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Hyperparathyroidism suppression and prevention of cardiovascular calcification and complication in chronic kidney disease patients – *Are 1,25 $(OH)_2$ vitamin D derivatives actually necessary?*

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SUMMARY

We reviewed the experimental and clinical data on whether 1α-OH vitamin D derivatives are actually necessary for suppressing uraemic hyperparathyroidism and preventing its deleterious skeletal, renal and cardiovascular complications.

Experimental data on parathyroid hormone synthesis and parathyroid hyperplasia suppression show that in spite of uraemia-induced resistance to calcitriol, supraphysiological serum levels of calcitriol are not necessary since in vitamin D receptor and 25-OH vitamin D 1αhydroxylase gene-deleted mice, hyperparathyroidism can be suppressed by a high calcium diet. Only normal bone growth necessitates appropriate activation of the VDR. However, VDR of parathyroid cell as well as of chondrocyte, osteoblast, macrophage and smooth muscle cell can be appropriately activated by intracrine formation of calcitriol, provided systemic levels of 25-OH vitamin D are sufficient.

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Supraphysiological serum levels of calcitriol account for the premature aging phenotype with vascular calcification of klotho $^{-/-}$ and FGF23 $^{-/-}$ gene-deleted mice, and in uraemic rats, normocalcemic calcitriol administration decrease survival by promoting vascular calcification, while a high calcium diet has the opposite effect.

In spite of uraemia-induced resistance to calcitriol, the hyperparathyroidism of predialysis and dialysis patients has been efficiently suppressed solely by vitamin D deficiency correction (S 25-OH vitamin D>20 ng/ml) associated with a calcium based oral phosphate binder in the Nephrology Centres of Amiens and Bordeaux. In spite of a high dose of $CaCO_3$ (up to 3.6 g elemental calcium per day) associated with 25-OH vitamin D deficiency correction, but without 1α-OH vitamin D, no independent link was observed between aortic calcification and calcium dose in our centre, where there has been no exposure to aluminium overload since 1980. Furthermore no inverse link between aortic calcification and bone mineral density was observed in contrast to what has been observed in the general population or the dialysis population of Erlangen.

Considering the high prevalence of vitamin D deficiency in the USA dialysis Centre (80% of patients with S25-OH vitamin D <15 mg/ml), the survival benefit observed in patients having received intravenous calcitriol or paricalcitol compared to those who have not may be just a reflection of the deleterious effect of vitamin D deficiency, since in addition to prevention of hyperparathyroidism and bone disease, the 'sunshine' vitamin D decreases the risk of diabetes, cardiovascular and cancerous diseases.

We conclude that there is as yet no proof that 1α-OH vitamin D derivatives are necessary in uraemic patients, provided their usual vitamin D insufficiency or deficiency has been corrected by plain or 25-OH vitamin D.

This statement is based on following data:

1. 1α-OH vitamin D derivatives do not suppress PTH synthesis more efficiently than 25-OH vitamin D does at physiological concentration. The reverse is potentially observed when 1α- OH vitamin D is associated with a non-calcium-based-oral-phosphate-binder (non-Ca-OPB) and compared with plain vitamin D or calcidiol associated with calcium-based-oral-phosphate-binder (Ca-OPB).
2. The less hypercalcaemic and hyperphosphataemic paricalcitol has been evaluated mainly against placebo in CKD patients very likely having a vitamin D insufficiency and calcium deficiency, since in the reported studies these parameters were not taken into account while recent ASN posters stress the high prevalence of vitamin D deficiency in American CKD patients. When paricalcitol has been compared with calcitriol, it has been found only marginally superior for suppressing PTH and preventing hypercalcaemia and hyperphosphataemia.
3. Effects of paricalcitol on bone biopsies of CKD patients have not been as well documented as those of calcitriol or alfacalcidol. When compared with calcidiol, alfacalcidol has been shown to be less efficient for osteoid mineralization.
4. In experimental uraemia, paricalcitol as calcitriol induces vascular calcifications whereas $CaCO_3$ and calcimimetics prevent them.
5. The better prevention of vascular calcification in dialysis patients with sevelamer compared with Ca-OPB was favoured by the inappropriate decrease of 1α-OHD derivatives, when associated with Ca-OPB, so that a higher incidence of hypercalcemia was induced.
6. The greater survival with oral alfacalcidol or intravenous calcitriol or paricalcitol was evi-

denced only in dialysis patients not receiving plain vitamin D or 25-OH vitamin D. Therefore it was likely due to the correction of the well established deleterious effects of vitamin D-insufficiency on diabetes prevention, cardiovascular remodelling and inflammation.

7. All cells implicated in PTH suppression, immunological modulation and cardiovascular remodelling have a receptor for 25-OH vitamin D and a 1α-hydroxylase enabling them to appropriately synthesise calcitriol, provided serum calcidiol is not insufficient.

INTRODUCTION

Since the discovery by Fraser and Kodicek[1] that 1α hydroxylation of 25-OH vitamin D increases vitamin D potency to stimulate active intestinal absorption of calcium and phosphate (and therefore its hypercalcaemic and hyperphosphataemic effects), these vitamin D dihydroxylated derivatives have been extensively used in the management of secondary hyperparathyroidism, the severity of which increases in parallel with the progression of renal failure. However, no long term head-to-head comparison with hard clinical outcome evaluation has ever been performed in CKD patients between these 1α-OH vitamin D derivatives and plain vitamin D, although administration of the latter (together with a calcium supplement of about 1000 mg/day) has been shown to reduce the fracture risk in elderly patients without overt chronic kidney disease but with some degree of vitamin D insufficiency, provided they adhere to the prescription[2,3]. Nevertheless, in the 2003 NKF/KDOQI[4], the intravenous use of 1α-OH vitamin D at each dialysis is recommended, without prior correction of the prevalent vitamin D insufficiency, in order to correct overt hyperparathyroidism, provided serum concentrations of calcium and phosphorus are below the recommended upper limit (2.37 and 1.78 mmol/l respectively).

