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see original article on page 134

Vitamin D, insulin resistance, and renal disease

A Remuzzi[1]

Chonchol and Scragg report the results of a population study on levels of 25-hydroxyvitamin D in patients with renal dysfunction. They demonstrate that these patients do not show vitamin D deficiency unless renal function is severely affected (GFR<29 mL/min/1.73m2), while vitamin D and renal function loss are independently associated with insulin resistance. These data provide more solid evidence than previous available studies on small patient groups, and pose new questions about the mechanisms responsible for progressive renal disease as well as potential effects of vitamin D supplementation.

Kidney International (2007) **71**, 96–98. doi:10.1038/sj.ki.5002047

The role of vitamin D deficiency in several pathological conditions has been the focus of several investigations in the last few years.[1] The complexity of the biological role of vitamin D metabolism makes it difficult to clearly delineate the role of vitamin D cascade in these pathophysiological systems. More evidence is now emerging on the role of vitamin D besides calcium and phosphate homeostasis. Thus, vitamin D is known also to regulate cell proliferation and differentiation and to modulate the immune system, and it is implicated in several endocrine functions (Figure 1).[2] In light of this broad spectrum of biochemical reactions, and the fact that vitamin D is produced by numerous differentiated cells and tissues,[3] it is likely that vitamin D is involved in several pathophysiological processes. Among these, vitamin D seems to be implicated in progressive kidney diseases; however, despite evidence of secondary hyperparathyroidism and reduced bone density, there is no direct evidence on the mechanisms by which vitamin D is involved in the development and progression of chronic renal diseases.

According to several reported studies, serum levels of vitamin D are decreased in patients affected by kidney diseases, as compared with the general population, in different stages of renal-function loss.[4] However, these studies, although they document kidney disease and renal function well, are restricted to a small number of patients. At variance, the article by Chonchol and Scragg[5] (this issue) provides some interesting data based on population data. To overcome the limitations of studies in small groups of patients, Chonchol and Scragg collected data from the Third National Health and Nutrition Examination Survey (NHANES III). The authors clearly demonstrate, by appropriate statistical analysis, that serum levels of 25-hydroxyvitamin D, a measure of blood stores of vitamin D, are effectively reduced in uremic patients, but only when renal function is severely lost (glomerular filtration rate ranging from 15 to 29 ml/min/1.73 m^2) as compared with that of subjects with normal renal function, whereas in patients affected by only mild or moderate loss of renal function the serum level of 25-hydroxyvitamin D is normal. In addition, the results of the statistical analysis showed that 25-hydroxyvitamin D levels and loss of renal function have independent inverse associations with insulin resistance,[5] suggesting that the relation between vitamin D and insulin resistance, if any, still has to be elucidated in more detail. Thus, the results of this study make some important contributions to the understanding of the pathophysiological role of vitamin D in progressive renal diseases and its possible implication for pharmacological therapy. In addition, they should guide future investigations of the potential role of vitamin D supplementation.

The theoretical possibility that vitamin D is involved in the pathophysiology of progressive renal disease is based on the fact that, besides secondary hyperparathyroidism, this molecule is involved in other cellular and metabolic functions known to be altered in renal diseases. One mechanism that has been better

