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ORIGINAL ARTICLE

Vitamin D and Parathyroid Hormone Levels in Prediction of the Prevalence of Cerebrovascular Accident in Geriatric Patients

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ABSTRACT

Background: Plasma 25- (OH) Vitamin D level and various disorders such as metabolic syndrome, type 2 diabetes mellitus, cardiovascular problems, dementia, chronic renal disease, chronic pulmonary disease, colorectal cancer were shown to be associated. However, recent studies indicate that parathyroid hormone (PTH) may also have an impact on the development of aforementioned disorders. In this study, we aimed to investigate plasma vitamin D and serum PTH status and cerebrovascular accident association in the elderly.

Material and Methods: Totally, 1078 adult patients aged 65 year-old or older (103 patients with a past medical history of stroke and 975 patients without stroke history) were included in this cross sectional study. After comprehensive geriatric assessment, laboratory investigations including plasma vitamin D and serum PTH levels were evaluated.

Results: The median of plasma 25- (OH) Vitamin D levels (16.28 *vs.* 18.00 ng/ml) was significantly lower and the median of serum PTH levels (58.7 *vs.* 54.9 pg/ml) was significantly higher in patients with stroke than in patients without history of stroke group (P=0.016 and P=0.019, respectively). Multivariate regression analysis revealed that only serum PTH level (OR=1.007, 95% CI=1.002-1.012, P=0.007) was an independent variable for stroke.

Conclusion: Our study supports the assumption that elevated PTH has a role in stroke risk stratification. We would like to emphasize that serum PTH level -even though it is in the reference range- may be a predictor of cardiovascular outcomes such as cerebrovascular accident in the elderly.

Key words: Vitamin D; Hyperparathyroidism; Parathyroid Hormone; Stroke

INTRODUCTION

Clinical trials reveal different aspects of vitamin D deficiency therefore it keeps the state of being a mysterious molecule. Besides the usual function on gut absorption of calcium and phosphorus, extra skeletal benefits are under investigation. Plasma 25- (OH) cholecalciferol level and various disorders were shown to be associated in the existing medical literature.

Immunologic functions, metabolic syndrome, type 2 diabetes mellitus and myocardial infarction, cerebrovascular accident, dementia, chronic renal disease, chronic pulmonary disease, some cancer types were all evaluated to date and were found to be associated with vitamin D abnormalities [1-18]. However, recent studies indicate that parathyroid hormone (PTH) may have an impact on the development of aforementioned disorders.

Hence, we aimed to find out if an association between vitamin D and PTH levels and cerebrovascular accident existed in the elderly population.

MATERIAL AND METHODS

Study design and the participants

Totally, 1078 adults over 65 years of age were included in this retrospective, cross-sectional study. Patients with malignancy or severe liver failure and on dialysis were excluded from the study. Barthel index of basic activities of daily living (BADL), Lawton-Brody instrumental activities of daily living (IADL), short form of mini nutritional assessment test (MNA-SF) [19] and Mini-mental state examination (MMSE)

[20] were used for comprehensive geriatric assessment of the patients. All patients were evaluated with medical history and standardized clinical examinations. Patients were divided into two groups according to presence or absence of a history of cerebrovascular disease. Cerebrovascular disease patients were defined as having ischemic cerebrovascular disease according to the patients' medical histories.

History of any chronic disease such as hypertension, diabetes mellitus, coronary artery disease, osteoporosis and stroke was noted for each patient. Body mass index (BMI) was also calculated.

This study was approved by Local Ethical Committee of Hacettepe University Faculty of Medicine.

Laboratory parameters

Hemogram, serum biochemistry including albumin, uric acid, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, calcium, fasting plasma glucose, sodium, potassium, total cholesterol, low density lipoprotein, high density lipoprotein, triglyceride, thyroid-stimulating hormone, plasma vitamin D and serum PTH levels were evaluated. Plasma 25-hydroxyvitamin D level was assessed to determine vitamin D status by high performance liquid chromatography (HPLC). Serum PTH levels were analyzed with electrochemiluminescence immunoassay.

