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Higher bone resorption excretion in South Asian women vs. White Caucasians and increased bone loss with higher seasonal cycling of vitamin D: Results from the D-FINES cohort study

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ABSTRACT

Few data exist on bone turnover in South Asian women and it is not well elucidated as to whether Western dwelling South Asian women have different bone resorption levels to that of women from European ethnic backgrounds. This study assessed bone resorption levels in UK dwelling South Asian and Caucasian women as well as evaluating whether seasonal variation in 25-hydroxyvitamin D [25(OH)D] is associated with bone resorption in either ethnic group.

Data for seasonal measures of urinary *N*-telopeptide of collagen (uNTX) and serum 25(OH)D were analysed from n = 373 women (four groups; South Asian postmenopausal n = 44, South Asian premenopausal n = 50, Caucasian postmenopausal n = 144, Caucasian premenopausal n = 135) (mean (±SD) age 48 (14) years; age range 18–79 years) who participated in the longitudinal D-FINES (Diet, Food Intake, Nutrition and Exposure to the Sun in Southern England) cohort study (2006–2007).

A mixed between-within subjects ANOVA (n = 192) showed a between subjects effect of the four groups ($P < 0.001$) on uNTX concentration, but no significant main effect of season ($P = 0.163$). Bonferroni adjusted Post hoc tests ($P \leq 0.008$) suggested that there was no significant difference between the postmenopausal Asian and premenopausal Asian groups. Season specific age-matched-pairs analyses showed that in winter ($P = 0.04$) and spring ($P = 0.007$), premenopausal Asian women had a 16 to 20 nmol BCE/mmol Cr higher uNTX than premenopausal Caucasian women.

The (amplitude/mesor) ratio (i.e. seasonal change) for 25(OH)D was predictive of uNTX, with estimate (SD) = 0.213 (0.015) and 95% CI (0.182, 0.245; $P < 0.001$) in a non-linear mixed model (n = 154). This showed that individuals with a higher seasonal change in 25(OH)D, adjusted for overall 25(OH)D concentration, showed increased levels of uNTX. Although the effect size was smaller than for the amplitude/mesor ratio, the mesor for 25(OH)D concentration was also predictive of uNTX, with estimate (SD) = −0.035 (0.004), and 95% CI (−0.043, −0.028; $P < 0.001$).

This study demonstrates higher levels of uNTX in premenopausal South Asian women than would be expected for their age, being greater than same-age Caucasian women, and similar to postmenopausal Asian women. This highlights potentially higher than expected bone resorption levels in premenopausal South Asian women which, if not offset by concurrent increased bone formation, may have future clinical and public health implications which warrant further investigation. Individuals with a larger seasonal change in 25(OH)D concentration showed an increased bone resorption, an association which was larger than that of the 25(OH)D yearly average, suggesting it may be as important clinically to ensure a stable and steady 25(OH)D concentration, as well as one that is high enough to be optimal for bone health.

Abbreviations: uNTX, urinary collagen type 1 cross-linked *N*-telopeptide; D-FINES, Diet, Food Intake, Nutrition and Exposure to the Sun in Southern England.

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1. Introduction

Despite the hypothetical increase in osteoporotic fracture risk due to smaller bone size in postmenopausal South Asian women [1] few studies have assessed bone health in this population group. Also, recent epidemiological research has suggested that US dwelling South Asian women have an increased prevalence of femoral neck osteoporosis [2] but have no differences in wrist fracture rates [2] compared with same-age Caucasian women, suggesting that bone health in South Asian women needs further elucidation.

Bone turnover markers are a known predictor of fracture risk [3] as well as giving valuable insight into the bone turnover related mechanisms underlying inter-individual differences in bone structure. However, there is a lack of information on bone turnover rates in South Asian women, either western dwelling, or dwelling in country of origin. Only three studies, to the authors' knowledge [4–6] have reported levels of bone turnover activity in migrant South Asian women living in Western countries. These studies found either no difference in bone turnover between South Asian and Caucasian populations [4,5] or no difference between older and younger South Asian women [6], the latter result of which is of concern considering the premenopausal status of the younger women. These cross-sectional studies highlight important similarities and differences between bone turnover in western dwelling South Asian and Caucasian women. However, there is still a need for studies to assess longitudinal change in bone turnover markers over the course of at least one year in South Asian women to see if these ethnic and age differences in bone turnover vary by season, and if so how.

There is also a need to understand the relationship between vitamin D status and bone resorption, specifically how this relationship may be mediated by season, menopausal status or ethnicity. It is known that adequate vitamin D status is important for bone health, with associations between bone turnover and 25(OH)D status being found in Caucasian populations in some studies [7,8]. However, it is relatively unknown as to whether there is an association between 25(OH)D status and bone turnover in South Asian women, with the only published study (UK) finding no cross-sectional relationship [4]. The known lower 25(OH)D status in many Western dwelling South Asian women, as compared to Caucasian women [4,9–11], suggests theoretically that the relationship between 25(OH)D and bone turnover may be stronger in South Asian women, but more research is required to establish whether this is the case.