This practice, although popular predominantly in the US because of a nation specific dialysis reimbursement policy[5], is now promoted outside the USA because of quite appealing cohort study results, showing a significant survival advantage in patients having received oral alfacalcidol[6] or intravenous calcitriol or paricalcitol[7], compared to those who have not.

Therefore we want to review here the present experimental and clinical data which would support the preferential use of 1α-OH vitamin D derivatives associated with non calcium-based oral-phosphate-binder (non Ca-OPB) over the plain vitamin D-insufficiency correction associated with calcium-based oral phosphate binder (Ca-OPB) for both parathyroid and bone outcomes, as well as vascular and mortality outcomes.

A. SUPERIORITY OF 1α-OH VITAMIN D DERIVATIVES + NON CA-OPB OVER VITAMIN D INSUFFICIENCY CORRECTION + CA-OPB, FOR HYPERPARATHYROIDISM SUPPRESSION AND BONE OUTCOMES?

A.1 Experimental data

Figure 1 summarizes the present understanding of PTH synthesis regulation and parathyroid cell proliferation in uraemia, a condition in which these two phenomena are closely related. The main stimulating factors of PTH synthesis and hyperparathyroid hyperplasia in uraemia are trends to increased serum phosphorus (SPO_4) levels and to decreased serum levels of calcium (SCa), calcitriol and bicarbonate. Low SCa and high SPO_4 prolong PTH mRNa half-life by inhibiting endonuclea-

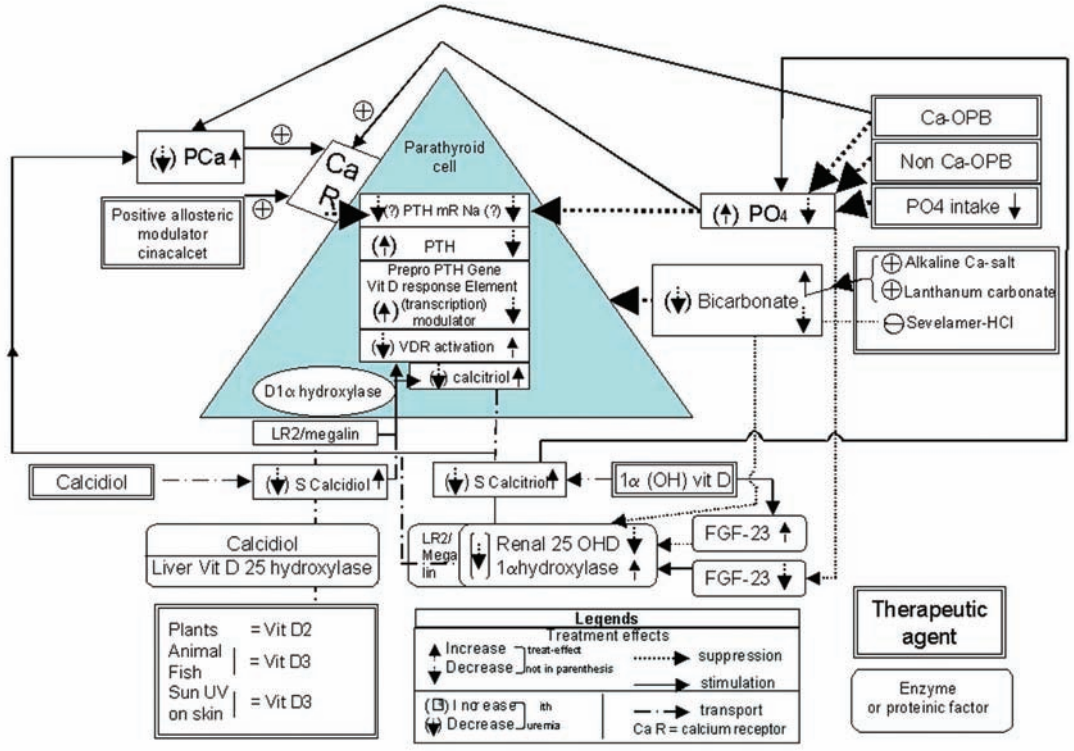

Figure 1 : Therapeutical interventions and suppression of PTH synthesis in uremia

ses[8], while low Scalcitriol decreases activation of the vitamin D receptor (VDR), resulting in increased transcription of the prepro-PTH-gene which has a vitamin D response element. The suppressive effect of VDR activation on this response element is furthermore hindered by uraemic toxins[9]. The mechanisms of uraemia-induced resistance to the effect of calcitriol and the early decrease of calcitriol levels[10] in uraemia have been the main intellectual justifications for not only correcting the low serum calcitriol levels, but even for increasing them to supraphysiological levels[9]. However, it can be seen from figure 1 and table I that supraphysiological levels of 1α-OH vitamin D result in a single PTH suppressive effect (PTH gene transcription decrease), its PTH-suppressing hypercalcaemic effect being counterbalanced by its PTH-stimulating hyperphosphataemic one. Furthermore, the latter results in down-regulation of the calcium sensor receptor[11] and in an increase in osteoblastic secretion of a phosphatonin, the fibroblast growth factor (FGF)-23[12,13]. The latter further suppresses the renal 25-OH vitamin D-1α-hydroxylase resulting in a greater decrease of endogenous synthesis of calcitriol. In contrast, primary use of alkaline calcium salt as phosphate-binder (such as $CaCO_3$ or calcium-acetate) has a greater cost-effective potential to suppress PTH since it corrects not only uraemia-induced hypocalcaemia and acidosis but also uraemia-induced hyperphosphataemia, the correction of this latter correcting the uraemia-induced down-regulation of the calcium receptor and decreasing

FGF-23[14] so that endogenous production of calcitriol is eventually increased.