Statistical Analysis

The numerical variables were investigated to determine whether or not they are normally distributed by using histograms, analytical methods and probability plots. Mean ±SD was used for normally distributed variables. Median (minimum-maximum) was used for skew distributed continuous variables. Categorical variables were presented with the numbers and frequencies of patients.

Pearson's x^2 test was used for evaluating the differences between categorical variables. Otherwise, Student's t test was applied for normally distributed continuous data and Mann-Whitney U test for skew distributed parameters. To investigate the correlation between cholesterol levels and plasma vitamin D levels, Spearman test was applied. Logistic regression analysis was used for identifying independent correlates for stroke. $P<0.05$ was considered as statistically significant. Statistical analyses were done by using the version 18.0 of SPSS (Statistical Package for Social Sciences) for Windows program.

RESULTS

One hundred and three patients with stroke and 975 patients without stroke were included in our study. Demographic properties, geriatric assessment test scores, laboratory parameters and co-morbidities of the participants were presented in Table 1 and Table 2. The mean age of the participants and the rate of gender were similar between two groups. When the degree of disability was assessed, it was found that the patients with stroke had more functional dependence than the patients without stroke (IADL scores were 12.89 ±4.35 *vs.* 14.47 ±3.12, $P<0.001$ respectively). Hypertension rate in stroke patients was higher than the patients without history of stroke (82.5% *vs.* 71.9%, P=0.021).

Serum total cholesterol (TC), low-density lipoprotein (LDL) and high density lipoprotein (HDL) levels were significantly lower in patients with stroke than in patients without stroke (P=0.002, P=0.008, $P<0.001$, respectively, the details were shown in Table 2). All patients were analyzed for any correlation between lipid and vitamin D levels. However, there were no significant correlations between vitamin D and TC (r=0.043, P=0.178), LDL (r=0.027,

Table 1. Demographic Properties, Geriatric Assessment Test Scores and Co-Morbidities of the Study Population

Parameters	Patients with stroke (n=103)	Patients without stroke (n=975)	P value
Age, years	71.90 ±5.67	72.23 ±6.47	0.627
Gender, male	38 (36.9 %)	314 (32.2%)	0.335
BMI, kg/m^2	26.68 ±4.50	28.00 ±16.25	0.491
MMSE score	24.89 ±5.60	26.03 ±4.55	**0.048***
BADL score	1.00 (0.00-20.00)	0.00 (0.00-20.00)	0.136
IADL score	12.89 ±4.35	14.47 ±3.12	**<0.001***
MNA-SF score	12.00 ±2.37	12.16 ±2.24	0.507
SBP, mmHg	147.50 ±21.88	145.21 ±21.71	0.316
DBP, mmHg	86.83 ±10.85	86.49 ±11.97	0.781
Hypertension	85 (82.5 %)	697 (71.9 %)	**0.021***
Diabetes mellitus	33 (32.0 %)	241 (25.0 %)	0.113
Coronary artery disease	39 (37.9 %)	285 (29.4 %)	0.076
Osteoporosis	61 (59.2 %)	584 (60.6 %)	0.789

BMI: Body mass index, MMSE: Mini mental state examination, BADL: Basic activities of daily living, IADL: Instrumental activities of daily living, MNA-SF: Mini nutritional assessment-short form, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Table 2. Laboratory Parameters of the Study Population

