THE INFLUENCE OF RENAL FUNCTION ON VITAMIN D METABOLISM IN THE VERY ELDERLY

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Abstract: Objectives: Hypovitaminosis D and chronic kidney disease (CKD) are highly prevalent in older adults. The factors correlating with 25-OH-vitamin D and PTH levels were analyzed in older adults with and without CKD. Design: We performed a cross-sectional analysis embedded within the BELFRAIL study. Setting: A population-based prospective cohort study of the very elderly in Belgium. Participants: 325 participants, all aged 80 or older. Measurements: Time of year and LAPAQ score were used as proxies for sunshine exposure. Vitamin D3 supplementation, gender, institutionalisation, age, level of education, and serum calcium and phosphorus level were examined as possible confounders in the analyses. Results: There was no correlation between the presence of CKD and low 25-OH-vitamin D levels, but there was a significant (p<0.01) correlation between CKD and high PTH levels. Among the participants with a normal eGFR, the LAPACQ score, vitamin D supplementation, season, log PTH value and eGFR were correlated with log 25-OH-vitamin D levels. Among the participants with CKD, only vitamin D supplementation, log PTH levels and serum calcium levels were correlated with log 25-OH-vitamin D levels. Gender, log 25-OH-vitamin D values, serum calcium and phosphorus levels and eGFR were correlated with log PTH values in the patients with normal eGFR. Log 25-OH-vitamin D values, serum phosphorus levels, vitamin D supplementation (p=0.07), season (p=0.10) and eGFR were correlated with log PTH values in the patients with CKD. Conclusion: Exposure to sunshine and an active lifestyle were correlated with higher 25-OH-vitamin D levels in older adults without CKD. The PTH level in patients with CKD may be influenced by the season.

Key words: Hypovitaminosis D, elderly, renal function, lifestyle, sunshine.

Introduction

Hypovitaminosis D is common in older adults in western society. In the Netherlands, only 18% of patients 65 years and older have normal 25-OH-vitamin D levels (1). In the same age group, chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², has a prevalence of approximately 30% (2-4). Therefore, many older adults suffer from CKD and hypovitaminosis D.

The metabolism of vitamin D has been well documented (5). Vitamin D is synthesized in the skin in response to solar UVB radiation and is absorbed from food via the intestines. In the liver, vitamin D is transformed into 25-OH-vitamin D. The majority of 25-OH-vitamin D becomes converted to 1,25-OH2-vitamin D in the kidneys. This hydroxylation reaction in the kidney is stimulated by parathyroid hormone (PTH).

A recently published review (6) concluded that daily vitamin D3 supplementation together with calcium supplementation leads to lower all-cause mortality rates (RR 0.94; 95% CI 0.91-0.98) and an increase in nephrolithiasis (1.17; 1.02-1.34). These conclusions are primarily limited to elderly women with a high risk of osteoporosis since in this subpopulation large RCT’s (7) were performed. Furthermore, the investigators only looked for the effects of vitamin D supplementation and a more active lifestyle; changes in diet and exposure to sunshine were not examined.

Before designing a new RCT to analyse the effects of factors like an active lifestyle, sunshine exposure and vitamin D supplementation on PTH and 25-OH-Vitamin D serum levels were analyzed in patients with and without CKD on the cross-sectional data the BELFRAIL study, a cohort of representative very elderly adults aged 80 years and older.

Methods

BELFRAIL Design

The BELFRAIL study (BFC80+) is a prospective, observational, population-based cohort study of subjects aged 80 and older in three well-circumscribed areas in Belgium. The study design and the characteristics of the cohort have been described in detail (8). Briefly, 29 general practitioner (GP) centres were asked to recruit consecutive patients aged 80 years and older. Only three exclusion criteria were used: the presence of severe dementia, the need for palliative care and medical urgency. The study protocol was approved by the Biomedical Ethics Committee of the medical school of the Université Catholique de Louvain, Belgium (B40320084685); all study participants provided informed consent.

Between November 2, 2008 and September 15, 2009, the subjects were included in the BFC80+ study. The GPs...
registered the background variables, such as age, gender, marital status, living situation and level of education, and current medication regimen. A research assistant assessed physical activity using the LASA Physical Activity Questionnaire (LAPAQ) (9). The LAPAQ is a face-to-face questionnaire that measures the frequency and duration of physical activities, such as walking outside, bicycling, gardening, light household tasks, heavy household tasks, and a maximum of two sport activities during the previous two weeks.

