12 Precision and Monitoring Change in BMD

Introduction

The aim of this section is to discuss the use of serial bone mineral density (BMD) measurements to measure changes in BMD and to emphasise how this differs from the use of BMD measurements in the diagnosis of osteoporosis. In order to monitor change it is first important to consider the clinical reasons why we need to measure changes, and then consider the limitations of BMD measurements in this situation. We may then define the most appropriate measurement site and the required interval between measurements to determine whether clinically important changes have occurred.

Rationale for Monitoring Changes in BMD
The aim of drugs used in the treatment of osteoporosis is to reduce the risk of fracture. Bisphosphonates, which are generally used as the first-line treatment for osteoporosis, usually lead to an increase in BMD in the order of 5 to 10% at the lumbar spine over the first two years of treatment. This change in BMD in response to treatment appears to be a poor predictor of the change in fracture risk. Nonetheless, serial BMD measurements may be useful to identify the 10 to 15% of individuals who fail to respond to treatment.

Identification of non-responders
Failure to respond may occur for a variety of reasons. Some patients do not comply with treatment, that is they do not take their medication, or do not take it correctly. Other patients do not respond to medication which they are taking correctly. This may be the result of poor absorption from the gut, which is a particular problem with the bisphosphonate drugs, or the patient may have an underlying medical condition which is causing bone loss such as thyrotoxicosis. Identification of non-responders enables investigation for underlying diseases and may indicate the need to change to another therapeutic agent.

Compliance with treatment
Another reason to monitor patients is to improve compliance. Most treatments for osteoporosis reduce the risk of vertebral fracture by approximately 50%. However, this means that many patients will have further fractures despite an optimal response to treatment. Most patients who sustain a further fracture will perceive this as treatment failure. If we are to encourage them to persist with treatment it is probably important to demonstrate to the patient that their treatment is working. Demonstration of treatment effect is of particular importance in the management of osteoporosis since much of the treatment we prescribe is preventative in nature, and does not improve the patient’s current symptoms. Indeed the treatment is often inconvenient to take, and may cause side-effects.
Measuring Changes in BMD
In order to confirm that an individual has responded to treatment, we need to be able to measure a significant increase in BMD. It is helpful at this point to consider the properties of an ideal measurement tool and to assess how well BMD measurements fulfill these criteria.

An ideal measurement to assess treatment response would have the following properties:

• **Show a change in response to the treatment being used**
  Data from clinical trials of treatment for osteoporosis suggest that the increase in BMD in response to anti-resorptive treatment differs between measurement sites (figure 1), and probably also between treatments, although there are few direct comparisons of different agents. The greatest increase is usually seen at the lumbar spine, with smaller changes seen at the hip, and smaller changes still at peripheral skeletal sites such as the forearm. The reason for the difference in response between different skeletal sites is probably related to the ratio of trabecular to cortical bone. The vertebral bodies contain a high proportion of trabecular bone which undergoes more rapid turnover than cortical bone, and may therefore be expected to show a greater response to treatment.

Some treatments lead to greater increases in BMD than the bisphosphonates. This may reflect a true increase in new bone formation, as is the case with teriparatide. Alternatively, it may reflect an artefactual effect, as in the case of strontium ranelate. With this treatment, strontium, which has a higher atomic weight than calcium, replaces calcium on the bone surface leading to an exaggerated increase in measured BMD.

• **Change by a greater amount than the error of the measurement**
  Any measurement has an inherent variability, so that a repeat measurement made under identical circumstances will be slightly different from the first. The magnitude of this variability may be described as the precision error, or reproducibility of the measurement. The precision error is greater for some bone density measurements than others (table 1). In order to monitor treatment response it is important to use a precise measurement since the increase in BMD with treatment is generally small and may otherwise be masked by measurement variability. The calculation of measurement precision is discussed later in this chapter.

• **Enable a response to be measured within a short time**
  The time taken to measure a treatment response will depend on the size of the response, the speed with which it occurs, and the precision of the measurement. Unfortunately, the change seen in response to treatment is not much larger than the precision of even the best BMD measurement and in most cases it is not possible to determine a treatment response in less than about 18 months. As may be seen later, in the case of some measurements the interval is much longer, and therefore not clinically useful.

