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## 14. RECENT APPROACHES TO THERAPY: IS THERE REAL PROGRESS?

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### 14.1 Introduction

“Real progress” must be considered a subjective term with regard to therapeutic advances in any field of medicine. Novel approaches may be of significance because of introducing new treatment targets, representing completely new mechanistic strategies or reaching major success rates when compared to standard approaches, respectively. Labelling strategies as “real progress” must however be done with caution in any case, because favorably influencing outcomes on short or intermediate term may still not change or even unfavorably alter long-term perspectives. Nevertheless, this brief article intends to address a couple of recent developments in the field of nephrology which either unexpectedly discovered a new avenue in an established therapeutic field, i.e. the use of active vitamin D analogues, or opens new perspectives in a disastrous disease, calciphylaxis (= calcific uremic arteriopathy [CUA]), which previously presented with mortality rates of 50 to 80%.

### 14.2 Vitamin D and survival

In each year's last issue of the TIME magazine, the ranking of the 10 most important breakthroughs of the current year is published in fields of culture, politics, music, economy, medicine etc. Surprisingly, in the year 2007 the realization of the importance of vitamin D, an old player in physiology and pathophysiology of the human body, was ranked among the 10 medical breakthroughs of the year. This was due to increasing awareness of the fact that vitamin D does not just play a role in calcium homeostasis and bone turnover, but acts as a pleiotropic steroid hormone controlling cell growth (anticancer effects), the immune system (antiautoimmune and antiinfectious properties) and cardiovascular functions (myocardial integrity). The vitamin D receptor (VDR) is virtually expressed in most tissues indicating a widespread biological importance of vitamin D signalling throughout the body (Table 14.1.)

System	Tissue
Endocrine	Parathyroid, pancreatic B cells, thyroid C cells
Cardiovascular	Arterial smooth muscle cells, cardiac myocytes
Musculoskeletal	Osteoblasts, chondrocytes, striated muscle
Gastrointestinal	Esophagus, stomach, intestine
Hepatic	Liver parenchymal cells
Renal	Tubules, JG apparatus (renin), podocytes
Reproductive	Testis, ovary, uterus
Immune	T cells, B cells, bone marrow, thymus
Respiratory	Lung alveolar cells
Epidermis	Keratinocytes, hair follicles
Central nervous system	Brain neurons

**Table 14.1.** Vitamin D receptor distribution (from: Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int* 2006;69:33-43).

Recent studies indicated that vitamin D deficiency was associated with impaired survival in all patient cohorts under investigation, i.e. in normal populations, in patients with chronic kidney disease (CKD) but not on dialysis as well as in CKD patients on dialysis. Moreover, treatment with active vitamin D analogues was consistently correlated with improved survival in CKD patients, while one recent study showed a beneficial relationship between vitamin D supplementation and survival in normal individuals. The caveat of these treatment reports, despite their consistency, was that they were all observational and thus not prospective interventional studies. This means that some degree of decision bias may have influenced final observations, and that these studies therefore do not prove any cause-and-effect relationships.

#### 14.2.1 Biology of cardiovascular vitamin D actions

One factor in order to judge such associations is biological plausibility, and these biological insights are mostly gained by interventional experimental research. One of the keys towards the understanding of vitamin D-related actions was the creation of VDR knockout (VDR<sup>-/-</sup>) mice. These animals showed a significant up-regulation of both renin gene expression and activation of angiotensin II. As a central pathophysiological readout, these VDR<sup>-/-</sup> mice developed severe left ventricular hypertrophy (LVH) associated with myocardial upregulation of renin gene expression (1). This observation deserves particular attention given the clinical fact that most dialysis patients develop into being calcitriol “knockouts” and show a high incidence of suffering from LVH. Bodyak *et al.* extended the experimental results by demonstrating that salt-induced myocardial hypertrophy could be completely prevented by treatment with the novel vitamin D receptor activator paricalcitol, independent on its influence on hypertension (2). These findings initiated the design of two clinical studies (PRIMO I in CKD stages 3b-4, and PRIMO II in CKD 5D) investigating the influence of paricalcitol on the potential of regressing LVH in

patients evaluated by both echocardiography as well as MR scan. Both PRIMO studies just started recruitment.

