

Depression is associated with low levels of 25-hydroxyvitamin D among Jordanian adults: results from a national population survey

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Abstract Although low serum 25-hydroxyvitamin D (25(OH)D) and elevated serum parathyroid hormone (PTH) have been associated with depression in clinical settings, this link in community-dwelling individuals is inconclusive. The present study aimed at examining the association between serum 25(OH)D and PTH levels and the presence of depression in a national population-based household sample of 4,002 Jordanian participants aged ≥ 25 years. The DASS21 depression scale was used to screen for depression, and serum concentrations of 25(OH)D and PTH were measured by radioimmunoassay. Multiple logistic regression models were used to explore the association between serum 25(OH)D and PTH levels and depression. The unadjusted odds ratio (OR) decreased linearly with increasing quartiles of serum 25(OH)D ($P_{\text{trend}} = 0.00$). The OR for having depression was significantly higher among individuals in the first and second quartiles (OR = 1.4, 1.23, respectively) than among those in the fourth quartile (P values = 0.00 and 0.03, respectively). This relationship remained significant after adjusting for age, sex, marital status, education, BMI, serum creatinine, number of chronic diseases (OR = 1.39 and 1.21 and P values = 0.00 and 0.05, respectively) and

after further adjustment for exercise, altitude, and smoking (OR = 1.48 and 1.24, respectively, and P values = 0.00 and 0.03, respectively). No significant association was found between serum PTH levels and depression. The decrease in risk of depression among participants started to be significant with serum 25(OH) D levels higher than 42.3 ng/ml (lower limit of the range of the third quartile). This value may help pinpoint the desirable level of serum 25(OH)D to be attained to help aid the prevention and treatment of depression.

Keywords Depression · Vitamin D · Parathyroid hormone · National survey · Jordan

Introduction

Depression is a highly prevalent mental disorder of worldwide distribution [1–3]. Depression seriously affects the way someone eats, sleeps, and works [4] and concomitantly disrupts social relationships, economic status, and sense of self-esteem. Moreover, the coexistence of depression and chronic diseases is a common finding, and its role in initiation and/or aggravation of these diseases is highlighted in research literature [5–7]. Serum 25 hydroxyvitamin D (25(OH)D) deficiency or insufficiency is a global health problem and estimated to affect one billion people worldwide [8]. A high prevalence of vitamin D deficiency and insufficiency was reported in different populations in the United States and Europe. In the United States, the prevalence of 25(OH)D levels <20 ng/ml is between 25 and 50% among healthy adults [9, 10]. In Europe, prevalence rates of vitamin D deficiency or insufficiency are even higher and range between 28 and 87% in healthy adults [11–13]. Even in sunny countries,

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30–50% of children and adults in Saudi Arabia, Australia, and Jordan had serum 25(OH)D deficiency below 20 ng/ml [14–16].

There is accumulating evidence of the association of serum (25(OH)D) levels with a wide range of physiological outcomes such as bone health, CVD, diabetes, hypertension, metabolic syndrome, and cancer. Surprisingly, there is scarcity in research exploring the association between serum 25(OH)D levels and depressive disorder, despite the fact that serum 25(OH)D deficiency is highly treatable and thus may enable the prevention of depression. Moreover, the wide distribution of receptors for 25(OH)D in the brain including regions involved in behavior such as cortex, cerebellum, and limbic system increased the plausibility to hypothesize that vitamin D deficiency is associated with neuropsychological dysfunctions such as depression. More recent cross-sectional studies and randomized clinical trials explored the association between 25(OH)D and depression with inconsistent findings. For while some of these studies [17–19] showed an inverse association between 25(OH)D level and depression, the findings from other studies [20–22] were not supportive of this association. The present study assesses the association between serum levels of vitamin D and depressive disorder using a nationally representative sample of Jordanian adults.

Materials and methods

The data in this study are a subset of a more comprehensive national population-based household sample. Details of the study design are reported elsewhere [23, 24]. Briefly, a complex multistage sampling technique was used to select the households, taking into consideration the geographic distribution of the population as well as the urban–rural residence. As the population is covered by an extensive network of health centers and because the study procedures have to take place in a medical setting, the selection households were health center-oriented. A systematic sample of households was selected from the population served by the selected health centers. The number of selected households was approximately proportional to the population in each region. In each selected area, all members of the selected households aged ≥ 25 years were invited to attend the health center in the next day after an overnight fast. Subjects on regular medications were asked not to take their medications early at that day and to bring all their medications with them to the survey site. The study was approved by the Ethical Committee for Research on Humans of the National Center for Diabetes, Endocrinology, and Genetics and supported by the Ministry of Higher Education. An informed consent was obtained from all participants, or their guardians, if children. Of the 9,000

subjects invited to participate, 5,640 subjects (1,607 men and 4,033 women) aged between 7 and 90 years responded. Of the total 7,658 adults aged 25 years and older who were invited to participate, 4,117 (53.8%) subjects responded and participated in the study. The main reason for none response was lack of time because of being at work.

