



Research paper

Association between low serum 25-hydroxyvitamin D and depression in a large sample of Chinese patients with type 2 diabetes mellitus



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ABSTRACT

Background: Because of the absence of data on the direct association between vitamin D and depression in patients with diabetes, we examined the association between vitamin D state (assessed by 25-hydroxyvitamin D [25(OH)D]) and the prevalence of depression in adult patients with type 2 diabetes mellitus (T2DM).

Method: Cross-sectional data were obtained from 2786 patients with T2DM recruited from a Chinese diabetes registry. Patients' records were reviewed to obtain data pertaining to age, sex, Body Mass Index (BMI), marital status, level of education, smoking status, duration of diabetes mellitus, use of insulin, and presence of additional illnesses. A multiple logistic regression analysis adjusted for potential confounders was used to assess independent associations between serum levels of 25 (OH)D and depression (defined by the Patient Health Questionnaire-9).

Results: Using the PHQ-9 cutoff value of ≥ 10 , 5.71% (159/2786; 95% CI: 4.85–6.57%) were considered to have depression. The serum 25(OH)D levels were significantly lower in diabetic patients with depression than those patients without depression [10.2(IQR, 7.6–15.2) ng/ml vs. 14.6(IQR, 10.7–19.8) ng/ml, respectively; $P < 0.0001$]. Multivariate logistic regression analysis considering traditional risk factors and other biomarkers showed an inverse relationship between serum 25 (OH)D levels and depression when serum 25 (OH)D were used as a continuous variable (OR, 0.84; 95% CI, 0.77–0.90; $P < 0.001$). Compared with the first quartile of serum 25 (OH)D levels, the second quartile OR for depression was 0.83 (95% CI, 0.75–0.92, $P = 0.012$). For the third and fourth quartiles, it was 0.40 (95% CI, 0.33–0.52, $P < 0.001$) and 0.15 (95% CI, 0.08–0.22; $P < 0.001$), respectively.

Conclusions: We observed a significant negative association between serum levels of 25 (OH)D and depression in Chinese patients with T2DM.

1. Introduction

Diabetes mellitus (DM) and depression are common in the china. The age-standardized prevalence of total diabetes and pre-diabetes in Chinese were 9.7% and 15.5%, respectively, accounting for 92.4 million adults with diabetes and 148.2 million adults with pre-diabetes (Yang et al., 2010). It was estimated that depressive disorders were the fourth leading cause of disease burden in women and seventh leading cause in men (Sweileh et al., 2014). Approximately 3.3% of Chinese will suffer major depressive disorder at some point in their lives (Gu et al., 2013). Depression is associated with poor health behaviors (Strine et al., 2008) and central obesity (Weber et al., 2000) that increase risk of type 2 DM (T2DM). Depressed adults have a 37% increased risk of

developing type 2 diabetes mellitus (Knol et al., 2006). Recent evidence has indicated that T2DM in the elderly is a risk factor for depression, cognitive dysfunction or dementia (Gorska-Ciebiada et al., 2015). Diabetes may increase risk of depression because of the sense of threat and loss associated with receiving this diagnosis and the substantial lifestyle changes necessary to avoid developing debilitating complications (Mezuk et al., 2008).

Vitamin D has been suggested to protect against depression. Jääskeläinen et al. (2015) raised the hypothesis that higher serum 25-hydroxyvitamin D [25(OH)D] concentrations protect against depression even after adjustment for a large number of sociodemographic, lifestyle and metabolic factors. Another study found that low vitamin D levels are associated with depressive symptoms, especially in

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persons with a history of depression (Hoang et al., 2011). Interestingly, Mauss et al. (2015) found that vitamin D deficiency is associated with prevalent DM in working older adults. Importantly, another study suggested that low levels of 25(OH)D at first trimester were an independent risk factor for developing gestational DM and associated with insulin resistance at second trimester (Lacroix et al., 2014). However, the data on the direct association between vitamin D and depression in patients with diabetes is absent. Therefore, the aim of this study is to examine the association between vitamin D state assessed by 25(OH)D and the prevalence of depression in adult patients with T2DM.

2. Patients and methods

2.1. Patients

Between July 2011 and December 2015, Chinese patients with T2DM aged between 25 and 80 years who underwent comprehensive assessments at our department were invited to participate in the study. The exclusion criteria were: type 1 diabetes, disabling disease or reduced life expectancy (e.g. severe heart failure, severe respiratory, neurological or psychiatric illness, or late stages of cancer) or difficulty in communication, use of possible or known cognition-impairing drugs in the previous 3 month, presence of neoplasm, a history of mental illness, inflammatory or infectious brain disease. In addition, patients already taking vitamin D supplements or psychotropic medications were also excluded. Written informed consent was obtained after having provided verbal and written information to participants or nearest relatives when relevant. Ethics approval was granted by The Ethics Committee for Medical Research at the first hospital of Hunan university of Chinese medicine.

