes of aging and the burden of disease that occur in this group and recording data in 2001, 2003, 2012, and 2015 (with measurement of mortality).

MATERIAL AND METHODS

To carry out the present work we used the MHAS database (25). The methodology was conducted by the Center for Population Studies at the University of Pennsylvania, Center for Research on Population at the University of Maryland and the Center for Demography and Ecology, University of Wisconsin, while the National Institute of Statistics, Geography and Informatics (INEGI) of Mexico performed fieldwork. Information related to various aspects, such as dynamics of health, family structure and intergenerational transfers, migratory behaviors and socioeconomic differences by income and property ownership was collected. The sample is representative of the non-institutionalized population component aged 50 years in 2000. Collecting data from the first round was conducted from May to October 2001 and a second round took place from June to September 2003 in which participants were re-interviewed in 2001, and a third and fourth round in the years 2012 and 2015 respectively. For the present analysis all subjects 50 years or older evaluated during the 2012 wave, with serum levels of vitamin D, who underwent a follow-up in 2015 and determined whether they were still living or not were selected. We excluded participants in who we could not determine the status of the studied variables (missing values). The MHAS is partly sponsored by the National Institutes of Health/ National Institute on Aging (grant number NIH R01AG018016) and the INEGI in Mexico. Data files and documentation are public use and available at www.MHASweb.org (25).

CATEGORIZATION OF VITAMIN D

Methodological parameters for determining levels of vitamin D can be found in the web page of the MHAS (25) and were described previously by Carrillo Vega et al. (6). Briefly, Biomarkers and vitamin D were obtained between October and November 2012, with trained personnel, who performed the peripheral venipuncture. After the venipuncture, the sample was centrifuged during 15 minutes to separate the serum, and stored in two 2-mL tubes. Serum vitamin D levels was measured with a chemiluminescent microparticle immunoassay (CMIA-Architect Abbott Laboratories. Abbott Park, IL, USA). The measurement interval of this CMIA ranged from 8 to 160 ng/mL, and the intra- and inter-assay coefficients of variation were < 10 %. Serum 25(OH) D levels were categorized into four groups, based on cut-points used in previous studies on vitamin D and frailty: < 15, 15-< 20, 20-< 30 and ≥ 30 ng/ml (10,11).

ANALYZED COVARIATES

We analyzed the following variables: gender, age, self-reported comorbidities such as hypertension or high blood pressure, diabetes or high sugar level in blood, cancer, lung disease, heart disease (heart attack), brain disease (stroke, stroke or transient ischemic attack), arthritis or rheumatism, kidney and/or liver infection, Pneumonia, Herpes Zoster, and Tuberculosis. For these comorbidities, we created the variable number of comorbidities, representing the sum of the latter, and have values ranging from 0 to 12. We also included: quality of vision, and hearing, frequency of smoking, and drinking. Cognitive status was evaluated through the cross-cultural cognitive examination, which has a sensitivity of 100 % and a specificity of 83 % for patients with dementia (26). Depressive symptoms were measured with a validated nine-item questionnaire (27). Functional assessment was obtained by the number of basic or BADL (bathing, dressing,

toileting, moving, eating and being continent, score 0-6) and instrumental activities of daily living or IADL (preparing hot food, buy food, taking medications and managing their money, score 0-4) for which require assistance. Mortality was reported in the fourth round of the survey in 2015. Missing values were considered in the case of respondents did not answer or replied, "do not know" on each of the variables analyzed. All subjects who participated in the study gave their informed consent at the time of interview.

STATISTICAL ANALYSIS

The analysis was performed by the method of complete cases (only those subjects without missing values in the variables analyzed) (28). Participants were characterized by using descriptive statistics, and included median, and interquartile range for quantitative variables, and absolute frequencies, and percentages in the case of qualitative variables. Chi square tests were used to determine differences between qualitative variables, and Kruskal Wallis test to demonstrate the difference between quantitative variables. *p* values lower than 0.05 were considered statistically significant. The variable survival time was calculated from the time in weeks between the date of the clinical evaluation of the third (2012) and the fourth wave (2015) evaluation or by the date of death. The degree of association of variables was measured with hazard ratio through Cox regression model. A minimum of 121 participants in each group was estimated to identify statistically significant difference in proportions between 0.15 and 0.025 through Chi square two-tailed test, power of 0.9 and alpha of 0.05 for mortality variable. All statistical analyses were performed using Stata/SE, version 12 (Stata Corporation, College Station, TX, USA).

