EFFECT OF VITAMIN D DEFICIENCY IN CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS: CLINICAL, LABORATORY & IMMUNOHISTOCHEMICAL STUDY

THESIS

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2017

بسم الله الرحمن الرحيم

Acknowledgement

I am thankful to ALLAH for granting me the will and power to finish this work.

I wish to express my greatest thanks and sincere appreciations to ***Prof. Dr. Mohamed Abd El-Raouf Masoud***, professor of otolaryngology, Faculty of Medicine, Ain Shams University, for his encouragement, for his generous assistance, fatherhood-relationship and helpful advices in the conduction of this work.

I wish to express my sincere gratitude and cardinal appreciations to my eminent ***Prof. Dr. Amr Gouda Shafik,*** professor of otolaryngology, Faculty of Medicine, Ain Shams University, for his continuous supervision, great help and giving much of his precious time and advices to make this work, kind cooperation and great encouragement during the preparation of this work.

I deeply thank ***Prof. Dr. Mohamed El-sharnouby,*** professor of otolaryngology, Faculty of Medicine, Ain Shams University, for his supervision, continuous efforts, valuable advices, brotherhood relation and sincere efforts in conduction of this study.

I wish to express my supreme gratitude to **Prof. Dr. Manal Ibrahim Salman**, Professor of pathology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.

I wish to express my great thanks and gratitude to **Dr. Hany Kassamy Mohamed**, Lecturer of Otorhinolaryngology, Ain Shams University, to whom I owe more than words that can express for his generous co-operation and support all of the time.

I am really grateful to all my Professors and Staff Members of ***Otorhinolaryngology department, Faculty of Medicine, Ain Shams University*** and all my teachers who taught me any word on the road of science.

Finally, there is no word that can express my deepest and sincere gratitude to ***my family*** that was and will always be beside me.

This work was partially supported by Ain Shams Faculty of Medicine Grants Office, grant number: 2016/6

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List of Abbreviations

Abbreviation	Meaning
1,25 $(OH)_2D$	1,25-dihydroxy vitamin D
1,25$(OH)_2D_3$	1,25 dihydroxy vitamin D_3
25(OH)D	25-hydroxy vitamin D
5-LO	5-lipoxygenase
AAO-HNS	American Academy Of Otolaryngology & Head Neck Surgery
aFGF	Acidic Fibroblast Growth Factors
bFGF	Basic Fibroblast Growth Factors
CA	Carbonic Anhydrase
CF	Cystic Fibrosis
CMC	Carboxymethyl Cellulose
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusistis Without Nasal Poyps
CRSwNP	Chronic Rhinosinusistis With Nasal Poyps
CysLTs	Cysteinyl Leukotrienes
ELISA	Enzyme-Linked Immunosorbent Assay
EPOS	European Position Paper On Rhinosinusitis And Nasal Polyps
ESS	Endoscopic Sinus Surgery
FESS	Functional Endoscopic Sinus Surgery
GC	Glucocorticoids
H&E	Hematoxylin And Eosin

HLA	Human Leukocyte Antigen
HSV-1	Herpes Simplex Virus-1
HSV-2	Herpes Simplex Virus-2
HSNF	Human sinonasal fibroblasts
IL	Interleukin
ILCs	Innate Lymphoid Cells
LMS	The Lund-Mackay Scoring
LTAs	Lt Antagonists
LTC4S	Leukotriene C4 Synthase
MBP	Major Basic Protein
NP	Nasal Polyposis
NR	Nutritional Rickets
OCSs	Oral Corticosteroids
PARC	Pulmonary And Activation-Related Chemokine
PCNA	Proliferating Cell Nuclear Antigen
PRRs	Pattern Recognition Receptors
PTH	Parathormone
SF-36	36-Item Short Form Survey
SNOT-22	Sino-Nasal Outcome Test
TLRs	Toll-Like Receptors
TNF	Tumor Necrosis Factor
UVB	Ultra Violet B Rays
VDRs	Vitamin D Receptors
VZV	Varicella-Zoster Virus

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ABSTRACT

This is an interventional clinical trial demonstrating the effect of vitamin D deficiency in chronic rhinosinusitis with nasal polyposis.

Methodology: Fifty patients with the clinical diagnosis of chronic rhinosinusitis with nasal Polyposis (CRSwNP) at Otorhinolaryngology outpatient clinic, Ain Shams University hospitals. Group I will be subdivided into 2 subgroups, group Ia: twenty five patients will receive vitamin D supplementation, while group Ib will receive local and systemic steroids.

Results: Chronic rhinosinusitis with nasal polyps' (CRSwNP) populations are vitamin D deficient, clinical improvement was noted in chronic rhinosinusitis with nasal polyps' (CRSwNP) population both by history and examination (reduction in nasal polyp size, decrease in mucosal edema, change of secretion consistency) after vitamin D3 supplementation,), but better response and improvement was demonstrated in the steroids treated group.

