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Abstracts

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## I001

### The Assessment of Fracture Risk: A Global Perspective

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For many years, the assessment of fracture risk and osteoporosis has been considered almost synonymous with bone mineral density (BMD) measurement. Indeed, diagnostic criteria for osteoporosis, based on absolute or relative BMD, were in practice often used as therapeutic thresholds. Whereas this had the merit of simplicity, we have now more knowledge about other risk factors associated with fracture risk and how these can be incorporated into an overall assessment of fracture risk.

When integrating risk factors, one has first to consider the expression of risk. A single and easy to use metric is useful. The *T* score has served this purpose in the past, but there is a growing consensus that the assessment should concentrate on fracture risk rather than on a biological variable, a similar evolution as, for example, in the field of cardiology, where CVD risk is the outcome of interest rather than blood pressure, although it remains an important intermediate.

Fracture risk can be expressed as a risk relative to other individuals of the same age, gender, ethnicity, or location in the world. For most purposes, the value of interest will not be the remaining lifetime risk but the absolute risk in the foreseeable future, i.e., the absolute risk in the 5 to 10 years ahead, as this is the timeframe for which an intervention will be considered. There are many potential clinical indicators for assessing this risk, but to be of practical value, they should be important risk factors, at least partially independent from each other, and sufficiently prevalent in the population considered. Several examples will be discussed, including body weight, previous fracture, family history, and lifestyle parameters. Finally, the integration of these risk factors with the assessment of bone (BMD, ultrasound or other) will be discussed.

## I002

### Combination Therapy for Osteoporosis

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Most standard therapies for osteoporosis reduce bone resorption and increase bone mineral density (BMD) modestly. Antiresorptive agents increase the mineralization of pre-existing bone matrix but do not increase bone formation or the amount of true bone tissue. Thus, they do not cure osteoporosis. Because single-agent antiresorptive therapy has, at best, modest effects on BMD, alternative strategies have been entertained.

Several studies have examined the effects of combinations of antiresorptive agents on BMD including bisphosphonates plus hormone therapy (HT) and bisphosphonates plus selective estrogen receptor modulators. Regardless of whether the two antiresorptive agents are started simultaneously or a bisphosphonate is added to ongoing HT, the incremental increases in BMD with two antiresorptive agents are small. It is unknown whether such additional increases in BMD will reduce fracture rates below those seen with single antiresorptive agents. In fact, it is theoretically possible that additional suppression of bone resorption may have adverse effects on bone strength and it is nearly certain that side effects will be more common with two antiresorptive agents than with one. Thus, combination antiresorptive therapy is generally not recommended.

Recently, parathyroid hormone (PTH) became available to treat both men and women with osteoporosis. Unlike antiresorptive agents, PTH administration increases bone formation and bone resorption. Because once-daily PTH increases bone formation more than it increases bone resorption, it increases BMD substantially and it causes the production of actual new bone. Because PTH also increases bone resorption, however, it would seem likely that combining PTH with an antiresorptive agent would increase BMD more than with either agent alone. When PTH is added to long-term continuous HT, BMD increases more than with continued HT alone. It is not clear from those observations, however, whether combination therapy is superior to PTH alone. Two recent studies have compared

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the effects of alendronate (ALN) alone, PTH alone, and PTH plus ALN on BMD in osteoporotic subjects. Surprisingly, both studies suggest that PTH monotherapy increases BMD of the spine more than does combination therapy or ALN alone. It is unknown whether these differences in BMD will be accompanied by differences in fracture rates. Nonetheless, at the present time, it seems prudent to use PTH alone rather than in combination with an antiresorptive agent.

**I003**

**Rab GTPAses and the Control of Membrane Traffic in Bone Cells**

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Small GTPases of the Rab family are key regulators of membrane traffic. Each cell type expresses a characteristic set of Rabs to control ubiquitous and specialised trafficking pathways. In bone cells, the importance of Rabs has been highlighted by several recent studies. Firstly, the discovery that biphosphonate drugs act by inhibiting protein prenylation, and consequently Rab function. Secondly, the realisation that understanding the molecular mechanisms of bone resorption in osteoclasts will be critical to find new therapeutic avenues to fight common bone diseases. I will discuss the importance of Rabs as regulators of membrane traffic and their involvement in disease, with a focus on osteoclasts.

**I004**

**Bone Dynamics and Vesicular Trafficking**

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Throughout life, the skeleton is continuously remodeled. Bone formation by osteoblasts and bone resorption by osteoclasts are processes that are completely dependent on vesicular trafficking. Signals, generated at the plasma membrane by growth factors, cell–cell and cell–extracellular matrix adhesion, converge to modulate their intracellular trafficking machinery to ensure correct and timely delivery of cargo and proteins.

In vivo, bone-depositing osteoblasts form a continuous cell layer on top of the newly deposited matrix. Here, extracellular-matrix proteins are secreted in a polarized fashion, i.e., away from neighboring capillaries and towards the existing bone surface. Enzymes involved in mineralization, specifically alkaline phosphatase, are localized to the basolateral plasma membrane highlighting polarized protein delivery. The exact mechanism responsible for this polarized delivery in osteoblasts has not been elucidated.

Since polarized trafficking depends on targeting information present both on the transport vesicle and the target membrane, the establishment of cell–cell junctions and their spatial arrangement provide important cues for the organization of polarized trafficking. In this light, we have shown that osteoblastic cells form functional tight junction-like structures in culture. Moreover, these cells contain a selected repertoire of proteins known to be essential for secretion. Via means of high-resolution immunolocalization studies, we provide evidence that in migratory osteoblasts, t-SNAREs and secreted matrix proteins are preferentially accumulated at the leading edge. A similar localization was also observed for lysosomal-associated proteins, linking for the first time lysosomes and their enzymatic content with the process of bone formation. Understanding the vectorial nature of the specific functions undertaken by osteoblasts and their regulation will be essential if stem cell maturation and function is to be controlled for therapy of osteoporosis and other bone diseases or for optimizing tissue engineering.

**I005**

**Membrane Trafficking and Podosomes**

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Focal delivery/exposure of matrix metalloproteases (MMP) is crucial for extracellular matrix (ECM) remodeling events during physiological and pathological processes alike. There are many mechanisms through which this occurs. For instance, in vivo, ECM degradation is confined to the immediate pericellular environment via the membrane type MMP (MT-MMP) which together with other proteins act as receptors/activators for soluble MMP. Clear molecular links between the MT-MMP and cytoskeleton proteins form the basis for their localization to limited districts of the plasma membrane (e.g., leading edge). In addition, secretory traffic is known to be polarized towards sites of active membrane reorganization, for instance, towards the leading lamella in wound-edge fibroblasts. It is now well-known that in vitro, ECM degradation by invasive cells occurs at specialized plasma-membrane structures (invadopodia or invasive podosomes) where a number of key proteins are concentrated, including regulatory cytoskeletal proteins, tyrosine kinases, integrins, and an MT-MMP. This implies that focal ECM degradation involves a tight coordination between trafficking processes, signaling events and cytoskeletal rearrangements.

Novel data will be presented concerning the regulation of the invadopodia/podosome machinery and the focalized targeting of MMP activity. In detail, morphofunctional studies will be presented describing (1) the regulatory cytoskeleton cascade controlling invadopodia structure; (2) the relationship between invadopodial protrusions and the ECM; and (3) the molecular and structural basis for polarized secretion towards the sites of ECM degradation (i.e., invadopodia and podosomes).