RESULTS

GENERAL CHARACTERISTICS OF THE PARTICIPANTS IN THE YEAR 2012

Baseline clinical and demographic characteristics of 1626 selected participants were grouped and analyzed according to vitamin D levels (Table I and Fig. 1). The groups of vitamin D levels < 15, 15-< 20, 20-29, and 30 or more, included 174 (9.3 %), 339 (20.8 %), 772 (47.4 %), and 341 (20.9 %) respectively. With regard to their general characteristics, those with lower levels of vitamin D were older, more often women, required more aid for activities of daily living, reported higher number of chronic diseases, and lower scores on cognition.

Table I. Demographic and health variables of respondents in the Mexican Health and Aging Study, according to serum vitamin D levels in ng/mL

	Less than 15	15 to < 20	20 to < 30	30 or more	
Variable	**n = 174**	**n = 339**	**n = 772**	**n = 341**	***p***
Age (years)	66 (58-73)	63 (56-70)	61 (55-68)	59 (54-66)	0.043
Grouped age					
50 to 59 years	49 (28.2 %)	125 (36.9 %)	351 (45.5 %)	174 (51 %)	
60 to 69 years	58 (33.3 %)	129 (38.1 %)	253 (32.8 %)	112 (32.8 %)	
70 to 79 years	41 (23.6 %)	62 (18.3 %)	123 (15.9 %)	40 (11.7 %)	< 0.001
80 to 89 years	23 (13.2 %)	21 (6.2 %)	40 (5.2 %)	14 (4.1 %)	
90 to 99 years	3 (1.7 %)	2 (0.6 %)	4 (0.5 %)	1 (0.3 %)	
100 years or more	0 (0 %)	0 (0 %)	1 (0.1 %)	0 (0 %)	
Gender					
Man	47 (27 %)	116 (34.2 %)	336 (43.5 %)	182 (53.4 %)	< 0.001
Woman	127 (73 %)	223 (65.8 %)	436 (56.5 %)	159 (46.6 %)	
Global self-reported quality of health					
Excellent	2 (1.1 %)	5 (1.5 %)	20 (2.6 %)	7 (2.1 %)	
Very good	6 (3.4 %)	13 (3.8 %)	27 (3.5 %)	18 (5.3 %)	0.265
Good	59 (33.9 %)	113 (33.3 %)	204 (26.4 %)	96 (28.2 %)	

(Continues on next page)

Table I (Cont.). Demographic and health variables of respondents in the Mexican Health and Aging Study, according to serum vitamin D levels in ng/mL

	Less than 15	15 to < 20	20 to < 30	30 or more	
Variable	**n = 174**	**n = 339**	**n = 772**	**n = 341**	***p***
Fair	89 (51.1 %)	169 (49.9 %)	449 (58.2 %)	188 (55.1 %)	0.068
Poor	18 (10.3 %)	39 (11.5 %)	72 (9.3 %)	32 (9.4 %)	
Use of glases	109 (62.6 %)	200 (59 %)	411 (53.2 %)	179 (52.5 %)	
Quality of vision with glasses					
Excellent	6 (3.4 %)	11 (3.2 %)	29 (3.8 %)	8 (2.3 %)	0.928
Very good	10 (5.7 %)	32 (9.4 %)	68 (8.8 %)	25 (7.3 %)	
Good	78 (44.8 %)	164 (48.4 %)	348 (45.1 %)	168 (49.3 %)	
Fair	70 (40.2 %)	106 (31.3 %)	268 (34.7 %)	119 (34.9 %)	
Poor	8 (4.6 %)	19 (5.6 %)	41 (5.3 %)	14 (4.1 %)	
Legally blind	0 (0 %)	0 (0 %)	1 (0.1 %)	0 (0 %)	
Use of hearing aid	4 (2.3 %)	2 (0.6 %)	12 (1.6 %)	5 (1.5 %)	0.367
Ever smoked	68 (39.1 %)	129 (38.1 %)	305 (39.5 %)	143 (41.9 %)	0.769
Currently drinks alcohol	38 (21.8 %)	86 (25.4 %)	211 (27.3 %)	96 (28.2 %)	0.295
Hypertension	82 (47.1 %)	145 (42.8 %)	344 (44.6 %)	117 (34.3 %)	0.007
Diabetes *mellitus*	50 (28.7 %)	98 (28.9 %)	156 (20.2 %)	42 (12.3 %)	< 0.001
Cancer	5 (2.9 %)	8 (2.4 %)	19 (2.5 %)	4 (1.2 %)	0.511
Pulmonary disease	17 (9.8 %)	18 (5.3 %)	54 (7 %)	16 (4.7 %)	0.11
Myocardial infarction	6 (3.4 %)	12 (3.5 %)	24 (3.1 %)	9 (2.6 %)	0.915
Cerebrovascular disease	3 (1.7 %)	4 (1.2 %)	12 (1.6 %)	5 (1.5 %)	0.958
Rheumatism	29 (16.7 %)	54 (15.9 %)	106 (13.7 %)	38 (11.1 %)	0.218
Kidney infection	5 (2.9 %)	2 (0.6 %)	15 (1.9 %)	4 (1.2 %)	0.174
Liver infection	19 (10.9 %)	22 (6.5 %)	79 (10.2 %)	31 (9.1 %)	0.209
Tuberculosis	1 (0.6 %)	0 (0 %)	4 (0.5 %)	1 (0.3 %)	0.577
Pneumonia	6 (3.4 %)	2 (0.6 %)	8 (1 %)	1 (0.3 %)	0.007
Herpes zoster	7 (4 %)	6 (1.8 %)	22 (2.8 %)	3 (0.9 %)	0.082
At least one fall	66 (37.9 %)	138 (40.7 %)	301 (39 %)	123 (36.1 %)	0.648
Cross-cultural cognitive	44 (33-60.6)	45.33 (33.33-59.67)	45.67 (34-58)	45.33 (33-58)	0.733
Number of chronic diseases	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-1)	< 0.001
Number of depressive symptoms	3 (1-6)	3 (1-5)	3 (1-6)	3 (1-5)	0.932
Help in at least one BADL	41 (23.6 %)	46 (13.6 %)	106 (13.7 %)	33 (9.7 %)	0.002
Help in at least one IADL	43 (24.7 %)	45 (13.3 %)	107 (13.9 %)	60 (17.6 %)	< 0.001
Body mass index	29.27 (25.8-32.7)	29 (25.83-31.81)	28.69 (25.67-32.12)	27.27 (24.27-30.32)	0.001

