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Association between Serum Concentration of Vitamin D and 1-Year Mortality in Stroke Patients

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Key Words
Acute stroke · Outcome · Prognosis · Vitamin D · Mortality

Abstract
Background: The prevalence of 25-hydroxyvitamin D [25(OH)D] deficiency is high in patients presenting with an acute stroke, and it may be associated with greater clinical severity and a poor early functional prognosis. However, no data about its impact on long-term prognosis is available. In this study, we aimed to assess the association between 25(OH)D levels and 1-year mortality in stroke patients. ***Methods:*** From February to December 2010, 382 Caucasian stroke patients admitted to the Department of Neurology of the University Hospital of Dijon, France, were enrolled prospectively. Demographics and clinical information including stroke severity assessed using the National Institutes of Health Stroke Scale score were collected. The serum concentration of 25(OH)D was measured at baseline. Multivariable Cox regression models were used to evaluate the association between 1-year all-cause mortality and serum 25(OH)D levels treated as either a log-transformed continuous variable or dichotomized (<25.7 and ≥25.7 nmol/l) at the first tertile of their distribution. ***Results:*** Of the 382 stroke patients included, 63 (16.5%) had died at 1 year. The mean 25(OH)D level was lower in these patients (32.3 ± 22.0 vs. 44.6 ± 28.7 nmol/l, p < 0.001), and survival at 1 year was worse in patients in the lowest tertile of 25(OH)D levels (defined as <25.7 nmol/l); log-transformed 25(OH)D levels were inversely associated with 1-year mortality (hazard ratio, HR = 0.62; 95% confidence interval, 95% CI: 0.44–0.87; p = 0.007), and patients with 25(OH)D levels <25.7 nmol/l were at a higher risk of death at 1 year (HR = 1.95; 95% CI: 1.14–3.32; p = 0.014). In multivariable analyses, the association was no longer significant but a significant interaction was found for age, and stratified analyses by age groups showed an inverse relationship between 25(OH)D levels and 1-year mortality in patients aged <75 years [HR = 0.38; 95% CI: 0.17–0.83; p = 0.015 for log-transformed 25(OH)D levels, and HR = 3.12; 95% CI: 0.98–9.93; p = 0.054 for 25(OH)D levels <25.7 vs. >25.7 nmol/l]. ***Conclusion:*** A low serum 25(OH)D level at stroke onset may be associated with higher mortality at 1 year in patients <75 years old. Further studies are needed to confirm these findings and to determine whether vitamin D supplementation could improve survival in stroke patients.

Introduction

The prevalence of 25-hydroxyvitamin D [25(OH)D] deficiency is high in patients presenting with an acute stroke [1, 2]. In a previous study, we demonstrated that

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low 25(OH)D levels were associated with both clinical severity at admission and a poor early functional prognosis in stroke patients [3]. In addition, a higher all-cause mortality has been reported in people with 25(OH)D deficiency [4, 5]. To investigate whether 25(OH)D levels could serve as a biomarker of long-term prognosis after stroke, we evaluated their association with mortality at 1 year.

Methods

The study methods have been described elsewhere [3]. Briefly, from February to December 2010, 386 consecutive Caucasian stroke patients with no premorbid handicap admitted to the University Hospital of Dijon, France, were enrolled. The 25(OH)D level measured within the first 24 h after admission was obtained in 382 patients (median value 35.1 nmol/l, interquartile range 21–57.8) of whom 42 had intracerebral haemorrhage and 340 had ischaemic stroke. Season of stroke onset, vascular risk factors, prestroke therapy, and acute treatment were recorded. Clinical severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS score). One-year all-cause mortality was assessed through death certificates. Information about vital status was complete.

