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Parathyroid hormone and rates of bone formation are raised in perimenopausal rural Gambian women

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Abstract

To investigate rates of bone turnover and calcium homeostasis in Gambian women, we recruited 103 peri- and postmenopausal women, aged 45 to 80+ years and 11 women of reproductive age. Fasting blood was analyzed for plasma osteocalcin, PTH, 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], total- and bone-specific alkaline phosphatase. Plasma and urinary calcium, inorganic phosphate, sodium, potassium, creatinine, and albumin and urine free deoxypyridinoline (Dpd) was also measured. Samples from 20 premenopausal and 31 postmenopausal women from Cambridge, UK were analyzed, using the same methodology for comparison.

For the Gambian women, peak calcium excretion occurred at around 50 years of age. For women aged ≥45 years, calcium excretion decreased by 3.0% per year of age (SE 1%; $P < 0.005$). In this age group, 25(OH)D also decreased with age ($P < 0.005$). Urinary sodium output, pH, and titratable acid output decreased (all $P < 0.05$) and total alkaline phosphatase ($P < 0.005$), osteocalcin ($P < 0.005$), and PTH ($P < 0.05$) increased with age.

Comparisons were made between the following groups of Gambian and British women: premenopausal, early (age 55–64 years)- and late (age 65+ years)-postmenopausal. Gambian women of all ages were lighter ($P < 0.001$), shorter ($P < 0.01$), and had higher plasma bone-specific alkaline phosphatase activity ($P < 0.05$) and higher concentrations of osteocalcin ($P < 0.05$), PTH ($P < 0.001$), 1,25$(OH)_2$D ($P < 0.001$), and 25(OH)D ($P < 0.001$). There were no consistent differences in calcitonin, while urinary free Dpd outputs were lower in the Gambians ($P < 0.001$). Plasma calcium, phosphate, and albumin ($P < 0.01$) were significantly lower. Urinary calcium, phosphate, sodium, and potassium excretion were lower, particularly in the postmenopausal group ($P < 0.001$). Although Gambian urine pH was more acidic, titratable acid output was lower ($P < 0.01$).

These data show that Gambian women with low dietary calcium intakes and good vitamin D status have low urinary calcium excretion and that menopausal changes in calcium and bone metabolism among Gambian women are similar to those seen in other populations.

In addition, they demonstrate that Gambian women of all ages have raised plasma PTH and 1,25$(OH)_2$D concentrations and raised markers of osteoblast activity. We postulate that high endogenous PTH concentrations may be beneficial to bone health in Gambian women, removing fatigue damage and improving bone quality.

Keywords: Bone formation; Gambian women; Perimenopausal; PTH; Osteoporosis

Introduction

The incidence of osteoporotic fractures in black populations of sub-Saharan Africa is low [1,15]. World projections are that osteoporotic fractures will increase in future years and a global "epidemic" of hip fractures is expected. Thus, the estimated 1.7 million hip fractures occurring world-wide in 1990 may rise to 6.3 million by 2050 [15]. Similar increases are projected in Africa where, based on anticipated demographic change alone, the proportion of world-wide hip fractures is likely to rise from 0.2% to 0.6% by the year 2050 [15].

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The low incidence of fractures in Africa may relate to a number of factors. In the past, it was proposed that the difference between Africans and Caucasians related to a higher bone mass as a result of a variety of diet, lifestyle, and genetic factors, as found in studies of African Americans [3–5,9,21,30,44]. However, our previous work in West Africa has demonstrated the low incidence of fractures in African women cannot be ascribed to a higher relative bone mass at any age [7,8,19,39,41].

Independently of bone mass, markers of bone turnover (particularly bone resorption) predict fracture risk in postmenopausal women [27]. A high plasma parathyroid hormone (PTH) concentration has also been shown to be associated with low bone mineral density (BMD) and increased risk of fracture, although these findings are not consistent which may be due partly to the failure of single time point sampling to address the circadian cycle of PTH secretion [4,16,17,20,23,33–37,45].