The data represent absolute frequencies and percentages or medians (interquartile range). Data were compared with chi squared or Kruskal Wallis. The number of chronic diseases is the sum of hypertension, diabetes, cancer, respiratory disease, acute myocardial infarction, cerebrovascular disease, rheumatism, kidney infection, liver infection, tuberculosis, pneumonia and herpes zoster.

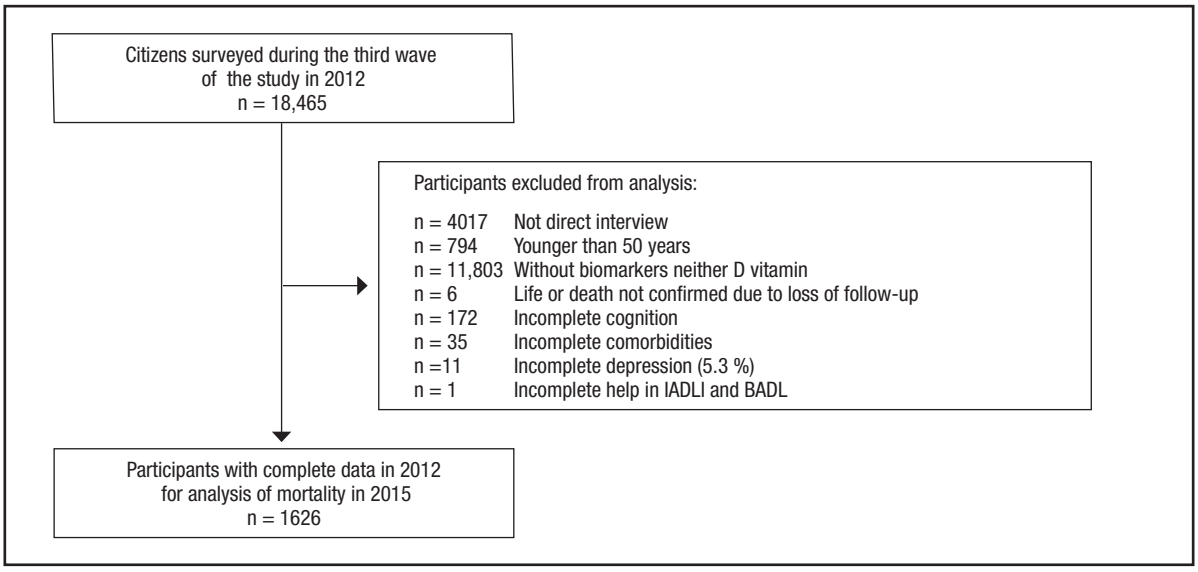

Figure 1.
Flowgram of the study.