From the nephrology perspective, the foremost indication of vitamin D treatment still remains secondary hyperparathyroidism (sHPT). In this regard, there is still uncertainty to which degree the potential of active vitamin D analogues to induce hypercalcemia and hyperphosphatemia in higher doses may incur unfavorable effects on CKD patients. While observational studies again do not point to a relevant risk association even in the highest quintiles of calcium, phosphate and iPTH levels, it can not be entirely excluded that individual elevations of the calcium x phosphate product under treatment may indicate overtreatment and risk. In experimental studies, paricalcitol is by far less calcitropic than the first and second generation active vitamin D analogues (calcitriol, 1-alpha, doxercalciferol), while in clinical trials this benefit seems somewhat less pronounced. Nevertheless, in uremic rats following 5/6-nephrectomy, it was recently shown that paricalcitol did not cause any medial calcification in the aortic wall, in dramatic contrast to animals treated with calcitriol or doxercalciferol, respectively. Lopez *et al.* presented data that the combination of a calcimimetic with paricalcitol was particularly effective to prevent vascular calcification, while the combination with calcitriol showed an intermediate effect. Low-dose calcimimetic combined with low-dose active vitamin D treatment may thus become the mainstay of effective sHPT treatment in the future.

#### 14.2.2 Vitamin D analogues and all-cause mortality

In the largest observational trials on the impact of active vitamin D treatment on survival in CKD 5D patients, it has to be noted that the survival benefits stretched well beyond cardiovascular outcomes (3). There are meanwhile numerous experimental reports as well as preliminary clinical studies in cancer patients demonstrating inhibitory effects on tumor cell growth (prostate, leukemia, colon). As one out of several mechanistic examples, metabolism and thus detoxification of the colon cell carcinogen lithocholic acid is facilitated through the vitamin D-dependent enzyme CYP3A9, thus genuine vitamin D deficiency may induce a specific risk for developing neoplasms of the colon.

Vitamin D deficiency is also linked to autoimmunity and as such to diseases including rheumatoid arthritis, multiple sclerosis and type I diabetes mellitus. Potentially even more interesting was the recent observation that availability 25-OH-vitamin D may be a key defense mechanism against intracellular pathogens such as mycobacterium tuberculosis. Macrophages endogenously “turn on” their 1-alpha-hydroxylase as well as their VDR following contact with mycobacteria, and 25-OH-vitamin D levels then determine whether the tuberculocidal protein cathelicidin is expressed in sufficient amounts (4). This breakthrough finding may be a prototypic for some anti-infectious properties related to vitamin D metabolism on a cellular level. The new therapeutic paradigm might be low to moderate “hormone replacement” instead of high-dose PTH suppression by active vitamin D analogues in CKD patients, in addition to the correction of insufficient 25-OH-vitamin D levels.

### 14.3 Definition of calciphylaxis

Calciphylaxis is a rare, but potentially life-threatening syndrome characterized by progressive and painful skin ulcerations associated with media calcification of

medium-size and small cutaneous arterial vessels (5). Calciphylaxis primarily affects patients on dialysis or after renal transplantation, however, exceptions have been reported in patients with normal renal function and in association with chronic-inflammatory disease, malignancy or primary hyperparathyroidism. Clinical manifestation of calciphylaxis is associated with high mortality of up to 80%, superinfection of necrotic skin lesions with subsequent sepsis significantly contributing to this dramatic outcome. However, many calciphylaxis patients also suffer from advanced cardiovascular disease characterized by severe calcifications of larger arterial vessels. There are currently no exact numbers on the incidence of calciphylaxis available. Based on small international surveys, incidence is estimated to be in the range of 1:1.000 to 1:1.500 cases in patients on chronic renal replacement therapy per year, but there is good reason to suspect underrecognition caused by mild cases or misdiagnosis in a relevant percentage of patients.

#### 14.3.1 Therapeutic options: old and new

Therapeutic approaches are limited in calciphylaxis. As pointed out above, the available data is restricted to case reports and small case-control studies, while prospective studies are not available. Once calciphylaxis is suspected or diagnosed in a uremic patient, the first therapeutic aim must be normalization of the calcium x phosphate product, i.e. by intensifying dialysis treatment, by using a low dialysate calcium and by high-dose treatment with (preferably calcium-free) phosphate binders. Reduction or withdrawal of active vitamin D treatment must be considered depending on the corresponding levels of PTH and calcium x phosphate product. In calciphylaxis patients with hyperparathyroidism and signs of high bone turnover, „emergency“ parathyroidectomy must be considered immediately. However, in such patients administration of calcimimetics may represent an effective therapeutic alternative -promising case reports on this conservative intervention have been published recently. Once progressive ulcerations and necrosis are observed, early broad-spectrum antibiotics should probably be initiated.

