Vitamin D deficiency: a neglected aspect of disturbed calcium metabolism in renal failure

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The vitamin D hormonal system

The vitamin D hormonal system comprises different metabolites derived from the precursor cholecalciferol (vitamin D₃), which is generated by actinic synthesis in the skin (under the influence of UV light) or is of dietary origin. Endogenous vitamin D belongs to the vitamin D₃ series, while some vitamin D supplements belong to the vitamin D₂ series. The latter (ergocalciferol) is of plant origin. In a first step these precursors are hydroxylated in the liver, thus forming the metabolite 25-hydroxy-vitamin D [25(OH)D] with a long half-life (3–4 weeks). 25(OH)D is a substrate for enzymes producing further vitamin D metabolites. 25(OH)D is the best indicator of vitamin D status [1]. By the action of 1-alpha-hydroxylase the most active metabolite 1,25-dihydroxyvitamin D or calcitriol is produced mainly in the kidney, but also in some extrarenal tissues. It has a short half-life (hours) and acts upon receptors in different target organs, both classical calcium-regulatory organs (intestine, bone, kidneys, parathyroids), and non-classical target organs such as the immune system, the beta cell and skin cells. [2]. The regulation of calcitriol synthesis in the kidney is achieved mainly through modulation of the activity of the renal 1-alpha-hydroxylase. This enzyme is predominantly expressed in the proximal tubular epithelium, but in man it also has been identified in the distal tubule. The reaction is normally not substrate-dependent, i.e. not dependent on the plasma concentration of the precursor substance 25(OH)D. It is stimulated by parathyroid hormone (PTH) and inhibited by phosphate. The concentrations of both PTH and phosphate tend to be abnormal in patients with chronic renal failure [3].

During the progression of renal failure, the capacity of the 1-alpha-hydroxylase to synthesise calcitriol decreases progressively because of the loss of functioning nephrons and because the concentration of serum phosphate is increasing. The diminution of the synthetic capacity occurs despite the compensatory increase in PTH concentration, which counteracts by stimulating 1-alpha-hydroxylase activity. Thus, serum calcitriol concentrations decrease, causing amongst others an impairment of intestinal calcium absorption and an escape of the parathyroids from the inhibitory influence of calcitriol [3,4]. The net result is secondary (renal) hyperparathyroidism, which to some extent succeeds in maintaining calcium homeostasis in early renal failure, but at the price of skeletal (osteitis fibrosa) and extra-skeletal complications. As renal failure progresses it becomes more and more difficult to maintain the serum calcium concentration within the normal range. In addition, patients often reduce their
dietary calcium intake spontaneously (because of anorexia) or upon medical advice (dietary restrictions of dairy products). As a result, serum calcium concentrations remain normal usually because PTH increases osteoclastic bone resorption [5].

Importance of 25(OH)D

In the past it was assumed that the 25(OH)D3 concentration is largely irrelevant because the biologically active metabolite 1,25(OH)2D3, which is synthesized in the kidney, is more potent, by a factor of more than 100. On the other hand, 25(OH)D is able to activate the vitamin D receptor, although with low affinity. As the concentration of 25(OH)D is higher by a factor of more than 100 compared with the concentration of 1,25(OH)2D3, many investigators believe that 25(OH)D contributes substantially to the overall vitamin D effect on target organs. To this one has to add the consideration that many tissues, for instance osteoclasts and vascular smooth muscle cells, express 1-alpha-hydroxylase activity. Although such locally produced 1,25(OH)2D3 does not make a major contribution to circulating 1,25(OH)2D3 [as reflected by the low 1,25(OH)2D3 concentrations in anephric individuals] the local 1,25(OH)2D3 concentrations in such tissues may be another matter and may actually importantly contribute to hypothetical local paracrine actions (e.g. in bone). Under normal circumstances, the activity of the renal 1-alpha-hydroxylase is strictly regulated by product inhibition and the synthesis of 1,25(OH)2D3 is not substrate-dependent. In contrast, in some pathological states including renal failure, renal 1-alpha-hydroxylase does become substrate-dependent. This implies that if the concentration of 25(OH)D3 is raised, the production of 1,25(OH)2D3 increases.