Statistical Analysis

25(OH)D levels were not normally distributed ($p < 0.001$ for the Shapiro-Wilk normality test) and were therefore log-transformed for the first series of analyses in which this variable was treated as continuous in statistical models. In the second series of analyses, 25(OH)D levels were dichotomized (<25.7 and ≥25.7 nmol/l) at the first tertile of their distribution. Survival curves were obtained using Kaplan-Meier analysis, and the log-rank test was used for comparisons between groups. Cox regression models were used to estimate hazard ratios (HRs) of 1-year mortality. The proportional-hazards assumption was tested using Schoenfeld residuals. Therefore, age (<60, 60–75, and ≥75 years) and NIHSS score (<6, 6–14, and >14) variables were categorized. In multivariable models, we introduced age, gender, 25(OH)D levels, and baseline characteristics with a p value <0.20 in unadjusted models. The reference used for the analyses based on 25(OH)D levels as a dichotomized variable was the upper 2nd and 3rd tertiles of 25(OH)D combined, corresponding to a 25(OH)D level ≥25.7 nmol/l. Backward selection was done using the likelihood ratio test to obtain the final model. Interaction terms were added to the models to test the modifying effect of confounding variables on the association between 25(OH)D level and 1-year all-cause mortality, using the likelihood-ratio test. Because there was a statistically significant interaction, stratified analyses by age groups were performed. Significance was set at $p < 0.05$. Statistical analysis was performed with STATA® 10.0 software (StataCorp LP, College Station, Tex., USA).

Ethics

This study was derived from the Dijon Stroke Registry, which was approved by the 'Comité National des Registres' (French National Committee of Registers) and the French Institute for Public Health Surveillance [6]. Authorization of the 'Commission Nationale de l'Informatique et des Libertés' (National Commission for the Protection of the Privacy of Electronic Data) was obtained.

Results

Of the 382 stroke patients, 63 (16.5%) had died at 1 year. The mean 25(OH)D level was lower in patients who had died (32.3 ± 22.0 vs. 44.6 ± 28.7 nmol/l, $p < 0.001$) and 1-year survival was lower in patients with low 25(OH)D levels (fig. 1).

In the first series of analyses, an inverse relationship between log-transformed 25(OH)D levels and 1-year mortality was observed (HR = 0.62; 95% confidence interval, 95% CI: 0.44–0.87; $p = 0.007$). In multivariable analyses adjusted for age, gender and NIHSS score, only a non-significant trend was noted (HR = 0.80; 95% CI: 0.54–1.17; $p = 0.247$). In stratified analyses by age groups, 25(OH)D levels tended to be inversely associated with 1-year mortality in patients aged 60–74 years (HR = 0.41; 95% CI: 0.16–1.02; $p = 0.056$) but not in those aged ≥75 years (HR = 0.95; 95% CI: 0.61–1.46; $p = 0.80$). Because of the small number of deaths in patients aged <60 years ($n = 4$), stratification was not possible for this age group. However, when patients aged <75 years were grouped together, the inverse association was found (HR = 0.38; 95% CI: 0.17–0.83; $p = 0.015$).

In the second series of analyses, low 25(OH)D levels dichotomized at the first tertile of their distribution were associated with 1-year mortality (HR = 1.95; 95% CI: 1.14–3.32; $p = 0.014$). After adjustment for age, gender and NIHSS score, the association was no longer significant (HR = 1.15; 95% CI: 0.67–1.98; $p = 0.613$). In stratified analyses, a significant association between low 25(OH)D levels and 1-year mortality was noted in patients aged 60–74 years (HR = 3.91; 95% CI: 1.00–15.29; $p = 0.05$) but not in those aged ≥75 years (HR = 0.89; 95% CI: 0.48–1.65; $p = 0.71$; fig. 2). When patients aged <75 years were grouped together, the association proved to be marginally significant (HR = 3.12; 95% CI: 0.98–9.93; $p = 0.054$).

Discussion

This study suggests that a low 25(OH)D level may be associated with an increased risk of 1-year mortality in those aged <75 years.

