

# Oral Presentations

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#### 1 Osteoporosis epidemiology: fracture, subsequent fracture and premature mortality

*Eisman JA*

Osteoporosis and Bone Biology, Garvan Institute of Medical Research, University of New South Wales and St Vincent's Hospital, Sydney, NSW, Australia  
 Correspondence to: Prof John Eisman, e-mail: j.eisman@garvan.org.au

Osteoporosis is an underrated, under-recognised and under-treated condition. This is in large part due to the totally misguided misconception that it is predominantly a problem for old women before they die. By contrast, it is now recognised to be a major problem for men as well as for women with its greatest impact in the relatively young old.

Any fracture that occurs without major trauma should be considered as a fragility, i.e. osteoporotic fracture, at least until excluded by investigations, including bone densitometry. Any and every fragility fracture signals increased risk of further fragility fractures of all types.

Although an initial fragility fracture is about one-half as common in men as in women of the same age, subsequent risk increases two-fold for women and four-fold for men. Hence, after any fragility fracture, the subsequent risk of another fracture is almost identical in men and women and equivalent to that of a man or woman 20 years older. The increase in risk is most marked for the first few years after the signal fracture and gradually returns to the population risk over the following 5–10 years.

Although the increased risk of premature mortality is well recognised after a hip fracture, in fact premature mortality is apparent after all types of fragility fractures with somewhat greater risk in women.

As for refracture risk, the premature mortality risk is most marked for the first few years after the signal fracture and gradually returns to the population risk over the following 5–10 years.

Finally the total direct and indirect health care cost of osteoporotic fractures has also been under-recognised.

Thus osteoporosis is a common health care problem that affects more than 50% of older women and about one-third of older men. It causes great health care costs, predisposes to initial and subsequent fractures as well as to premature mortality. It requires and deserves considerably greater health care focus.

#### 2 National guideline for the diagnosis and management of osteoporosis

*Hough FS, Ascott-Evans B, Brown S, Cassim B, de Villiers T, Lipschitz S, Pettifor J, Sonnendecker E*

National Osteoporosis Foundation of South Africa (NOFSA)

Correspondence to: Prof Stephen Hough, e-mail: fsh@sun.ac.za

*Objective:* This project is an update of the clinical guideline published by NOFSA in 2000 which aims to improve the efficacy of the diagnosis and management of patients with, or risk of OP.

*Outcomes:* Prevention of osteoporotic fractures and a reduction in the morbidity and mortality were the major considerations.

*Evidence:* Systematic reviews and the highest level of evidence (RCTs, meta-analyses) were employed; GRADE was used to describe the quality of evidence and strength of recommendation.

*Key recommendation:* 1) Greater awareness about OP and better access to health care for those suffering from OP are needed. 2) Local research and the formulation of a health economic strategy for managing OP in this country is required. 3) A diagnosis of OP is currently based on evidence of a fragility fracture or a low BMD (T-score < -2.5). 4) Use axial DXA to measure BMD and to diagnose OP. Use NHANES III young female ref. data in postmenopausal women and older men, of all races. Use Z-scores in younger individuals. QUS cannot be used to confirm a diagnosis, but is useful to assess fracture risk. 5) Limited laboratory tests are required to exclude PHPT an OM as causes of low BMD, and secondary OP. 6) Distinguish between diagnostic and interventional thresholds. 7) Treat when T-score < -2.5 or fractures presents; use clinical risk factors/FRAX in those with osteopenia. 8) Non-pharmacologic measures are important. 9) No ideal drug can be recommended – individualise therapy. 10) Follow-up is important, but beware of pitfalls.

#### 3 Assessment of bone density and microstructure with special reference to children and adolescents

*Rizzoli R*

Division of Bone Diseases, Department of Rehabilitation and Geriatrics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Correspondence to: Prof Rene Rizzoli, e-mail: rizzoli@cmu.unige.ch or Rene.Rizzoli@medecine.unige.ch