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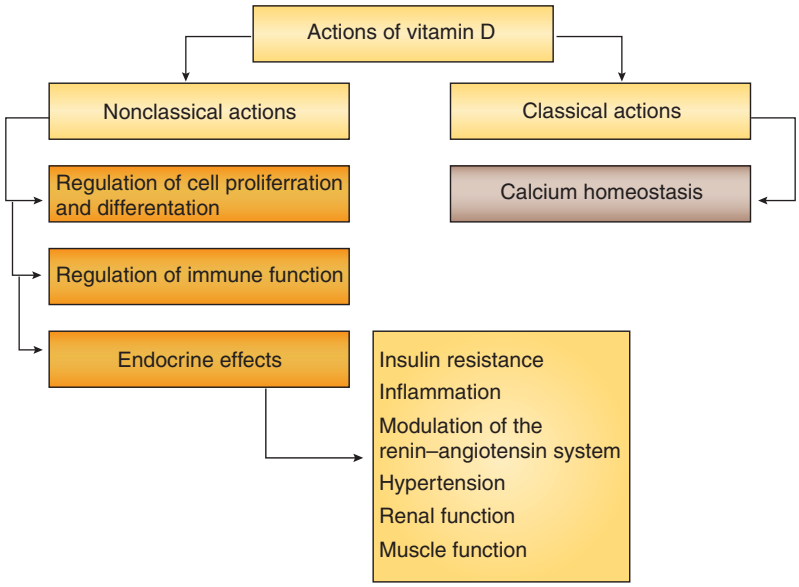

Figure 1 | Besides classical functions of vitamin D, there is now emerging evidence that other actions of this hormone are important in the regulation of organ and systemic functions.

characterized in the progression of renal disease is the activation of the renin–angiotensin system. Relevant experimental and clinical observations demonstrate that the antagonism of the biological action of angiotensin II prevents or ameliorates renal structural and functional changes.[6] The observation that vitamin D acts as a negative endocrine regulator for the renin–angiotensin system[7] would indicate a potential involvement of vitamin D in the progressive loss of renal function. Another possible mechanism that could relate vitamin D and progression of renal disease is the involvement of vitamin D in cell cycle regulation and cell differentiation.[3] It is of interest that vitamin D supplementation decreased podocyte loss and hypertrophy in the classical model of experimental renal disease progression, the surgical reduction of renal mass in the rat.[8] There is also experimental evidence that vitamin D is related to insulin resistance,[9] a condition frequently observed in patients affected by progressive renal disease. Finally, vitamin D is known to modulate the functioning of immune cells such as T lymphocytes and monocytes,[10] which are frequently involved in the immunological reactions associated with renal disease progression.

On the basis of this body of evidence and of these theoretical considerations, it has been suggested that vitamin D has a potential role in kidney disease progression and that consequently vitamin D supplementation should be adopted to prevent renal disease and cardiovascular events in these patients. The Kidney Disease Outcomes Quality Initiative guidelines also recommend measurements of 25-hydroxyvitamin D serum levels in patients with advanced chronic renal disease. However, the data provided by Chonchol and Scragg[5] clearly indicate that serum levels of 25-hydroxyvitamin D are not significantly reduced in patients affected by renal disease unless the glomerular filtration rate is lower than 29 ml/min/1.73 m^2, suggesting a condition not characterized by vitamin D deficiency until the disease is in the advanced stage. These data pose two challenges. The first is to identify the role of vitamin D in the pathophysiological mechanisms responsible for these diseases, especially in the initiation and the first stage of progression. The second is related to the potential effects of vitamin D supplementation therapy in these patients. On the basis of the data reported by Chonchol and Scragg,[5] both these issues need to be further elucidated.

In addition, clinical data demonstrate beneficial effects of vitamin D supplementation in these patients, even in the early phase of the disease.[4] How this relates to the previously mentioned normal level of vitamin D should be studied in more detail. On the basis of this consideration, vitamin D supplementation in these patients should be carefully evaluated in order to gain more evidence on the effective target of these therapies and the potential results that could be obtained in slowing the rate of renal disease progression. On the other hand, the data of Chonchol and Scragg[5] do confirm that vitamin D is deficient in uremic patients in the advanced stage of the disease. These results are important for the understanding of the cardiovascular events that frequently affect patients with end-stage renal disease. At the moment, deeper knowledge of the relative importance of the previously mentioned biological systems, linked to vitamin D, for the cardiovascular morbidity and mortality in these patients is needed. Hopefully, the large-population data provided by Chonchol and Scragg[5] will stimulate experimental and clinical studies with the aim to investigate the effective role of vitamin D in the early phase of the disease, when serum levels of the vitamin D cascade are not significantly affected, as well as in the late phase that is characterized by vitamin D deficiency.