Data collection

All field work was carried out between July 1 and November 30, 2009. Participants attended the health centers in the morning (8–11 am) with a minimum fasting time of 10 h.

A pilot-tested structured questionnaire was developed and administered by trained interviewers. The questionnaire gathered information on age, sex, level of education, marital status, amount of exercise per week, smoking habit, and the most common chronic diseases. Two questions related to physical activity were modified from the Leisure Time Exercise Questionnaire (LTEQ) to assess the physical activity of participants [25]. Participants were asked about the frequency and duration of performing strenuous, moderate, and mild exercise in the past week. More than 10 examples of common specific activities were given. Participants reporting >150 min of moderate or strenuous exercise (i.e., 5 days/week of 30 min activity daily) were classified as meeting current physical activity guidelines for healthy adults [26]. Chronic disease score was generated by summing up the number of most common diseases mentioned by the participant and has medication(s) for this/these diseases. Chronic diseases include cardiac disease, lung disease, diabetes mellitus, hypertension, lung diseases, asthma, irritable bowel disease, osteoarthritis, and osteoporosis. The score of this variable ranges between 0 and 9 and was categorized into 0, 1, 2, and 3 or more diseases.

Depressive disorder was measured using the Arabic version [27] of the depression (D) scale of the Depression Anxiety Stress Scales (DASS21) [28]. The instrument is the short form of Levibond and Levibond's 42-item self-report, which measures three distinct negative affective states of depression, anxiety, and stress [29]. DASS21 instrument has been validated for use in clinical and non-clinical populations and found to have adequate convergent and discriminant validity and can be validly used to measure the constructs of depression anxiety and stress [30, 31]. Reliability of the three scales is considered excellent [30], with Cronbach's alpha at 0.91 for the DASS depression scale [32]. The DASS depression scale assesses anhedonia, hopelessness, dysphoria, self-depreciation, devaluation of life, lack of interest or involvement, and experience of anxious affect. Participants were asked to use a 4-point frequency scale (0 = did not apply to me at all, 1 = applied to me to some degree or some of the time,

2 = applied to me to a considerable degree or a good part of the time, 3 = applied to me very much or most of the time) to indicate how much the statement applied to them over the past week. Scores of the DASS21-Depression (DASS21-D) were calculated by summing up the scores of depression items. The sum score was then multiplied by a factor of 2 to estimate the score of the original Depression Anxiety Stress Scale of the 42 items [31]. Participants' scores on DASS21-D scale range between 0 and 42. The DASS scale manual used cutoff points of 0–9, 10–13, 14–20, 21–27, and ≥ 28 to classify participants into 5 levels of severity of depression (normal, mild, moderate, severe, and extremely severe, respectively) [33]. For this analysis, participants who scored ≥ 14 on DASS depression scale were considered depressed.

Anthropometric measurements including weight and height were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters. Socio-demographic variables used in the analyses included age, sex, educational status, and marital status. Lifestyle variables include smoking and exercise. Altitude was measured as the height in meters above sea level.

Biochemical assays

Serum samples were transferred immediately from the health centers in cold boxes filled with ice to the central laboratory of the National Center for diabetes and endocrinology in Amman. Serum 25(OH)D concentrations were determined using radioimmunoassay (BIOSOURCE Europe S.A., Nivelles, Belgium). The intra- and inter-assay coefficients of variation (CVs) values were 5.6 and 11%, respectively. The limit of detection was 0.6 ng/ml. Serum PTH level was measured using Electrochemiluminescence (ECLIA-PTH) assay (Roche Diagnostics, Mannheim, Germany). The detection limit of the assay was 1.2 pg/ml, and the intra- and inter-assay coefficients of variation were below 5%. Serum creatinine was measured using Enzymatic assays.