Figure 1 additionally shows that parathyroid cells have a LR2/megalin receptor which allows calcidiol to be transported to a mitochondrial 1αhydroxylase[15]. This intracrine calcitriol production by the parathyroid cell may explain why the Slatopolsky group[16] could show in cultured bovine parathyroid cells that physiological concentration of calcidiol could suppress PTH synthesis as strongly as the maximal dose of calcitriol**.**

Because it has been claimed that calcitriol is necessary to normally synthesise megalin in order to transport calcidiol to the 1αhydroxylase[17-20] and that uraemic toxin interferes with the suppressive effect of VDR activation on the PTH gene vit D-response element[9], the intracrine production of calcitriol by parathyroid cell in a uraemic milieu may be insufficient. This would still justify pharmacologically-induced high serum calcitriol levels all the more in that the expression of the VDR (depressed in uraemia) would be enhanced by calcitriol but not by calcium[21].

However, this speculation is dismissed by the fact that in non uraemic mice which VDR or 25-OH vitamin D-1αhydroxylase-gene has been deleted[22,23], the resulting severe hyperparathyroidism and bone demineralisation can be simply prevented by just increasing the dietary Ca:PO_4 ratio to 2. This possibility is all the more remarkable in that the calcium--receptor expression remains likely down--regulated since it has been shown that this receptor is upregulated by vitamin D, but not by calcium[24]. As simple adjustment of the Ca/PO_4 ratio can prevent hyperparathyroidism in mice without VDR or calcitriol, why should supraphysiological levels of serum calcitriol be necessary to suppress PTH in uraemic patients or rats?

In fact in uraemic rats, a high calcium diet without 1α-OH vitamin D supplement efficiently suppresses PTH and mitigates hyperphosphatemia[25]. This is not astonishing since we have pointed out the potentially greater PTH-synthesis-suppressive effect of Ca-OPB compared with calcitriol. Furthermore high calcium, as low phosphate diet prevents parathyroid hyperplasia by the same molecular mechanisms triggered by 1α-OH vitamin D derivatives[11]: increase of cyclin-dependent kinase inhibitor p27 and decrease of transforming growth factor α. The superiority of calcium--receptor activation over that of VDR in the prevention of hyperparathyroidism has been actually evidenced in non uraemic mice thanks to gene deletion of the Ca-receptor. This results in a fatal hyperparathyroidism which can be rescued only by further genetic deletion of the prepro PTH gene[26] or of the glial cells missing 2 gene[27] in order to respectively prevent synthesis of PTH or parathyroid formation. In uraemic rats, preliminary results indicate that the calcium-receptor "positive allosteric modulator" "cinacalcet" prevents hyperparathyroidism and parathyroid hyperplasia as well as a high calcium diet without calcitriol[28] and may even promote its regression[29], a fact never reported with calcitriol.

It should be noted however that calcium can not completely replace calcitriol, since in 25-OH vitamin D-1hydroxylase-deleted mice, a high calcium diet does not prevent skeleton longitudinal growth impairment[23]. Paradoxically, calcitriol excess may have a bone mineralization deleterious effect since the defectuous mineralization of endomembranous bone observed in vitamin D-24 hydroxylase gene deleted mice associated with high circulating calcitriol levels can be improved only by the vitamin D-1α-hydroxylase gene deletion[30].

A.2 clinical data evidencing PTH suppression in CKD patient by just vitamin D insufficiency correction and Ca-OPB

In predialysis CKD patients

Massry and Llach[31] showed as early as 1985 that a simple low phosphate diet could decrease serum PTH levels even without decreasing serum phosphate concentration (but decreasing 24 hour phosphaturia) while increasing calcium intestinal absorption and calcium phosphate balance. This benefit of phosphate intake decrease on PTH was explained 2 years later by Portale *et al* who showed that it was related to serum calcitriol increase[32]. This PTH suppression by low phosphate diet explains the positive effect of this diet on the Ca-PO_4 balance previously shown in 1943 by Liu and Chu[33] who did not have the PTH dosage available. The long term efficiency (2 to 5 years) of a low phosphate diet associated with higher calcium intake and non hypercalcaemic 25-OH vitamin D repletion in suppressing PTH and correcting osteitis fibrosa or osteomalacia histological lesions was confirmed by our group[34] and the Bordeaux group[35,36]. In contrast, placebo-controlled studies in vitamin D and calcium deficient predialysis CKD patients, showed that hypercalcaemic and hyperphosphoraemic dose of alphacalcidol[37] or non hypercalcaemic dose of calcitriol[38] could not suppress baseline elevated PTH levels, being able only to prevent their further increase. An actual decrease of PTH with an increase of bone mineral density with alfacalcidol compared with placebo was reported only in a Danish study[39]. However in this study, the serum calcitriol levels did not increase in the alfacalcidol group, while the calcidiol levels [which at baseline evidenced a vitamin D deficiency (13 ng/ml)], increased more in the alfacalcidol group, challenging the responsibility of this latter in the bone density increase.

It is interesting to point out that at the last ASN meeting in 2005, a great concern was expressed regarding the high prevalence of vitamin D insufficiency (30 % with 25 OH vit D = 30-15 ng/ml) or deficiency (60 % with 25-OH vitamin D < 15 ng/ml) in CKD patients grade 3-4, in spite of the 2003 K/DOQI recommendation to correct it. This prevalence was particularly high in winter and in the African Americans because of their skin pigmentation (this latter decreasing skin formation of native vitamin D_3) and because of their prevalent lactase deficiency inducing milk intolerance[40]. Vitamin D insufficiency prevalence is also high in Japan's CKD patients[41], even though their diet is usually rich in fish. Interestingly, preliminary results of vitamin D insufficiency correction by ergocalciferol (50000 U first week + daily 1000 U) which increased S 25-OH vitamin D from 19 to 30 ng/ml, showed that intact PTH could be decreased by 10 % (200/177 pg/ml) after 3 months while SCa and SPO_4 did not significantly increase (9.3/9.4 and 4.0/4.0 mg/dl)[42], confirming the previous longer term French experiences.

In dialysis patients

The severity of vitamin insufficiency in American dialysis patients is still worse than in predialysis CKD patients, since some degree of vitamin D deficiency (S25-OH Vit D < 15 ng/ml) is present in 83 % and severe deficiency (< 5 ng/ml)[43] present in 5 %.

