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# Balanced calcitriol treatment to make children grow

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**Short stature is an important clinical problem in children with chronic kidney disease. Calcitriol is used as standard therapy to control secondary hyperparathyroidism, but its effect on linear growth remains controversial. Sanchez and He report multiple effects of calcitriol on chondrocyte proliferation and maturation that might help to clarify this controversy.**

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Growth impairment is a major problem in children suffering from chronic kidney disease (CKD). The North American Pediatric Renal Trials and Collaborative Studies reports that at the time of entry to the registry, 37% of children with CKD have severe linear growth delay, defined as body length below the third percentile for age.[1] Linear growth of long bones is achieved by endochondral bone formation. A cartilaginous precursor template is produced by chondrocytes, which go through a coordinated program of proliferation, maturation, and hypertrophic differentiation, in the growth plate. As chondrocytes become hypertrophic, they undergo apoptosis and hereby initiate cartilage matrix mineralization. After vascular invasion, by which osteoblasts and osteoclasts are supplied to the growth plate, the cartilage matrix is replaced by bone.

In addition to protein malnutrition, metabolic acidosis, and anemia, both growth hormone resistance and renal osteodystrophy are important, recognized factors contributing to growth retardation in these young patients. Accordingly, in order to improve bone growth, patients are treated with recombinant human growth hormone and/or 1,25-dihydroxyvitamin $D_3$ (calcitriol, $1,25(OH)_2D_3$), which is administered in the first place to prevent secondary hyperparathyroidism and the accompanying high bone turnover. Several studies showed that recombinant human growth hormone exerts a positive effect on chondrocyte proliferation *in vitro* and on longitudinal bone growth in uremic rats and children with CKD. On the other hand, the effect of calcitriol on bone growth seems to be far more complex. The results of experimental as well as clinical studies, investigating the effect of calcitriol therapy and the way it is administered (daily versus intermittently) on long bone growth in uremia, are not unequivocal. Daily, but not intermittent, calcitriol therapy has been shown to increase bone growth in uremic rats[2] and children[3] with CKD, whereas other studies revealed that both treatment strategies are equally effective in growth improvement.[4] Contrary to these observations, the development of low bone turnover and the subsequent failure in growth enhancement has also been reported in calcitriol-treated CKD patients.[5]

Sanchez and He[6] (this issue) investigated this controversy by comparing the effect of daily and intermittent calcitriol therapy on the expression of chondrocyte proliferation and differentiation markers in the growth plates of 5/6 nephrectomized rats (Figure 1). Because longitudinal bone growth results mainly from endochondral bone formation, it is interesting to study the molecular alterations in the proliferative and hypertrophic zone of the epiphyseal growth plate under calcitriol treatment in addition to changes in body and tibial length as outcome parameters. Daily as well as intermittent calcitriol administration resulted in an increased expression of proliferation and differentiation markers in growth plate chondrocytes, but also in an increased expression of proliferation inhibitors, probably explaining why neither calcitriol dosing regimen improved the impaired body and tibial growth in uremic rats, as discussed by the authors.[6]

Both parathyroid hormone (PTH) and $1,25(OH)_2D_3$, two factors regulating each other's production in the parathyroid gland and the kidney, respectively, can play a regulatory role in bone growth. In the setting of CKD, the regulation of these hormones is seriously disturbed. Severe secondary hyperparathyroidism in CKD, characterized by a high bone turnover and often accompanied by an impaired mineralization and the presence of bone marrow fibrosis, can ultimately affect bone growth. In addition, the $1,25(OH)_2D_3$ deficiency due to the impaired renal function can also contribute to the reduced growth in pediatric CKD patients.

However, despite the harmful effects of excessive serum PTH concentrations on bone turnover, this hormone, when present in its normal concentration range, tightly regulates bone metabolism, including bone growth. The stimulating effect of PTH on endochondral bone formation is demonstrated by an increased long bone length, increased epiphyseal volume, and upregulated chondrocyte proliferation and differentiation, as well as an increased matrix mineralization, in 25-hydroxyvitamin D-1α-hydroxylase and PTH double-knockout mice treated with PTH for 10 days.[7] *In vitro* experiments showed that incubation of rabbit chondrocytes with PTH inhibited the terminal differentiation toward hypertrophic chondrocytes.[8] The finding that the PTH/PTHrP receptor is mainly expressed in the lower proliferative and the matrix-forming zone (upper hypertrophic zone) is consistent with the proliferative effect of PTH on growth plate chondrocytes. However, Xue *et al.*[9] recently found that PTH deficiency resulted in only a slight decrease in longitudinal bone length, but a significant reduction in trabecular bone volume. In contrast, 25-hydroxyvitamin