Some data are available concerning the use of sodium thiosulfate and of bisphosphonates in the treatment of calciphylaxis. Thiosulfate is available as a chelating agent indicated for the treatment of cyanide intoxication. On the one hand, it possesses a high affinity to calcium ions, which may interfere with calcium and phosphate precipitation producing soluble calcium thiosulfate which can potentially be removed by dialysis. On the other hand, thiosulfate may also interfere with the local inflammation process by antioxidant properties. Both concepts currently lack proof.

It is currently unclear, whether bisphosphonates interact with extraosseous calcification processes via their antiresorptive bone effects or via direct peripheral pyrophosphate-like effects at the tissue sites. Pyrophosphates are small molecules acting as potent inhibitors of calcification at local tissue sites, while pyrophosphate deficiency causes severe soft-tissue calcifications in experimental animals as well as in humans (“Idiopathic Infantile Arterial Calcification”) (6). Although case reports on beneficial effects of pamidronate in calciphylaxis patients have recently been published, caution is advised concerning uncritical use of bisphosphonates in this patient group unless adynamic bone disease (ABD) is excluded or highly unlikely,

since ABD will be aggravated by these compounds, especially in renal failure patients.

### 14.3.2 Vitamin K and calciphylaxis: a novel pathomechanistic concept

Matrix Gla protein (MGP) is a 10 kD protein exclusively expressed in vascular smooth muscle cells (VSMC) and chondrocytes (6). This protein requires post-translational vitamin K-dependent  $\gamma$ -carboxylation for activation. Accordingly, warfarin treatment suppresses MGP activation. Knockout of the MGP gene in mice (MGP<sup>-/-</sup>) causes severe media calcification of large arteries with subsequent rupture of the ossified aorta -MGP<sup>-/-</sup> mice actually die of internal arterial hemorrhage at the age of 6-8 weeks. MGP acts purely as local inhibitor, systemic overexpression is not capable of counteracting arterial calcification induced by MGP<sup>-/-</sup>. Analogously, media calcification can also be induced by treatment with vitamin K antagonists. In rats, warfarin-induced vascular calcification can be partially reversed by feeding supraphysiological doses of vitamin K1 or K2 following withdrawal of warfarin, whereas calcification progresses when only low doses of vitamin K are fed (7).

Case reports already suggested a relatively high coincidence between warfarin treatment and calciphylaxis. The German registry branch of the "International Cooperative Calciphylaxis Network" (ICCN) collected 50 cases of calciphylaxis during the least 1.5 years and found that 42% of these patients had been on warfarin treatment when calciphylaxis developed (Ketteler M, Brandenburg VM, unpublished). Therefore, and based on the biological plausibility related to MGP inactivation, warfarin withdrawal and switch to heparin use is most probably warranted and urgently recommended, despite a lack of clear-cut prospective clinical evidence. Subsequent high-dose vitamin K supplementation may have to be addressed by future studies in this patient group and may even develop into a protective therapeutic means. Current and emerging treatment strategies of calciphylaxis are listed in Table 14.2.

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#### General approaches:

- Lowering of calcium x phosphate product (by phosphate binders, increasing dialysis dose, reduction of calcium exposure, reduction or withdrawal of vitamin D therapy)
- Parathyroidectomy (in cases of severe secondary or tertiary hyperparathyroidism)
- Broad-spectrum antibiotics (ulcerating disease with signs of inflammation)
- Professional interdisciplinary wound treatment

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#### Potential approaches:

- Withdrawal of vitamin K antagonist treatment (switch to heparin or platelet aggregation inhibitors depending on indication)
- Cinacalcet (in cases of secondary or tertiary hyperparathyroidism and contraindications against parathyroidectomy)
- Bisphosphonates (caution: only if adynamic bone disease can be excluded)
- Sodium thiosulfate
- Hyperbaric oxygen therapy

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#### Approaches under evaluation:

- High-dose vitamin K substitution?
  - Fetuin-A induction by anti-inflammatory agents?
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**Table 14.2.** Current and future therapeutic strategies for calciphylaxis (adapted from: Ketteler M and Biggar P. *Calciphylaxis: Epidemiology, Pathophysiology and Therapeutic Options*. BANTAO J 2008;6:1-5).

## 14.4 Summary

Among many recent developments of therapeutics in the nephrology field, e.g. new phosphate binders such as sevelamer carbonate and lanthanum carbonate, long-acting ESA's such as C.E.R.A., novel therapeutics in the transplant field, new indications for powerful biologicals such as rituximab etc., the biology of vitamin D and the new promise of successfully counteracting calciphylaxis appear to be this reviewer's "personal highlights". Still, even these perspectives will have to prove their reliability and validity in the future.

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