**Laboratory tests**

Blood samples were collected in the morning. All measurements were performed in the laboratories of the Cliniques Universitaires St Luc, Brussels. The UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA) was used to measure creatinine (IDMS), calcium and phosphorus levels. 25-OH-vitamin D levels were measured on the LIAISON® (DiaSorin, Saluggia, Italy), and parathyroid hormone (PTH) levels were measured using the UniCel® Dxl 800 Immunoassay System (Beckman-Coulter, Brea, USA).

**Main study parameters**

**Vitamin D metabolism**

The participants were categorised into groups based on their 25-OH-vitamin D levels using previously published (10, 11) cut-offs: <10 ng/ml (deficient), 10-19 ng/ml (insufficient), 20-29 ng/ml (hypovitaminosis) and >30 ng/ml (normal). In addition, dichotomous classifications were used: <20 ng/ml (low 25-OH-vitamin D) and > 20 ng/ml (normal 25-OH-vitamin D). The participants were also divided into two groups based on their PTH levels using a cut-off of 60 pg/ml (12).

**Renal function**

The abbreviated Modification of Diet in Renal Disease (MDRD) equation was used to calculate the estimated glomerular filtration rate (eGFR): eGFR (mL/min/1.73 m²) = 175 x (Scr)\(^{-1.154}\) x (age)\(^{-0.203}\) x (0.742, if female) (13).

The patients were divided based on their eGFR according to the CKD classification system from the US National Kidney Foundation (14): >60, 45-60, 30-45 and <30 mL/min/1.73 m². Additionally, the participants were divided as having CKD (eGFR < 60 mL/min/1.73 m²) or having a normal eGFR (>60 mL/min/1.73 m²).

**Confounders**

The season during which blood was collected (either October-March or April-September) and the LAPAQ score (measured as 5 categories: a score of 0 and the 4 gender-adjusted quartiles; or as dichotomous categories: a score of 0 + the 2 lowest gender-adjusted quartiles and the 2 highest gender-adjusted quartiles) were used as proxies for sunshine exposure in the period prior to blood collection. Vitamin D3 supplementation (yes or no), gender, institutionalisation (yes or no) and level of education (high or low) were considered to be potential confounders for 25-OH-vitamin D and PTH levels.

**Statistical analyses**

The prevalence of each of the vitamin D levels (deficient, insufficient, hypovitaminosis, and normal) was compared using a Kruskal-Wallis test. Odds ratios were used to compare the 25-OH-vitamin D levels and PTH levels with the different stages of CKD and were calculated using binary logistic regression. P-values were used to assess significance. After logarithmic transformation, the serum vitamin D and PTH levels were used as the dependent variables in multivariate linear regressions. In the multivariable analysis, p values of >0.10 were considered to be non-significant (NS). All analyses were performed using SPSS, version 16 (SPSS Inc. Chicago, IL, USA).

**Results**

The PTH and 25-OH-vitamin D levels were measured in 325 participants. Appendix 1 shows the comparison of these 325 participants with the entire BELFRAIL study population; no significant differences were observed. The characteristics of the BELFRAIL study population have been described previously (8). Briefly, of the 325 participants aged 80 and older in our study, 203 (63%) were women, and 33 (10%) were institutionalised. The prevalence of CKD was 46%, and the mean eGFR was 64 mL/min/1.73 m². 13% of the participants had normal vitamin D levels, 21% had hypovitaminosis D, 33% had vitamin D insufficiency and 33% had vitamin D deficiency. There were differences between the eGFR subgroups in terms of the serum PTH and phosphorus levels and LAPAQ scores as shown in table 1. The institutionalised participants had a higher prevalence of vitamin D deficiency (45% versus 31%), and the participants who took vitamin D supplements had a lower prevalence of vitamin D deficiency (7% versus 33%) and a higher prevalence of normal 25-OH-vitamin D levels (40% versus 7%). The participants who provided blood samples from October-March had a higher risk of vitamin D deficiency (41%) than those who provided blood samples from April-September (28%).

Table 2 demonstrates the relationship between eGFR and serum 25-OH-vitamin D and PTH levels, using 3 models to adjust for confounders. A relationship between eGFR and 25-OH-vitamin D levels was not found in any model only a trend (p = 0.09) in the third model. However, in all of the models, there was a significant (p<0.01) correlation between eGFR and serum PTH levels.

Gender, LAPAQ score, vitamin D supplementation, season, log PTH, serum calcium and eGFR were significantly associated with 25-OH-vitamin D levels (p <0.05). For participants with a normal eGFR (see table 3), the LAPAQ score, vitamin D supplementation, season, log PTH values and eGFR were correlated with log 25-OH-vitamin D values. Among the participants with CKD, vitamin D supplementation, log PTH values and serum calcium levels were correlated with the log 25-OH-vitamin D values (see table 3).