Introduction

Nasal polyps (NP), a subgroup of chronic rhinosinusitis, remains one of the most difficult challenges in clinical rhinology, as its etiology and pathophysiology are still controversial. Medical treatment is unsatisfactory, and, because of frequent recurrences, repeated surgical interventions are often necessary. According to literature, patients with recalcitrant chronic rhinosinusitis with nasal polyposis (CRSwNP) and if low serum Vitamin D level is correlated with NP, we design the following study.

Many cytokines are believed to be involved in the development of NP. Besides tissue eosinophilia, the other histological characteristic of NP is tissue remodeling that includes basement membrane thickening, gland modifications, ECM accumulation and edema. Matrix metalloproteinases (MMPs), a family of zinc- and calcium-dependent endopeptidases that can collectively degrade almost all ECM components, is a key player in the process of airway remodeling. MMPs produced by inflammatory cells appear to be responsible for microvascular permeability leading to edema and cell transmigration, and ECM remodeling in asthmatic airways(2-3). Many studies also have mentioned the occurrence of tissue remodeling and the involvement of matrix metalloproteinases (MMPs) in the formation of nasal polyps(4). Upon stimulation, nasal fibroblasts, via production of collagens and fibronectin, are known to promote extracellular matrix generation and tissue remodeling.

In recent years, increasing evidence has revealed new actions of vitamin D (VD) derivatives, such as their regenerative influence on immunological processes or their anti-proliferative and anti-inflammatory properties. There are many papers talking about the role of Vitamin D (VD) in the pathogenesis and manifestation of airway disease(6) and showed that VD deficiency is related to severity of asthma and pulmonary function(3-11). Maternal VD intake from foods during pregnancy may be negatively associated with risk of asthma and allergic rhinitis in childhood(7). In vitro, VD derivatives could inhibit IL-6 and IL-8 expression in human nasal polyp fibroblast cultures(12), regulate RANTES and IL-8 production in normal human dermal fibroblasts(13), and MMP-9 production in keratinocyte(14). The facts that nasal polyps and asthma share characteristic inflammatory features and histopathological findings of airway remodeling had motivated us to investigate the possibility that VD is also involved in the regulation of remodeling process and inflammatory cascade occurring with nasal polyp.

In order to study the role of vitamin D in the pathogenesis and manifestation of chronic rhinosinusitis with nasal polyp, we design the following study.

In vivo: We try to determine if serum Vitamin D level is lower in patients with chronic rhinosinusitis with nasal polyp (CRSwNP) and if low serum Vitamin D level is correlated with the severity of CRSwNP.

In vitro: We will use the cultured nasal polyp-derived fibroblasts to investigate the in vitro effect of vitamin D derivatives (calcitriol and tacalcitol) on the production of Matrix Metalloproteinase (MMP)-2 and MMP-9 by nasal polyp-derived fibroblasts...

Methods

Patients with latest diagnosis of CRSwNP undergoing elective sinus endoscopic surgery were recruited. All subjects with CRSwNP met diagnostic criteria as established by EPOS2007(15). Subjects with asthma, allergy (determined by Phadiotop), chronic systemic inflammatory disease, smoking, and malignancies will be excluded. Demographic characteristic information was collected. The severity of CRSwNP was assessed with the Lund-Mackay score and polyp grading system.

In vivo: Vitamin D status was assessed by measuring circulating 25-hydroxvitamin D (25OHD) by using commercial chemiluminescence immunoassay. Then, we will use Chi-square to test the difference of blood VD level in both groups.

In vitro: Resected polyp were used for primary fibroblast culture. The 4th to 8th passage of human fibroblasts were used for the experiments. MMP-2 and MMP-9 were measured by ELISA and Western blot according to manufacturer’s protocol.

Results

(1) In vivo testing: serum 25(OH) vitamin D level

Demographic data of the patients studied were presented in Table 1. There were no significant differences between patients with CRSwNP and Chronic Rhinosinusitis without polyps (CRSsNP) control subjects in age, sex distribution, or body mass index. Serum 25(OH) vitamin D levels (ng/mL±SD) were significantly lower in patients with CRSwNP (21.4 ng/mL±SD) than in those with CRSsNP (28.8 ng/mL±SD) (P<0.001).

Disease severity VS serum 25(OH) vitamin D levels

Serum 25(OH) vitamin D was inversely related to polyp grade (Figure 1). r=-0.63, p=0.001. Serum 25(OH) vitamin D was also inversely related to LMScore (Figure 2), and total IgE level (data not shown), but these did not each statistically significant.

Conclusions

In vivo study, we demonstrated that serum 25OHD levels in CRSwNP patients were significantly lower than those in CRSsNP patients. Serum 25OHD level was significantly and inversely related to the size of nasal polyps. We postulated that low vitamin D level might fail to reduce the level of cytokines released by inflammatory cells and fibroblasts, which might lead to the results of perpetuation of chronic inflammatory cascade. In vitro study, we had successfully demonstrated that Vitamin D could significantly suppress the TNF-α-induced MMP-2 and -9 secretion from cultured nasal polyp fibroblasts. Thus patients with vitamin D deficiency, low vitamin D level might fail to reduce the secretion of MMPs and result in perpetuation of chronic inflammatory sinus diseases.

The study on the influence of VD derivatives on inflammatory processes in NP may shed a light not only on the mechanism of its etiology but also prove their potential use in the pharmacotherapy of NP. Therefore, our results raise the possibilities for the development of more and specific types of treatment in nasal polyposis and warrant further investigation.

Vitamin D Decreases in Vitro Secretion of Matrix Metalloproteinase 2 and 9 from Nasal Polyp-derived Fibroblasts

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