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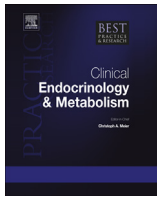

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Monitoring of osteoporosis therapy

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Over the past two decades, major advances have been made in the number and range of agents available for the treatment of osteoporosis, all with proven anti-fracture efficacy. Unfortunately, compliance with these treatments is not optimal, and a number of patients could be considered as non-responders. Consequently, monitoring anti-osteoporotic therapy could be part of successful osteoporosis management. Currently, no formal well-accepted clinical practice guidelines are available for monitoring anti-osteoporosis therapies. Changes in bone mineral density and bone turnover markers, while on therapy, have potential value in monitoring treatment but their assessment and, consequently, their benefits could be limited by metrological and clinical issues. Moreover, their effectiveness is probably drug dependant. Recommendation for the standardisation of the methodology when analysing the potential relevance of tools for the monitoring of osteoporosis therapy is needed.

Introduction

Osteoporosis is a major health problem worldwide. It is defined as a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk. Technological developments for the measurement of bone mineral density (BMD) have led to diagnostic criteria that are widely applied. The World Health Organization diagnostic criterion for osteoporosis is a BMD measurement equal to or more than 2.5 standard deviations below the young female reference mean (T-score ≤ -2.5 standard deviation) [1]. In addition,

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there have been major advances in the number and range of agents available for treatment, all with proven anti-fracture efficacy [2]. These agents have differing modes of action in protecting against fracture, and this needs to be taken into account when developing monitoring strategies. Important gaps in the clinical management of osteoporosis include the identification of individuals who would best benefit from intervention and, for those on treatment, the optimal manner in which response to treatment should be monitored.

The goal of pharmacological therapy is to reduce fracture risk by increasing bone strength. The ideal method of evaluating success with drug therapy would be to compare pre-treatment fracture risk with post-treatment fracture risk, or directly to measure changes in bone strength. For individual patients in clinical practice, we must rely on surrogate markers (biomarkers) that are correlated with bone strength and fracture risk. A working group of the National Institutes of Health defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention," with applications that include "use for prediction and monitoring of clinical response to an intervention" [3]. It has been proposed that an acceptable biomarker for osteoporosis therapy should meet established standards for accuracy, precision, and reliability, with well-defined quality control procedures, standardized data acquisition, and methods for analysis, and show (a) biological plausibility, (b) a significant association between the biomarker and fracture in the target non treated population, (c) consistent biomarker changes in response to treatment, and (d) that changes in biomarker predict the fracture reduction on treatment [4]. Moreover, another requirement is that if the biomarker indicates a lack of response, appropriate changes in management can be made by the health care prescriber and, in the case of poor adherence to treatment, patient behaviour can be modified [5]. At last, in a world with limited health-care resources, monitoring should also be cost-effective [5].

Even though anti-osteoporosis treatment can be associated with a decrease in the incidence of vertebral and non-vertebral fractures, development of a new fracture does not necessarily represent failure of therapy. Indeed, at best, pharmacological agents reduce fracture rates by 30–70% [2]. Therefore, an efficient monitoring of osteoporosis therapy could help to determine the effectiveness of a treatment strategy and guide management decisions.

Tools to monitor osteoporosis therapy

The most widely used tools to monitor osteoporosis therapy in clinical practice are Dual X-ray Absorptiometry (DXA) and Bone Turnover Markers (BTMs). Consequently, the next sections will present a critical review of the evidence supporting the use of BMD and BTMs to monitor treatment effect as well as their clinical applications. However, it should be acknowledged that other tools have been developed to assess properties of bone [6,7]. Quantitative ultrasound measures the speed of sound and broadband ultrasound attenuation at peripheral skeletal sites, but there is no clear evidence that these parameters are clinically useful in monitoring therapy. Quantitative Computed Tomography (QCT) and peripheral QCT measure volumetric BMD in trabecular and cortical bone, but could hardly be recommended as a monitoring tool in clinical practice because it is more expensive, less widely available, and exposes the patient to a higher dose of ionizing radiation than DXA. Finite element analysis has not been validated as an outcome measure in clinical trials and cannot be recommended as a monitoring tool. At last, high resolution magnetic resonance imaging and high resolution peripheral QCT at peripheral skeletal sites measure trabecular microarchitecture but are not validated tools to measure treatment effect.

BMD by DXA

Several national and international guidelines, including the International Society for Clinical Densitometry (ISCD), recommend BMD measurements for the routine monitoring of treatment. In particular, the ISCD states [8] that (a) Serial BMD testing can monitor response to therapy by finding an increase or stability of bone density; (b) Serial BMD testing can evaluate individuals for non-response by finding loss of bone density, suggesting the need for re-evaluation of treatment and evaluation for secondary causes of osteoporosis; (c) Follow-up BMD testing should be done when the expected