The first head-to-head comparison between calcitriol (0.5-1.5 µg/day) and plain vitamin D (400-1200 U/day)[44] in dialysis patients showed that calcitriol was more hypercalcaemic and PTH suppressive. One year later we showed that at isohypercalcemic dose alfacalcidol and calcidiol had a comparable PTH suppressive effect associated with a comparable improvement of histological osteitis fibrosa. However, bone mineralization was greater with calcidiol as sug-

gested by a greater increase in mineralization front, whereas the increase in the SCa x SPO_4 product was comparable[45]. In a long term cohort study we could show that alfacalcidol could correct osteitis fibrosa only in patients whose SPO_4 phosphate was controlled, pointing out the necessity of phosphate binder for PTH and osteitis fibrosa improvement[46]. In a British placebo controlled study with bone biopsies, it could be shown that calcitriol did actually improve osteitis fibrosa but at the price of inducing painful osteomalacia in relation with higher doses of aluminium-phosphate binders[47]. Because we realized in 1980 the potential toxicity of aluminium phosphate binders[48], we first showed that it could be replaced by $CaCO_3$ at higher dose. We subsequently performed a controlled randomized trial in dialysis patient whose PTH was adequately suppressed with 3.6 g elemental calcium as $CaCO_3$, by maintaining half of them on this treatment while in the other half oral calcium dose was decreased to 1.2 g and alfacalcidol was introduced in association with $Al(OH)_3$. After 6 months, serum levels of Ca, PO_4 and PTH were comparable, but that of aluminium increased in the alfacalcidol group[49]. The long term efficiency and safety of dialysis hyperparathyroidism control by high dose of $CaCO_3$ in dialysis patients was later confirmed by bone biopsies which documented in a few patients a low bone turnover pattern with normal bone volume not associated with hypercalcemia[50].

In contrast, in patients such as the Toronto patients[51] who had been exposed to $Al(OH)_3$, aluminic adynamic bone disease was associated with bone volume decrease and marked hypercalcaemia. Independently of PTH level, the prevalence of hypercalcaemia was proportional to the aluminium overload but inversely related to calcium load.

The efficiency of hyperparathyroidism control by high dose of $CaCO_3$ and correction of vitamin D deficiency (year throughout mean serum calcidiol between 20-25 ng/ml) was confirmed by our 1996 cross sectional study[52] of 64 patients dialyzed for 4-5 years with a mean age of 60 years: 2/3 of them had their annual mean monthly measured intact PTH level <220 pg/ml while prevalence of modest hypercalcaemia (>2.6 mmol/l and hyperphosphataemia (>2 mmol/l) was respectively 2 and 7 %. Furthermore their midshaft radius cortical bone had a DXA bone mineral density Z score of *-0.*5 i.e. not significantly different to gender and age matched control.

In 2003[53], with the availability of sevelamer, we performed a 5 month controlled study in which (after randomization) half of the patients, previously treated with a dialysate calcium of 1.50 mmol/l + vitamin D deficiency correction + $CaCO_3$ were switched to sevelamer + higher dialysate calcium (if SPO_4 was >1.8 mmol/l) or to alfacalcidol (if SPO_4 was <1.8 mmol/l), while calcidiol supplementation was discontinued. This conversion to sevelamer was associated with comparable control of SCa and PO_4 concentrations, comparable decrease of Scalcidiol (from 22 to 8 ng/ml) and not significantly greater increase of SPTH (from 186 to 247 pg/ml in the sevelamer group and from 145 to 180 pg/ml in the $CaCO_3$)[53]. Although not significantly greater in our study, the increase of PTH with sevelamer substitution to Ca-OPB has usually been significant on a longer term, as shown in the "treat to goal study" in which for 1 year the intact PTH levels were 100 pg/ml higher in the sevelamer group[54]. The dramatic decrease S 25-OH vitamin D in our study was explained by the winter season (November – May). This highlights the critical importance of systematic correction of vitamin D deficiency also in dialysis patients, especially in winter, in spite of the fact that such supplementation had not been recommended by 2003 K/DOQI. However even in September and

in Algeria, dialysis patients have a high prevalence of vitamin D deficiency[55] which explains why we could show a strong inverse correlation between SPTH and Scalcidiol levels, independent of serum concentrations of Ca, PO_4, bicarbonate and calcitriol. This observation has been recently confirmed in a Hungary[56] dialysis centre, this latter furthermore showing an inverse correlation between Scalcidiol and bone mineral density.

Regarding the relative PTH suppression efficiency of high dose of $CaCO_3$ versus oral or intravenous calcitriol, their comparatibility was evidenced by the Durham group[57]. In a 6 month randomized trial performed on patients dialyzed with a 1.25 mmol/l dialysate calcium and receiving at baseline 2 g/day of elemental calcium, this group found that oral calcium increase to 6 g/day suppressed PTH as well as oral or intravenous calcitriol associated with $Al(OH)_3$. Interestingly the increase of serum Ca and PO_4 into the recommended range was less high with $CaCO_3$ than with oral or intravenous calcitriol, in spite of the adjunction of Al OH_3.

Such comparison of the PTH suppressive effect with high dose of Ca-OPB does not exist for newer less hypercalcaemic and less hyperphosphaturic 1α-OH vitamin D derivatives such as paricalcitol, maxicalcitol or hectrol. The PTH suppressive effect of these new derivatives has been mainly assessed against placebo in patients with probable vitamin D insufficiency (25-OH vitamin D was not documented in these trials but recently documented at <15 ng/ml in 83% of an American dialysis centre). Furthermore, their hyperparathyroidism was mild (since their baseline PTH, while on a low PTH stimulating dialysate calcium, was inferior to 700 pg and associated with low SCa and mild hyperphosphataemia). Comparative studies of these derivatives with calcitriol are rare and have shown no difference either for maxicalcitol[58] or a modest advantage for paricalcitol; this derivative decreased PTH below the recommended upper limit, slightly more rapidly (within 87 instead of 108 days) and decreased the duration of hypercalcaemic or hyperphosphataemic periods from 3 to 0.25 hundred patient years[59].