VITAMIN D LEVELS AND THEIR ASSOCIATION WITH MORTALITY AT THE YEAR 2015

After a mean follow up of 162.1 weeks (95 % CI 161.3-162.9), the number of deaths among participants was 22 (12.6 %), 10 (2.9 %), 24 (3.1 %), and 8 (2.3 %) in those with vitamin D levels <15, 15-<20, 20-29, and 30 or more, respectively ($p<0.001$). The unadjusted relative risk was 5.421 (95 % CI 2.465-11.92, $p<0.001$) and 1.257 (95 % CI 0.5024-3.147 $p=0.8021$) and 1.325 (95 % CI 0.6015-2.919 $p=0.4829$) for the participants with vitamin D levels <15, 15-<20, 20-29, respectively, which after adjusting for covariates, levels of vitamin D lower of 15 remained statistically significant (Table II).

DISCUSSION

The objective of this analysis was to determine the association between low levels of vitamin D and mortality in Mexican population, from the database of the Mexican Health and Aging Study (MHAS).

When reviewing the clinical characteristics of the members of the groups, it was found that levels of vitamin D lower than 15 were associated with older age, female sex, lower scores on cognition, required more aid in BADL, and more chronic diseases, which agrees with the findings of Dobnig et al.(15), and Schottker et al. (17), in German population, as well as by Pilz, and colleagues (16), in Netherland. Consistency was clear in age and comorbidities such as diabetes, but in those studies, neither cognition nor functionality were measured.

We found a striking association of mortality with levels of vitamin D below 15 ng/ml. This association remained even after adjusting for confounding variables such as age, sex, number of chronic diseases, cognition score, and number of basic and instrumental activities of daily living for requiring support, and depression scale score. These results are consistent with findings from other studies that used the similar cut point used

Table II. Vitamin D serum levels (ng/ml) in participants from the Mexican Health and Aging Study, and its association with mortality

	***n* = 1625**	
Variable	***p***	**HR (CI 95.0 %)***
< 15	0.006	3.276 (1.401-7.66)
15 to 20	0.87	0.923 (0.357-2.393)
20 to < 30	0.972	1.015 (0.447-2.302)
30 or more		1

*HR: hazard ratio. *Adjusted for age, sex, number of depressive symptoms, number of chronic diseases, cognitive score and help in at least one BADL.*

in the present study (15-17,29). In the report by Vogt et al. (29), the result is partially explained by frailty status, while in that performed by Dobnig et al. (15), mortality was associated with the groups of participants with median levels of 6 and 13 ng/ml. Mean level of vitamin D was 12 ng/ml in the group of participants with higher mortality in the study of Pilz et al. (16), and below 12 ng/ml in the study of Schottker et al. (17).

Possible explanation for this association, is that the vulnerability could be a marker of another underlying disorder, and is associated with social or environmental factors that may increase the risk of mortality (30). In this case, one possible explanation is frailty syndrome. It has been associated with vitamin D levels below 15 ng/ml found by Ensrud et al. (10) and Pabst et al. (11), while Gutierrez Robledo et al. (12), report it at levels below 12 ng/ml. Frailty is associated with higher mortality (31,32), which could explain the association of the number of deaths found at vitamin D levels below 15.

Both, frailty syndrome and hypovitaminosis D are very common among older persons in Latin America (4,33). Their association has been well established (10-12,29). Although evidence is still limited, several authors have proposed to supplement enough vitamin D (800 to 2000 IU daily) to reach a serum level of 30 ng/ml to help in the prevention and control of frailty (34). A growing number of voices propose to create strategies to improve the status of vitamin D in older adults and the general population to decrease the burden of disease (35) as well as mortality (36,37).

The present study has some limitations. First, the medical conditions of the study population and the activities of daily living are self-reports on the state of health, although several studies have found consistency in self-reports and direct measurements (38). Second, the loss of subjects during follow-up, and analysis of complete cases may have influenced the study results, and produced selection bias (39). It is well known that subjects who do not complete the performance measures in population studies (probably like those not included in the present analysis) are expected to be less healthy, and more likely to die (40), increasing the possibility of survival bias. Despite these limitations, this study has many strengths, including its large sample size of men and women living in the community (which makes it generalizable), its prospective design, the ability to evaluate multiple medical conditions and factors that have been reported previously with an association with adverse outcomes.

CONCLUSION

Vitamin D levels below 15 constitute a marker of risk, of a higher mortality in community-dwelling Mexican population aged 50 years and older.

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