• **Be safe, and preferably cheap, reliable and convenient**
  All the techniques in routine use for BMD measurement (Dual energy x-ray absorptiometry – DXA, Quantitative ultrasound – QUS and Quantitative computed tomography - QCT) are suitable for monitoring in terms of safety and convenience, although they may be unsuitable for the reasons outlined above. The unit cost varies between techniques but providing the machines are utilised to their full capacity the costs are not prohibitive.
It may be seen that BMD measurement does not fulfill the criteria for an ideal measure of treatment response. Biochemical markers of bone turnover have potential advantages over serial BMD measurements for the purposes of monitoring osteoporosis therapy. Changes in the biochemical markers are rapid, and often exceed measurement error within 3 to 6 months. The change in bone turnover markers also appears to be more predictive of the change in fracture risk than does change in BMD. However, there remain limitations to the use of the biochemical markers in clinical practice and they are currently only available for clinical use in a few centres in the UK.

At the present time therefore, BMD measurement remains the most accessible measure of treatment response. However, some BMD measurements are superior to others. The main limitation of BMD measurements to detect change is that the magnitude of change in response to treatment is similar to the measurement variability. It is important to understand how the variability influences the choice of measurement, and its interpretation.

**Measurement Reproducibility (Precision)**

There are a number of sources of variability of BMD measurements which it is helpful to consider separately:

**Machine**

Small changes result from the error of the technique. Daily phantom scans should be performed under standardised conditions to identify clinically relevant changes which could reflect faults with the scanner, such as detector deterioration. The use of quality control procedures is addressed in section 9. There are systematic differences between machines, even from the same manufacturer. It is therefore essential that the same machine is used to make serial measurements.

**Operator**

Error may be introduced by the operator at any stage in the process of scan acquisition or analysis. It is therefore essential to take great care to follow the manufacturer’s guidelines as closely as possible. Particular care should be taken to position the patient correctly, and to use identical scanning parameters on each subsequent scan, and reanalyze previous measurements if required. These factors are covered in detail in sections 8 and 10.

**Patient**

In most cases the greatest variability between scans results from the patient. A change in BMD over time may represent disease progress or response to treatment, but it is important to be alert to the possibility of artefactual change which may lead to misinterpretation of the result. Errors may result from significant weight change, or the inclusion of artefacts within the region of interest. Progression of degenerative change of the spine, aortic calcification, or a new vertebral fracture will all artificially increase the measured BMD2. These factors are discussed in section 10.

It may be seen that careful attention to detail will eliminate many of the factors causing variability. Some variability however cannot be avoided and it is important to quantify this in order to determine the least significant change for any measurement.
Calculation of Precision Error

It is usual to determine the short term reproducibility of a BMD measurement by making duplicate measurements of a group of subjects with repositioning between scans. Measurements may be made on the same day, or within a short period. Table 1 compares typical precision errors for commonly used BMD measurements. The precision error may be calculated as a coefficient of variation as follows:

\[
CV = \frac{\text{global estimate of the SD of the repeat measurements}}{\text{mean}} \times 100\%
\]

(the global estimate of the SD is equivalent to the root mean square taken from analysis of variance of the repeated measurements)

<table>
<thead>
<tr>
<th>MEASUREMENT</th>
<th>PRECISION ERROR (COEFFICIENT OF VARIATION, %)</th>
<th>LEAST SIGNIFICANT CHANGE, %</th>
<th>RESPONSIVENESS TO ANTI-RESORPTIVE TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA - AP lumbar spine</td>
<td>1.0</td>
<td>2.8</td>
<td>Good</td>
</tr>
<tr>
<td>DXA – femoral neck</td>
<td>2 to 3</td>
<td>5.6 to 8.4</td>
<td>Moderate</td>
</tr>
<tr>
<td>DXA – total hip</td>
<td>1.5</td>
<td>4.2</td>
<td>Moderate</td>
</tr>
<tr>
<td>PDXA – forearm</td>
<td>1.0</td>
<td>2.8</td>
<td>Poor</td>
</tr>
<tr>
<td>QUS - BUA (calcaneus)</td>
<td>2 to 5</td>
<td>5.6 to 14</td>
<td>Unknown</td>
</tr>
<tr>
<td>QUS – SOS (calcaneus)</td>
<td>0.5</td>
<td>1.4</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 1

Reproducibility of techniques which may be considered for use in monitoring changes in BMD. Typical values for precision error within an osteoporotic population are shown. The wide range of precision error for broadband ultrasound attenuation (BUA) reflects differences between the systems available to measure QUS.