This is the first study to assess the prognostic value of low 25(OH)D levels on post-stroke mortality. Several ex-

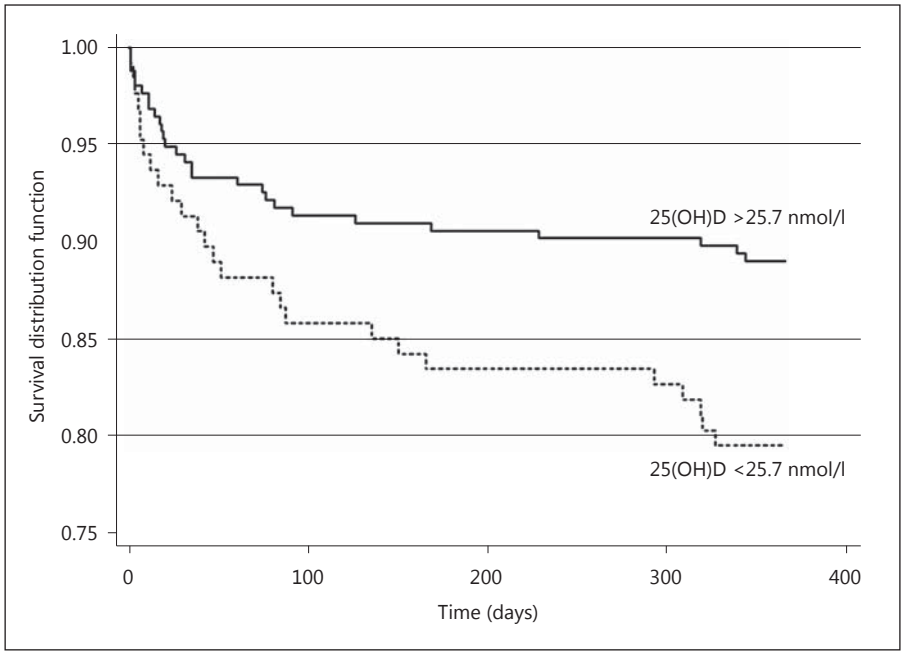

Fig. 1. Kaplan-Meier estimates of 1-year survival stratified by 25(OH)D levels (log-rank test 0.01).

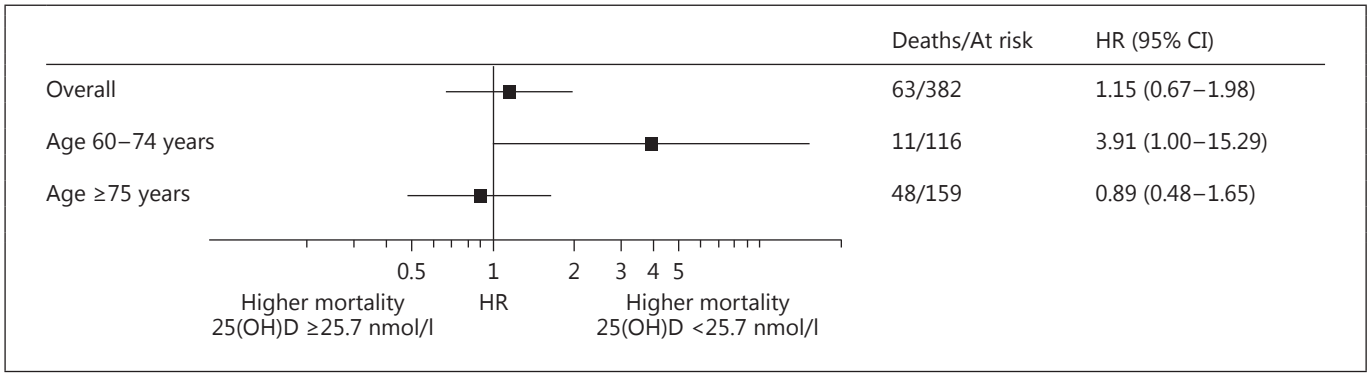

Fig. 2. Association between 25(OH)D levels and 1-year mortality in multivariable analyses. Models adjusted for 25(OH)D levels, gender, NIHSS (<6, 6–14, ≥14), and age groups (except for stratified analyses).