Factors impairing the accumulation of bone during growth are implicated in the pathogenesis of osteoporosis. During bone mineral accrual, there is a marked increase in bone dimensions with little changes in volumetric density, then bone size varies little throughout life, beyond the continuous and slight expansion of bone outer

dimensions. Traumatic fractures affect nearly one out of two healthy children, with a peak incidence concomitant to peak height velocity. It has been hypothesised that bone fragility during adolescence results from a transient deficit in bone mineral accrual relative to bone size. In healthy adolescent boys fracture history was associated with lower aBMD and trabecular vBMD at weight-bearing skeletal sites. Indeed, subjects with a positive fracture history had lower femoral neck and total hip aBMD as compared to boys without fractures. In addition, boys with a fracture history displayed at the distal tibia lower trabecular vBMD and number, and greater trabecular spacing. Patients with inflammatory bowel diseases have low bone mass and may be at increased fracture risk. In 90 young patients with Crohn's disease, ulcerative colitis and undetermined colitis, 31 subjects reported at least one clinical fracture. Higher total hip aBMD was associated with lower fracture risk. Trabecular vBMD, bone volume fraction, trabecular thickness and the homogeneity of trabecular distribution were all significantly lower at both radius and tibia in the fractured group compared to the non fractured one. Although more than 60% of the variance of peak bone mass, the amount of bone present in the skeleton at the end of its maturation process, is genetically determined, the remainder is likely influenced by factors amenable to positive intervention, such as adequate dietary intake of dairy products as a natural source of calcium and proteins, vitamin D, and regular weight-bearing physical activity. Inflammatory diseases or nutritional deficit during adolescence could negatively influence bone mass accumulation and microstructural development. Thus, optimising bone mineral mass and structure during childhood and adolescence may contribute to fracture risk reduction during adolescence and possibly in the elderly.

#### 4 Ethnic differences in DXA and pQCT measures between South African children, aged 13 years

<sup>1,2</sup> *Micklesfield LK*, <sup>1</sup> *Norris SA*, <sup>1</sup> *Pettifor JM*

<sup>1</sup> MRC Mineral Metabolism Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa

<sup>2</sup> ESSM, Department of Human Biology, University of Cape Town, Cape Town, South Africa

Correspondence to: Dr Lisa Micklesfield, e-mail: lisa.micklesfield@uct.ac.za

We have previously shown that whole body (WB), lumbar spine (LS) and proximal femur (PF) BMC is higher in black children compared to white children at nine years of age, after adjustment for differences in body size. The influence of puberty on these differences in BMC, as well as on pQCT measures in South African children, is unknown.

We collected DXA and pQCT data on the Bone Health subsample of the Birth to Twenty longitudinal cohort at 13 years of age ( $n = 128$  white: 61 boys, 67 girls;  $n = 345$  black: 179 boys, 166 girls). Black groups were shorter, had less % lean mass and greater % fat mass than their white counterparts, and black boys were lighter and at an earlier stage of pubertal development compared to white boys. Adjusting for height, WB and LS BMC were higher in the black girls compared to the white girls, while LS BMC was higher in the white boys than black boys. Distal (4%) radius and tibia total areas (TotA), adjusted for height, were significantly higher in black girls but no different between the boys. All 38% tibia pQCT values, adjusted

for height, including TotA, cortical area and thickness, periosteal circumference and polar bone stress-strain index, were greater in the black children compared to their white peers. At the 66% sites of the forearm and lower leg, at which muscle (MCSA) and fat (FCSA) cross-sectional areas were measured, leg MCSA was higher in the white groups compared to the black groups and at the forearm in white boys compared to black boys. There was no difference in FCSA between the ethnic groups at either site. Although all bone values were higher in the black children and MCSA was higher in the white children, there was a significant correlation between leg MCSA and tibia 38% CoA in all groups. Ethnic differences in DXA measures are replicated by distal pQCT at 13 years, however more robust differences between ethnic groups were present at the predominantly cortical site.

#### 5 Heterogeneity in fracture pathogenesis in urban South African children: the birth to twenty cohort

*Thandrayen K*, *Norris SA*, *Micklesfield LK*, *Pettifor JM*

MRC Mineral Metabolism Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa

Correspondence to: Dr K Thandrayen, e-mail: Kebashni.thandrayen@wits.ac.za

South African black children fracture less than white children. Differences in bone mass and structure, and physical activity, may be contributing risk factors. The aim of this study was to investigate the association between fracture prevalence, bone mass and physical activity in urban South African children.

Using the Bone Health subsample of the Birth to Twenty longitudinal study, we retrospectively obtained information of lifetime fractures until age 15 years. Bone mass (measured by DXA), anthropometric data, physical activity scores and pubertal status were obtained at age 10 and 15 years.

