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Vitamin D status in relation to physical performance, falls and fractures in the Longitudinal Aging Study Amsterdam: A reanalysis of previous findings using standardized serum 25-hydroxyvitamin D values

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ABSTRACT

The Longitudinal Aging Study Amsterdam (LASA) is an ongoing prospective cohort study in a representative sample of Dutch older persons. In previous LASA studies, lower serum 25-hydroxyvitamin D (25(OH)D) values, as assessed by a competitive protein binding assay or radioimmunoassay, have been associated with decreased physical functioning, falls and fractures. Recently, serum 25(OHD) values in LASA were standardized using the Vitamin D Standardization Program (VDSP) protocol as part of the European ODIN project. In the current manuscript, the influence of standardizing serum 25(OH)D values will be discussed using the associations with physical functioning, falls and fractures as examples.

1. Introduction

About 30% of community-dwelling older persons aged 65 years or over falls every year, and about 15% is a recurrent faller [1]. Falls may lead to serious injuries, such as fractures. Lifetime osteoporotic fracture risk lies between 40 and 50% in women and 12–22% in men [2]. The individual burden of falls and fractures is high. Both falls and fractures may lead to restriction of physical activities, decreased physical function, loss of independence, an increase of health service use, nursing home admission, lower quality of life, higher mortality risk and high costs for society [3–10].

Vitamin D is important for calcium homeostasis and healthy bones [11]. Severe vitamin D deficiency is associated with rickets and osteomalacia, and also with muscle weakness. The vitamin D receptor is expressed in skeletal muscle [12], and VDR-null mice show smaller muscle fiber size and abnormal expression of major muscle-specific genes [13,14]. Functional decline and falls are both related to an increased fracture risk [15,16].

In previous studies of the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective cohort study, associations were reported between serum 25-hydroxyvitamin D (25(OH)D) and physical functioning, falls and fractures. Lower serum 25(OH)D values were associated with loss of muscle strength [17], lower physical performance and decline in physical performance [18,19], functional limitations and functional decline [20], falls [21] and fractures [22].

Serum 25(OH)D in LASA was analyzed using a competitive protein binding assay in 1995/96 and radioimmunoassay at other timepoints. As there is considerable variability both within and among various laboratory assays [23], there is an urgent need for standardization. The Vitamin D Standardization Program (VDSP) developed a protocol to standardize existing serum 25(OH)D data using standards provided by the National Institute of Standardization Technology [24,25]. The validity of the program has been shown in an Irish survey [23,26].

The aim of the current study is to reanalyze previously reported associations between serum 25(OH)D and physical performance, falls and fractures in the LASA study using standardized serum 25(OH)D values. In addition, the importance of standardization of serum 25(OH) D values in existing studies will be discussed as well as the importance of observational vitamin D research.

2. Methods

2.1. Design and participants

The Longitudinal Aging Study Amsterdam (LASA) is an ongoing prospective cohort study in a representative sample of Dutch older persons. The aim of this cohort is to study predictors and consequences of changes in physical, cognitive, emotional and social functioning in

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older persons [24]. A random sample of men and women aged 55 years and over, stratified by age, sex, urbanization grade and expected 5-years mortality rate was drawn from the population registers of eleven municipalities, in three regions of the Netherlands. In total, 3107 persons were enrolled in the baseline examination in 1992/93. For the current study, persons who participated in the medical interview in 1995/96, and were born in or before 1930 (aged 65 years and older as of January 1, 1996), were selected (n = 1509). In 1352 of these persons, blood samples were drawn and valid serum 25(OH)D could be determined in 1320 samples. Data on physical performance were assessed in 1995/96 and 1998/99 (n = 1234 in the cross-sectional analysis; n = 979 in the longitudinal analyses). Falls were prospectively assessed during one year (n = 1231). Fractures were prospectively assessed during six years (n = 1311). The Medical Ethics Committee of the VU University Medical Center gave approval for the study, and all persons gave informed consent.

2.2. Physical performance, falls and fractures

Physical performance was assessed by three tests: time needed to walk three meters along a rope, turn 180 ° and walk back (walking test); time needed to stand up from and sit down on a chair five times with arms folded across the chest (chair stands test); and the ability to perform the tandem stand (one foot placed behind the other on a straight line) for at least ten seconds (tandem stand) (adapted from [27]). For the walking test and chair stands test, scores one to four were given according to the quartile of the distribution of time needed. Score zero was given to those respondents who could not complete the test. The tandem stand was categorized as follows: unable (score 0), able to hold position for 3–9 s (score 2), and able to hold position for at least 10 s (score 4). Total physical performance sum score ranged from zero to twelve with twelve indicating good physical performance.

Decline in physical performance during three years of follow-up was defined using the Edwards-Nunnally Index, which is an index that adjusts for regression to the mean [28]. Changes in physical performance were dichotomized into decline versus no decline (stable or improvement) using a critical value of 1.96 [18].

