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Effect of vitamin D replacement on hip structural geometry in adolescents: A randomized controlled trial

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ABSTRACT

Background: We have shown in a randomized controlled trial that vitamin D increases bone mass, lean mass and bone area in adolescent girls, but not boys. These increments may translate into improvements in bone geometry and therefore bone strength. This study investigated the impact of vitamin D on hip geometric dimensions from DXA-derived hip structural analyses in adolescents who participated in the trial.

Methods: 167 girls (mean age 13.1 years) and 171 boys (mean age 12.7 years) were randomly assigned to receive weekly placebo oil or vitamin D_3, at doses of 1400 IU or 14,000 IU, in a double blind placebo-controlled 1-year trial. DXA images were obtained at baseline and one year, and hip images were analyzed using the hip structural analysis (HSA) software to derive parameters of bone geometry. These include outer diameter (OD), cross sectional area (CSA), section modulus (Z), and buckling ratio (BR) at the narrow neck (NN), intertrochanteric (IT), and shaft (S) regions. Analysis of Covariance (ANCOVA) was used to examine group differences for changes of bone structural parameters.

Results: In the overall group of girls, vitamin D supplementation increased aBMD (7.9% and 6.8% in low and high doses, versus 4.2% in placebo) and reduced the BR of NN (6.1% and 2.4% in low and high doses, versus 1.9% in placebo). It also improved aBMD (7.9% and 5.2% versus 3.6%) and CSA (7.5% and 5.1% versus 4.1%) of the IT and OD of the S (2.4% and 2.5% versus 0.8% respectively). Significant changes in the OD and BR of the NN, in the overall group of girls remained, after adjusting for lean mass, and were unaffected with further adjustments for lifestyle, pubertal status, and height measures. Conversely, boys did not exhibit any significant changes in any parameters of interest. A dose effect was not detected and subgroup analyses revealed no beneficial effect of vitamin D by pubertal stage.

Conclusions: Vitamin D supplementation improved bone mass and several DXA-derived structural bone parameters, in adolescent girls, but not boys. This occurred at a critical site, the femoral neck, and if maintained through adulthood could improve bone strength and lower the risk of hip fractures.

Introduction

The amount of bone mass acquisition during adolescence is a determining factor for the risk of developing fractures later in life [1]. Although genetic factors play an important role in defining the individual's bone mineral density and content, environmental factors also exert an important influence on bone mass acquisition and its maintenance [2–4]. Several studies have shown that modifiable lifestyle factors such as dietary intake of calcium and vitamin D, and physical activity, with high impact weight bearing activities, can enhance bone mass accrual during growth [5–13].

Dual energy X-ray absorptiometry (DXA) technology is commonly used to assess bone mass and density in a highly precise, safe, and non-invasive way. However, the conventional analysis of the DXA data does not capture bone geometric and structural parameters that can be considered more appropriate for understanding the impact of any therapeutic intervention on bone mechanical integrity. It is also more difficult to assess the relationship between bone strength and body anthropometric measures when using BMD [14–16].

As a result, Beck et al. developed a program, known as the hip structural analysis (HSA) software, to estimate bone geometric properties and thus strength using the conventional DXA image data, based on principles that were first described by Martin and Burr [17]. Many

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investigators have used the HSA program to characterize bone geometry and strength [15,16,18–20]. This method can allow an assessment of the biomechanical basis for fracture risk reduction of various established interventions, through an understanding of their influence on bone geometry [21]. Indeed, high impact physical activities, and the age at which these activities are practiced, have been shown to have an effect not only on bone mineralization, but also on its geometric properties [19,22–25].

The effect of vitamin D supplementation on bone density has been extensively studied in adults, but much less in children and adolescents [10,13,26–32]. Indeed, these and numerous other studies demonstrate that the crucial role vitamin D plays in normal bone physiology in children is an important determinant of skeletal health in adults. It plays an important role in calcium homeostasis and skeletal mineralization through its endocrine effects on its target organs, bone, kidney, and intestine, and maintenance of normal circulating calcium and phosphate levels. The presence of the vitamin D receptor within the skeletal muscle suggests as well a role for vitamin D in muscle function [33,34].

Our randomized controlled clinical trial in school children showed that vitamin D supplementation had a positive impact on bone musculoskeletal parameters in girls in general and at pre-menarcheal stages in particular. Lean mass significantly increased in both low dose and high dose groups, and so did other bone parameters such as lumbar spine BMD in low dose, and trochanter BMC of both treatment groups [13]. However, to our knowledge, no study has assessed the effect of vitamin D supplementation on bone geometry, in any age group, including adolescence, a critical time for bone mass accrual. The purpose of our investigation was to examine the relationship between baseline vitamin D levels and HSA parameters and the impact of vitamin D supplementation in pre- and post-pubertal children on bone geometry and structure.

Methods

The analyses of the current study are post-hoc exploratory analyses using data from a randomized double blind placebo controlled trial on adolescent healthy subjects.

