Response to "Concerns regarding the use of 3D-DXA"

We thank the Editor for the opportunity to respond to the Letter to the Editor: “Concerns regarding the use of 3D-DXA” in relation to our recent publication, Harding et al., *Bone*, 136, 2020, 115362 [1].

The Letter author writes “It is my understanding that it is not possible to measure the cortical parameters from a two-dimensional dual-energy X-ray absorptiometry (DXA) image.”

This is correct. Technically, all so-called ‘measures’ from indirect densitometry are estimates, but more to the writer’s point, it is typically not possible to parse out cortical from trabecular bone from a standard areal BMD exam. The 3D-DXA modelling software was built from a database of Quantitative Computed Tomographic scans of the proximal femur, to develop a statistical shape and density model; technical details of the modelling algorithm have been published previously [2, 3].

**Concerns about the statistical model:**

The Letter author writes “…if you have a dataset of DXA images with…an overall increase in areal BMD, a 3D-DXA analysis will produce an increase in volumetric density together with an increase in cortical thickness.”

We understand the basis for the author’s opinion but provide evidence to the contrary in Figure 1. The statistical model used by the 3D-DXA technology is based on the principles of statistical shape and appearance modelling, which have been largely used to model bone shape and density distribution [4]. As mentioned by the author of the letter, in those approaches, no explicit parameter describes the cortical thickness or density. This, however, does not mean that cortical thickness and density variations cannot be captured by the model independently from integral bone density variations. Figure 1 shows an example of two instances of the statistical model used by the 3D-DXA technology. The two instances have the same integral vBMD, but a different cortical (and trabecular) vBMD. This demonstrates that the statistical model used by 3D-DXA incorporates cortical density variations independently from integral bone density variations.

*Figure 1: These two instances of the statistical model used by 3D-DXA have the same integral vBMD (268 mg/cm³). The instance in the left image has a higher average cortical vBMD (853 mg/cm³) and a lower trabecular vBMD (132 mg/cm³), compared to the instance of the right image (cortical vBMD of 595 mg/cm³ and trabecular vBMD of 192 mg/cm³).*

**Ability of 3D-DXA to analyse the cortex from DXA scans:**
With respect to the concern about the ability of 3D-DXA to discriminate the cortex from DXA scans, we refer the author to several published clinical trials. In a recent study [5], DXA scans collected during the ACTIVE trial were retrospectively analysed using 3D-DXA. The patients had received either 18-months treatment of Abaloparatide, Teriparatide or placebo. The study reported a similar increase in integral vBMD at 18 months for both treatment groups (4.2% Abaloparatide and 3.9% Teriparatide, non-significant difference). Both Abaloparatide and Teriparatide groups exhibited a similar increase in trabecular vBMD at 18 months (8.7% vs 8.8%, respectively) and cortical thickness (1.5% vs 1.5%, respectively). However, the changes reported for the cortical vBMD following Abaloparatide treatment were significantly greater (1.2%), than Teriparatide (0.3%, p<0.01).

In another study [6], DXA scans of patients treated with Alendronate, Denosumab or Teriparatide were analysed by 3D-DXA. Both Denosumab and Alendronate treatment caused a marked increase in integral vBMD (3.8% Denosumab group and 2.0% Alendronate group). However, the treatment effect on the cortex was very different between drugs. While a significant 1.8% increase in cortical thickness was reported following Denosumab treatment (p<0.05), Alendronate treatment had no effect on cortical thickness (0.05%, non-significant). In the same study, both Denosumab and Teriparatide treatment effected similar changes in trabecular vBMD (7.7 mg/cm$^3$ Denosumab and 6.2 mg/cm$^3$ Teriparatide), while the effect on cortical vBMD was very different between groups (14.9 mg/cm$^3$ Denosumab and -8.0 mg/cm$^3$ Teriparatide) (Figure 2).

![Figure 2](image)

**Figure 2:** Average changes in vBMD observed in the mid-coronal plane following Denosumab (left) and Teriparatide (right) treatment (adapted from [3]). The blue represents an increase while the red represents a decrease. The left image shows an increase in vBMD in both compartments, while the right image shows an increase in trabecular vBMD and a decrease in vBMD in the cortex. $\Delta$Trab and $\Delta$Cort indicate the average changes at 24 months in trabecular vBMD and cortical vBMD, respectively.

The results of these clinical studies demonstrate the ability of 3D-DXA to capture changes in the cortex, independent of integral bone changes.

We have recently demonstrated excellent repeatability of vBMD and femoral neck strength from 3D-DXA analyses of pairs of same-day repeated proximal femur scans from 10 healthy women [7]. We also showed that mean bone accrual following 8 months of bone-targeted exercise using 3D-DXA Hip analysis exceeded repeatability values in the femoral neck and cortical regions.
Taken together, we believe the secondary 3D-DXA Hip outcomes reported in Harding et al., *Bone*, 136, 2020, 115362 [1] are an informative and valid representation of changes beyond aBMD that may occur at the proximal femur in response to a recognised bone-targeted exercise intervention.

**References**


Kind regards,

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