

# Clinical Update

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## POSTMENOPAUSAL OSTEOPOROSIS, DIAGNOSTIC TOOLS, FRACTURE RISK ASSESSMENT AND TREATMENT

### CU1.1

#### Update on Tools for Diagnosis and Monitoring Osteoporosis. DXA, TBS, VFA, Microindentation and Biomarkers.

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Dual energy X-ray absorptiometry (DXA) is currently the reference technique to diagnose osteoporosis, estimate fracture risk and monitor antiosteoporotic therapy. However, there are other determinants of bone strength that cannot be evaluated by only measuring bone mineral density (BMD), which are those related to bone quality such as the bone microarchitecture and bone tissue characteristics, among others. In addition, it is important to know the effect of different antiosteoporotic treatments in determinants of bone strength other than BMD, especially after long-term therapy. In recent years several diagnostic tools addressed to evaluate different aspects of bone quality have been developed, allowing better evaluation of bone strength. In this sense, the trabecular bone score (TBS), a texture parameter computed from DXA images, seems to analyse bone microarchitecture, thereby enhancing the bone assessment made by BMD measurement by adding the dimension of bone quality. In addition, DXA-assisted vertebral fracture assessment (VFA) is a useful method to detect the presence of vertebral fractures, an important and frequently overlooked risk factor for further fractures, allowing evaluation of BMD in the same session. Other methods such as the bone microindentation testing provides direct *in vivo* estimation of bone material strength measured in the cortical bone of the tibia. Finally, although there are several discrepancies about the use of bone turnover markers in clinical practice, it should be noted that they can predict fracture risk and treatment-induced changes, accounting for a substantial proportion of fracture risk reduction. Nevertheless, controlling sources of variability and adopting international reference standards are necessary in this field. In summary, the integration of several new tools related to other aspects of bone quality may improve not only the identification of patients at high-risk of fracture but also the therapeutic approach and monitoring of these patients.

### CU1.2

*Abstract not available*

### CU1.3

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### CU1.4

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### CU1.5

*Abstract not available*

## VITAMIN D – SKELETAL AND NON-SKELETAL EFFECTS

### CU2.1

#### An Update on the Effects of Vitamin D on the Skeleton

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Vitamin D deficiency can cause secondary hyperparathyroidism and bone loss, mineralization defects, and in the long term rickets and osteomalacia. Vitamin D stimulates calcium and phosphate absorption from the gut, making these available for bone mineralization which mainly is a passive process. New laboratory observations show effects of vitamin D metabolites on osteoblast function and possibly mineralization. The prevalence of rickets is low in affluent countries but higher in some countries in Asia and Africa, and also in non-western immigrants. The global prevalence of osteomalacia depends on definition and can be estimated from biopsy and autopsy series, conservatively at about 1 %. Osteomalacia has been observed as a cause of hip fractures in the elderly. Vitamin D status is estimated according to serum 25-hydroxyvitamin D as deficient (<25 nmol/l) or insufficient (25-50 nmol/l) or adequate (>50 nmol/l). Low serum 25(OH)D (<50 nmol/l) has been observed in 50 to 80% of older persons, and in about 50% of all adults at least during winter. This results in a seasonal increase of parathyroid hormone and bone loss. The deficit of bone mineral density as a consequence of elevated PTH can be estimated at 1-2.5%. Clinical trials with vitamin D versus placebo in older persons have shown an increase of BMD of about 2%. Randomized clinical trials with vitamin D with or without calcium have shown a decrease of fracture incidence in 7 of 19 trials, no effect in 10 and an increase of fracture incidence in 2 trials. Most meta-analyses showed a decrease of fracture incidence with the combination of vitamin D and calcium, but no effect of vitamin D alone. The effect on fracture incidence could result from an increase of bone mineralization or a decrease of fall incidence.

**CU2.2**

*Abstract not available*

**CU2.3**

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**CU2.4****Vitamin D and Cancer**

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Vitamin D is not really a vitamin but the precursor to the potent steroid hormone Calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>). Calcitriol, originally known for its regulation of calcium metabolism and bone homeostasis, has widespread extra-skeletal actions throughout the body including beneficial effects on the development and progression of cancer. The vitamin D receptor (VDR) is expressed in most tissues of the body. Most cancer data have been accumulated for colon, breast and prostate cancer but a benefit from vitamin D may be found in many cancers. Calcitriol regulates numerous extra-skeletal pathways that could play a role in determining cancer risk and prognosis including pathways involved in proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis and metastasis, and it therefore has the potential to affect cancer development and growth. Vitamin D status, which is determined by sunlight exposure, diet and supplements, might reduce the risk of developing cancer, and the appropriate regulation of cancer-relevant pathways by vitamin D might also have a place in the treatment of cancer. Multiple cell culture and animal models of cancer support a role for dietary vitamin D<sub>3</sub> and calcitriol in retarding cancer development and progression; however, data from human clinical trials are thus far inconsistent. Randomized control trials in humans do not yet exist to conclusively support a beneficial role for vitamin D, however accumulating results from preclinical and some clinical studies strongly suggest that vitamin D deficiency increases the risk of developing cancer and that avoiding deficiency and adding vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome. If adequate vitamin D concentrations do reduce risk, ensuring that people receive sufficient vitamin D would be an easily available, economical and safe modality to reduce cancer incidence and mortality.

**CU2.5****Vitamin D in Pregnancy**

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Low concentrations of 25-hydroxyvitamin D, the major circulating storage form, are common in the general population. Over recent decades, there has been increasing evidence for a role of vitamin D in disease pathogenesis far beyond the musculoskeletal system. Thus, many studies have investigated whether low levels of circulating 25-hydroxyvitamin D have a detrimental effect on pregnancy outcomes, for both mother and offspring, and whether supplementation with vitamin D might ameliorate such effects. We comprehensively surveyed this literature in a recent systematic review, funded by NIHR HTA. Suggestive positive associations were observed between maternal 25-hydroxyvitamin D concentration/ vitamin D supplementation during pregnancy, and offspring birthweight, serum calcium concentrations and bone mass, with some evidence for a protective effect of maternal 25-hydroxyvitamin D concentrations on pre-eclampsia. Overall, though, there was insufficient evidence to recommend vitamin D supplementation in pregnancy for any single health outcome. Such findings reinforce the need for high quality randomised control trials, such as the UK MAVIDOS Maternal Vitamin D Osteoporosis study, a multicentre, randomised, placebo-controlled, double-blind trial of 1000IU/day vitamin D3 (cholecalciferol) versus placebo from 14 weeks gestation till delivery of the offspring, in which the primary outcome is offspring DXA-measured bone mass, with pregnancy outcomes assessed as secondary endpoints. This study, which is currently in the analysis-phase, will test, in an interventional setting, earlier observations linking low maternal 25-hydroxyvitamin D concentration to reduced offspring bone mass, and gain valuable information regarding the role of vitamin D in pregnancy for other health outcomes. Such a rigorous interventional approach is essential to enable research questions to be adequately answered, such that alterations to public health policy maybe confidently based on robust evidence.