B. SUPERIORITY OF 1α-OH VITAMIN D DERIVATIVES + NON CA-OPB OVER VITAMIN D INSUFFICIENCY CORRECTION + CA-OPB FOR DECREASING VASCULAR CALCIFICATION AND CARDIOVASCULAR RISK?

B.1 Experimental evidences of vascular calcification and mortality risk increase with 1α-OH vitamin D derivatives but not with high oral calcium load without concomitant use of 1α-OH vitamin D

In FGF-23 as well as *klotho* gene null mice, the premature-aging phenotype is associated with vascular calcification and premature death as well as with high serum calcitriol levels. Decreasing these calcitriol levels in *klotho* mutants by dietary means or ablating vitamin D 1α-hydroxylase in FGF-$23^{-/-}$ mice resulted in marked improvement of this phenotype and longer survival[60]. This longer survival is all the more remarkable since single deletion of the vitamin D-1α-hydroxylated gene leads to stimulation of the renin angiotensin system and to hypertension[61].

In uraemic rats (5/6 nephrectomy), compared with vehicle treated animals, even non hypercalcaemic dose of calcitriol decreases survival, in association with more rapid progression of renal failure, more severe hypertension and extensive aortic calcifications[62]. This vascular procalcifying effect of calcitriol at non hypercal-

caemic dose has been confirmed by other teams in uraemic rats after adenine intoxication whereas vehicle or a new calcimimetic (AMG 601) was without this effect[63]. Although in the 5/6 nephrectomized rats, paricalcitol (3 µg/kg – 3 times/wk for 8 weeks) has been shown to increase less aortic calcification than calcitriol (1 µg/kg/wk x 8 weeks)[64], an *in vitro* study[65] has shown that in human coronary smooth muscle cell culture exposed to high concentration of phosphate, not only calcitriol but also paricalcitol increased, dose dependently, their calcification when compared with vehicle or to the calcimimetic R-568.

In contrast, a high calcium diet in uraemic rats increases survival in association with less enhanced resistance artery relaxation, severe hypertension, less proteinuria, slower progression of renal failure and no vascular calcification, while the angiotensin II-AT1 receptor is under expressed in the kidney[25,66]. The same vascular protective effect of higher calcium diet has been also observed in uraemic $ApoE^{-/-}$ mice prone to premature atherosclerosis: this diet decreased aortic calcification in association with decreased serum phosphorus[67]. This beneficial effect of high calcium diet has been even reported by the Slatopolsky group in uraemic rats although they had a high phosphate diet[68].

B.2 Clinical evidences for acceleration of renal failure progression and increased vascular calcification risk with 1α-OH vitamin D derivatives but not with high oral dose of Ca-OPB plus vitamin D deficiency correction

1α-OH vitamin D derivatives increase active absorption of calcium and phosphate, predisposing to hyperphosphataemia and hypercalcaemia, predominant phosphocalcic risk factors for visceral and vascular calcification and clinical complications[69].

Furthermore, by increasing active calcium-absorption in the duodenojejunum, calcitriol decreases the quantity of calcium available for complexing oxalate, hence an increased oxalate absorption by the colon. This explains why oral and intravenous calcitriol increase serum calcium oxalate saturation product and therefore vascular calcification risk.

These deleterious effects of 1α-OH vitamin D derivatives may explain that in predialysis CKD patients, early placebo-controlled trials with calcitriol or alfacalcidol have reported acceleration of renal failure progression[70]. In contrast with our treatment based on vitamin D insufficiency correction by 25-OH vitamin D_3 and 1.2 to 2.4 elemental calcium such as Ca-CO_3, we found a decrease of the slope of 1/Screatinine, suggesting a less rapid progression of renal failure[34].

In dialysis patients, these deleterious serum changes favour calcification of vessels and various organs such as the heart and the lungs. This has been first evidenced by an autopsy study from Los Angeles paediatric hospitals[71]. It showed that 60% of demised uraemic children had visceral and vascular calcification and that the degree of calcinosis was greater with male gender, age, duration of dialysis and SCa x SPO_4 product elevation. Independently of these parameters, the calcinosis was however more severe with calcitriol than with plain vitamin D_2 or D_3 or dihydrotachysterol. In spite of these results, 1α-OH vitamin D was not discontinued in favour of plain or 25-OH vitamin D while CaOPB replaced $Al(OH)_3$, and dialysate calcium was decreased to 1.25 mmol/l. Ten years later the L.A. paediatric team performed an electron beam evaluation of the coronary and aortic calcification in ESRD children and young adult put on dialysis 5-10 years earlier and showed that coronary calcification was absent in the 23 patients whose age was below 20 but present in 14 out

of 16 aged 20-30 years. Presence of calcification was associated with a 10 year older age and 10 years longer duration on dialysis as well as with a higher SCa x SPO_4 product and higher oral calcium load, but this association were not adjusted to 1α-OH vitamin D dose or serum calcitriol levels. This adjustment has been, however, performed in a British study[72] which showed that independently of age and serum Ca and PO_4 product, *calcitriol levels were directly related with vascular calcification extension*.

The risk of hypercalcaemia and vascular calcification is logically enhanced when Ca-OPB rather than non Ca-OPB are given in association with 1α-OH vitamin D, even though the short term CARE study[73] showed a more rapid and greater decrease of serum phosphorus and SCa x SPO_4 product with calcium acetate than with sevelamer. This was shown in the "Treat to Goal Study"[54] in which sevelamer was compared with Ca-OPB. However, other factors than lower incidence of hypercalcaemia linked to lower calcium load could account for the vascular calcification greater protective effect of sevelamer since serum levels of bicarbonate, LDL cholesterol and C-reactive protein (CRP) were lower, while PTH (and therefore bone turnover) were 100 pg/ml higher with sevelamer. Concomitant use of 1α-OH vitamin D with Ca-OPB in patients previously overloaded with aluminium further increases the risk of vascular calcifications because of the long term aluminium-induced adynamic bone disease which prevents calcium and phosphate deposition in the bone. This goes towards explaining the independent association of vascular calcification with the dose of Ca-OPB observed in the works of the Gerard London group[74]. Interestingly, although this group showed independent association between vascular calcification with mortality and oral calcium load, they were unable to show a direct association between mortality and oral calcium dose.