White males who fractured had greater metabolic physical activity scores at age 10 and 15 years. At 10 years, white males who fractured had greater BA at all sites and BMC at the radial (R), hip neck (HN) and spinal (LS) sites. At 15 years, white males who fractured had similar findings: BA was higher at the whole body less head (WBLH); hip (H) and LS; and BMC was higher at R, H, HN and WBLH. HN BMC adjusted for BA was higher at age 15 years in white males with fractures but not at age 10 years. At 10 years, black males who fractured had lower R and H BMD and lower H BMC compared to those that did not fracture. After BA adjustments; all R and TH BMC were lower at 10 years in black males with fractures; and at 15 years TH, HN, R and UD BMC remained low. Black females who fractured had lower radial UD BMC at 15 years. There were no significant differences in BMC at age 10 years in black or white females and at age 15 years in black males and white females who did or did not fracture.

In conclusion, the pathogenesis of fractures differs between ethnic groups. Lower bone mass in black males and increased physical activity in white males appear to be contributory risk factors.

## 6 Exercise and bone

*Micklesfield LK*

MRC Mineral Metabolism Research Unit, Department of Paediatrics,  
University of the Witwatersrand, Johannesburg, South Africa

Correspondence to: Dr Lisa Micklesfield, e-mail: lisa.micklesfield@uct.ac.za

The role of exercise in the prevention of osteoporosis changes with age. Although there is no definite answer as to when an individual will reach their peak bone mass, several studies have shown that more than 90% of total body bone mineral density is achieved by the age of 20 years. Therefore, childhood and adolescence is a very important “window of opportunity” during which to optimise the factors that influence bone mineral density, such as physical activity and calcium intake.

High impact and weight-bearing exercise are most important in maintaining bone mineral density in adults. Weight-bearing exercise includes any activities in which an individual bears their own body weight, such as walking, jogging, tennis and stair-climbing. Research has shown these activities to be more beneficial for bone mass than activities that are not weight-bearing, such as swimming and cycling. However, any activity that involves the muscle pulling on the bone is beneficial in maintaining bone mass, and is certainly preferable to no activity at all. For this reason, weight training should be included in any exercise programme designed to prevent osteoporosis. This has been confirmed by research published in the *Journal of Bone and Mineral Research* that has reported that women who participated in an 8-month weight-training exercise programme showed an increase in bone mineral density of 1.2% at the lumbar spine, which was significantly different to the women who did not participate in the exercise programme and showed a decrease of 0.8% in lumbar spine bone mineral density.

The beneficial role of exercise in older adults is due more to a reduction in the risk of falling, and therefore a reduction in the risk of fracture. The risk of falling is reduced by improvements in strength, co-ordination and balance that result from regular participation in an exercise programme.

The benefits of exercise on the bone will only be maintained for as long as the exercise programme is followed. Therefore, exercise needs to become a way of life, and should be included as an integral part of any osteoporosis prevention programme.

## 7 Audit of DXA scans at GSH between 2007–2010 from Departments of Gastroenterology and Endocrinology

*Kalla AA, Bewerunge L, Fataar AB*

Departments of Medicine and Nuclear Medicine, University of Cape Town, South Africa

Correspondence to : Asgar Ali Kalla, e-mail: kallaa@iafrica.com

The purpose of this study was to do an audit of DXA scans from two departments and to see the prevalence of osteoporosis in these two groups.

All patients studied in the Nuclear Medicine department between October 2007 and February 2010 and who had lumbar spine L1–L4 measurements with the same LUNAR machine were selected for analysis. Age, sex, height, weight, source, and BMD parameters were recorded in all patients.

There were 256 patients from endocrinology (58 male) and 154 from GIT (54 male). The mean age of the endocrine group was 56 years while the GIT group mean age was 45.4. In the endocrine group 77 (30%) patients had osteoporosis at the lumbar spine compared with 23 (15%) in the GIT group. Using total hip T-scores, there were 25 (10%) in the endocrine group compared with 4 (3%) in the GIT group. At the femoral neck, osteoporosis was present in 42 (16%) of the endocrine group and only 6 (4%) of the GIT group. The correlation coefficient between total femoral T-score and spine ( $r = 0.73/r = 0.63$  endoc/GIT) was slightly higher than with femoral neck T-score ( $r = 0.7/r = 0.58$  endoc/GIT).