The aim of this study was to investigate rates of bone turnover and calcium homeostasis in relation to menopause in a rural West African community accustomed to a low calcium intake [40], and to study changes in calcium and bone metabolism in relation to age. In addition, we compared data from Gambian and British women, collected and assayed using the same methodologies, to investigate possible underlying biochemical differences that might contribute to the lower fracture incidence in African populations.

Methods

Subjects

A census of three rural villages in The Gambia, West Africa was performed. All female residents aged over 45 years were identified (n = 258). In order to avoid systematic bias in sampling, over an 18-month-period, subjects were randomly selected from the population database each month, stratified by age. Of these, 103 (40%) women participated in the study, comprising 98% of those invited to take part. A small number of younger women were also recruited, as a comparator group. The majority of younger women in the villages were pregnant or lactating and so could not be included in the study. The age range of this comparator group was 26 to 38 years and the mean random plasma estradiol concentration was 466 SD302 pmol/L [6]. The villages of Keneba, Manduar, and Kanton Kunda in West Kiang are 150 km from the capital Banjul and are reached via the main road from the coast and then a 20-km dirt track. The Medical Research Council (MRC) has maintained a research station in Keneba for more than 50 years and continued demographic surveillance ensures that the ages of residents are precisely known.

The comparative British data were from women living in Cambridge, UK, who had participated in other studies of calcium and bone metabolism under the same collection conditions as the Gambian subjects and whose biochemistry was measured contemporaneously in the same laboratory. The UK samples were collected during Spring and Summer months (March to September inclusive) thus avoiding the Winter nadir in British 25(OH) vitamin D levels.

Subjects were suffering from no known illnesses and were taking no medications known to affect calcium metabolism. For some analytes particularly for the UK subjects, it was not possible to analyze a number of samples because of insufficient sample volume and freezer malfunction. However, no attempts were made to interpolate for missing data.

Fasting blood specimens were collected on a single occasion. Blood specimens were collected before 9 a.m. using pre-cooled syringes and bottles containing EDTA for intact PTH and Lithium Heparin for the other analytes, to assist the separation of the plasma. Blood samples were immediately spun down and frozen to less than −20°C. 24-h urine samples were collected into acid-washed plastic containers, and kept cool using ice packs. Additionally, in The Gambia, women were frequently visited in the field to encourage complete sampling. Samples were retrieved from the cold boxes every few hours during the day and refrigerated in the laboratory. At the end of the collection, each individual's urine fractions were pooled and mixed, the total volume was recorded, and urinary pH was measured. Urinary titratable acid output was measured by direct titration to pH of 7.4. Aliquots were then stored for the measurement of free deoxypyridinoline (Dpd) and a sample acidified with 200 μL of concentrated hydrochloric acid to 20 mL of urine producing a 1% solution was retained for estimation of calcium, phosphate, and creatinine excretion. The Gambian samples were transported on dry ice to the Cambridge laboratory for analysis.

In The Gambia, informed consent was obtained from all participants according to the methods advocated by the MRC/Gambia Ethics Committee. In Cambridge, written informed consent was obtained. Ethical approval for the study was received from both the MRC/Gambia Ethics Committee and the Ethical Committee of the MRC Dunn Nutrition Unit, Cambridge, of which the Nutrition and Bone Health Group of MRC Human Nutrition Research and MRC Keneba were formerly a part.

Sample analyses

The details of the biochemical assays performed and the coefficients of variations (CV) for [intra-/inter-assays] comprised: plasma osteocalcin [5.0%/6.0%] and intact PTH [7.0%/6.0%] were measured by RIA (Incstar, Stillwater, MN); plasma 25-hydroxyvitamin D [25(OH)D] (10.0%/9.0%) and 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$] (5.0%/4.0%) (after immunoextraction) were analyzed using RIA (Incstar, Stillwater, MN and IDS, Bolden,