VITAMIN D RECEPTOR ACTIVATION INCREASES SERUM SCLEROSTIN IN CKD PATIENTS: A RANDOMIZED CLINICAL TRIAL

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INTRODUCTION

Sclerostin is an osteocyte glycoprotein which interacts with major endocrine and autocrine factors regulating bone mineral balance. 1,25(OH)2VD dose-dependently increases the expression of sclerostin gene in osteoblasts in vitro. However, there is still no information on the effect of activated forms of vitamin D on circulating sclerostin. Within the context of a randomized, double blinded clinical trial (1) we tested the effect of vitamin D receptor activation (VDRA) by paricalcitol (PCT) on serum sclerostin and other MBD biomarkers.

METHODS

Measurements were performed in the whole cohort of stage G3-4 CKD patients enrolled in the PENNY trial (n=88). After baseline measurements, patients were randomized to receive 2 µg PCT capsules (n=44) or matching placebo (n=44) daily, for 12 weeks. Sclerostin and the main CKD-MBD biomarkers were measured in all patients of both study arms (no sample was missing) at baseline, after 12 weeks of PCT/Placebo treatment and two weeks after PCT/Placebo withdrawal.

RESULTS

At baseline sclerostin correlated directly with age (r=0.36, P=0.001), gender (r=0.33, P=0.002) and three main somatometric measurements [height (r=0.36, P=0.001), weight (r=0.42, P=0.001), waist circumference (r=0.35, P=0.001)] as well as with diabetes (r=0.22, P=0.04) and C Reactive Protein (r=0.29, P=0.005) and inversely with cholesterol (r=-0.28, P=0.008). Among CKD-MBD biomarkers, sclerostin associated inversely with serum phosphate (r=-0.26, P=0.01) and directly with 1,25(OH)2VD (r=0.22, P=0.04), but was independent of serum calcium, PTH, 25OHVD and FGF23 (all P>0.14). PCT treatment increased sclerostin levels (from 166.7 pg/ml to 182.4 pg/ml) as compared to placebo (from 180.4 pg/ml to 167.3 pg/ml; between group difference: P=0.03) and this effect went along with the expected PTH suppression (PCT -75.1 pg/ml; Placebo +20.5 pg/ml; P<0.001), a marked rise in FGF23 (PCT +107.0 pg/ml; Placebo -20.2 pg/ml; P=0.001) and a reduction in 1,25(OH)2VD levels (PCT -24.3 pg/ml; Placebo:-5.5 pg/ml; P<0.001). The PCT driven sclerostin rise and the accompanying changes on CKD-MBD biomarkers almost entirely reverted two weeks after stopping PCT and placebo. No effect of seasons was found on the rise in the serum sclerostin increase induced by PCT (P for the effect modification > 0.38).