The precision error is not only influenced by the measurement technique and site of measurement but also by the characteristics of the subjects. For instance the precision error tends to increase in an elderly or osteoporotic population due to factors such as greater difficulty in repositioning, and the lower mean BMD. Knowledge of the precision within an appropriate group is important in the interpretation of BMD changes.

Least Significant Change

Knowing the precision of a measurement helps us to interpret serial measurements made in an individual. The magnitude of change which must be measured to be sure that the change is real, and not simply the result of a measurement error may be referred to as the least significant change. This represents the 95% confidence limits for the measured change. Another way of describing this is that 95 times out of a hundred, a change greater than the least significant change will be real. The least significant change is calculated as \(2.8 \times CV\). For example, if a measurement has a precision error of 1%, the least significant change will be 2.8%.
Longitudinal Sensitivity
Neither the precision error nor the least significant change of a measurement allow us to compare the clinical utility of measurements made by different methods, or at different sites in assessing change. This is because a comparison of two measurements must also take into account the change seen in those particular measurements in response to treatment. The longitudinal sensitivity of a measurement gives an idea of its clinical utility, and may be used to compare different measurement techniques. It may be defined as the ratio of the change with treatment to the precision of the measurement and is sometimes referred to as the signal to noise ratio.

Standardised Coefficient of Variation (SCV)
Similarly, the clinical utility of different methods to diagnose osteoporosis cannot be determined by direct comparison of their precision. In this case it is because the difference in each measurement between healthy individuals and those with osteoporosis (the dynamic range) needs to be considered. This may be done by use of the SCV which is calculated as follows:

\[
\text{SCV} = \frac{\text{global estimate of the SD of repeat measurements}}{\text{difference between mean value for healthy young adults and individuals with osteoporosis}}.
\]

Optimal Clinical Approach to Assessment of Treatment Response
Knowledge about the comparative longitudinal sensitivity of BMD measurements allows us to define the best approach to use in clinical practice. Although measurement of the proximal femur, or even a peripheral skeletal site such as the forearm or calcaneus may be an appropriate measurement to use to in the assessment of fracture risk, the best measurement for monitoring change in BMD is usually that of the lumbar spine. The reason for this is firstly because the spine appears to show a greater change in response to treatment compared to other skeletal sites, and secondly because the measurement at the spine is precise. In other words the lumbar spine measurement shows good longitudinal sensitivity to change.

The precision of lumbar spine measurements in clinical practice is usually approximately 1%. A change of more than 3% may therefore be considered to be significant. In contrast, a change at the proximal femur is not significant until it is greater than about 6%. Figure 1 shows data from a study of the use of alendronate in the treatment of postmenopausal osteoporosis. In this study an average subject showed a change in LS-BMD of greater than 3% within six months. In other words, more than 50% of patients could be described as having shown a response to treatment by this time. In contrast, the average response at the femoral neck did not exceed the least significant change of 6% even by the end of the three year study.
This shows data from a study of the treatment of postmenopausal osteoporosis with alendronate. The change in BMD as a percentage of the baseline value is shown over the three years of the study at three skeletal sites. The magnitude of the increase in BMD was much greater at the spine than at either the femoral neck or the distal radius. Adapted from Liberman et al3.

The timing of a repeat measurement is also related to the longitudinal sensitivity. Figure 2 illustrates the proportion of individuals exceeding the least significant change after a year of treatment. This will be dependent on the measurement site, which affects both the least significant change and the magnitude of the treatment response. In this study, which examined the use of cyclical etidronate in the treatment of postmenopausal osteoporosis4, only 40% of subjects could be classified as responders after one year. In practice repeat measurements are usually made after two years or more. In summary, BMD measurements may be used to determine the response to treatment in individual patients. The magnitude of the response to treatment is similar to the measurement variability of most BMD measurements and the choice of measurement is influenced by both the reproducibility of the measurement, and the anticipated response to treatment at that skeletal site. Treatment response is usually determined by serial measurements of the lumbar spine, repeated after 1 to 2 years of treatment.
This shows data from a study of the treatment of postmenopausal osteoporosis with etidronate. The annual change in BMD at the lumbar spine as a percentage of the baseline value is shown for the women treated with etidronate (left) and those receiving calcium as a placebo (right). The shaded area shows the least significant change for this measurement. This illustrates the number of individuals who could be identified as responders (above shaded area) and non-responders (below shaded area) after one year of treatment. 60% of patients treated with etidronate did not show a significant change in BMD during this time. Adapted from Storm et al. 4.

References