OSTEOPOROSIS PROFILE

Introduction

Human bone mass normally decreases from its adult peak with advancing age. This is especially so in women after the menopause, since post-menopausal oestrogen deficiency may trigger the activity of the osteoclasts, the cells responsible for bone resorption. This can cause an acceleration of bone remodelling, producing the condition known as osteoporosis, an avoidable skeletal condition characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to an increased risk of fracture. A diagnosis of osteoporosis is based either on the presence of a minimal trauma fracture or on the WHO's definition of osteoporosis, which is itself based on the bone mineral density (BMD) T score. A T-score of the spine, hip or wrist that is 2.5 SD's or more below the reference mean (i.e. a T score of −2.5 or less) suggests a diagnosis of osteoporosis. While the lifetime risk of osteoporosis for a 50-year-old man it is one in five, for a 50-year-old woman it is estimated at one in two [1].

Prevention of osteoporosis can be:

- primary, which involves preventing bone loss from occurring,
- secondary in which the progression of bone loss is inhibited to avert the development of fractures, or
- tertiary in which patients with existing fractures are treated to prevent subsequent fracture [1].

Although osteoporosis is relatively common, the diagnosis is often not made until after a fracture has occurred, so there is a good case for osteoporosis screening. Nutritional status is of key importance and is currently a major health issue, since many osteoporosis sufferers are introduced to anti-resorptive treatment without adequate prior nutritional assessments – which must limit the value of such treatments.

Biomarkers of bone formation and resorption

Markers of bone formation and resorption can be used to estimate bone turnover rates and are of particular value in identifying "fast" bone losers (mainly post-menopausal females). To predict bone loss one should, in principle, measure the balance between formation and resorption of bone – i.e. the amount of bone matrix mineralised and de-mineralised - at a particular time. This is not possible, but a number of studies [2,3,4,5] have shown that biochemical markers can be used as independent predictors of fracture, especially of the spine and hip. For example, in osteopenic women [5] the 10-year probability of fracture amounted to 26% if alkaline phosphatase was elevated vs. only 6% in women with normal enzyme levels. Since plasma calcium levels are usually normal in osteoporosis, even if the bones are deficient, serum alkaline phosphatase is of some value in the monitoring of the rate of bone mineralisation [6].

Another approach to the estimation of bone breakdown is to measure the urinary excretion of the N-terminal fragments of mature type I collagen, which is cleaved from collagen during the osteoclastic resorption of bone. Since continuous remodelling takes place in bone, the N-terminal telopeptide (NTX) is released at a rate proportional to bone resorption activity [7]. Urine NTX is currently the biomarker of choice for monitoring osteoporosis treatment.

Nutritional risk factors

Calcium is the major cation of bone, with skeletal calcium being indirectly affected by dietary calcium intake and the amount of calcium lost from the body in urine or sweat. Bone is continuously broken down and re-

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formed and thus has a on-going requirement for calcium, but also for energy and for other nutrients including phosphorus, copper, manganese, zinc, magnesium, vitamin C and vitamin D.

Vitamin D deficiency, together with poor calcium intake, is a major risk factor for osteoporosis and osteoporotic fracture [8]. [See the separate Biolab datasheet "Vitamin D"]. Optimum levels of vitamin A (retinol) are also required for bone metabolism; overconsumption of vitamin A is thought to interfere with the action of vitamin D and contribute to the development of osteoporosis [9].

Phosphorus is required as a component of bone, but there is also concern that excessive phosphorus intake (for example from carbonated drinks) can stimulate PTH secretion, causing calcium release from bone and its loss in the urine.

55% of body magnesium is skeletal, and one third of skeletal magnesium is exchangeable and can be used to maintain extracellular levels, which are of prime importance for neuromuscular excitability and cardiac function) [10]. Poor magnesium intake, or losses from the extracellular fluid, can therefore deplete bone magnesium and the magnesium content of cells around the body, including erythrocytes. Bone magnesium is required for some 300 metabolic enzymes, including all energy-transfer reactions using ATP. Magnesium deficiency can also affect PTH secretion from the parathyroid glands and thus directly interfere with calcium and phosphate metabolism.