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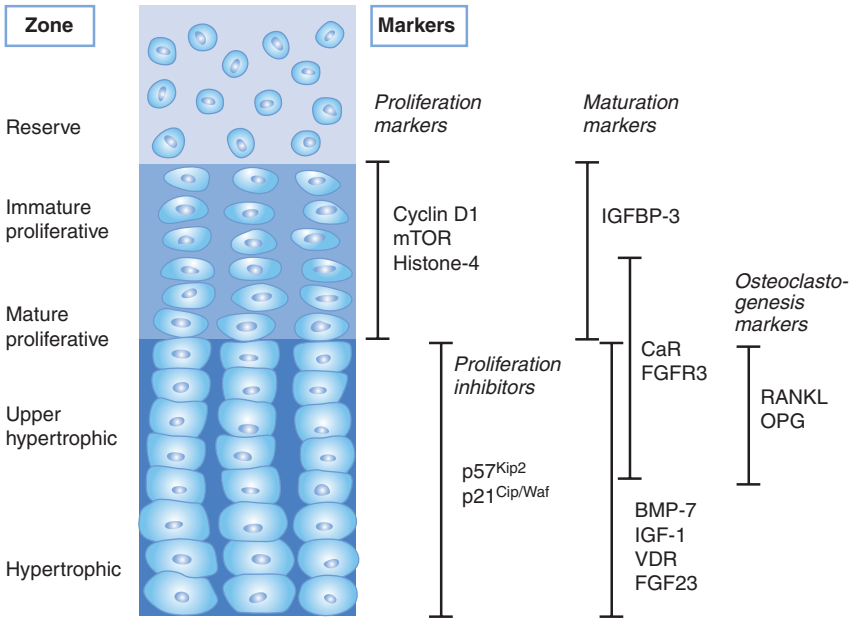


**Figure 1 | Expression of proliferation, differentiation, and osteoclastogenesis markers and proliferation inhibitors in the different zones of the growth plate in uremic rats, reported by Sanchez *et al.*[6]** Both daily and intermittent calcitriol enhanced chondrocyte proliferation and maturation. In addition, the expression of the proliferation inhibitors $p57^{Kip}$ and $p21^{Cip/Waf}$ was also upregulated under calcitriol treatment. The upregulation of both - proliferation markers and proliferation inhibitors may explain why calcitriol administration did not increase bone growth in uremic rats. mTOR, mammalian target of rapamycin; IGFBP-3, insulin-like growth factor-binding protein-3; CaR, calcium receptor; FGFR3, fibroblast growth factor receptor 3; BMP-7, bone morphogenetic protein-7; IGF-1, insulin-like growth factor-1; VDR, vitamin D receptor; FGF-23, fibroblast growth factor-23; RANKL, receptor activator of NF-KB ligand; OPG, osteoprotegerin.

D-1α-hydroxylase knockout mice exhibit a smaller reduction in trabecular bone volume, but a significant decrease in bone length. These findings suggest that $1,25(OH)_2D_3$ plays a more decisive role in endochondral bone formation, and thus bone growth, compared with PTH. Furthermore, it has been demonstrated that $1,25(OH)_2D_3$ regulates chondrocyte proliferation and differentiation *in vitro*.

As shown by experimental and clinical studies, calcitriol can exert both positive and negative effects on longitudinal bone growth in uremic subjects. This controversy may be due to different administered doses of calcitriol used in experiments and the remaining endogenous $1,25(OH)_2D_3$ production, which in turn depends on the degree of renal failure. The significance of the calcitriol dose for its effect is demonstrated in cell culture experiments: a high calcitriol concentration in the medium inhibits cell proliferation, whereas a low concentration has a stimulatory effect.[10] In this view, the observation of an increased expression of proliferation markers, along with an upregulation of proliferation inhibitors in growth plate chondrocytes of uremic rats treated with daily or intermittent calcitriol, supports the idea that the balance between proliferative and antiproliferative effects can modify the net effect on endochondral bone growth and that this balance can turn over in either direction depending on substantial differences in calcitriol concentration.

Impaired growth leading to small adult stature has been demonstrated to affect psychosocial well-being and quality of life, as well as to entail increased mortality risk in children with CKD.[11] The disturbances in the growth hormone–insulin-like growth factor-1 axis that is one of the etiological factors in growth retardation accompanying CKD can be treated with recombinant human growth hormone, which has been shown to effectively improve growth and adult height in these patients. However, in case of uncontrolled hyperparathyroidism and renal osteodystrophy, growth hormone therapy is contraindicated. Moreover, increased PTH levels and calcitriol deficiency also negatively affect bone growth, in a way that is still incompletely understood. The results presented by Sanchez and He[6] illustrate the complex regulation of endochondral bone formation process by calcitriol and put in perspective the difficult exercise clinicians are confronted with in young CKD patients, when trying to find the optimal balance between adequate treatment of secondary hyperparathyroidism on the one hand and the risk of PTH oversuppression leading to adynamic bone disease on the other hand. Therefore, the evaluation and validation of new markers in addition to PTH to assess and follow up bone status in these patients, together with studies investigating whether calcitriol analogues or calcimimetics can facilitate achievement of this delicate balance necessary to maintain bone growth, are of particular interest.

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