# Role of Vitamin D in Bronchiectasis (CF versus Non CF Patients)

Thesis

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# INTRODUCTION

Cystic fibrosis (CF) is the most common lethal autosomal recessive respiratory disease in the western world with an estimated incidence of 1 per 300 live births. Most patients with CF succumb to respiratory failure from chronic pulmonary failure infections ***(Eastham et al., 2014).***

CF is caused by dysfunction of the CF transmembrane conductance regulator (CFTR) protein, a chloride channel present on epithelial cells. Thus, CFTR mutations affect the respiratory, gastrointestinal, hepatobiliary, and reproductive systems as well as sweat glands.

Vitamin D deficiency in patients with CF can arise from various causes including pancreatic exocrine Insufficiency, lack of outdoor activity and alterations of vitamin D metabolism ***(Collawn & Matalon, 2014).***

Due to fat malabsorption resulting from pancreatic insufficiency, higher oral dose of vitamin D are necessary to correct and maintain optimal vitamin D status in patients with CF ***(Salvatore et al., 2012).***

Non-cystic fibrosis (non-CF) bronchiectasis often start in childhood with a significant impact on adult morbidity. Bronchiectasis is conventionally used as a descriptive term for an irreversible pathological state characterized by chronic suppurative airway disease manifested clinically by chronic

productive cough and radiologically by bronchial dilation and often thick-walled bronchi ***(Bastardo et al., 2013).***

Vitamin D deficiency occurs frequently in patients with cystic fibrosis (CF) & non CF bronchiectasis. Vitamin D is important for optimal mineralization of bone. Vitamin D deficiency in these patients can arise from various causes including pancreatic exocrine insufficiency, lack of outdoor activity, and alterations of vitamin D metabolism ***(Vanstone et al., 2015).***

The mechanisms by which vitamin D may exert its beneficial actions in chronic lung diseases are likely related to the role vitamin D in modulating the adaptive and innate immune response. Higher vitamin D status is associated with better lung function and that vitamin D therapy may help recovery from pulmonary exacerbations of bronchiectasis in both CF& non-CF patients ***(Cutting et al., 2015).***

Vitamin D may have a role in preserving lung function according to the Third National Health and Nutrition Examination Survey (NHANES III), there was a positive correlation between vitamin D status and lung function as assessed by the forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) ***(Aris et al., 2011).***

The potential mechanisms by which vitamin D may preserve lung function based on studies in cystic fibrosis and

other chronic lung disease include improved airway remodeling in response to injury, decreased airway inflammation, and decreased airway bacterial colonization.

Vitamin D has been established to enhance the innate immune system by up-regulating antimicrobial peptides such as human cathelicidin (hCAP18 or its cleaved protein LL-37) ***(Paccou et al., 2010).***

Invading microorganisms can bind to toll-like receptors on alveolar macrophages which result in up-regulation of the 1α-hydroxylase and increased production of the active form of vitamin D (1,25(OH)2D) and the vitamin D receptor (VDR) ***(Grober et al., 2013).***

The locally produced 1,25(OH)2D can induce expression of cathelicidin by macrophages and monocytes to clear the infection by the invading microorganisms.Specific to CF, locally produced 1,25(OH)2D can potentially enhance airway concentrations ofLL-37 to decrease colonization of airway pathogens such as Pseudomonas aeruginosa and Bordetellabronchiseptica ***(Hall et al., 2012).***

Vitamin D can also down regulate pro-inflammatory cytokine in macrophages and may also reduce the inflammation in the CF airway. Vitamin D may also have beneficial effects on induction of reactive nitrogen and oxygen intermediates and

induction of autophagy to help clear infections ***(Salvatore et al., 2011).***

**Vitamin D & Innate immunity**

The presence of VDR in cells of the innate immune system, such as dendritic cells, peripheral blood mononuclear cells, activated T lymphocytes, and even quiescent CD4 T cells along with the presence in macrophages and dendritic cells of the enzymes responsible for activation and degradation of vitamin D (1a-hydroxylase, and 25-hydroxyvitamin D-24-hydroxylase, respectively), implies that vitamin D has an active part in innate immunity ***(Pincikova et al., 2016).***

Dendritic cells have a critical role in innate immunity and can promote the differentiation of naïve $CD4^+$ T cells to either effector or regulatory T-cells (Treg).vitamin D can affect the stimulatory characteristics of DCs and change the balance towards the induction of $CD4^+CD25^+Foxp3^+$ Treg. It can also enhance recruitment of Treg cells at inflammatory sites. This suppressive, anti-inflammatory function of vitamin D may contribute to the limitation of chronic bronchial inflammation and have a beneficial effect in the control of the disease ***(Abreu et al., 2014).***

**Vitamin D & Adaptive immunity**

Vitamin D also plays a role in modifying adaptive immunity. The administration of vitamin D decreases Th1

cytokine secretion and inhibits T-cell proliferation. Vitamin D was also shown to either inhibit or enhance Th2 cell differentiation and production of Th2 cytokines. Vitamin D exhibits an inhibitory effect on IFN-γ production through IL-12, and it can also suppress IL-4, and IL-13 expression induced by IL-4 ***(Muthian et al., 2016).***

Regarding B cells, it is known that treatment with $1,25(OH)_2D$ hinders proliferation and differentiation to IgG secreting plasma cells. Vitamin D reduces the expression in Th17 cells of IL-17, which is a cytokine found elevated in the sputum and the lungs of CF patients. Aspergillus fumigatus, has been implicated as a common cause of both CF and non-CF bronchiectasis ***(Adorini et al., 2012).***

Recently, it was shown that CF patients with allergic bronchopulmonary aspergillosis (ABPA) had increased Th2 reactivity, and this was associated with lower serum vitamin D levels. When $1,25(OH)_2D$ was added to $CD4^+$ T cells isolated from these patients, the induction of IL-5 and IL-13 by Aspergillus decreased and Th2 responses of $CD4^+$ T cells were reduced ***(Liu et al., 2012).***