Statistical analysis

A total of 4,002 (1,008 men and 2,994 women) out of 4,117 adults participants were included in our analysis, after excluding those with missing values for any of the study variables. Data were analyzed using the Statistical Package for Social Sciences software, SPSS (SPSS Inc., Chicago, IL, USA) version 16.

Frequency distribution was used to describe the dichotomous variable of depression and other categories of participants' characteristics.

Bivariate analyses were performed to test for independent distribution of plasma 25(OH)D categories as well as for other participants' characteristics among levels of depression using χ^2 test.

The odds ratios (OR) and their *p* values were estimated by performing multiple logistic regression models to test the association between 25(OH)D and depression. In the multivariable analyses, depression was treated as dependent variable and serum 25(OH)D was treated as independent variable. Serum 25(OH)D was tested in two different forms: dichotomous (a cutoff value of <30 and ≥ 30 ng/ml) and categorical using quartiles of 25(OH)D levels. The selection of 30 ng/ml as a cutoff point was based on the observation that the biological relationship between 25(OH)D and PTH levels starts to be non-linear at serum 25(OH)D level of approximately 30 ng/ml and that the healthful range of serum 25(OH)D starts at 30 ng/ml [8]. Serum parathyroid hormone (PTH) was also tested in two different forms: dichotomous at cutoff point of <65 and ≥ 65 ng/l and categorical using quartiles of PTH levels. The 65 ng/l is the upper limit of normal values of PTH used by the laboratory where PTH was analyzed, which is based on the manufacturer's instructions. A *P* value of ≤ 0.05 was considered statistically significant.

Results

Of all participants, 1,272 (31.8%) reported having moderate to extremely severe depression. The percentages of adults reported having depression differed significantly by gender, level of education, marital status, number of chronic diseases, BMI, and smoking status, but not by age, physical activity, or altitude (Table 1).

Individuals with serum 25(OH)D <30 ng/ml had significantly higher rate of depression (35.9%) than those with 25(OH)D ≥ 30 ng/ml (30.1%) (*P* value = 0.00). Participants with serum PTH values higher than 65 ng/l had higher rate of depression (38.4%) than those with serum PTH values ≤ 65 ng/l (31.5%). This difference in depression approached the level of significance at *P* value of 0.08 (Table 1).

Results of multiple logistic regression analyses indicated that the unadjusted OR for having depression was significantly higher among adults with 25(OH)D <30 ng/ml (OR = 1.32) than those with 25(OH)D level of ≥ 30 ng/ml (*P* value = 0.00). This relationship remained significant after adjusting for socio-demographic and health characteristics (age, sex, marital status, education, BMI, serum creatinine, and number of chronic diseases) (OR = 1.34, *P* value = 0.00) and after further adjustment for physical activity, altitude, and smoking status (OR = 1.38, *P* value = 0.00) (Table 2).

Table 1 Frequency distribution of adults reported having depressive disorder (scored ≥ 14 on DASS21-D score $\times 2$) by selected characteristics ($N = 4,002$)

Variable	Overall <i>n</i> (%)	Depressed (DASS score ≥ 14) <i>n</i> (%)	<i>P</i> value
Age (years)			
25 to <40	1,575 (39.4)	523 (33.2)	0.17
40 to <60	1,886 (47.1)	587 (32.1)	
≥ 60	541 (13.5)	162 (29.9)	
Sex			
Men	1,008 (25.2)	213 (21.1)	0.00
Women	2,994 (74.8)	1059 (35.4)	
Education			
<High school	1,754 (43.8)	657 (37.5)	0.00
High school	973 (24.3)	310 (31.9)	
>High school	1,275 (31.9)	305 (23.9)	
Marital status			
Married	3,358 (83.9)	1,044 (31.1)	0.00
Divorce/widow	308 (7.7)	132 (42.9)	
Single	336 (8.4)	96 (28.6)	
Number of chronic diseases			
0	2,700 (67.5)	817 (30.3)	0.00
1	829 (20.7)	268 (32.3)	
2	363 (9.1)	138 (38.0)	
≥ 3	110 (2.7)	49 (44.5)	
BMI (kg/m^2)			
<30.0	2,027 (50.6)	612 (30.2)	0.03
≥ 30	1,975 (49.4)	660 (33.4)	
Smoking			
No	3,367 (84.1)	1,041 (30.9)	0.00
Yes	635 (15.9)	231 (36.4)	
Physical activity			
Sedentary	2,719 (67.9)	875 (32.2)	0.23
Meets guidelines	1,283 (32.1)	397 (30.9)	
Altitude(m above sea level)			
<600	1,510 (37.7)	458 (30.3)	0.24
600–1,000	1,822 (45.5)	588 (32.3)	
>1,000	670 (16.8)	226 (33.7)	
PTH (ng/l)			
<65	3,851 (96.2)	1,214 (31.5)	0.08
≥ 65	151 (3.8)	58 (38.4)	
25(OH)D (ng/ml)			
<30	1,172 (29.3)	421 (35.9)	0.00
≥ 30	2,830 (70.7)	851 (30.1)	
		Mean	Standard deviation
Serum creatinine (mg/dl)		0.69	0.20