Zinc is also necessary for bone formation. As an enzyme co-factor, zinc is required for bone mineralisation and the development of bone structure. Systemic zinc deficiency reduces the concentration of zinc in bone.

Interpretation of results

The reference interval for serum alkaline phosphatase is 35 - 104 IU/L. The activity of alkaline phosphatase increases with accelerated bone loss, since there is increased deposition of bone as well as a greater increase in bone breakdown in this condition. Children (before puberty) have increased activities of this enzyme reflecting normal bone growth.

The reference interval for Collagen Type 1N telopeptide (Urine NTX) is 5 – 65 nmol of bone collagen equivalents (BCE) per mmol of urine creatinine. Normal adult levels of urine N-terminal telopeptide (NTX) suggest normal bone turnover, but values are increased during the growth phase in childhood. Moderate elevation of urine N-terminal telopeptide (NTX) suggests unbalanced bone re-modelling characteristic of osteoporosis, while a marked elevation of urine N-terminal telopeptide (NTX) (two-fold or greater) suggest the presence of additional bone disease, such as osteopenia.

Plasma calcium and phosphate concentrations reflect the net balance between bone mineralisation and resorption, as well as intestinal absorption and renal excretion [10]. These processes are regulated by parathyroid hormone (PTH) and by vitamin D. Adequate vitamin C status and normal levels of vitamin A are also pre-requisites for healthy bone mineralisation.

Plasma levels of copper, manganese and zinc that are below the quoted reference intervals suggest deficiency of these elements, which can contribute to a poor rate of bone mineralisation. Supplementation with these trace elements has been shown to produced beneficial effects on bone density as compared to subjects supplemented with calcium alone[10].

Measurements on early morning (e.m.), second void urine samples, collected between 8.00 am and 11.00 am, can also be used to assess excretion rates of calcium, phosphorus, magnesium and zinc, with the result normalised as the molar ratio to creatinine. The reference ranges shown on the osteoporosis profile report are for adults, not children, whose high urine output of calcium and phosphorus reflects normal bone growth.

Urine calcium can also be used in the assessment of vitamin D status; if the serum vitamin 25-hydroxy cholecalciferol is > 200 nmol/L and the UCa/Cr is > 0.60, that is evidence for vitamin D toxicity. An increase in osteoclastic bone resorption will also raise the UCa/Cr. Vitamin D deficiency, or a calcium-restricted diet, may reduce the UCa/Cr ratio to < 0.25. Low sodium diets tend to decrease UCa/Cr, while a high sodium intake and excretion increases UCa/Cr.

Urine phosphate is more influenced by diet than is urine calcium because of the greater proportion of dietary PO_4 absorbed from the gut. High circulating vitamin D and PTH cause phosphaturia by increasing the renal clearance of phosphate.

Phosphaturia also causes loss of magnesium in the urine. A low Mg value in an e.m.u. suggests magnesium deficiency, but a normal result does not exclude magnesium deficiency, which can be checked by red cell magnesium measurement.

The wide reference interval for urine zinc reflects the poor intake of zinc in many subjects. Zinc is required for both osteoblastic and osteoclastic activity [11,12,13,14].

Patient preparation: the patient should abstain from taking supplements containing the minerals and vitamins measured in the profile for 48 hours prior to venipuncture.

Specimen requirements: the following blood specimens are required **-** 2 clotted SST (serum separator, yellow top) tubes, 1 trace element-free (blue top) potassium EDTA tube, 1 lithium heparin (green top) tube, together with 15 mL of a second void e.m.u. (early morning urine, collected between 8.00 am and 11.00 am) in a plastic, screw cap container. A postal sample kit can be supplied and the osteoporosis urine element profile is also available separately.

Turn around time: 8 working days.

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