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**Institutionen för klinisk vetenskap, intervention och teknik
(CLINTEC), Enheten för pediatrik**

Vitamin D insufficiency in cystic fibrosis: prevalence, consequences and intervention

AKADEMISK AVHANDLING

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av

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ABSTRACT

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease in Caucasians. The major cause of morbidity and mortality is lung disease, characterized by a vicious circle of infection and inflammation. Management of CF requires a multifaceted approach, where intensive chest physiotherapy is combined with aggressive antibiotic treatment, and tight nutritional follow-up. Vitamin D insufficiency has high prevalence among CF patients worldwide. Vitamin D is crucial for maintaining healthy skeleton. Recently, extraskeletal functions of vitamin D have been described. These include immunomodulatory and glucose-lowering properties. Due to lack of relevant studies, vitamin D supplementation in CF is recommended only as one of the means of maintaining bone health. The aim of this thesis was to increase our current understanding of the impact of vitamin D supplementation in CF patients, and provide data needed for designing an efficient vitamin D supplementation policy.

First of all, we showed that a majority of Scandinavian CF patients had a suboptimal serum 25-hydroxyvitamin D (s25OHD) level (**Paper I**), and that the vitamin D doses needed to increase it were high. Cholecalciferol was more efficient at increasing s25OHD than ergocalciferol, and s25OHD monitoring was needed (**Paper III**).

Secondly, we propose that vitamin D induces a broad spectrum of immunomodulatory actions in CF. In the well-defined Scandinavian CF population (n=898), s25OHD was associated negatively with serum total IgG, and positively with lung function (FEV1) in a robust multiple linear regression (MLR) model (**Paper I**). In line with that, three months long ergocalciferol supplementation in Stockholm CF patients decreased serum total IgG and IgM, whereas cholecalciferol decreased expression of the costimulatory molecule CD40 on dendritic cells. Patients receiving any form of vitamin D decreased T cell activation and IL-8 levels at the end of the supplementation. On the other hand, certain mechanisms of innate immunity were enhanced, such as MCP-1 and sTREM-1. Soluble CD14 increased only in patients reaching $92 < \text{s25OHD} < 97$ nmol/L, which suggests bell-shaped relationship between s25OHD and soluble CD14. Notably, increase in s25OHD levels was associated with positive changes in lung function and in respiratory quality of life scores (**Paper III**).

Moreover, we demonstrated that $\text{s25OHD} < 30$ nmol/L, $\text{s25OHD} < 50$ nmol/L, and vitamin D insufficiency degree are independent determinants of HbA1c values in Scandinavian CF patients in a MLR model. This indicates that vitamin D may have glucose-lowering properties in CF. In addition, $\text{s25OHD} < 30$ nmol/L and vitamin D insufficiency degree determined the risk of CF-related diabetes (**Paper II**).

In **Paper IV** we aimed to assess the ability of CF bronchial epithelial (CFBE) cells to convert the inactive 25OHD to the active $1,25(\text{OH})_2\text{D}$, which is an important mechanism ensuring adequate local concentrations of the biologically active $1,25(\text{OH})_2\text{D}$ *in vivo*. Upon addition of 25OHD (100 nmol/L), the amplitude of the increase in $1,25(\text{OH})_2\text{D}$ was smaller for the CFBE cells than the non-CF human bronchial epithelial cells (12.0 versus 33.2 pmol/L). These results indicate that cells harbouring mutations in *cfr* may have impaired ability to activate vitamin D.

In conclusion, this thesis contributes to the understanding of the multifunctional importance of vitamin D in CF. It creates hypotheses about role of vitamin D in chronic inflammation, diabetes and lung function, which need to be studied further.