Patients referred for DXA scan at our hospital from the endocrine department are more likely to be osteoporotic than those referred from the GIT clinic. This may relate to the different indications and threshold for requesting BMD studies in these different departments. These differences may also be due to the younger age of GIT patients referred for DXA scans.

## 8 Dietary protein and bone: Devil or Angels?

*Rizzoli R*

Division of Bone Diseases, Department of Rehabilitation and Geriatrics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Correspondence to: Prof Rene Rizzoli, e-mail: rizzoli@cmu.unige.ch or Rene.Rizzoli@medecine.unige.ch

Peak bone mass (PBM) is a significant determinant of fracture risk later in life. Genetics accounts for more than 70% of PBM variance. Nutritional intakes modulate the genetic effects. Protein intakes are positively correlated to bone growth and bone mass accumulation in children and adolescents. Milk and dairy products provide large amounts of calcium, phosphorus, and other nutrients like proteins. In a balanced diet, about 70% of dietary calcium comes from milk and dairy products. In children and adolescents, intervention studies with dairy products show positive effects on bone mass accrual. Dairy products are associated with significantly greater total and cortical areas at the distal third of radius, suggesting a possible effect on bone modelling.

Nutritional deficiencies play a significant role in osteoporosis in the elderly. A low protein intake could be particularly detrimental for both the acquisition of bone mass during childhood and adolescence, and for the conservation of bone integrity with aging. Protein undernutrition can favour the occurrence of hip fracture by increasing the propensity to fall as a result of muscle weakness and of impairment in movement coordination, by affecting protective mechanisms, such as reaction time, muscle strength, and thus reducing the energy required to fracture an osteoporotic proximal femur, and/or by decreasing bone mass. Various studies have found a relationship between the level of protein intake and calcium-phosphate or bone metabolism and have come to the conclusion that either a deficient or an excessive protein supply could negatively affect the balance of calcium. In a prospective study carried out on more than 40 000 women in Iowa, higher protein intake was associated with a reduced risk of hip fracture. The association was particularly evident with protein of animal rather than vegetal origin. There is a positive correlation between bone mineral mass and spontaneous protein intake in women. In a longitudinal follow-up in the frame of the Framingham study, the rate of bone mineral loss was inversely

correlated to dietary protein intake. Increasing protein intake has a favourable effect on BMD in the elderly receiving calcium and vitamin D supplements. Thus, whereas a gradual decline in calorie intake with age can be considered as an adequate adjustment to the progressive reduction in energy expenditure, the parallel reduction in protein intake may be detrimental for maintaining the integrity and function of several organs or systems, including skeletal muscles and bone.

## 9 Differentiating adipose-derived stromal cells (ADSCs) into osteoblasts: not all ADSCs are created equal

<sup>1</sup> Sadie-Van Gijsen H, <sup>2</sup> Smith W, <sup>2</sup> du Toit EF, <sup>1</sup> Hough FS, <sup>1</sup> Ferris WF

<sup>1</sup> Department of Medicine, Stellenbosch University, Stellenbosch, South Africa

<sup>2</sup> Department of Biomedical Sciences, Stellenbosch University, Stellenbosch, South Africa

Correspondence to: Dr Hanél Sadie-Van Gijsen, e-mail: hsadie@sun.ac.za

**Objective:** We wished to compare the osteoblastic potential of adipose-derived stromal cells (ADSCs) from subcutaneous and visceral adipose depots from lean and diet-induced obese rats, to assess whether metabolic status affects osteoblast differentiation.

**Methods:** ADSCs were isolated from subcutaneous and visceral adipose tissue from lean and diet-induced obese male Wistar rats. Cultured cells were treated with osteoblast differentiation media (OM) and examined for alkaline phosphatase activity and matrix mineralisation, both indicative of osteoblast differentiation. The expression of the osteoblast-associated transcription factors Runx2 and Msx2 was measured using RT-PCR.

