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IMPACT OF ACTIVE VITAMIN D AND CALCIUM PREPARATION ON VASCULAR CALCIFICATION MARKERS IN HEMODIALYSIS PATIENTS WITH HYPOCALCEMIA INDUCED BY CALCIMIMETICS

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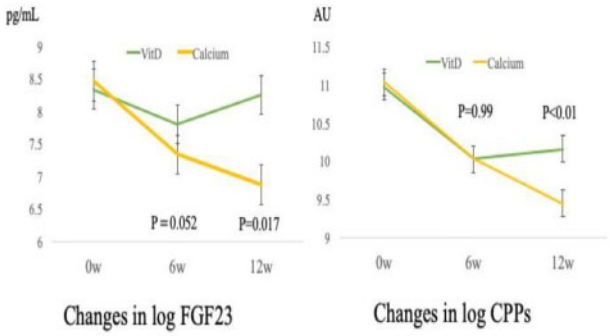
BACKGROUND AND AIMS: Recently, we demonstrated the efficacy of etelcalcetide for control of secondary hyperparathyroidism (SHPT) in the DUET trial; a 12-week multicenter, open-label, randomized (1:1:1), parallel-group study treated with etelcalcetide + active vitamin D (Group E+D), etelcalcetide + oral calcium

preparation (Group E+Ca), or control groups (Group C) in 124 subjects undergoing maintenance hemodialysis. Moreover, we also showed that active vitamin D was useful in correcting hypocalcemia induced by calcimimetics, but the oral calcium preparation was superior for suppression of hyperphosphatemia. In this post hoc analysis, we evaluated vascular calcification markers, fibroblast growth factor 23 (FGF23) and calciprotein particles (CPPs), in patients using etelcalcetide (n = 77) extracted from the registrants of the DUET trial.
METHOD: Serum levels of FGF23 and CPPs were measured at baseline, 6 weeks and 12 weeks after start of the trial. Skewed data (FGF23 and CPPs) were transformed to natural logarithm to achieve normal distribution prior to statistical analysis. The changes in log CPPs and log FGF23 were estimated in a linear mixed model with each treatment group, time point, and interaction of the treatment group and time point as the fixed effects. We compared these changes between treatment the groups using a linear mixed model and also the Tukey-Kramer method to correct for multiplicity. Additionally, we exploratory examined the correlations among changes of FGF23, CPPs and other biomarkers related to bone mineral metabolisms, iPTH, Ca, P, and calcium-phosphate product, tested by Spearman's rank correlation coefficient.
RESULTS: The decreases at the 12-week time point after the trial start in log FGF23 were estimated -1.13 pg/mL in Group E+Ca and -0.10 pg/mL in Group E+D in a linear mixed model, respectively. Similarly, the decreases in CPPs were estimated -1.60 AU in Group E+Ca and -0.82 AU in Group E+D, respectively. Changes of both FGF23 ($P = 0.017$) and CPPs ($P < 0.001$) in Group E+Ca significantly decreased compared with those in in Group E+D by Tukey-Kramer multiple-comparison test at 12 weeks after the trial start, while both changes in CPPs and FGF23 could not reach the significant differences between two groups at 6 weeks after the trial start (Figure 1). Reductions in FGF23 positively correlated with reductions in calcium ($\rho = 0.42$, $P < 0.01$) and phosphate ($\rho = 0.48$, $P < 0.01$) at 6 weeks after the trial start, and in calcium ($\rho = 0.30$, $P < 0.01$) and phosphate ($\rho = 0.70$, $P < 0.01$) at 12 weeks after 6 weeks of the trial start), but there was no correlation with reductions in iPTH at any time point. Reductions in CPPs positively correlated with reductions only in phosphate at 6 weeks after the trial start ($\rho = 0.47$, $P < 0.01$) and at 12 weeks after 6 weeks of the trial start ($\rho = 0.54$, $P < 0.01$).



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CONCLUSION: In this analysis, vascular calcification markers were significantly decreased in Group E+Ca compared to those in Group E+D. Further studies should be needed, our study suggests that oral calcium preparation may have an advantage against vascular calcification rather than active vitamin D for the correction of hypocalcemia induced by etelcalcetide in hemodialysis patients with SHPT.