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Expanding role for vitamin D in chronic kidney disease: importance of blood 25-OH-D levels and extra-renal 1alpha-hydroxylase in the classical and nonclassical actions of 1alpha,25-dihydroxyvitamin D(3).

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Abstract

Recent advances in the understanding of vitamin D have revolutionized our view of this old nutritional factor and suggested that it has much wider effects on the body than ever believed before. In addition to its well-known effects on calcium/phosphate homeostasis, vitamin D, through its hormonal form, 1alpha,25-dihydroxyvitamin D(3) or calcitriol, is a cell differentiating factor and anti-proliferative agent with actions on a variety of tissues around the body (e.g., skin, muscle, immune system). By influencing gene expression in multiple tissues, calcitriol influences many physiological processes besides calcium/phosphate homeostasis including muscle and keratinocyte differentiation, insulin secretion, blood pressure regulation, and the immune response. The incidence of various diseases including epithelial cancers, multiple sclerosis, muscle weakness as well as bone-related disorders has been correlated with vitamin D deficiency/insufficiency and has led to a re-evaluation of recommended daily intakes both in the normal subject and CKD patient. Critical developments have been the emergence of the value of blood 25-OH-D measurement as a tool in predicting vitamin D-related problems and this has in turn emphasized the importance of the extra-renal version of the 1alpha-hydroxylase, the enzyme responsible for the final step in vitamin D activation. The widespread expression of this extra-renal enzyme supports the view that it exists to boost intracellular concentrations of calcitriol within some target tissues in order to modulate a unique set of genes specifically in those tissues, a process which is therefore dependent upon circulating 25-OH-D. For CKD patients with their tendency to vitamin D substrate insufficiency coupled with their documented loss of the renal 1alpha-hydroxylase in late stages, this new information has profound implications. Physicians must start to manage the vitamin D insufficiency by vitamin D supplements throughout stages 1-5 whilst continuing to provide calcitriol replacement therapy, in the form

of calcitriol or its analogs, in stages 3-5.

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