Further analysis of data, using the quartile categories of serum 25(OH)D, indicated that the unadjusted OR for having depression increased linearly across the quartiles of serum 25(OH)D ($P_{\text{trend}} = 0.00$). The OR for having depression was significantly higher among individuals in the first and second quartiles (OR = 1.4 and 1.23,

respectively) than among those in the fourth quartile (P values = 0.00 and 0.03, respectively) (Table 2). Using multiple logistic regression analyses, this relationship remained significant after adjusting for age, sex, marital status, education, BMI, serum creatinine, and number of chronic diseases (OR = 1.39 and 1.21 and P values = 0.00

Table 2 Unadjusted and adjusted odds ratios and their level of significance of logistic regression analyses for the association between serum levels of 25(OH)D and PTH with depression severity ($N = 4,002$)

Variable	<i>n</i>	Depression (DASS D score ≥ 14)					
		Model 1		Model 2		Model 3	
		OR	<i>P</i> value	OR	<i>P</i> value	OR	<i>P</i> value
25(OH)D							
≥30 ng/ml	2,830	1		1		1	
<30 ng/ml	1,172	1.32	0.00	1.34	0.00	1.38	0.00
Quartiles of 25(OH)D (ng/ml)							
>63.22	1,000	1		1		0.1	
42.31–63.22	1,006	1.05	0.61	1.01	0.96	1.05	0.63
27.61–42.30	997	1.23	0.03	1.21	0.05	1.24	0.03
≤27.60	999	1.4	0.00	1.39	0.00	1.48	0.00
P_{trend}			0.00		0.00		0.00
PTH(ng/l)							
<65	385	1		1		1	
≥65	151	1.36	0.08	1.24	0.22	1.33	0.1
Quartiles of PTH (ng/l)							
<16.1	993	1		1		1	
16.1 to <24.0	985	1.15	0.16	1.28	0.01	1.19	0.11
24.0 to <35.0	1,013	1.06	0.58	1.18	0.1	1.1	0.36
>35.0	1,010	1.05	0.6	1.11	0.31	1.08	0.43

Model 1 unadjusted; *model 2* adjusted for age, sex, marital status, education, BMI, serum creatinine, and number of chronic diseases; *model 3* adjusted for confounders in model 2 plus smoking, exercise, and altitude

and 0.05, respectively) and after further adjustment for exercise, altitude, and smoking (OR = 1.48 and 1.24, respectively, and P values = 0.00 and 0.03, respectively) (Table 2).

Results of multiple logistic regression analyses indicated that the unadjusted OR for having depression was higher among adults with serum PTH levels ≥ 65 ng/l (OR = 1.36) than those with serum PTH levels < 65 ng/L. This relationship, however, was not statistically significant (P value = 0.08). The relationship between serum PTH levels and depression remained not significant after adjusting for socio-demographic and health characteristics (age, sex, marital status, education, BMI, serum creatinine, and number of chronic diseases) (OR = 1.24 and P value = 0.22) and after further adjustment for physical activity, altitude, and smoking status (OR = 1.33 and P value = 0.1) (Table 2).

Further analysis of data, using the quartiles of serum PTH values, indicated that the likelihood for having depression was not significantly associated with serum levels of PTH ($P_{\text{trend}} = 0.56$). Using multiple logistic regression analyses, this relationship remained non-significant after adjusting for age, sex, marital status, education, BMI, serum creatinine, and number of chronic diseases and after further adjustment for exercise, altitude, and smoking (Table 2).

Discussion

At the outset, a word of caution in interpreting the study data is in order. First, the cross-sectional design used in this study provide a “snapshot” of distribution of depression and serum levels of 25(OH)D at a specific point in time. Other study designs such as randomized clinical trials provide more in-depth understanding of the associations under study. However, the design of the study has strong external validity as it represents real-life situation and is an important step before proceeding into more controlled studies. Second, the response rate in this study was 53.8%, which carries the possibility that more patients with depression had turned down our invitation to participate as part of their lack of interest in doing things. However, this self-selection bias may underestimate the prevalence rate of depression but not the association of depression with serum levels of 25(OH)D.

