Abstract: Objective: To examine whether low serum 25-hydroxyvitamin D (25OHD) concentration were associated with low muscle strength while taking into account the effects of potential confounders among a cohort of community-dwelling women aged 75 years and older. Design: Cross-sectional study corresponding to the baseline assessment of the EPIDOS study. Setting: Five French cities including Amiens, Lyon, Montpellier, Paris and Toulouse. Participants: Randomized sample of 440 women included in the EPIDOS study. Measurement: Maximal isometric voluntary contraction strength of the lower limb and hand with computerized dynamometers, serum 25OHD and parathyroid hormone concentration. Age at baseline evaluation, number of chronic diseases, body mass index (BMI), use of calcium drug, practice of a regular physical activity, serum calcium concentration and clearance of creatinine were used as covariables. Subjects were separated into 3 groups based on serum 25 OHD levels with the following cut-off values: < 15 ng/ml, 15-30 ng/ml and > 30 ng/ml. Results: More than 90% of women had a serum 25OHD insufficiency (i.e. < 30ng/ml) and 40.2% had a related secondary hyperparathyroidism. The mean value of muscle strength was not different among the 3 groups of women (174.9±53.2 for serum 25OHD < 15 ng/ml versus 175.9±52.6 for serum 25OHD 15-30 ng/ml versus 173.4±53.1 for serum 25OHD > 30 ng/ml with P=0.946 for quadriceps, and 56.1±13.2 for serum 25OHD < 15 ng/ml versus 57.1±13.5 for serum 25OHD 15-30 ng/ml versus 61.1±12.7 for serum 25OHD > 30 ng/ml with P=0.064 for handgrip). There was no significant association between serum 25OHD concentration and quadriceps strength (crude β = 0.03 with P = 0.891 and adjusted β = -0.04 with P = 0.837). Univariate linear regression showed a significant association between serum 25OHD concentration and handgrip strength (crude β = 0.16 with P = 0.049) but not while using an adjusted model (adjusted β = 0.13 with P = 0.106). Conclusions: The findings of this study do not support the hypothesis of a relationship between low serum 25OHD concentration and low muscle strength. Further research is needed to corroborate and explain this finding.

Key words: Vitamin D, muscle strength, older adults.

Introduction

Muscle is a target site for 25-hydroxyvitamin D (25OHD) and 1,25-dihydroxyvitamin D (1,25 (OH)2D) (1-3). These both vitamin D metabolites act on muscle cell via genomic and non-genomic pathway and, thus, may influence muscle function (1, 4). It has been suggested that chronic low serum 25OHD concentration could be associated with muscle weakness defined as the inability to exert strength with ones muscles to the degree that would be expected given the individual’s general physical fitness (1-4). However, the relationship between low serum 25OHD concentration and low muscle strength is not fully established among older adults because findings from observational clinical studies are controversial. Some studies have shown that 25OHD insufficiency (i.e. < 30ng/ml) as well 25OHD deficiency (i.e. < 15ng/ml) were associated with muscle weakness (4-8), while others failed to find any relationship (9, 10).

Divergences between studies may result from a lack or an insufficient control of confounders that may modify the relationship between serum 25OHD concentration and muscle strength. Firstly, it has been shown that secondary hyperparathyroidism associated with low serum 25OHD concentration may directly provoke muscle weakness (11-13). Secondly, a low calcium concentration may also be a modulator of muscle strength by acting on 1,25 (OH)2D and on parathyroid hormone (PTH) production (13, 14). Thirdly, age, unhealthy status, malnutrition, level of physical activity are health and life style factors that may also change the relationship between serum 25OHD concentration and muscle strength (15, 16).

Whilst the effects of confounders of the relationship between serum 25OHD concentration and muscle strength are well-identified, few studies have examined their joint effects (4, 15, 16). These studies have highlighted that muscle weakness could be related to confounders and not to low serum 25OHD concentration. Furthermore, Bischoff et al. (10) showed that the relationship was complex and depend on the type of vitamin D metabolites. Although decrease in leg extensor strength in Bischoff ‘s study was explained by sex, age, body mass index...
(BMI), and serum 1,25 (OH)2D but not 25OHD level in older adults, there was a positive correlation between both vitamin D metabolites and lower limb muscle strength while using a univariate model.