On the contrary, a difference in the hypercalcaemic and hyperphosphataemic effect between calcitriol and paricalcitol may be responsible for a difference in dialysis patient survival. This has been suggested by the first Cohort study of Teng[75] who showed a lower 3 year mortality with Zemplar® than with Calcijex® (18 *versus* 22 %), while the first year increase was respectively 6.5 *versus* 8 % for SCa and 12 *versus* 14 % for SPO_4.

Regarding the vascular safety of oral Ca-OPB at doses greater than the 1.5 g/day elemental calcium upper limit recommended by the KDOQI, the Amiens experience is, however, reassuring. In this centre, in which aluminium intoxication by the dialysate was prevented since 1978 and by phosphate binder since 1980, we have been repeatedly [52,76,77] unable to show any independent link between the $CaCO_3$ dose and the extension of the vascular calcification, even though the mean daily dose of elemental calcium given as phosphate binder was around 3.2 g while the serum 25-OH was between 20-25 ng/ml and the prevalence use of 1α-OH vitamin D of 17 %. Interestingly in our patients, in contrast to the Framingham general population[78], to a postmenopausal population[79] and to the dialysis patients of Erlangen[80], we could not find an inverse correlation between aortic calcification extension and bone mineral density, suggesting that our treatment could prevent calcium mobilization from bone to the aorta. This contrasts with the observation in a general population that aortic calcification has been inversely correlated with serum calcitriol, the possible explanation being that low serum calcitriol reflects low calcidiol levels and that both stimulate PTH and therefore bone loss with vascular calcification.

Thus the danger of vascular calcification increase with Ca-OPB has been evidenced only in the "Treat to Goal study" in which Ca-OPB were associated with 1α-OH vitamin D derivatives which dose was not appropriately decreased in order to prevent higher incidence of hypercalcaemia.

B.3 The survival and renal benefit associated with calcitriol or paricalcitol has been shown only in dialysis patients with probable vitamin D-insufficiency

In the Japanese dialysis cohort study[6] (treated with oral alfacalcidol therapy) and in the second cohort study of Teng et al[7] (treated with Calcijex® or Zemplar®), a survival advantage was observed in the treated cohorts compared with the not treated ones. Calcidiol levels were not measured in these patients, but were probably low, both in Japan[41] and in the USA (as shown by La Clair[81]) as well by the more recent studies presented at the 2005 ASN meeting[40,43]. Therefore it is likely that the higher rate of mortality among patients who did not receive 1α-OH vitamin D derivatives was simply a reflection of their poor vitamin D status. Indeed "Sunshine vitamin" repletion is associated not only with a lower risk of bone disease, but also with a lower risk of developing diabetes, cardiovascular disease, cancer, immunological and infectious diseases[82]. The beneficial effects of vitamin D might be mediated directly - even in uraemic patients - by calcidiol, which serum concentration is 10^3 higher than that of calcitriol or by *in situ* transformation of calcidiol into calcitriol at the level of immunocompetent cells or vascular smooth muscle cells, which have 25-OH-vitamin D-1α hydroxylase[83]. The mechanism by which vitamin D prevents these diseases independently of mineral metabolism regulation has been recently reviewed by Andress[17] and Levin[84]. Inflammation is now regarded as a key pathogenic mechanism in atherosclerosis and vitamin D has long been known to possess immunoregulatory activities and to downregulate nuclear factor KB (NF-KB) which triggers inflammation via multiple cytokines and over expression of metalloproteinase by the macrophages involved in plaque destabilization. This was clinically proven by Timms *et al*[85] who pointed out in an Indo-Asian population apparently healthy but prone to vitamin D deficiency that plasma metalloproteinase MMP9 and CRP were inversely correlated with serum 25-OH vitamin D. One year after this population received 3 quarterly injections of cholecalciferol (Vitamin D_3), MMP9 and CRP decreased. Vitamin D may also play an indirect role in the pathogenesis of heart failure by promoting left ventricular hypertrophy (LVH). Low levels of serum calcidiol have been associated with high levels of N-terminal proatrial natriuretic peptide, a predictor of congestive heart failure and LVH severity, as well as of poor left ventricular function[86,87]. In this vitamin-D-deficient dialysis patient, intravenous calcitriol for 15 weeks could decrease LVH and improve LV function. In 148 post menopausal women[88] (>70 years of age) with vitamin D deficiency (calcidiol <20 ng/ml) but no renal failure nor cardiovascular complication) 8 weeks supplementation with 1200 mg of calcium alone in association with 800 IU vitamin D_3 compared with calcium supplementation alone resulted in a higher S calcidiol (26 *vs.* 17 ng/ml), in a 17% lower PTH level and a 9% lower SBP, so that 81% against 47% of patients decreased their SBP by 5 mmHg or more. The correlation between SBP decrease and PTH decrease was stronger in the group treated with vitamin D + calcium than in the group treated with calcium alone (r=0.49 *vs.* 0.23).

Thus, the second study by Teng and colleagues supports the hypothesis that the beneficial 'non-mineral' effects of 1α-OH vitamin D derivatives override their deleterious hypercalcaemic and hyperphosphataemic effects (which mainly occurred when administered together with a calcium-based OPB). However this observational study does not evidence that 1α-OH vitamin D derivatives confer a survival benefit compared to vitamin D insufficiency correction, since this latter was not granted.

In predialysis CKD patients an antiproteinuric effect of oral paricalcitol has been more recently reported[89]. However these patients were also very likely vitamin D insufficient since this study was performed in the USA where the prevalence of vitamin D insufficiency was 83% in 2005[81], 2 years after the KDOQI recommendations had asked to correct it.

C. HOW TO IMPROVE THE EFFICIENCY AND SAFETY OF URAEMIC HYPERPARATHYROIDISM TREATMENT THANKS TO EVIDENCE-BASED GUIDELINES?