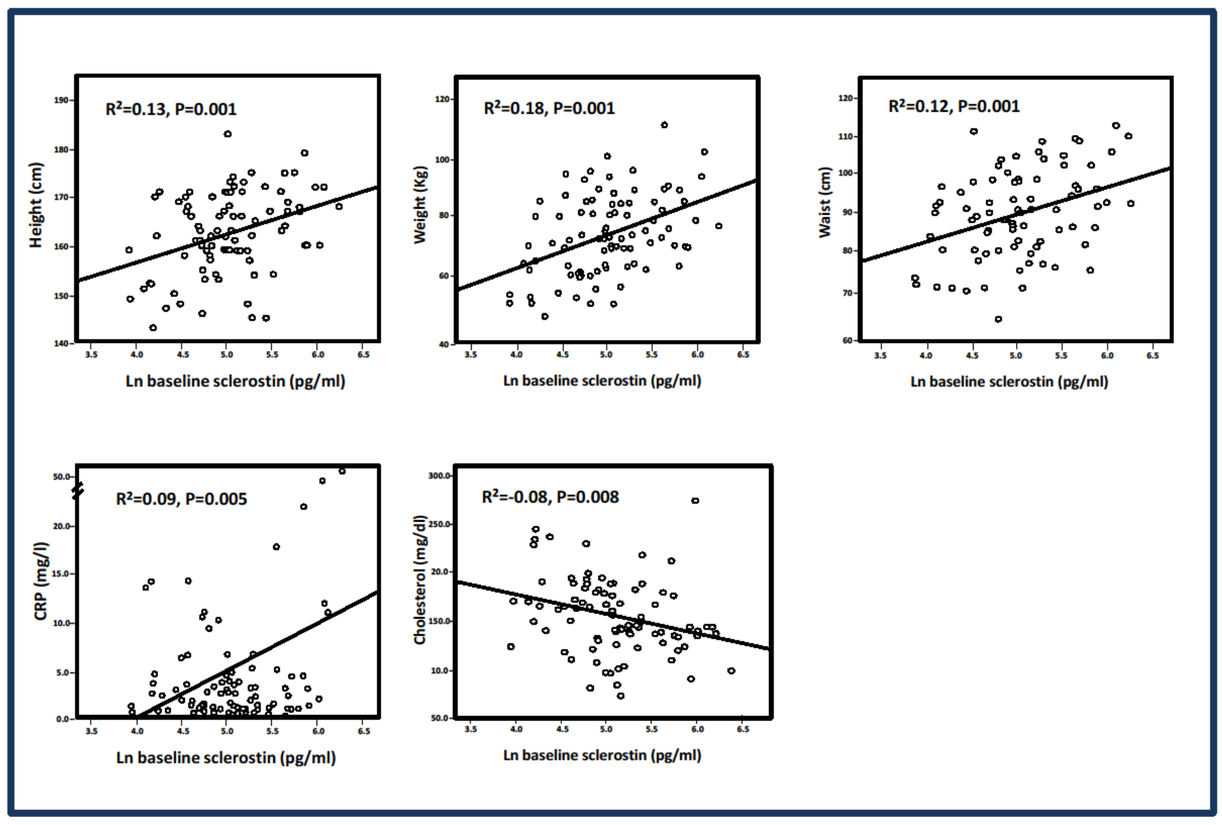

Fig. 1. Baseline correlates of sclerostin

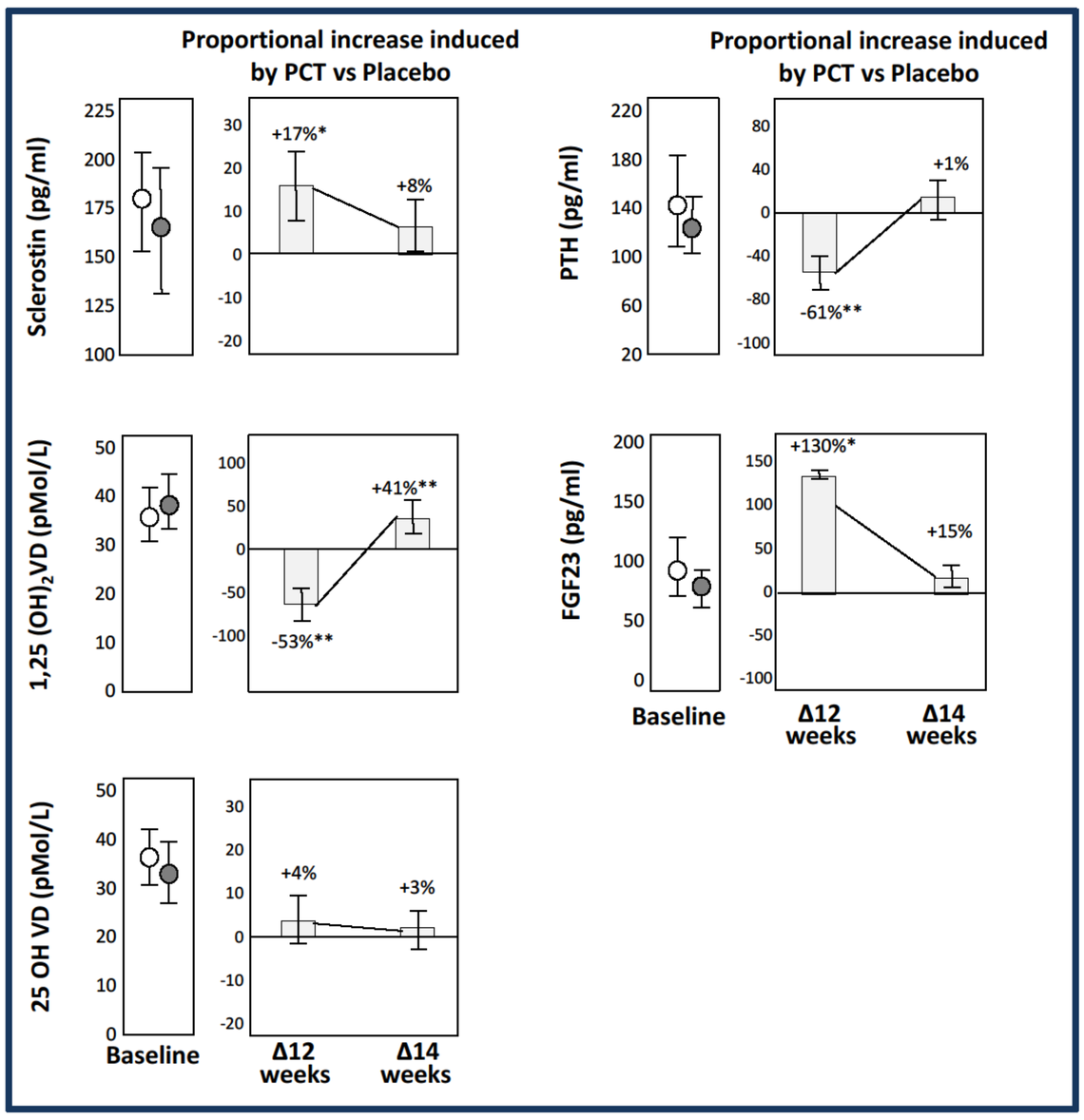

Fig. 2. Proportional increase of sclerostin, 1,25 $(OH)_2$ Vitamin D, 25 OH Vitamin D, PTH, FGF23 induced by PCT versus Placebo

CONCLUSIONS

Within the framework of a randomized clinical trial in CKD patients, vitamin D activation by paricalcitol increases serum sclerostin as compared to placebo. These findings further highlight the interconnectedness of CKD-MBD biomarkers and suggest that the PCT-induced increase in serum sclerostin is a counter-regulatory response aimed at modulating the effect of vitamin D receptor activation on mineral bone metabolism.

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