Acquiring more information about low serum 25OHD concentration-related changes in muscle strength adjusted for the effects of confounders among older adults could add to our knowledge of low serum vitamin D-related adverse muscle outcomes. Furthermore, in view of previous findings on the interrelated relationships between muscle strength and serum 25OHD, PTH, and calcium concentration, the respective influences of each serum variable on muscle weakness need to be explored. Thus, the objective of the study was to examine whether low serum 25OHD concentration were associated with low muscle strength while taking into account the effects of serum and clinical confounders among women aged 75 years and older using data from the EPIDOS study.

Methods

Participants

We studied a randomized sample of 440 subjects included in the EPIDOS study which is a community-dwelling observational prospective cohort study designed to evaluate the risk factors for hip fracture among more than 7500 healthy older women aged 75 years and older. The sampling and data collection procedures have been described elsewhere in detail (17). In summary, from 1992 to 1994, 7598 subjects sampled from electoral lists were recruited in five French cities including Amiens, Lyon, Montpellier, Paris and Toulouse after having given their written informed consent. Exclusion criteria were inability to walk independently, hip fracture or bilateral hip replacement, inability to understand or answer the study questionnaires. Included participants received a full medical examination in each local clinical center by trained nurses which included structured questionnaires, information about chronic diseases, clinical examination and anthropometrics measurements. The study was conducted in accordance with the ethical standards set forth in the Helsinki declaration (1983). The local ethics committee of each city approved the project.

Muscle strength measures

The procedure consisted of the evaluation of the maximal isometric voluntary contraction (MVC) strength of the lower limb and hand with computerized dynamometers. Before testing for both muscle strength measures, subjects were allowed to practice the isometric movements and a trained evaluator gave standardized verbal instructions regarding the test procedure. Furthermore, subjects were instructed to push against the dynamometers as hard as they could and the maximal peak pressure expressed in Newton per square meter was recorded. The highest value of MVC strength recorded was used in the present data analysis. Quadriceps strength was assessed using a strain gauge system attached to a chair upon which subjects were seated with both hips and knees flexed at 90° angle. The leg to be tested was fixed to the lever arm on an analog strain gauge to measure strength. The seat position was adjusted for the leg length. Three MVC were recorded for the dominant and the non-dominant leg, and analyzed off-line. Secondly, a hydraulic hand dynamometer (Martin Vigorimeter, Medizin Tecnik, Tutlingen, Germany) was used to measure the handgrip strength. The size of the grip was adjusted so that the subject felt comfortable. The subject stood upright with the arm vertical and the dynamometer close to the body. The test was performed one time on each side.

Serum measures

Fasting early morning venous blood was collected from resting subjects for the measurement of serum 25OHD, PTH, calcium, creatinine and albumin. Sera were stored at -100°C until analysis. Serum 25OHD concentration was measured by radioimmunoassay (Incstar Corp., Stillwater, MN). With this method, there is no interference of lipids, which is often observed in other non chromatographic assays of 25OHD. The intra- and interassay precisions were respectively 5.2 % and 11.3 %. (range in normal adults aged 20-60 yr, 30-125 ng/ml). Intact PTH (iPTH) was measured by immunochemoluminometric assay (Magic Lite, Ciba Corning Diagnostic, Medfield, MA; normal range for adults 20-60 year of age, 11-55 pg/ml). The intra- and interassay precisions were 5.2-6.8% and 5.0-5.5% respectively. Serum calcium, albumin and creatinine were determined using automated standard laboratory methods. Because of the high prevalence of hypoalbuminemia in older adults, the serum concentration of albumin and calcium were used to correct the calcium value (calcium corrected value = Ca + 0.02 [46-albumin]). The calcium corrected value was used in the subsequent analysis. The clearance of creatinine was calculated from the Cockcroft formula ([(140-age years) / creatinine mol/l] x 1.04). All measurement was performed locally at the University Hospital at Lyon, France.

Clinical covariates

Age at baseline evaluation, number of chronic diseases, BMI, use of calcium drug and practice a regular physical activity were used as clinical confounders in data analysis. Confounders were obtained from a physical examination and a health status questionnaire to target comorbidities (hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson’s disease and depression). Practice of a regular activity was reported with a self-reported structured questionnaire. Type, frequency and duration of recreational physical activities including walking, gymnastics, cycling, swimming or gardening were recorded. A regular physical activity was considered if the subjects practiced at least one recreational physical activity for at least one hour a week for the past month or more. BMI was calculated as weight (kg)/height^2 (m). Weight was measured with a beam balance scale and height with a height gauge.