Using a large national population-based household sample of adult men and women aged 25 years and older, we examined whether the occurrence of depression, measured using the DASS21-D instrument, is associated with serum levels of 25(OH)D and PTH. Our data show that lower serum 25(OH)D levels are associated with a higher prevalence of rates of depression among the Jordanian population. This association persists after adjusting for the

potential confounders of age, sex, education, marital status, BMI, number of chronic diseases, serum creatinine level, physical activity, smoking, and altitude. The odds of depression (DASS D ≥ 14) increase by 38% across insufficiency categories of 25(OH)D level and by 48% across decreasing quartiles of 25(OH)D level. Serum PTH levels are not associated with depression either in the unadjusted or in multivariate-adjusted analyses. There is a paucity of research examining the association between depression and serum 25(OH)D and PTH levels in community-dwelling people. We are aware of only four other population-based studies [17, 18, 20, 21] that have specifically examined this association. The findings of this study are consistent with the European Men Ageing Study (EMAS) [17] on men 40–79 years of age and with the Longitudinal Ageing Study Amsterdam (LASA) [18] on men and women aged ≥ 65 years. However, our results conflict with the National Health and Nutrition Examination Survey (NHANES) [20] on American men and women aged ≥ 20 years and with data from a cross-sectional study on middle-aged and older Chinese men and women [21]. Our results are consistent with the Lee et al. [17] and Hoogendijk et al. [18] studies even after performing separate analyses (data not shown) on the age groups ≥ 65 years men and women and for the age groups 40–79-year-old men. The agreement in findings between our study and those of European studies negates the effect of ethnicity as an explanation for the differences in findings reported in the Zhao et al. [20] and Pan et al. [21] studies. Moreover, it is clear that these studies have used measures for depression (the PHQ-9 scale was used in Zhao et al. [20] study, and the CES-D scale was used in the Pan et al. [21] study) that differ from the DASS21-D scale used in our study. The scores of depression obtained using the CES-D, PHQ-9, and DASS-9 have been validated and used widely in non-clinical settings; thus, the bias accrued from the use of different measures of depression should not be a plausible explanation for the differences in findings in these studies. Therefore, the differences in findings with other studies could possibly be related to cultural and/or social differences or to certain biological factors mediating the relationship between serum 25(OH)D levels and/or its receptors and depression. Several interpretations are put forth to determine the link of low levels of serum 25(OH)D in the pathogenesis of depression. The abundance in the distribution of target neurons of 25(OH)D suggests the influence of 25(OH)D on synthesis levels of several aminergic and peptidergic messengers (acetylcholine esterase, serotonin, testosterone, thyroid hormone, tyrosine hydroxylase messenger RNA, melatonin [34, 35]), which have been linked to the pathogenesis of depression [36]. The reduction in levels of endogenous melatonin was associated with endogenous depression through desynchronization of the sleep-wake cycle. In their literature

review, Martin-de-Souza et al. [37] provided suggestive evidence that depression arises “...from genetic or metabolic predisposition in conjunction with environmental factors such as stressful life events.” They concluded that proteome analyses have a potential in exploring the pathophysiology of depression. Moreover, the findings from animal studies [38, 39], clinical trials [40], and prospective research [41] suggest several direct and indirect pathways through which low 25(OH)D levels are implicated in the pathogenesis of depression.

The present study shows that the decrease in the risk of depression among participants began to be significant with a serum 25(OH)D level higher than 42.3 ng/ml (the lower limit of the range of the third quartile). This value may be of clinical interest in determining the sufficiency/deficiency levels of serum 25(OH)D for the prevention and treatment of depression. More evidence from prospective research or clinical trials on the optimal level of serum 25(OH)D is needed to prevent or treat depression.

In conclusion, the results from this study, which were obtained from a large national population sample of Jordanian adults, demonstrate a significant association between depression and serum 25(OH)D levels. However, no significant association is found between depression and serum PTH concentrations. In conclusion, the results from this study that was obtained from a large national population sample of Jordanian adults showed a significant association between depression and serum 25(OH)D levels but no association was found between depression and serum PTH concentrations.

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Conflict of interest The authors declare that they have no conflict of interest.

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