Conclusion: Vitamin D role in pathogenesis of CRSwNP is now just beginning to be better understood. While it remains unclear whether Vitamin D deficiency is causational in this disease, there is likely a role for its use as a disease-modifying, more specific agent (either alone or as a synergistic agent to traditional therapeutics) in treatment (or prophylaxis) of patients with recurrent or recalcitrant cases, or cases not candidate for surgery (either unfit or refusing).

Keywords: Vitamin D, nasal polyps, bFGF, sinusitis

INTRODUCTION

Nasal polyposis is a common nasal disease with a high rate of recurrence **(Franzke et al., 2012).** The pathogenesis of nasal polyposis is still unclear, but the disease is believed to be a manifestation of complex inflammatory reactions **(Zaravinos et al., 2009).**

Nasal polyposis is marked by an eosinophilic infiltrate, massive tissue edema, proliferation of stromal and epithelial elements, and thickening of the basement membrane **(Pawankar, 2003)** whereas chronic rhinosinusitis without nasal polyposis (CRSsNP) is characterized by more prominent fibrosis of the extracellular matrix and lacks a profound eosinophilic infiltrate **(Fokkens et al., 2012).**

Basic fibroblast growth factor (bFGF) is a multifunctional protein that is a member of a family of heparin-binding polypeptide growth factors that are involved in numerous biological activities including cellular proliferation and differentiation, neoangiogenesis, and tissue remodeling **(Kim et al., 2006).** bFGF is thought to play a significant role in airway remodeling in the setting of chronic inflammation due to its ability to promote migration and/or proliferation of vascular

endothelial cells, myofibroblasts, and fibroblasts **(Skevaki et al.,2012).**

Basic fibroblast growth factor (bFGF) RNA was significantly upregulated in tissue samples taken from antrochoanal polyps when compared to controls and patients with CRSsNP, and in studies specifically looking at CRSwNP, bFGF was elevated at both the mRNA and protein levels when compared to controls **(Mahfouz et al., 2006).** bFGF interacting with fibroblasts may also be a key component in polyp development **(Kim et al., 2006).**

There is evidence to suggest that nasal polyposis fibroblasts are responsive to vitamin D. Topical calcitriol, the active form of vitamin D, has been shown to inhibit nasal polyposis fibroblast proliferation in a dose-dependent fashion & these antiproliferative effects were maximized when combining calcitriol with budesonide. Although this study did not determine a mechanism by which vitamin D affects nasal polyposis fibroblasts, the authors concluded that vitamin D may downregulate vitamin D receptor dependent chemokines that play an important role in nasal polyposis formation **(Rostkowska-Nadolska et al., 2009).**

Despite many pharmacological treatments, in most cases the outcomes are unsatisfactory and recurrences require surgery. At present, steroids in a long term topical and oral forms are the

primary in the therapy for nasal polyposis. Due to well-known side effects related to steroid intake, this therapeutic option is often rejected. All of these factors indicate the need for the investigation of new agents suitable for treating nasal polyposis **(Blomqvist et al., 2001).**

Vitamin D (VD) and its different analogues, besides their classic role as regulators of calcium and phosphor homeostasis, have emerged as a large family of antiproliferative agents. Such properties suggested vitamin D potential as a therapy for chronic inflammatory diseases **(Rostkowska-Nadolska et al., 2009).**

Vitamin D (VD) is a potent immunomodulatory steroid hormone involved in growth and differentiation of many cell types and regulative influence on immunological processes or their anti-proliferative and anti-inflammatory properties **(Mathieu et al., 2002)**. And increasing evidence suggests vitamin D may be involved in other Th2-skewed airway disorders **(Brehm et al., 2009).**

Vitamin D deficiency, in particular, has been linked to a high rate of both infectious and inflammatory diseases, including those of the upper and lower airways, such as rhinosinusitis, pneumonia, influenza A, and otitis media **(Pinto et al., 2008).** Patients with CRSwNP have been shown to have to be vitamin D

-deficient, and that deficiency is associated with more severe disease **(Mulligan et al., 2012).**

Recently, it was found that patients with chronic rhinosinusitis and allergic fungal rhinosinusitis demonstrate insufficient levels of vitamin D (<32 ng/ml) when compared with controls. Chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic fungal rhinosinusitis (AFRS) have insufficient levels of circulating 25-OH vitamin D3 (VD3). Compared with control and CRSwNP, AFRS and CRSwNP have significantly lower plasma vitamin D levels **(Mulligan et al., 2012).**

Medical University of South Carolina laboratory previously demonstrated an association between vitamin D insufficiency/deficiency in adult and pediatric patients with CRSwNP and AFRS **(Van Bruaene et al., 2012).** This association was again demonstrated in a study from Taiwan that also noted an inverse correlation between serum levels of vitamin D and severity of nasal polyposis **(Wang et al., 2013).** They concluded that vitamin D deficiency was associated with worse disease scores and postulated that low levels of vitamin D may fail to reduce the level of cytokines released by inflammatory cells and fibroblasts, thus contributing to the perpetuation of chronic inflammation.