**Results:** For both lean and obese rats, OM treatment induced osteoblast differentiation in subcutaneous ADSCs (scADSCs) but not in visceral ADSCs. In addition, scADSCs from obese rats had reduced osteoblastic potential compared to scADSCs from lean rats. Msx2 expression was found to be up-regulated during osteoblastic differentiation of scADSCs from lean rats, but to a lesser extent in scADSCs from obese rats. Msx2 expression is therefore positively associated with the osteoblastic potential of ADSCs.

**Conclusions:** The osteoblastic potential of cultured ADSCs is influenced by the adipose tissue depot from which the cells were originally isolated, as well as the metabolic status of the donor animal. These cells retain a "memory" of their origin after *in vitro* expansion. In addition, the expression of Msx2 may be considered as a marker of osteoblastic potential in ADSCs.

## 10 Glucocorticoids up-regulate MKP-1 and inhibit proliferation in naïve mesenchymal stromal cells and primary pre-osteoblasts

Sanderson M, Sadie-Van Gijsen H, Hough FS, Ferris WF

Division of Endocrinology, Department of Medicine, Faculty of Health Sciences, Stellenbosch University, Stellenbosch, South Africa

Correspondence to: William Ferris, e-mail: wfferris@sun.ac.za

**Objectives:** Glucocorticoids (GCs) induce osteoporosis by diminishing osteoblast numbers. In the immortalised preosteoblast cell line

MBA 15.4, GCs decrease mitosis by increasing the expression of the dual-specificity phosphatase (DSP) MKP-1 which switches off the proliferative ERK pathway. Overexpression of MKP-1 results in decreased proliferation in MBA 15.4 cells, whereas knock down of expression using siRNA reverses the anti-proliferative effects of GCs. Consequently, MKP-1 was viewed as the primary conduit for the anti-osteoblastic effects of GCs in the MBA 15.4 cell line. However, MKP-1<sup>-/-</sup> homozygous knockout mice were not resistant to GC-induced osteoporosis as expected and therefore there was disparity between the immortalised MBA 15.4 and *in vivo* data. Therefore the effects of GCs on primary stromal cell proliferation and signalling were examined to clarify this.

**Methods:** Rat adipose-derived stromal cells (ADSCs) were differentiated into an osteoblastic phenotype and the effects of the GC dexamethasone on proliferation, ERK activation and MKP-1 expression were measured.

**Results:** GCs induce MKP-1 expression, inhibit mitogen-induced ERK activation and decrease cellular proliferation in both naïve ADSCs and ADSCs differentiated into an osteoblastic phenotype.

**Conclusion:** The disparity between data from primary preosteoblasts and MKP-1<sup>-/-</sup> homozygous knockout mice infers degeneracy in the anti-proliferative effects of GCs *in vivo*.

## 11 Calcium and vitamin D homeostasis during pregnancy and lactation

Pettifor JM

MRC Mineral Metabolism Research Unit, Department of Paediatrics, Chris Hani Baragwanath Hospital and the University of the Witwatersrand, Johannesburg, South Africa

Correspondence to: Prof John Pettifor, e-mail: John.Pettifor@wits.ac.za

Pregnancy and lactation place considerable demands on maternal calcium homeostasis. These increased calcium demands are met by increased maternal intestinal calcium absorption, reduced renal calcium excretion or increased bone resorption. Based on these increased requirements, it has been customary to recommend increased maternal calcium intakes during both pregnancy and lactation, however are these recommendations necessary or based on scientific evidence?

Few longitudinal studies have been conducted to assess bone loss during pregnancy, but those that have suggest that some 3% of bone mass may be lost at the trochanter region of the proximal femur with smaller losses at the lumbar spine and none at the whole body, radius or femoral shaft. Despite the increased bone resorption, intestinal calcium absorption increases some 50 - 70%, while urine calcium excretion also increases. During lactation, bone loss is even greater with approximately 5% being lost at the lumbar spine. The maximum rate of loss occurs in the first three months of lactation with bone loss diminishing thereafter. Once lactation ceases there is a rapid return of bone mass to pre-pregnancy levels. There is little or no evidence that the number of pregnancies or the duration of lactation has any long term effects on bone mass in women as they enter the postmenopausal period. There is no convincing evidence that calcium supplementation ameliorates the degree of bone loss or increases the rate of recovery during weaning. Furthermore, supplementation has no effect of breast milk calcium concentrations during lactation. However there are a few studies that suggest that

calcium supplementation during pregnancy may influence foetal or neonatal bone mass.