Finally, the results of Chonchol and Scragg[5] also indicate that renal dysfunction and vitamin D have independent inverse associations with insulin resistance, while in the general population there is evidence of close association between insulin sensitivity and serum levels of 25-hydroxyvitamin D. Thus, more complex mechanisms may relate these pathological manifestations, and more focused experimental and clinical research may help to elucidate them in the near future with the aim of avoiding unrealistic expectations for therapeutic approaches that have potential use in a large patient population.

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see original article on page 146

Insulin resistance and protein catabolism in non-diabetic hemodialysis patients

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Chronic kidney disease (CKD) is associated with complex metabolic changes including insulin resistance. Siew *et al.* have highlighted an important relationship between insulin resistance and skeletal muscle protein turnover. If insulin resistance is implicated in sarcopenia of CKD, further research will be required to determine whether interventions that improve insulin sensitivity improve clinical outcomes and cardiovascular risk in CKD.

Kidney International (2007) **71**, 98–100. doi:10.1038/sj.ki.5002045

One of the most important predictive factors of survival on dialysis is the presence of malnutrition.[1,2] Previous studies have demonstrated that a significant proportion of hemodialysis patients and chronic ambulatory peritoneal dialysis patients are malnourished. These patients have increased morbidity and mortality and a poorer quality of life as compared with patients who are adequately nourished. Impaired nutrition may be measured by a variety of methods, but those methods that measure body composition directly (total-body nitrogen analysis and dual-energy X-ray absorptiometry) demonstrate that lean body mass is reduced in patients with renal impairment.[3,4] These changes are demonstrable at the initiation of dialysis and are likely to develop in patients with mild to moderate chronic kidney disease (CKD). Negative nitrogen balance and sarcopenia can result from decreased protein anabolism or increased protein catabolism or both. The balance between these factors and relative contributions of other conditions that cause sarcopenia are still to be defined. Decreased protein anabolism may result from disuse of muscles, suboptimal protein intake, intercurrent illness, and medications, whereas increased protein catabolism can result from acidosis, microinflammatory processes related to increased cytokines, oxidative stress, and the reduced actions of anabolic hormones such as insulin.

The increased mortality and morbidity observed in dialysis patients with malnutrition or depleted muscle mass are principally due to an increase in cardiovascular events.[5] In view of this, it is important not only to understand the mechanisms by which sarcopenia may occur, but also to understand the association between altered body composition and clinical outcomes in CKD. Recent literature has highlighted the effects of chronic inflammation and oxidative stress in predisposing CKD patients to malnutrition and increased vascular disease.[6] Chronic inflammation may predispose to impaired nutritional status by enhancing protein catabolism. Associations between chronic inflammation, measured as elevated C-reactive protein or proinflammatory cytokines, impaired nutritional status, and subclinical and clinically overt vascular disease, have been documented in patients at the commencement of dialysis. Furthermore, systemic inflammation may result in reductions in total cholesterol levels, which may account for the altered epidemiological association of an inverse relationship between total cholesterol levels and mortality reported by some investigators in dialysis patients.

Although the malnutrition, inflammation, atherosclerosis hypothesis may explain many of the clinical associations of malnutrition in dialysis patients,[6] CKD is associated with complex metabolic changes, and Siew *et al.*[7] (this issue) now highlight the importance of another metabolic effect of CKD — insulin resistance. It is well documented that insulin resistance is a feature of advanced CKD, and there is some evidence that insulin resistance occurs in mild to moderate CKD. The cause of insulin resistance in non-diabetic CKD is not apparent, but it may be related to central adiposity, the micro-inflammatory environment, or other metabolic defects. Insulin resistance has been shown to be an independent predictor of survival in dialysis patients.[8] It has been hypothesized that insulin resistance may increase vascular risk in dialysis patients in the same way observed in the general population, because of the tendency of vascular risk factors to cluster in subjects who are insulin resistant.

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