It is for the above reason that it is widely believed at present that low 25(OH)D3 concentrations are undesirable in the patient with renal failure [6]. We believe that the importance of 25(OH)D3 in chronic kidney disease has been underestimated in the past. The reluctance to correct low serum 25(OH)D3 concentrations goes back to early observations that the long half-life of vitamin D and 25(OH)D renders the control of hyperparathyroidism and abnormal calcium metabolism more difficult. In case of overdosing long lasting episodes of hypercalcaemia may be provoked. There also was a lack of consensus regarding which concentrations of 25(OH)D are optimal. Observations in the general population indicate that PTH concentrations are lower, the rate of intestinal calcium absorption is higher and less mineral is released from the skeleton when 25(OH)D concentrations are in the range of 20 ng/ml (50 nmol/l) or higher. These observations have led recently to upward revision of what is felt to be the optimal concentration of 25(OH)D. This issue is particularly important in the dialysis population, because these mostly elderly individuals have an inactive life style with reduced exposure to sunshine and UV light, thus reducing actinic synthesis of vitamin D [7–9].

What is the concentration of 25(OH)D in the general population? The distribution of values follows a Gaussian curve and the mean value depends on age. The age-dependent decline in 25(OH)D3 is not desirable, however, because for the reasons given above it is associated with diminished intestinal calcium absorption, increased resorption of skeletal mineral and increased PTH concentrations. Based on a study in a Spanish population sample [9], these considerations led us to postulate that it is necessary to re-define the normal values of 25(OH)D [9,10].

Factors influencing 25(OH)D concentrations

The factors influencing 25(OH)D concentrations can be grouped into three broad categories [1]. (i) First, factors which affect the cutaneous synthesis of vitamin D under the influence of UV B radiation. These factors comprise age, melanin concentration in the skin and conditions modulating the intensity of sun exposure such as season of the year, latitude, altitude and type of clothing. (ii) Secondly, nutritional factors, although under normal circumstances the dietary supply of vitamin D makes only a minor contribution to overall vitamin D status. Dietary sources of vitamin D comprise raw and cooked fish and dairy products as well as polyvitamin preparations containing vitamin D or (in the USA) food items enriched with vitamin D, such as milk products and vegetable fats [1]. (iii) Thirdly, the 25(OH)D3 concentration is modulated by factors which affect the metabolism of vitamin D. Examples include substances which diminish intestinal absorption or interrupt the intestinal reabsorption of vitamin D metabolites (enteric recirculation) as well as drugs which alter the activity of hepatic CYP enzymes and accelerate the catabolism of 25(OH)D into inactive vitamin D metabolites in the liver.

These complex relationships explain why highly variable 25(OH)D3 concentrations are found in different populations. As an example, 25(OH)D deficiency (<10 ng/ml; 25 nmol/l) has been reported in almost 100% of an elderly population with low sun exposure [11]. Similarly, the Seneca study on healthy elderly Europeans showed that 36% of men and 47% of women had 25(OH)D concentrations <12 ng/ml (30 nmol/l). Paradoxically, inhabitants of Southern countries (Spain and Greece) had the lowest 25(OH)D3 concentrations, possibly as a result of less exposure to the sun and specific dietary habits [12]. It is because of restricted sun exposure that paradoxically in Saudi Arabia, presumably the country with one of the highest intensities of sunshine, elderly women have the lowest reported concentrations of 25(OH)D, certainly because they are veiled and live indoors. In North America, 57% of acute admission of symptomatic patients to general wards had 25(OH)D concentrations <15 ng/ml (37.5 nmol/l) [13].
Re-defining normal serum concentrations of 25(OH)D

It has been known for a long time that osteomalacia occurs at 25(OH)D concentrations \( \leq 5-7 \text{ ng ml} \). It is also known that secondary hyperparathyroidism and osteopenia occur at concentrations \( \leq 10-12 \text{ ng ml} \). In the early days, concentrations \( \geq 18-20 \text{ ng ml} \) were considered adequate [14,15]. As mentioned above, the ‘optimal’ concentration of 25(OH)D has been revised upwards to levels \( \geq 40 \text{ ng ml} \) or \( 100 \text{ nmol l} \). The following classification has been proposed:

(i) Hypovitaminosis D: concentrations between 20 and 40 ng/ml (50 and 100 nmol/l).
(ii) Vitamin D insufficiency: plasma concentration between 10 and 20 ng/ml (25–50 nmol/l).
(iii) Vitamin D deficiency: 25(OH)D concentrations \( \leq 10 \text{ ng ml} \) (25 nmol/l) [16].

A recent study sponsored by the European Community had been conducted in a random sample of 302 volunteers (149 women, 153 men) above 54 years of age (mean 68 ± 8 years). A high prevalence of low 25(OH)D concentrations and secondary hyperparathyroidism was found as shown in Figure 1 [8,9].