Full details on the study protocol, subject selection, evaluation, and data collection are available under Supplementary methods, and the CONSORT diagram as Supplementary Fig. 1.

Subjects

Subjects were those who completed the one year randomized double blind placebo controlled vitamin D trial [13]. The trial included 179 and 184 apparently healthy girls and boys respectively, recruited from 4 schools from the Greater Beirut area to ensure balanced representation geographically and socio-economically [35], between December 2001 and June 2002. Over 93% of the study participants (168 girls and 172 boys) returned for their scheduled one year assessment [13]. The age group chosen was 10–17 years, a critical age for bone mass accretion [36]. Subjects were included in the study if they were considered healthy, based on careful physical examination, and had no history of any disorders or medications known to affect bone metabolism [35]. The study was approved by the Institutional Review Board, and informed consent was obtained from all study subjects and their parents.

Intervention and data collection

Subjects were randomly assigned in a double-blind manner to receive weekly placebo oil, or a vitamin D_3 preparation, given as low dose vitamin D (1400 IU [35 μg/week]), i.e. the equivalent of 200 IU/day, or high dose vitamin D (14,000 IU [350 μg/week]), i.e. the equivalent of 2000 IU/day (Vigantol oil, Merck KGAa, Germany) for 1 year. The randomization process, dose selection, quality assurance and monitoring have been previously described in full detail [13]. The calculation of the sample size was performed based on the expected outcomes of the randomized clinical trial as detailed in the study by El-Hajj Fuleihan et al. [13]. At 12 months, the number of subjects with HSA data included in the current analyses included 111 subjects (55 girls, 56 boys) in placebo group, 113 subjects (58 girls, 55 boys) in low dose, and 114 subjects (54 girls, 60 boys) in high dose groups.

Each subject had a baseline physical examination, including height, weight, and Tanner stages. Standing height was measured in triplicate using a wall stadiometer and average value was reported. Weight was recorded while the subject was wearing light clothes without shoes using a standard clinical balance. Pubertal status was measured by one of three physicians who were contributing to the study, according to the established criteria of Tanner [37]. Menarcheal status was determined by these physicians by inquiring with the study subjects about their menarcheal status at study entry. Because of the small number of subjects in each Tanner stage subgroup, study subjects were divided into two discrete pubertal sub-groups for each gender, pre- ($n = 33$) and post-menarche ($n = 134$) in girls, and early (Tanner I ($n = 45$) and II ($n = 47$)) vs. late (Tanner III ($n = 30$), IV ($n = 30$), V ($n = 19$)) puberty in boys, as was implemented in the original reports of the trial [13,38]. Assessment of calcium intake, exercise, sun exposure, and history of fractures was made at baseline and follow-up [35]. Exercise frequency was assessed based on a questionnaire inquiring about the average number of hours spent on sports per week. Calcium intake was evaluated through a food frequency questionnaire that stressed the consumption of dairy products by adolescents in the Lebanese population. Frequency of sun exposure was reported as the average number of hours spent in the sun for weekdays and weekends, and the prorated average was reported.

Measurement of serum 25-hydroxy vitamin D [25(OH)D] levels

Serum 25(OH)D was measured at baseline and 12 months by a competitive protein binding radio-immunoassay using the Incstar Kit (Diasorin, Incstar, Saluggia, Italy), with intra- and inter-assay CVs less than 13% at a serum concentration of 47 ng/ml. All samples were assayed together in the same run at the end of the study.

Areal bone mineral density (aBMD) measurements

BMD of the hip and total body compositions were determined at baseline and 1 year using a Hologic 4500A densitometer (Hologic, Bedford, MA; software version 11.2:3). In our center, the mean ± SD precision of the aBMD measurements, expressed as the CV, for 280 same-day duplicate scans performed during the study duration was less than 1.2 ± 0.9% for the spine, total hip, femoral neck, trochanter, and one third radius. Similar values were obtained for total body aBMD and BMC, lean mass, and fat mass.

Hip structural analysis

Proximal femur scans were analyzed at Dr Beck's laboratory, Johns Hopkins University (Baltimore, MD, USA) using the HSA program [20,39,40]. The HSA program uses conventional DXA image data to derive geometric properties of transverse bone cross-sections that are 5 mm thick in three regions. These regions, as illustrated in Fig. 1, are: the narrow neck (NN) across the narrowest segment of the femoral neck, the intertrochanteric (IT) region along the bisector of the neck–shaft angle, and the shaft at a length equivalent to 1.5 times minimum neck diameter distal to the intersection of neck and shaft axes. For each region the distribution of bone mass across the bone was extracted and the outer diameter (cm), bone cross-sectional area exclusive of soft tissue (CSA, cm^2), and cross-sectional moment of inertia (CSMI, cm^4) were directly measured from the bone mass profile. The outer diameter (OD) is a direct descriptive measure that measures the distance