In addition to that of overall average yearly 25(OH)D concentrations, degree of annual fluctuation in 25(OH)D could also theoretically influence bone health. This is because changes in 25(OH)D substrate have a large impact on the activity of the 1-hydroxylase enzyme, which is one of the main hydroxylase enzymes controlling 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] levels, and at physiological concentrations of 25(OH)D is working well below its Michaelis-Menten constant [K_m]. Large changes in the activity of the 1-hydroxylase enzyme could occur as a result of large seasonal fluctuations in 25(OH)D and have an impact on $1,25(OH)_2D$ concentration [12]. Some previous research studies in Caucasian populations have found no relationship between seasonal fluctuation of 25(OH)D and bone resorption [13] or no acute effect of vitamin D supplementation during winter time (to blunt the seasonal rhythm) on bone resorption or formation markers [14]. However, data from South Asian and Caucasian populations in the D-FINES (Vitamin **D**, **F**ood **I**ntake, **N**utrition and **E**xposure to **S**unlight in Southern England) cohort study suggested that a larger change in 25(OH)D over the course of a year was associated with increased bone turnover [uCTX], in comparison to those with a smaller change in 25(OH)D [15]. However, subject numbers were relatively small and only sCTX levels were measured.

The present work is a larger follow-up analysis of the D-FINES cohort. We investigate whether there is a difference (within and between seasons) in bone resorption (uNTX) between Caucasian and South Asian women, when adjusted for confounding factors, as well as examining whether there is a relationship between serum 25(OH)D concentration and bone resorption in either ethnic group. We also determine the relative abilities of seasonal change and average 25(OH)D to predict bone resorption over the course of one year, using a non-linear mixed modelling approach. Based on the results of our previous analysis [15], as well as the above literature, it was hypothesised that South Asian women would have increased bone resorption as compared with their Caucasian counterparts. It was also predicted there would be an association between 25(OH)D status and bone resorption within seasons, and that individuals showing a high degree of seasonal fluctuation in 25(OH)D over the course of the year would also show higher bone resorption than those with a lower degree of seasonal fluctuation in 25(OH)D.

2. Materials and methods

2.1. Study design

Subjects had taken part in the 2006–2007 UK Food Standards Agency D-FINES study (Project N05064) [9], whereby they attended the University of Surrey once per season for one year (four visits) for sampling of blood for measurement of 25(OH)D status and of urine for measurement of uNTX, as well as for collection of anthropometric, dietary and lifestyle information. Data from n = 373 women (South Asian postmenopausal n = 44, South Asian premenopausal n = 50, Caucasian postmenopausal n = 144, Caucasian premenopausal n = 135) was available for analysis. Menopausal status was derived from the date of the last menstrual period (self-reported), with postmenopausal status being defined as the participant having had no menstrual periods for >-3 months. Any postmenopausal women who had used hormone replacement therapy in the last year were excluded from the study. Further details regarding the D-FINES study, including subject recruitment, study procedure, other exclusion criteria and background information have been previously reported [9]. In accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, ethical reviews were obtained from relevant Research Ethics Committees (National Health Service NHS REC 06/Q1909/1, and University of Surrey EC/2006/19/SBMS). Written, informed consent was obtained from all participants.

2.2. Biochemical measurements

Measurement of uNTX was undertaken at the University of Sheffield (Metabolic Bone Centre, Northern General Hospital, Sheffield, UK), funded by a grant (number 225) from the National Osteoporosis Society (2011). Measurements were undertaken using the automated Vitros ECi, Ortho Clinical Diagnostics analyser (Rochester NY, USA) and were adjusted for creatinine (Cr) excretion. Serum 25(OH)D was measured by the Vitamin D Research Group at the University of Manchester, using the manual IDS enzyme immunoassay (Immunodiagnostic Systems Ltd., Boldon, Tyne and Wear, UK) with inter-assay and intra-assay coefficients as described previously [9].

2.3. Statistical methods, including non-linear mixed modelling analysis

Ethnic and menopausal status differences in uNTX were analysed using mixed between-within subject analysis of variance (ANOVA; women with all four uNTX measurements). Within-season ANCOVA was also conducted (using all women with at least one uNTX measurement) to allow for the analysis of data from women who did not have full data for uNTX for all seasons (to reduce the impact of attendance bias). For the premenopausal women only, an age-matched analysis was also undertaken due to a biologically significant age difference between the two premenopausal groups (mean (SD) for age: 34.0 (5.6) years in the Caucasians and 39.0 (8.5) years in the South Asians). The premenopausal South Asian women were individually matched to one