Maternal vitamin D status is important in determining neonatal vitamin D status and the vitamin D excretion in breastmilk. Customary vitamin D supplements are inadequate to maintain maternal vitamin D status during pregnancy or to ensure infant vitamin D status during breastfeeding. In conclusion, there is no evidence that calcium supplementation influences maternal bone loss or recovery, but maternal vitamin D status is important for the wellbeing of the neonate and infant. Thus calcium is not recommended as a routine supplement during this period of calcium stress, however vitamin D supplements are.

## 12 Longitudinal assessment of vitamin D status in urban South African children

Poopedi MA, Norris SA, Pettifor JM

MRC Mineral Metabolism Research Unit, Birth to Twenty Research Programme, University of the Witwatersrand, Johannesburg, South Africa

Correspondence to: Mr Machuene Ananias Poopedi, e-mail: machuene.poopedi@wits.ac.za

The aim of the study was to determine changes in 25(OH)D status over a period of three years in urban South African children.

**Methods:** 25(OH)D levels were analysed in 385 children aged 10 years, 310 children aged 11 years and 261 children aged 12 years, but only those children who had data for two or more years were included. The children formed part of the Birth-to-Twenty longitudinal cohort. Children with chronic illness, on medication or on any drugs and on minerals known to affect bone mass were excluded from the study.

**Results:** The mean 25(OH)D values were very similar in each of the two ethnic groups over the three years of measurement. In order to assess the degree of tracking in 25(OH)D values over the three years, Z-scores were calculated for each of the children's 25(OH)D annually. 25(OH)D Z-scores in both in black and white children correlated positively but poorly between the years, (blacks Y10 vs Y11 vs Y12,  $r = 0.2$ ;  $r = 0.2$ ;  $r = 0.6$  respectively) and (whites Y10 vs Y11 vs Y12,  $r = 0.5$ ,  $r = 0.4$ ;  $r = 0.5$  respectively). Furthermore children with high or low concentrations of 25(OH)D at year 10 did not maintain their relative positions in years 11 or 12.

**Conclusions:** Although the majority of children were vitamin D replete, the values of 25(OH)D did not show clinically significant tracking over three years of measurement, suggesting that a single measurement of 25(OH)D cannot be used to reflect vitamin D status over a prolonged period. These findings probably reflect variable environmental factors influencing vitamin D status on an annual basis.

**Conflict of interest:** None

## 13 Vitamin D status of mothers and their newborns in Soweto

Ranchod H, Thandrayen K, Pettifor JM

MRC Mineral Metabolism Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa

Correspondence to: Dr K Thandrayen, e-mail: Kebashni.thandrayen@wits.ac.za

Vitamin D deficiency and rickets has made a surprising resurgence in many parts of the world, despite a clearer understanding of predisposing factors and attempts at preventative strategies.

**Aim:** To assess the vitamin D status in mother-infant pairs in Soweto, at birth.

**Methodology:** A prospective, descriptive study of 87 black mothers and their infants (Ballard score gestational age > 37 weeks) from Chris Hani Baragwanath Hospital labour ward that were born between February and April 2008. Blood samples were collected from cord blood and mothers immediately after delivery, with their consent.

**Results:** The mean age of the mothers was  $27.2 \pm 5.8$  years (mean  $\pm$  standard deviation) with an average weight of  $75.2 \pm 14.9$  kgs and height of  $160.3 \pm 5.9$  cms. The mean gestational age of the newborns was  $39.5 \pm 0.9$  with birth weight of  $3.2 \pm 0.4$  kgs. Newborn calcium levels were  $2.43 \pm 0.14$  mmol/l and maternal levels were  $2.12 \pm 0.15$  mmol/l. Three (3.4%) mothers and four (4.6%) newborns were vitamin D deficient (25 OHD < 12 ng/ml) whereas 18 (20.7%) of the mothers and 7 (8%) of the newborns were vitamin D insufficient (25 OHD 12–20 ng/ml).

**Conclusion:** Twenty five percent of Sowetan black pregnant mothers were vitamin D insufficient/deficient and 13% of the infants were vitamin D insufficient/deficient. Thus, there is a need for vitamin D supplementation during pregnancy to high risk mothers and their breastfed infants.