Falls were prospectively assessed during one year using a calendar. Participants were asked to report their falls weekly on a calendar and to send the calendar to our institute every three months. Recurrent falls were defined as two or more falls during one year.

Fractures were assessed using a calendar in the first three-year period. Participants were instructed to complete a set of questions regarding fractures every three months, and to send the calendar to our institute. In the second three-year period, fractures were assessed by an interview at the end of the period. For each fracture, the exact date was asked and verified with the general practitioner or hospital. More than ninety percent of the fractures included in the analyses could be verified. In case of persons who dropped out or were deceased, the general practitioner was interviewed about potential fractures and the circumstances of the fractures. All fractures were considered osteoporotic, except for head/hands/fingers/feet/toes fractures and fractures caused by traffic accidents, which were excluded from the analyses.

2.3. Original serum 25(OH)D values

Morning blood samples were obtained in 1995/96 and 2009. In 1995/96, subjects were allowed to have tea and toast, but no dairy products. For the measurements in 2009, blood was collected after an 8-h fast. The blood samples were centrifuged and stored at −80°C. Serum 25(OH)D measurements took place in 1997/98 (samples collected in 1995/96) and 2010/11 (samples collected in 2009). In 1997/98, a competitive protein binding assay was used (Nichols Diagnostics Capistrano, CA, USA) and in 2010/11, a radioimmunoassay was used (Diasorin, Stillwater, Minnesota, USA). The interassay coefficient of variation was 11% on average levels of 27 nmol/L and 141 nmol/L for the Nichols assay, and 10% at average levels of 30 nmol/L and 65 nmol/L for the Diasorin assay. All measurements were performed at the Endocrine Laboratory of the VU University Medical Center.

Table 1
Percentage of people at risk using different cut-off values for the original and standardized serum 25(OH)D values.

	Original 25(OH)D	Standardized 25(OH)D
Serum 25(OH)D in 1995 (Nichols), mean age 75.6 ± 6.6		
< 25 nmol/L	11.3%	10.2%
< 30 nmol/L	17.5%	17.3%
< 50 nmol/L	48.4%	53.2%
< 75 nmol/L	82.4%	91.6%
Serum 25(OH)D in 2009 (Diasorin), mean age 71.5 ± 7.7		
< 25 nmol/L	1.5%	2.4%
< 30 nmol/L	3.8%	4.6%
< 50 nmol/L	26.5%	28.5%
< 75 nmol/L	67.6%	68.1%

25(OH)D = serum 25-hydroxyvitamin D.
Standardization was performed according to the Vitamin D Standardization Program protocol [29].

2.4. Standardized serum 25(OH)D values

In 2015, serum 25(OHD) values were standardized using the Vitamin D Standardization Program (VDSP) protocol as part of the European ODIN ("Food-based solutions for optimal vitamin D nutrition and health through the life cycle") study [29]. In total, 166 frozen samples from 1995/96 and 159 frozen samples from 2009 were reanalyzed in Ireland by a standardized and certified LC–MS/MS method, which was traceable to the National Institute of Standards and Technology higher-order Reference Measurement Procedure. The resulting serum 25(OHD) values were used to develop master regression equations, which were used to recalibrate the datasets of 1995/96 and 2009, respectively.

2.5. Statistical analyses

Prevalence data of low vitamin D status using different cut-off values for serum 25(OH)D were calculated using both the original as well as the standardized serum 25(OH)D values. Secondly, physical performance, falls and fractures were reanalyzed using standardized serum 25(OH)D values. For comparability issues, the same approach was used as in the original manuscripts [18,21,22]. In short, for physical performance, the average score including 95% confidence interval (95% CI) was calculated for both the original as well as standardized serum 25(OH)D values (per 10 nmol/L). Decline in physical performance during three years of follow-up was analyzed using logistic regression analysis. The analysis was adjusted for the following baseline variables: age, sex, number of chronic diseases, degree of urbanization, body mass index and alcohol use. For falls, an optimal cut-off point was chosen based on the prevalence data of recurrent falls stratified according to standardized serum 25(OH)D (< 25 nmol/L, 25–50 nmol/L, 50–75 nmol/L, > 75 nmol/L). The association between standardized serum 25(OH)D and recurrent falls was analyzed using logistic regression analysis. The analysis was adjusted for the baseline variables age, sex, season, body mass index, number of chronic diseases, creatinine, cognition, smoking and alcohol use. For fractures, an optimal cut-off point was chosen by calculating the difference in fracture risk for different cut-off values ranging from 25 to 75 nmol/L. The association between standardized serum 25(OH)D and time to first osteoporotic fracture was analyzed using a Cox Proportional Hazards Model. The analyses were adjusted for the baseline variables age, sex, season, education, body mass index, number of chronic diseases, creatinine level, cognition, smoking, and alcohol use. The confounders differed slightly between outcomes to match the original analyses. For a