2.2. Clinical assessment

Demographic variables and possible risk factors were recorded in a standardized interview. Sociodemographic details (age, sex, body mass index [BMI], duration of diabetes, level of education, smoking status, marital and employment status), family history of diabetes and mental illness, cardiovascular metabolic indices, complications (hypertension, dyslipidemia, coronary heart disease, stroke, retinopathy, sensory neuropathy, peripheral vascular disease and chronic kidney disease), lifestyle factors, self-care and use of medications were documented. Blood pressures (BP) and anthropometric measurements were collected. Diabetic retinopathy was examined by fundoscopy or retinal photography. Peripheral sensory neuropathy was assessed by graduated tuning fork and monofilament.

Physical exercise was measured using the short version of the International Physical Activity Questionnaire (IPAQ), a self-reporting instrument that asks for an estimate of total weekly physical activity (walking/vigorous and moderate intensity activity) during the previous week. Physical activity levels were categorized into three (low, moderate, and high) categories following the scoring rule of IPAQ (Craig et al., 2003). The 4-item Morisky scale was used for medication adherence (Morisky et al., 1986).

2.3. Depression measurement

Participants were requested to complete the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. It consists of nine questions derived from the DSM-IV diagnostic criteria for major depression. In a previous validation study in Hong Kong Chinese type 2 diabetic patients, the optimal cutoff score to detect depression was 7 with 82.6% sensitivity and 73.7% specificity (Zhang et al., 2013). In this study, we used the widely accepted cutoff point of 10 (88% sensitivity

and 88% specificity in the original validation study with most participants being Caucasians) to detect probable depression in our study according to previous studies (Kroenke et al., 2001; Manea et al., 2012).

2.4. Laboratory tests

Fasting blood samples were collected in 5 ml tubes within 24 h after admission at 7:00–8:00 AM, were quickly centrifuged to separate the serum from the cells and were then immediately frozen at -80°C until analysis. All samples were analyzed in duplicates. Serum 25(OH)D levels were measured on the E601 modular (Roche Diagnostics, Mannheim, Germany) with a calibration range from 3 to 70 ng/ml. The intra-assay and inter-assay coefficients of variability were 1.8–4.4% and 2.6–5.2%, respectively. Fasting for blood glucose (FBG), glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (Hs-CRP), total cholesterol, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglyceride and renal function were also tested.

2.5. Statistical analysis

The results are expressed as percentages for categorical variables and as median (interquartile range, IQR) for the continuous variables. The relation of serum 25(OH)D with depression was investigated with the use of logistic regression models. Correlations among continuous variables were assessed by the Spearman rank-correlation coefficient. Proportions were compared using the Chi-square test, and the Mann–Whitney test was used to compare continuous variables between groups. We used crude models and multivariate models adjusted for all significant outcome predictors and report odds ratios (ORs). ORs were also calculated according to equal quartiles of the distributions of serum 25(OH)D, and trends across these quartiles were tested by using conditional logistic regression models. For multivariate analysis, we included confounders, known risk factors, and other significant predictors as assessed in univariate analysis. Further, receiver operating characteristic curves (ROC) was used to test the overall prognostic accuracy of the 25(OH)D and other markers and results were reported as area under the curve (AUC). All statistical analysis was performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

3. Results

After excluding 45 patients with incomplete data, 2786 Chinese patients with T2DM were included in the analysis. The median age of the participants was 59 years (IQR, 48–67), 51.5% were female ($n=1435$), and median diabetes duration was 7.0 (IQR: 3.0–12.0) years. The median PHQ-9 score was 3 (IQR, 1–5). Using the PHQ-9 cutoff value of ≥ 10 , 5.7% (159/2786; 95% CI: 4.9–6.6%) were considered to have depression. Among those patients with depression, only 13.2% (21/159) start to take psychotropic medications after the diagnosis. The baseline characteristics of patients presenting with depression or not were described in Table 1.

Patients with depression were older and more frequently were female, obesity, unmarried or widowhood, family history of mental illness, lower education, and higher blood levels of Hs-CRP, FBG, HbA1c and lower 25(OH)D. No association was found between complications or duration of diabetes and the presence of depression (Table 1). The results indicated that the median serum level of 25 (OH) D was 14.6 (IQR, 10.4–19.7) ng/ml. The serum 25(OH)D levels were significantly lower in diabetic patients with depression than those patients without depression [10.2 (IQR, 7.6–15.2) ng/ml vs. 14.6 (IQR, 10.7–19.8) ng/ml, respectively; $P < 0.0001$]. The lower serum 25(OH) D levels at admission corresponded to the higher PHQ-9 score ($r = -0.553$, $P < 0.0001$). In addition, 25(OH)D was also correlated with

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