## 14 Osteoporosis treatment: Who to treat? When to start? When to stop?

Eisman JA

Osteoporosis and Bone Biology, Garvan Institute of Medical Research, University of New South Wales and St Vincent's Hospital, Sydney, NSW, Australia

Correspondence to: Prof John Eisman, e-mail: j.eisman@at.garvan.org.au

A decision about osteoporosis treatment depends upon the balance of risk and benefit just as in every other medical condition.

The level of risk of fracture can be calculated now using well-developed risk algorithms available as web-based decision tools. These include the WHO FRAX<sup>®</sup> and the Australian Garvan Dubbo-based Fracture Risk Calculator <fractureriskcalculator.com>. In these risk algorithms, prior fracture, low BMD, advancing age are common risk factors. The Garvan calculator adds falls while the WHO FRAX<sup>®</sup> adds a range of clinical risk factors, including corticosteroid use, smoking and alcohol amongst others. Both of these tools require validation within their country of use and for both men and women. However it is critical that neither tool can make the treatment decision, each can only indicate an approximate 5 or 10-year level of risk, which has to be considered in conjunction with the individual patient's concerns and medical history and prognosis.

In most countries, public authorities support costs of treatment after any low trauma fracture. However the low trauma nature of these fractures is under-recognised; only 20–30% of women and 5–10% of men actually receive recommended therapy. Bone densitometry is a useful adjunct, but it does not have to be in the osteoporotic range (i.e. T-score < -2.5) to warrant therapy. In fact, most fragility fractures occur in women (and men) with bone density in the osteopenic range.

This is simply because, although each such individual's risk is lower, there are so many more people in this BMD grouping. In the face of this evidence, there is a growing support for basing the support of the costs of treatment upon the estimated absolute risk.

Importantly, a range of treatments are now available that are well tolerated and are effective in reducing risk by 50–70% for spine fractures and by 15–30% for non-spine fractures:

- Vitamin D insufficiency is common especially in institutionalised or housebound elderly and should be replaced. Calcium intake is often sub-optimal and also should be improved. Importantly other effective therapies have been validated on the basis of adequate vitamin D and calcium status.
- Sex hormone therapy reduces the risk of all types of fragility fracture including hip fractures in postmenopausal women. However, there are concerns precluding a recommendation for long-term therapy. There are neither safety nor fracture efficacy data for testosterone 'replacement' in men.
- The selective oestrogen receptor modulator (SERM, raloxifene) has somewhat lesser efficacy against spine fractures and non-spine fracture efficacy has not been demonstrated.
- Tibolone, another sex steroid-like therapy, reduces fracture risk but has not been widely supported because of concern about increased risk of vascular events in older women.
- Bisphosphonates are the mainstay of treatment by oral daily, weekly or yearly intravenous regimens. They reduce the risk of all types of fragility fracture including hip fractures.
- Strontium ranelate daily reduces fracture risk in women, including in older individuals, although its precise mode of action is still being explored.
- Teriparatide, a synthetic form of parathyroid hormone, has an anabolic effect when administered daily and reduces fracture risk in both men and women.
- Denosumab, a RANK ligand inhibitor, reduces the risk of all types of fragility fracture including hip fractures.

An interruption study of alendronate in women (FLEX) has led to the concept of a drug "holiday". This study was small, in women with mild osteoporosis and in any case the interrupted arm had significantly more clinical spine fractures. This study along with concerns about osteonecrosis of the jaw and atypical femoral fractures have led, misguidedly in my view, to unnecessary concerns and inappropriate treatment cessation particularly of bisphosphonates. Importantly, in this regard, the likelihood of osteonecrosis of the jaw and atypical femoral fractures with standard therapy appears to have been exaggerated.

Moreover recent data suggest that anti-resorptive therapy may reverse the premature mortality associated with osteoporosis and not entirely by reducing fracture risk.

As these data become clearer, the balance of risk and benefit for osteoporosis therapy may dramatically change. However, even without such new data, the risk-benefit equation is such that many more women and men should already be undergoing investigation and having treatment for osteoporosis.

## 15 An update on the promise of SERMS.

[de Villiers](#). Cape Town

## 16 HIV and Osteoporosis. [S Brown](#).

## 17 Prevalence of low bone mineral density in HIV-positive South Africans on anti-retroviral therapy. [J Dave](#).