Parameters	Patients with stroke (n=103)	Patients without stroke (n=975)	P value
Vitamin D, ng/ml	16.28 (1.07-63.00)	18.00 (1.07-120.00)	**0.016***
PTH, pg/ml	58.70 (23.40-397.00)	54.90 (7.90-410.00)	**0.019***
Albumin, g/dl	4.14 ±0.34	4.20 ±0.37	0.146
Uric acid, mg/dl	5.83 ±1.80	5.43 ±1.91	0.050
ESR, mm/h	17.00 (2.00-63.00)	17.00 (1.00-117.00)	0.530
CRP, mg/dl	0.40 (0.10-3.20)	0.35 (0.10-20.10)	0.773
Hemoglobin, g/dl	13.67 ±1.18	13.76 ±1.27	0.465
WBC, /µl	7045.54 ±2222.50	6750.23 ±1960.05	0.155
Platelet, /µl	250386.50 ±75357.11	250436.00 ±69340.19	0.995
Vitamin B12, pg/ml	295.95 (103.00-787.90)	270.00 (31.00-1200)	0.529
Folate, ng/ml	11.44 ±5.51	11.66 ±5.35	0.696
BUN, mg/dl	19.13 ±7.28	18.82 ±6.28	0.637
Creatinine, mg/dl	0.97 ±0.41	0.91 ±0.28	0.106
ALT, U/L	19.85 ±11.54	19.75 ±9.19	0.923
AST, U/L	22.78 ±11.88	22.39 ±9.58	0.706
ALP, U/L	159.02 ±87.89	166.32 ±82.38	0.398
GGT, U/L	21.00 (8.00-250.00)	19.00 (0.92-196.00)	**0.049***
Calcium, mg/dl	9.48 ±0.75	9.65 ±0.55	**0.029***
FPG, mg/dl	104.62 ±33.75	107.19 ±41.66	0.559
Sodium, mmol/L	141.49 ±2.96	141.94 ±2.99	0.148
Potassium, mmol/L	4.40 ±0.42	4.48 ±0.43	0.110
Total Cholesterol, mg/dl	196.60 ±51.00	211.79 ±45.52	**0.002***
LDL- Cholesterol, mg/dl	112.87 ±46.61	124.01 ±39.26	**0.008***
HDL- Cholesterol, mg/dl	52.86 ±11.38	57.22 ±14.38	**<0.001***
Triglyceride, mg/dl	155.50 ±85.53	144.07 ±75.94	0.197
TSH, ulU/ml	1.23 (0.00-3.97)	1.18 (0.00-100.00)	0.410

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, FPG: Fasting Plasma Glucose, TSH: Thyroid-stimulating hormone, GGT: Gamma-glutamyltransferase, ALP: alkaline phosphatase, ALT: Alanine aminotransferase, AST: aspartate aminotransferase, BUN: Blood Urea Nitrogen, PTH: Parathyroid Hormone, WBC: White blood cell

P=0.398), HDL (r=0.049, P=0.125), and triglyceride (r=−0.015, p=0.652). When the analysis was done separately according to the patient groups, there were no correlations between TC (r=−0.072, p=0.472), LDL (r=0.047, p=0.638), HDL (r=0.029, p=0.770), triglyceride (r=−0.079, p=0.431) and vitamin D levels in patients with stroke. In addition, the rates of using anti-hyperlipidemic drugs or statins were similar between the groups of the patients with stroke and without stroke (50.7% *vs.* 44.6%, P=0.327).

The median of plasma 25-OH vitamin D levels (16.28 *vs.* 18.00 ng/ml) was significantly lower and the median of serum PTH levels (58.7 *vs.* 54.9 pg/ml) was significantly higher in patients with stroke than control group (P=0.016 and P=0.019 respectively).

We had no clinical information about the rate of hyperparathyroidism in the patients with or without history of stroke. But, there were 134 patients (12.4% of all patients) with serum PTH levels above the reference range. The median serum PTH level in these patients was 111 pg/ml (min-max: 88.2-410 pg/ml). Also, percentage of the patients with history of stroke was higher in the patients with serum PTH levels above the normal range than the patients with serum PTH levels in normal range (14.9% *vs.* 6.9%, P=0.003).

Serum gamma-glutamyl (GGT) transferase levels (21 U/L *vs.* 19 U/L) were higher and serum calcium levels (9.48 mg/dl *vs.* 9.65 mg/dl) were lower in patients with stroke than patients without stroke (P=0.049 and P=0.029, respectively).

All parameters which were found to be significantly different in univariate analysis, including MMSE, IADL scores, presence of hypertension, vitamin D, GGT, calcium, LDL, HDL and TC levels were evaluated by using multivariate analysis to assess whether or not these parameters were correlated with stroke. Multivariate regression analysis showed that only serum PTH level (OR=1.007, 95% CI=1.002–1.012, P=0.007) was an independent risk factor for stroke.

