

EDITORIAL

Population differences in parameters of bone and mineral metabolism — the African fracture paradox

The World Health Organisation (WHO)'s definition of osteoporosis is based on the relationship between low bone mineral density (BMD) and consequent increase in bone fragility and susceptibility to fracture.¹ As such, a risk factor (i.e. low BMD) has been elevated to assume the status of a diagnostic criterion.²

In South Africa, the incidence of osteoporosis in white, Asian and mixed-race populations appears to be similar to incidence rates in developed countries. Osteoporotic fractures are, however, 10 times less prevalent in our black populations,³ which is also the case in the USA.⁴ Whereas the lower prevalence of fractures in Afro-Americans is readily explained on the basis of an approximate 15% higher BMD in this population compared with Caucasians, vertebral BMD in black and white South Africans appears to be quite comparable.⁵ How can the 10-fold lower prevalence rates of osteoporotic fractures documented in our black populations be explained?

Whereas BMD is quite specific (85%) it does lack sensitivity, and more than 50% of individuals at risk of sustaining an osteoporotic fracture may have a normal BMD.² Moreover, although bone mass is thought to account for up to 70% of the variance in bone strength *in vitro*, recently examined components of bone quality are thought to contribute significantly. These include differences in skeletal macroarchitecture (bone size and geometry), microarchitecture (cortical thinning, porosity; trabecular size, number, connectivity), material properties (mineralisation, microfracture, collagen cross-linking), and bone turnover (resorption, formation). Furthermore, osteoporotic fracture risk is multifactorial, comprising skeletal abnormalities of bone quantity (BMD) and quality, interrelated with independent risk factors such as age, genetic predisposition, previous fractures and the propensity to falls.⁶

Age, independent of BMD, is one of the best-known risk factors for osteoporotic fracture, and various changes in bone quality and turnover have been proposed to explain this observation.^{7,8} Given the differences in current life expectancy between white and black populations in this country, older black women may increasingly represent a population at risk for osteoporosis. Up to 80% of the variation in peak BMD is determined *genetically*; a genetic predisposition to osteoporotic fracture, independent of BMD, has however also been demonstrated.⁹ Polymorphisms in a number of genes (e.g. those encoding the oestrogen receptor, collagen, growth

factors, etc.) have been proposed to explain this observation. In large osteoporosis drug trials like the FIT¹⁰ and MORE¹¹ study, a *history of vertebral fractures* was shown to increase the risk of a subsequent vertebral fracture 3 - 5-fold. *Falls*, especially sideways falls, are incriminated in more than 80% of femoral neck fractures.² Various therapeutic interventions may decrease fracture prevalence, not only by increasing bone strength but also by improving neuromuscular co-ordination and muscle strength (vitamin D) or reaction time (oestrogen), and therefore prevent body sway and falls.¹²

A *high bone turnover* is well known to result in trabecular perforation and decreased interconnectedness, which markedly increase the likelihood of fracture, independent of BMD.^{8,13} In this issue of the *Journal*, Kruger and co-workers (p. 103) employ biomarkers of bone turnover to assess the influence of urbanisation-induced changes in diet and physical activity on the bone and mineral metabolism of black South African women. They conclude that urbanisation in older women (55 - 65 years) results in a decreased calcium intake, an increase in serum parathyroid hormone (PTH) levels and an increase in serum NTx, a biochemical marker of bone resorption. In a group of active growing girls (age 15 - 25 years) increased bone resorption could not be demonstrated, despite similar low intakes of calcium. Instead, bone formation appeared to be suppressed, as reflected by a markedly decreased mean serum osteocalcin level. Interestingly, the serum bone specific alkaline phosphatase (BSAP), another biomarker of bone formation, was not decreased by urbanisation. This observation remains to be explained, but could have resulted from a concomitant mineralisation defect induced by the low calcium intakes, which would have tended to increase BSAP levels. The age range 15 - 25 years is also rather wide, and may have included subjects at various stages of pubertal development, which complicates interpretation. Tanner staging or biochemical assessment of sex hormone levels would have provided a better understanding of these observations. Likewise, subjects included in the older age group (55 - 65 years) may have had varying degrees of hypo-oestrogenaemia, which would have impacted on biochemical parameters of bone resorption.

Although the study of biochemical markers of bone turnover has improved insights into the pathophysiology of metabolic bone diseases like osteoporosis, we do have to take cognisance of a number of limitations.¹⁴⁻¹⁶ Technical difficulties in their

measurement still constitute a major problem in the assessment of individual patients. Serum markers have a variability of 5 - 15%, but some urine markers have an overall coefficient of variation of up to 35% despite an analytical precision error of around 10%.^{14,15} Other technical limitations involve storage stability, variations between assays and the lack of internationally agreed standards. Circulating osteocalcin also reveals a significant circadian variation with a peak around 04h00 and a trough at 17h00. Timing of blood sampling is therefore crucial. Seasonal variations, as well as variations in the metabolism and hepatic/renal clearance of not only calcitropic hormones like vitamin D¹⁷ but also biomarkers, need to be considered. Finally, biochemical markers reflect total skeletal (largely cortical) metabolism and cannot localise a regional abnormality in bone metabolism, i.e. markers are not site-specific. Discrepancies between the biochemical and histomorphometric assessment of bone turnover therefore exist.

Finally, the interpretation of biomarker data remains complex. Whereas a high bone turnover has been clearly demonstrated as an independent risk factor for osteoporotic fracture,¹³ recent evidence suggests that a markedly suppressed bone turnover may also predispose via effects on micro-crack and fatigue damage. Not surprising is the fact that both the decreased¹⁸ and the increased¹⁹ bone turnover reported in black populations compared with whites have been proposed to explain the lower fracture prevalence in these subjects.

Clearly we have much to learn! The generation of local data on fracture incidence, BMD and qualitative parameters is paramount. Quantitative and qualitative differences in these parameters of bone health, which are increasingly documented in the various populations of our country, and the window of opportunity created by experiments of nature like the urbanisation-induced changes exploited by Kruger and colleagues in their current paper, will not only improve our local understanding of metabolic bone disorders but also provide opportunities to gain insights into the very

fundamental mechanisms which underlie the global predisposition to osteoporotic fracture.

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