In order to prove that paricalcitol grants cost effective survival or renal benefit, as well as optimal PTH suppression in terms of parathyroidectomy and fracture risk, this drug associated with non-Ca-OPB has to be compared to Ca-OPB associated with correction of vitamin D insufficiency (25-OH vitamin D >30 ng/ml) in randomized studies performed both in predialysis and dialysis patients.

In order to refine the odds of such trials, we have itemised the changes of independent factors influencing both PTH suppression and vascular calcification prevention with various therapeutic strategies in two tables.

Table I illustrates how the combination of *vitamin D-insufficiency correction + Ca-OPB is likely superior for suppressing PTH* over the combination of 1α-OH vitamin D + non Ca-OPB. For these latter we have illustrated the case not only with sevelamer HCL but also with sevelamer-carbonate and lanthanum-carbonate which are now on the market and with nicotinamide which has been recently shown to decrease serum phosphate in Japanese dialysis patients as efficiently as the formerly used Ca-OPB[90].

It should be noted that the net number of factors suppressing PTH is the difference between the number of PTH suppressing factors minus the number of PTH increasing ones. Table I shows that this net number of PTH suppressing factors is 4 for correction of vitamin D insufficiency + Ca-OPB and only 1, 2 or 3 with 1α-OH vitamin D + non Ca-OPB. When the use of the calcimimetic cinacalcet is considered for further suppressing PTH, its combination with higher dose of Ca-OPB for preventing cinacalcet-induced hypocalcaemia is much more PTH-suppressive than its combination with higher dose of 1α-OH vitamin D. Indeed in predialysis patients, use of higher dose of Ca-OPB also prevents the worsening of hyperphosphataemia secondary to cinacalcet-induced PTH suppression in predialysis patients, whereas 1α-OH vitamin D derivatives worsen hyperphosphataemia. The resulting net number of PTH suppressing factors in *predialysis patients* after addition of cinacalcet is then *5 when Ca-OPB is combined* and *only one when 1α-OH vitamin D dose* in increased. In *dialysis patients* without diuresis, cinacalcet-induced PTH suppression does not induce SPO_4 increase by stimulation tubular PO_4 reabsorption but decreases SPO_4 by inhibiting bone PO_4 release. The resulting net number of PTH suppressing factors in dialysis patients after cinacalcet addition is *8 when Ca-OPB dose is increased* and only *3 when 1α-OH vitamin D dose is increased*. The clinical relevance of this rough estimation of PTH modulating factors in dialysis patients is given by our comparison of the results of two early trials with cinacalcet: in the first trial[91] the dose used was 50 mg and it decreased intact PTH from 640 to 460 pg/ml while the SPO_4 decreased by 7.5 %; in the second trial[92] the dose used was 100 mg, but it did not decrease more PTH than in the first study in which baseline PTH was comparable. Furthermore SPO_4 did not significantly decrease (2.6%). The only explanation for this discrepancy that we could find was the following:

TABLE I
PTH suppression in CKD patients

Vitamin D insufficiency correction + calcium based oral phosphate binder (Ca-OPB)
is potentially superior to
1α-OH vitamin D administration + non calcium based oral phosphate binder (non Ca-OPB)

This superiority is further increased when cinacalcet is added
while doses of Ca-OPB *or* 1α-OH vitamin D are increased to prevent cinacalcet-induced hypocalcemia

	Therapeutic measures	PTH suppressing factors					PTH increasing factors			Net number of PTH-suppressive factors
		VDR activation	Ca R Sensitization	SCa increase	SPO_4 decrease	Sbicarbonate increase	SCa decrease	SPO_4 increase	Bicarbonate decrease	
	Vitamin D insufficiency correction + Ca-OPB	+		+	+	+				1 + 3 = 4
Non Ca-OPB	***1α - OH vitamin D***	+		+				+		1
	Lanthanum CO_3				+	+				+ 2 = 3
	Sevelamer-HCl				+				+	+ 0 = 1
	Sevelamer-CO_3 (c)				+	+				+ 2 = 3
	Nicotinamide				+					+ 1 = 2
	1αOH vit D + sevelamer-HCl	+		+	+			+	+	1
	+ Cinacalcet (a) and higher ***1α-OH vit D***		⊕	+			⊕	⊕+		0 = 1
	Predialysis									
	Dialysis	+	⊕	+	⊕		⊕	+		+ 2 = 3
	Vit D insufficiency correction + Ca-OPB	+		+	+	+				4
	+ Cinacalcet (a) and higher ***Ca-OPB***									
	Predialysis		⊕	+	+		⊕	⊕		+ 1 = 5
	Dialysis		⊕	+	⊕+	+	⊕			+ 4 = 8

(a) When Cinacalcet is added its effect on PTH suppressing or increasing factors is noted by a ⊕ while the effect of higher doses of 1α-OH vit D or CaOPB are noted by a simple +

whereas in the first study no change in 1α-OH vitamin D therapy occurred, in the second study, calcitriol or paracalcitriol was more frequently initiated [93] (table II).

Our estimation is limited by the fact that the intrinsic potency of each considered factor has not been taken into account. It is likely that changes in serum bicarbonate are less potent than changes in serum concentrations of phosphate and calcium or than the changes in activation of the parathyroid VDR or of the calcium receptor. Regarding activation of these latter receptors, experimental evidences suggest that activation of Ca-receptor has a greater suppressive effect than that of the VDR for prevention of parathyroid hyperplasia[63]. Changes in SPO_4 is also likely to be very powerful since it acts not only directly on the parathyroid cells for PTH synthesis and secretion modulation but also on the FGF-23 and therefore on the 1α-hydroxylase of 25-OH vitamin D, as well as on the expression of the calcium receptor.

Table III illustrates the changes of the net number of factors increasing and decreasing vascular calcification risk. Since low calcitriol in relation with low calcidiol levels in the general population is associated with increased coronary calcification, normalization of calcidiol has been granted with a vascular calcification protective effect. When Ca-OPB is associated to the vitamin D insufficiency correction, the net number of calcification-preventing factor remains 1 because the protecting effect of lower SPO_4 and Soxalate is counterbalanced by the opposite effect of SPO_4 and Sbicarbonate increase.