Discussion

In this study, we aimed to show whether there is a relationship between elevated serum PTH, plasma vitamin D levels and unfavorable cardiovascular outcomes, particularly with cerebrovascular accident. Plasma vitamin D levels were found to be lower and serum PTH levels were higher in patients with stroke than without stroke. And also, increased serum PTH levels were found to be an independent risk factor

for development of stroke. Minimal but statistically significant increase in cerebrovascular accident risk was found in concordance with the following studies.

One of the major targets of PTH in the body is vascular endothelium and smooth muscle [21]. Acute elevation of PTH is shown to cause vasodilation by inducing endothelial nitric oxide release and smooth muscle relaxation; however, chronic elevation of PTH causes systemic hypertension due to vasoconstriction related to intracellular calcium accumulation in vascular smooth muscle [22, 23]. This effect may cause hypertension in patients with hyperparathyroidism and this situation may explain why the risk of ischemic stroke is higher in these patients [24]. In our study, we have found that hypertension prevalence was higher in stroke group, and also serum PTH levels, even though they are in the reference ranges, were higher in this group.

Grandi et al. [25] evaluated patients with stable coronary heart disease regarding development of cardiovascular end-points. They found that above-normal levels of PTH were an independent risk factor for unfavorable cardiovascular end-points, including myocardial infarction, stroke and death due to cardiovascular diseases.

Lishmanov et al. [26] reported that only hyperparathyroidism or cardiovascular disease history (HR=1.3 vs. 5.9, respectively) were significantly associated with increased incidence of cardiovascular events in stage 3 and 4 chronic renal disease patients. Other parameters were corrected calcium, phosphorus, calcium-phosphorus product, and 25-OH vitamin D. However, they were not found to have an impact over development of cardiovascular events.

In the light of the aforementioned studies, PTH level seems to be a more important predictor of cerebrovascular accident development and our results match with these.

In our study, other findings of lower IADL and MMSE scores in stroke group were not surprising as it is well-known that cerebrovascular accident can compromise physical and mental status. So, functional dependence causing low physical activity and deprived sunshine of patients with stroke can be associated with low levels of vitamin D. Also, hypertension prevalence was higher in stroke group as expected.

Serum cholesterol levels were unexpectedly lower in stroke group. The comparison of two groups in terms of anti-hyperlipidemic usage revealed no difference between groups. The dietary differences between groups might have contributed to this result. However, serum triglyceride as it is more affected by diet than cholesterol, MNA test and albumin levels as indirect predictors of nutritional status were not different. Eventually genetic and familial factors can explain this variable result. In addition, low cholesterol levels are also discussed to be associated with stroke in the literature. High total and low HDL cholesterol levels were found to be associated with increased risk of ischemic stroke, and also, the lowest levels of total cholesterol were found to be associated with increased risk of hemorrhagic strokes [27, 28]. Lewington et al reported consistent results with our findings indicating that cholesterol was inversely associated with stroke mortality in patients aged 70 years and older [29].

The most valuable feature of the study was the large participant population. Also, we were able to easily reach relevant data to assess common risk factors of stroke between groups.

To the best of our knowledge, there is no any superiority of PTH to Vitamin D to predict cardiovascular disease risk stratification. Both testing have been shown to be related to increased risk of cardiovascular diseases [30–33]. But, in the elderly patients, there are not enough data to show this relation. In the light of our findings, we think that elevated levels of serum PTH may have an important role in risk stratification of ischemic stroke in elderly people.

Our study has some certain limitations. Firstly, this is a cross-sectional study. Secondly, because this study is designed retrospectively, our results should be supported by prospective studies. Another limitation is that we grouped patients who have stroke or not according to medical histories, solely. So, we did not use radiological evidence to rule out cerebrovascular diseases that may have caused silent infarcts. Additionally, the plasma vitamin D and serum PTH levels were measured at the time of the patients' enrollment to the study; however for the stroke group, we could not reach the levels of these parameters at the time of cerebrovascular accident.

Despite its limitations, our study supports the assumption that increased level of PTH has an important role in cardiovascular disease such as ischemic cerebrovascular disease risk stratification. We would like to emphasize that PTH level -even though it is between reference range- may be a predictor of cardiovascular outcomes such as cerebrovascular disease in the elderly. The causal relationship however waits to be proven by further studies.

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