planations could account for the divergent findings according to age groups. The absence of an association between low 25(OH)D levels and mortality in older patients could be related to the fact that age is by itself a strong predictor of post-stroke survival, and a potential deleterious effect of low 25(OH)D levels could be too small to be detected in the elderly. The relatively small population size could have made the study underpowered. Moreover, we cannot exclude the possibility that residual confounding factors, including dementia or a poorer health status, may have been missed.

The association between low 25(OH)D levels and mortality in patients aged <75 years is more convincing. This result is consistent with those from other studies, which demonstrated that 25(OH)D deficiency was associated with greater all-cause mortality [4, 5]. In addition, other works reported a deleterious effect of low 25(OH)D levels on survival in patients with various diseases including chronic kidney disease [7], heart failure [8, 9], and myocardial infarction [10]. The reasons why a low 25(OH)D level may increase the risk of post-stroke mortality remain uncertain. It could be hypothesized that it may result from an increase in vascular events in patients

with 25(OH)D deficiency [11], even though a recent study showed that the greater mortality in individuals with low 25(OH)D levels was not explained by a similar inverse association with ischaemic heart disease or stroke [5]. In the absence of available data, we were not able to assess the causes of death in our study. Finally, we cannot exclude the possibility that low 25(OH)D levels may simply reflect poor health, which could account for the observed association with death. Indeed, several medical conditions, including cancer, dementia, or other chronic diseases, are associated with 25(OH)D deficiency because of limited sun exposure, physical impairment, and inadequate nutrition, and could also be associated with premature death in stroke patients.

To conclude, further studies are needed to confirm our findings and to determine whether vitamin D supplementation could improve survival in stroke patients.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

References

1 Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA: Reduced vitamin D in acute stroke. Stroke 2006 37:243–245.

2 Carda S, Cisari C, Invernizzi M, Bevilacqua M: Osteoporosis after stroke: a review of the causes and potential treatments. Cerebrovasc Dis 2009;28:191–200.

3 Daubail B, Jacquin A, Guilland JC, Hervieu M, Osseby GV, Rouaud O, Giroud M, Béjot Y: Serum 25-hydroxyvitamin D predicts severity and prognosis in stroke patients. Eur J Neurol 2013;20:57–61.

4 Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S: Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. Am J Clin Nutr 2012;95:91–100.

5 Skaaby T, Husemoen LL, Pisinger C, Jørgensen T, Thuesen BH, Fenger M, Linneberg A: Vitamin D status and incident cardiovascular disease and all-cause mortality: a general population study. Endocrine 2013;43:618–625.

6 Béjot Y, Rouaud O, Jacquin A, Osseby GV, Durier J, Manckoundia P, Pfitzenmeyer P, Moreau T, Giroud M: Stroke in the very old: incidence, risk factors, clinical features, outcomes and access to resources: a 22-year population-based study. Cerebrovasc Dis 2010;29:111–121.

7 Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S: Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. Am J Kidney Dis 2011;58:374–382.

8 Liu LC, Voors AA, van Veldhuisen DJ, van der Veer E, Belonje AM, Szymanski MK, Silljé HH, van Gilst WH, Jaarsma T, de Boer RA: Vitamin D status and outcomes in heart failure patients. Eur J Heart Fail 2011;13:619–625.

9 Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, Admon D: Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012;14:357–366.

10 Correia LC, Sodré F, Garcia G, Sabino M, Brito M, Kalil F, Barreto B, Lima JC, Noya-Rabelo MM: Relation of severe deficiency of vitamin D to cardiovascular mortality during acute coronary syndromes. Am J Cardiol 2013;111:324–327.

11 Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD: Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819–829.