

Biochemical Predictors of Bone Mineral Density and Fracture Susceptibility: Results from a Maltese Study

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Introduction

Osteoporosis is a multifactorial skeletal disease characterised by low bone mass and micro architectural deterioration, leading to increased fracture susceptibility [1,2]. In Malta, 20% of women and 6% of men aged 50 years and older are estimated to be affected with Osteoporosis [3]. Fracture is the most significant clinical consequence of osteoporosis, with the most common, debilitating, and costly fractures being those of the spine, hip and wrist [1]. A number of environmental and genetic risk factors are known to affect bone mineral density (BMD), which in turn impacts fracture outcome [4,5]. Furthermore, other parameters reflecting calcium homeostasis, matrix mineralisation, and bone formation can also be targeted and measured in blood. Levels of serum calcium, serum albumin, and total serum alkaline phosphatase (sALP) are suggested as potential indicative markers of osteoporosis and/or fracture susceptibility, and increased frailty [5,6].

The role of calcium and albumin in bone

Bone is a versatile, physiologically dynamic organ composed of an inorganic phase (60-70%) and an organic phase (30-40%). Most of the inorganic phase (90-95%) consists of calcium hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) and to a much lesser extent of water and impurities [7]. The hydroxyapatite crystals interact with water in the bonematrix and extracellular fluid for the exchange of ions to aid in bone mineralisation. The organic phase, also known as the extracellular matrix (ECM), is mainly composed of type I collagen, a smaller portion of non-collagenous proteins (15%), as well as specialised proteins such as proteoglycans, growth factors, and matrix metalloproteinases. One-fourth of the total non-collagenous protein content is composed of exogenous albumin, which affects matrix mineralisation and bone cell proliferation thereby controlling hydroxyapatite crystal growth [8]. These protein levels also affect levels of Insulin Growth Factor 1 (IGF-1), which in turn play a role in bone remodeling [9].

Metabolically, this endocrine organ is primarily a major source of minerals, particularly calcium and phosphorus, which are involved extensively in calcium and phosphate homeostasis, to an extent that bone is compromised in favour of maintaining a constant serum calcium level in the body. The key players involved in this bone calcium mobilisation are parathyroid hormone (PTH) and vitamin D [10], which promptly come into play to normalise serum calcium levels by increasing or decreasing calcium losses through the intestines and kidneys [11]. Indeed, two scenarios are possible. In primary postmenopausal bone loss, serum calcium levels increase due to the increased bone resorption rate. To compensate for the high serum calcium level, PTH levels are low thereby decreasing gastrointestinal

and/or tubular calcium reabsorption [11]. In addition, a decline in oestrogen at menopause decreases plasma volume due to an increase in urinary output, which in turn increases serum albumin concentration [12]. Since blood calcium is primarily bound to albumin, higher circulatory total calcium levels are seen at menopause [13]. In fact, Maltese postmenopausal women below the age of 60 years were found to have considerably higher total serum calcium levels, which were negatively correlated with hip BMD [6]. Conversely, with ageing, a decline in gastrointestinal and/or tubular reabsorption of calcium results in an overall decline in serum calcium levels. To counterbalance the low serum calcium levels, calcium is mobilized from bone following secondary increases in PTH and subsequently vitamin D [14]. This results in osteoporosis and an increased fracture risk. Maltese postmenopausal women above the age of 60 years, who sustained more than one fracture or an osteoporotic hip fracture, had the lowest serum calcium levels when compared to age-matched controls [6]. Similar results were observed for serum albumin levels in women with a fracture history, with lowest levels observed in those who sustained a hip fracture. Lowest levels were recorded in older postmenopausal women [6] indicating that a low protein intake and possibly malnutrition negatively affect bone health [15]. The association between low protein levels and hip fracture risk in the elderly is well known [15,16], with authors reporting the use of serum albumin as a marker of frailty [16]. However, the association with BMD is still inconclusive [6,17]. A decline in the overall well-being and functional status in older individuals due to malnutrition, distress, and coexisting secondary disorders, is also accompanied by a decrease in levels of calcium and albumin amongst others [18].

Total sALP and BMD

Total sALP is frequently used as a marker of bone metabolism reflecting osteoblast activity and hence new bone formation. Maltese postmenopausal women with an osteoporotic BMD at the hip and who sustained an osteoporotic hip fracture had lower total sALP levels in comparison to age-matched controls [6]. The use of sALP as a specific marker of fracture risk remains controversial, with most studies reporting no association [19,20]. It is important to note the time at which blood is collected, since sALP levels return back to baseline approximately ≥ 8 weeks post-fracture or possibly remain elevated in the case of delayed or non-union fractures [19,20], therefore giving falsely elevated results.

Physical activity and levels of serum calcium, albumin and total sALP

Physical activity, especially weight-bearing exercise, is a well-known determinant of healthy bone mass and increased bone strength. Low

physical activity is thus considered a significant risk factor for low BMD and increased fracture risk, most importantly at the hip [21]. Levels of serum biochemical parameters are also correlated with levels of physical activity. Reduced physical activity and immobilization favour osteoclastogenesis, thereby decreasing osteoblast stimulation and sALP levels [22]. Serum calcium and albumin levels are also affected by the rate of physical activity performed. High physical activity is associated with intermittent PTH stimulation, which increases calcium absorption (reducing bone calcium mobilisation) and increases IGF-1 levels, which translate into higher albumin levels [23]. Indeed, Maltese postmenopausal women who reported a low level of physical activity had reduced levels of all three biochemical parameters [6].

Conclusion

In conclusion, levels of total serum calcium, albumin and sALP are suggestive of possible markers of hip BMD and/or increased fracture risk.

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