In contrast when 1α-OH vitamin D is given for inducing high calcitriol levels, four vascular calcification promoting factors are present. When 1α-OH vitamin D plus non-Ca-OPB are combined, the number of factors promoting vascular calcification varies from 1 to 4 according to the phosphate-binder; the best combination is with sevelamer-HCl (only 1 factor favouring calcification) because of its bicarbonate and LDL cholesterol decreasing effect[54] and with nicotinamide because of its HDL-cholesterol increasing effect[90]. Lanthanum carbonate does not improve the deleterious effect of 1α-OH vitamin D on vascular calcification (4 factors) because its hypophosphataemic effect is counterbalanced by its alkalinization effect[94]. The same effect is anticipated with sevelamer-carbonate which may replace sevelamer HCl on the market.

TABLE II

For correcting cinacalcet-induced hypocalcemia. Combination of cinacalcet with higher dose of Ca OPB compared with introduction of 1α-OH Vit D is more SPTH and SPO4 suppressive at equal cinacalcet dose

(Mansour J KI 2003;64:2624)

	Lindberg J (KI 2003)		Quarles LD JASN 2003	
Cinacalcet dose mg/d	50	placebo	100	placebo
Intact PTH pg/ml	637/460	632/701	626/451	583/552
SPO4 Change %	- 7.5	+ 11	- 2.6	+ 11
New patients put on 1αVit D	0	0	14/31	7/31

Addition of cinacalcet in order to improve PTH suppression when intact PTH remains above the recommended upper limit[4], whereas 1α-OH vitamin D derivatives are introduced or their doses increased (as advised in the earlier cinacalcet trials) for correcting the cinacalcet-induced-hypocalcaemia will potentially further worsen the vascular calcification risk. This is due to the fact that 1α-OH vitamin D induces four additional calcification promoting factors (increase in serum concentrations of calcitriol, calcium, phosphate and oxalate) whereas cinacalcet decreases SPO_4 only in dialysis patients, but increases SPO_4 in predialysis patients[95]. This explains why the net number of factors promoting calcifications is five in predialysis patients and only three in dialysis patients.

TABLE III

Prevention of vascular calcification risk in CKD patients

Vitamin D insufficiency correction + calcium based oral phosphate binder (Ca-OPB)

is potentially superior to

1α-OH vitamin D administration + non calcium oral based phosphate binder (non Ca-OPB)

This superiority is further increased when cinacalcet is added

while greater doses of Ca-OPB *or* 1α-OH vitamin D are used to prevent cinacalcet-induced hypocalcemia.

Therapeutic measures		Vascular calcification suppressing factors					Vascular calcification increasing factors					Net number of Vasc calcif suppressing factors
		Normal Scalcidiol (a)	SCalcium decrease	SPO4 decrease	Sbicar bonate Decrease	S oxalate decrease	Dyslipi demia correction (b)	High SCalcitriol	SCa increase	SPO4 Increase	Sbicar bonate Increase	Soxalate increase	
Vit D insufficiency correction + Ca-OPB		+		+		+			+	+	+		+ 0 = 1
1α - OH vitamin D	**Lanthanum CO3**			+				+	+	+		+	+ 0 = - 4
+ Non Ca-OPB	**Sevelamer-HCl (c)**			+	+		+				+		+ 3 = - 1
	Sevelamer-CO3 (c)			+									+ 0 = - 4
	Nicotinamide (c)			+			+						+ 2 = - 2
1α - OH vit D + sevelamer-HCl				+	+		+	+	+	+		+	- 1
+ cinacalcet (b) and higher	***Predialysis***		⊕					+	+	⊕+		+	- 4 = - 5
1α - OH vit D	***Dialysis***		⊕	⊕				+	+	+		+	- 2 = - 3
Vit D insufficiency correction + Ca-OPB		+		+		+			+		+		+ 1 = 2
+ cinacalcet (b) and higher	***Predialysis***		⊕	+		+			+	⊕	+		0 = 1
Ca-OPB	***Dialysis***		⊕	+		+			+		+		+ 1 = 2

(a) Since low calcitriol in relation with low Calcidiol serum level is associated with increased coronary calcification normalisation of Scalcidiol has been granted a vascular calcification protective effect.

(b) When Cinacalcet is added its effects on vascular calcification modulating factors are noted by a ⊕ while the effects of higher dose of Ca-OPB or 1α vitamin D are noted by a simple +.

In contrast, use of cinacalcet + higher dose of Ca-OPB *(*when PTH suppression is not sufficient with the basic suppressive treatment by vitamin D insufficiency correction + Ca-OPB), does not increase the calcification risk in predialysis patients because the higher oral calcium load for keeping SCa constant, prevents the hyperphosphataemic effect secondary to cinacalcet-induced PTH suppression, whereas the increase of Sbicarbonate is compensated by the Soxalate decrease. In dialysis patients this latter approach adds one net protecting factor (decrease in SPO4 and Soxalate being counterbalanced just by increase in Sbicarbonate).

CONCLUSION

1α-OH vitamin D derivatives in general and Paracalcitol in particular are not actually necessary for correction of uraemic hyperparathyroidism and may induce deleterious skeletal and cardiovascular complications.

Therefore, Vitamin D insufficiency prevention plus Ca-OPB should remain the two primary components for correction of uraemia-induced hyperparathyroidism, in predialysis as well as in dialysis patients, because they constitute the most cost-effective and likely safest measures. When this basic treatment is unable to keep serum concentrations of PTH, Ca and PO_4 in their recommended ranges then other approaches should be considered, such as combination of paricalcitol + non Ca-OPB or use of calcimimetic with higher dose of Ca-OPB, the latter approach having an expected greater potency both for suppressing PTH and preventing vascular calcification.

However, only a long term trial evaluating these two add-on treatments on hard clinical outcomes (fractures and parathyroidectomy, vascular calcification and complications) will be able to establish their actual cost effectiveness and safety.

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