Increased fetuin-A levels following treatment with a vitamin D analog

To the Editor: Fetuin-A is one of the several potential vascular calcification inhibitors in chronic kidney disease (CKD) patients; it seems to protect from precipitation of calcium phosphate under extra-osseous calcification stress by organizing a fetuin–mineral complex (FMC).[1]

Vitamin D has been demonstrated to promote ectopic calcifications by different mechanisms that also include fetuin-A exhaustion as a result of FMC formation. This hypothesis was supported by *in vivo* evidence in rats fed with toxic doses of vitamin D,[2] which induced ectopic calcifications and reduction of circulating fetuin-A; however, this mechanism has never been investigated in humans. In addition, Matsui *et al.*[1] recently reported a slight decrease in serum fetuin-A levels and a marked rise in FMC in uremic rats with very high levels of calcium × phosphorus (Ca × P) product.

We studied fetuin-A serum level variations in hemodialysis patients suffering from secondary hyperparathyroidism, before and after the administration of a vitamin D analog (paricalcitol).

We treated 10 consecutive hemodialysis patients with hyperparathyroidism, who had never received vitamin D treatment, with i.v. paricalcitol 5 μg thrice weekly; we obtained their sera before the first paricalcitol administration (t0), and after 1 week (t1), 4 weeks (t4), and 8 weeks (t8); serum levels of fetuin-A (measured using a human fetuin-A ELISA kit, Epitope Diagnostics, San Diego, CA), high-sensitivity C-reactive protein (hsCRP), total intact parathyroid hormone (PTH), and serum calcium and phosphorus levels were measured. The results are shown in Figure 1.

Contrary to that reported in rats, we observed, comparing t8 with t0, a progressive and statistically significant increase in serum fetuin-A levels ($P = 0.01$); there was also an increase in the Ca × P product ($P = 0.42$) and a decrease in PTH ($P = 0.07$) and hsCRP levels ($P = 0.06$), but these changes were not statistically significant. Because it is well known that inflammation, as assessed by hsCRP, may condition fetuin-A synthesis, we investigated whether changes in fetuin-A correlated with changes in hsCRP; in our patients there was no significant correlation between these two parameters ($r = -0.188$, $P = 0.60$); therefore, the increase in fetuin-A we observed after paricalcitol treatment did not seem to be accounted for by changes in the inflammatory status of our patients.

The increase in fetuin-A serum levels could be due to hepatic stimulation of fetuin-A synthesis induced by vitamin D through its action on the hepatocyte vitamin D receptor. In agreement with our data, serum levels of 1–25 OH dihydroxy-vitamin D in untreated CKD patients were found to correlate with serum fetuin-A levels.[3]

In conclusion, although vitamin D may elicit vascular calcification through an increase in the Ca × P product, in humans it is apparent that it may also activate a counter-regulatory mechanism that leads to an increased production of fetuin-A. These data lend further support to the view that vitamin D may exert pleiotropic effects on different organ systems, as reviewed by Verstuyf *et al.*[4] in a recent issue of *Kidney International*.

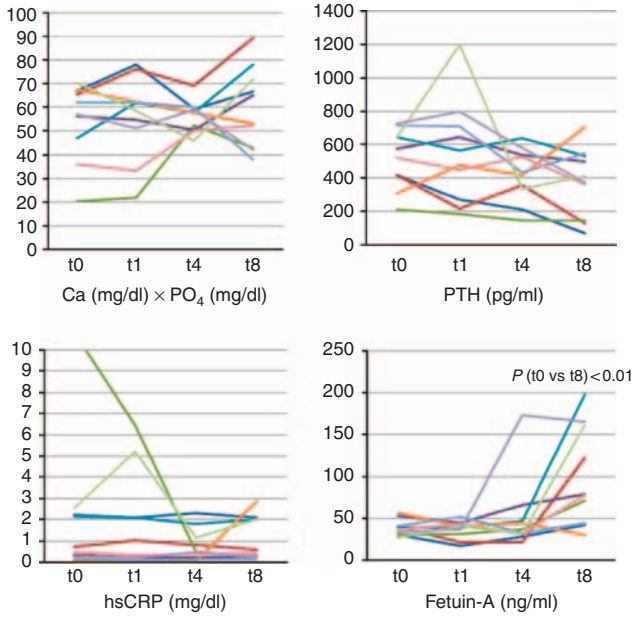

Figure 1 | Serum levels of fetuin-A, Ca × P product, parathyroid hormone (PTH), and high-sensitivity C-reactive protein (hsCRP) in the 10 patients studied, before (t0) and after 1 week (t1), 4 weeks (t4), and 8 weeks (t8) of paricalcitol treatment.

1. Matsui I, Hamano T, Mikami S *et al.* Fully phosphorylated fetuin-A forms a mineral complex in the serum of rats with adenine-induced renal failure. *Kidney Int* 2009; **75**: 915–928.
2. Price PA, Williamson MK, Nguyen TMT *et al.* Serum levels of the fetuin-mineral complex correlate with artery calcification in the rat. *J Biol Chem* 2004; **279**: 1594–1600.
3. Mehrotra R, Westenfeld R, Christenson P *et al.* Serum fetuin-A in nondialyzed patients with diabetic nephropathy: relationship with coronary artery calcification. *Kidney Int* 2005; **67**: 1070–1077.
4. Verstuyf A, Carmeliet G, Bouillon R *et al.* Vitamin D: a pleiotropic hormone. *Kidney Int* 2010; **78**: 140–145.

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The Author Replies: Manenti *et al.*[1] observed a significant increase in serum fetuin-A levels starting a few weeks after thrice-a-week paracalcitol treatment of 10 patients on chronic hemodialysis. The simple consequence could be that such