Editorial

Vitamin D Deficiency in Cardiovascular and Renal Disease: New Light Shed on an Old Enemy

The fat-soluble secosteroid hormone vitamin D is best known for its role in bone metabolism. From a historical perspective, the study of vitamin D deficiency has been intimately related to the study of (possible treatment of) rickets. Although diseases characterized by bone deformations have been described in ancient medical writings from the 1st and 2nd centuries, it was Galen who described the classic bone deformities noted in rickets [1, 2]. More clear descriptions originate from the 17th century, reporting rickets to be endemic in England [1]. In the early 20th century, observations that artificial UV light or sunlight provides protection against rickets coincided with results suggesting that rickets may be the consequence of a nutritional deficiency [3, 4]. The responsible vitamin was identified by McCollum *et al.*, who stated in their paper in the *Journal of Biological Chemistry* in 1922: "These experiments clearly demonstrate the existence of a fourth vitamin whose specific property, as far as we can tell at present, is to regulate the metabolism of the bones" [5]. This "fourth vitamin" was named vitamin D.

Once vitamin D deficiency had been identified as the cause of rickets, halfway the 20th century many governments decided to have foods (e.g. dairy and orange juice) fortified with vitamin D in order to conquer this deforming disease. Since then, rickets has become rare in the Western world. However, rickets can be considered "the tip of the vitamin D–deficiency iceberg" [6], as less severe vitamin D deficiency may compromise optimal function of several organ systems, such as the cardiovascular and renal system. A growing number of recent studies indicate that the sum of vitamin D generated in the skin and obtained from the diet is insufficient to maintain adequate circulating vitamin D levels in a considerable part of the population worldwide, as reviewed by Dr. Holick in this issue [7]. Thus, although rickets has become rare, the extent of the vitamin D deficiency pandemic, estimated to affect about a billion people worldwide, and its health consequences are matters that urgently require attention.

This Special Issue addresses the potential role of vitamin D deficiency in the pathogenesis and progression of cardiovascular and renal disease. A number of renowned authors will tackle the question whether vitamin D deficiency may be a risk factor for cardiovascular disease, and whether treatment with vitamin D (analogues) could be a beneficial intervention in cardiovascular and/or renal disease.

A first important hurdle in epidemiological research to investigate the association between vitamin D levels and certain diseases is a methodological one. Most experts agree that vitamin D deficiency can be defined as a low circulating level of the pro-hormone 25-OH vitamin D. However, it is uncertain which is the optimal method to properly measure 25-OH vitamin D levels, not in the last place since vitamin D levels are in the nanomolar range and many structurally highly similar metabolites exist. In this issue, Dr Carter, involved in the DEQAS (vitamin D external quality control programme) initiative, provides an excellent overview comparing various laboratory measurements and exploring the possibilities and pitfalls of these techniques [8].

In spite of methodological issues, a number of epidemiological studies have related vitamin D deficiency to increased risk of cardiovascular disease, but robust data from large randomized controlled trials are lacking. In this issue, Dr. Meems *et al.* systematically review the available data addressing potential cardioprotective effect of vitamin D analogues in heart failure [9], while the possible relationship between vitamin D deficiency and vascular disease is covered by Brewer *et al*. [10].

Although vitamin D may directly protect the heart and/or blood vessels, there could also be more indirect protective pathways. For example diabetes mellitus, a major risk factor for cardiovascular disease, may be modulated by vitamin D analogues. Indeed several studies suggest that vitamin D supplementation could be beneficial in diabetic subjects, although major question are still unanswered. Dr. Boucher addresses the potential relationship between vitamin D deficiency and diabetes [11].

In many patients, atherosclerosis results in end-organ damage on the long term. Besides the heart and vasculature, atherosclerosis may affect the kidneys and brain. Recent studies in diabetic animal models have revealed that vitamin D protects against diabetic nephropathy on top of standard treatment, in an impressive manner [12]. But also in non-diabetic renal disease, treatment with vitamin D analogues is beneficial [13]. Dr. Mirković provides an overview of recent studies on renoprotective effects of vitamin D in this Special Issue [14]. Dr. Pilz *et al*. will summarize all available data on the cerebroprotective potential of vitamin D (analogues) [15].

In summary, the potential protective role of vitamin D and/or its synthetic analogues is currently under investigation for a wide range of complex diseases. The preliminary positive findings documented until now suggest that vitamin D has pleiotropic effects, and raise the question whether vitamin D deficiency may be a universal risk factor for multifactorial disease. In the last paper of this issue, we will attempt to identify a limited number of molecular pathways shared by several types of complex disease, that could be regulated by vitamin D [16].

Ultimately, clinical trials should provide the evidence that vitamin D supplementation could indeed provide cardiovascular and/or renal protection. As such trials are currently ongoing, the coming years will hopefully bring answer to the question whether vitamin D could be a new cornerstone therapy for the treatment of cardiovascular and renal disease.

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