3.1 Factors in the Development of Osteoporosis

In women an age-related slow decrease is accelerated to an acute loss of bone in the menopausal and postmenopausal periods, and then followed by a gradual and progressive decline in bone mineral density (BMD) with age. In men, bone loss begins somewhat later, but it is due, as in women, to increased osteoclastic resorption, which is a direct consequence of decreases in steroid hormones, i.e. hypogonadism. The decrease in steroid hormones also directly impacts cells which have the oestrogen receptors alpha or beta such as the bone marrow mesenchymal progenitor cells responsible for the production of osteoblasts and adipocytes. Oestrogen promotes osteoblastogenic differentiation and inhibits adipogenesis. Therefore, with advancing age, bone formation is decreased as a direct consequence of a shift in the balance of production of the two cell lineages, in favour of adipocytes.

Many investigations have addressed the question of additional factors and pathways which regulate and control the differentiation of the mesenchymal progenitor cells in one direction or the other. The results of these investigations have implicated genomic, hormonal, for example intermittent parathyroid hormone (PTH), and various other pathways, including Wnt signalling as well as other ligands and receptors which influence mesenchymal stem cell differentiation and could tip the balance in favour of osteoblasts or adipocytes. For example, Wnt signalling favours osteoblastogenesis. It should be emphasized that the Wnt signalling pathway is involved in many biological processes from embryonic development to insulin secretion in adulthood. Some investigations have correlated the antagonism of oxidative stress to Wnt signalling in advancing age as a decisive contributing factor to the development of atherosclerosis, insulin resistance, hyperlipidaemia and involutional osteoporosis.

Earlier investigations implicated inhibition of gap-junctional communications between osteoblastic progenitors as responsible for the mesenchymal switch to adipogenesis. More recent studies have demonstrated that a ligand-activated transcription factor, known as PPAR gamma 2 in the mesenchymal stem cells participates in the control of adipogenic differentiation. Moreover, studies in animals have demonstrated that vitamin D3 inhibits adipogenesis and induces osteoblastogenesis, with a reduction in PPAR gamma 2. However, the net result of the activities of all the factors involved, after the decline in oestrogen levels, is production of adipocytes, not osteoblasts.

It is of interest that in animals, during periods of simulated microgravity, a mesenchymal switch from osteoblasts to adipocytes also occurs, due to changes in many factors and pathways. Returning to humans, it is postulated that similar changes may take place as a consequence of immobilization, disuse and in age-
related osteoporosis. Many investigations into all the mechanisms of osteopenia/osteoporosis are ongoing, as well as into the possibilities for potential interventions in the future.

3.2 Definition of Osteoporosis

The word osteoporosis literally means porous bone, indicating that the bone density is low and the bones are thin. But bone does not fracture due to thinness alone. In the early 1990s a consensus meeting of the World Health Organisation (WHO) defined osteoporosis as:

“A systemic skeletal disorder characterized by a low bone mass and by microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture”.

The first Consensus Conference on Osteoporosis of the new millennium proposed a new definition of osteoporosis as:

“A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture”.

However, in order better to understand the aetiology of osteoporotic fractures and the effects of therapy on the risk of occurrence of fractures, it is essential to recognize the factors that govern bone strength. The strength of an individual bone (and of the whole skeleton) depends on its mass, shape and the quality of the bone itself (Fig. 3.1).

Numerous large studies have already confirmed the connection between bone density, bone strength and fracture risk. Density is responsible for 60–90% of the strength of bone. From the outside, however, osteoporotic bones may even have the same size and look like normal bones, but inside they are brittle, with a thin cortex and a disrupted (or even localized lack of) trabecular network.

Low bone mass has proved to be the most important objective predictor of fracture risk. The lower the bone mass, the weaker the bone and the less force required to cause a fracture. Therefore, according to the WHO (The WHO Study Group 1994) osteoporosis in postmenopausal women was also defined in terms of bone density measurement and based on a comparison of the patients’ measurement to the standard peak adult bone mass (PABM) as follows:

“Osteoporosis is present when the bone mass is more than 2.5 standard deviations (SD) below that of healthy premenopausal adult females, the T-score”.

However, taking into consideration the multifactorial nature of bone fragility, an up-dated position paper was issued by the WHO and the International Osteoporosis Foundation (2007).

This proposed that “osteoporosis” is no longer diagnosed as such, but by a total individual 10-year

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**Fig. 3.1.** Progressive architectural deterioration of cancellous bone: increased osteoclastic resorption cavities and marked attenuation of cancellous bone (osteopenia); disconnected trabeculae, no longer a network (established osteoporosis)