The 25(OH)D concentration depends not only on age, but also on the season. During winter and spring time, the prevalence of individuals with low concentrations of 25(OH)D (\( <18 \text{ ng ml} \) or \( <45 \text{ nmol l} \)) was 72\% in individuals <65 years and 80\% in individuals >65 years. During summer time, the respective prevalence rates were 50 and 58\%. The prevalence of secondary hyperparathyroidism showed an inverse relation to the 25(OH)D\(_3\) concentration. In contrast, the concentration of 1,25(OH)\(_2\)D\(_3\) did not correlate with the PTH concentration. As shown in Figure 1, the prevalence of secondary hyperparathyroidism was particularly high in individuals with 25(OH)D\(_3\) concentrations \( <10 \text{ ng ml} = 25 \text{ nmol l} \). It was also surprisingly high, however, in individuals with 25(OH)D\(_3\) concentrations which until recently were still considered ‘normal’ [8,9].

In this study, as long as elderly individuals had an excellent renal function, i.e. a serum creatinine \( <1 \text{ mg dl} \) in men and \( <0.8 \text{ mg dl} \) in women, PTH concentrations were normal even when 25(OH)D\(_3\) concentrations were \( \sim 18-30 \text{ ng ml} \) (45–75 nmol/l). In elderly individuals with higher serum creatinine concentrations, normal PTH concentrations were only found if 1,25(OH)\(_2\)D\(_3\) concentrations were >30 ng/ml (75 nmol/l). It is obvious that apart from normal calcitriol concentrations, sufficiently high 25(OH)D concentrations are necessary if stimulation of the parathyroid gland is to be avoided.

It is of interest to compare serum 25(OH)D\(_3\) and 1,25(OH)\(_2\)D\(_3\) concentrations. In these elderly individuals, 1,25(OH)\(_2\)D\(_3\) concentrations were consistently within the normal range (\( >20 \text{ pg ml} \)) and only 4\% had relatively low concentrations in the range 10–20 pg/ml. This contrasts with the observation that 25(OH)D concentrations were within the normal range (\( >20 \text{ ng ml} \); 45 nmol/l) in only 40\% of individuals. If the more recently proposed threshold of \( >30 \text{ ng ml} \) (75 nmol/l) is adopted only 7\% of the individuals had normal 25(OH)D\(_3\) concentrations.

The advantage of paying close attention to 25(OH)D\(_3\) concentration

The above study suggests that in elderly individuals with mild to moderate renal dysfunction, elevated PTH concentrations are found even when 1,25(OH)\(_2\)D\(_3\) concentrations are within the normal range, as soon as the concentration of 25(OH)D is low. We emphasize that it does not matter whether mild to moderate renal function originates from age-dependent decline.
in renal function or is the result of chronic primary renal disease or is seen in patients with well functioning renal transplants which obviously have low filtration rates. We postulate that it makes a lot of sense to maintain the 25(OH)D concentration in the upper normal range, i.e. above the threshold of 30 ng/ml (75 nmol/l) in all individuals. It is hoped that this simple strategy will help to reduce the prevalence of secondary hyperparathyroidism in individuals with or without primary renal disease.

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References
10. Holick MF. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. Osteoporos Int 1998; 8: S24–S29
11. Scharla SH. Prevalence of subclinical vitamin D deficiency in different European countries. Osteoporos Int 1998; 8: S7–S12

Peritoneal-dialysis-related peritonitis: the art of rope-dancing

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Introduction

Although incidence rates of peritonitis have decreased substantially with the introduction of the flush-before-fill double-bag principle, and the emergence of improved connection systems [1], peritonitis remains an Achilles tendon for peritoneal dialysis (PD) [2]. Mortality directly related to peritonitis is low, but peritonitis episodes cause psychosocial problems and are in the long run related to both technique failure and mortality [3]. Repetitive or protracted peritonitis episodes can also damage the peritoneal membrane [4]. Despite the overall decreasing incidence of peritonitis, mortality and technique failure attributable to it did not improve. This is due to the greater severity of infections caused by Gram-negative and *Staphylococcus aureus* infections, two types of infections that are less related to connection systems, and the incidence of which has remained stable [5]. Although infection rates in haemodialysis are at least as high as those in PD [6], most nephrologists and many patients will point to the risk of peritonitis as one of the reasons not to perform PD. Because of all these arguments, prevention and treatment of peritonitis are still a matter of great concern.

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