Effect of calcifediol on chronic rhinosinusitis, a randomized clinical trial

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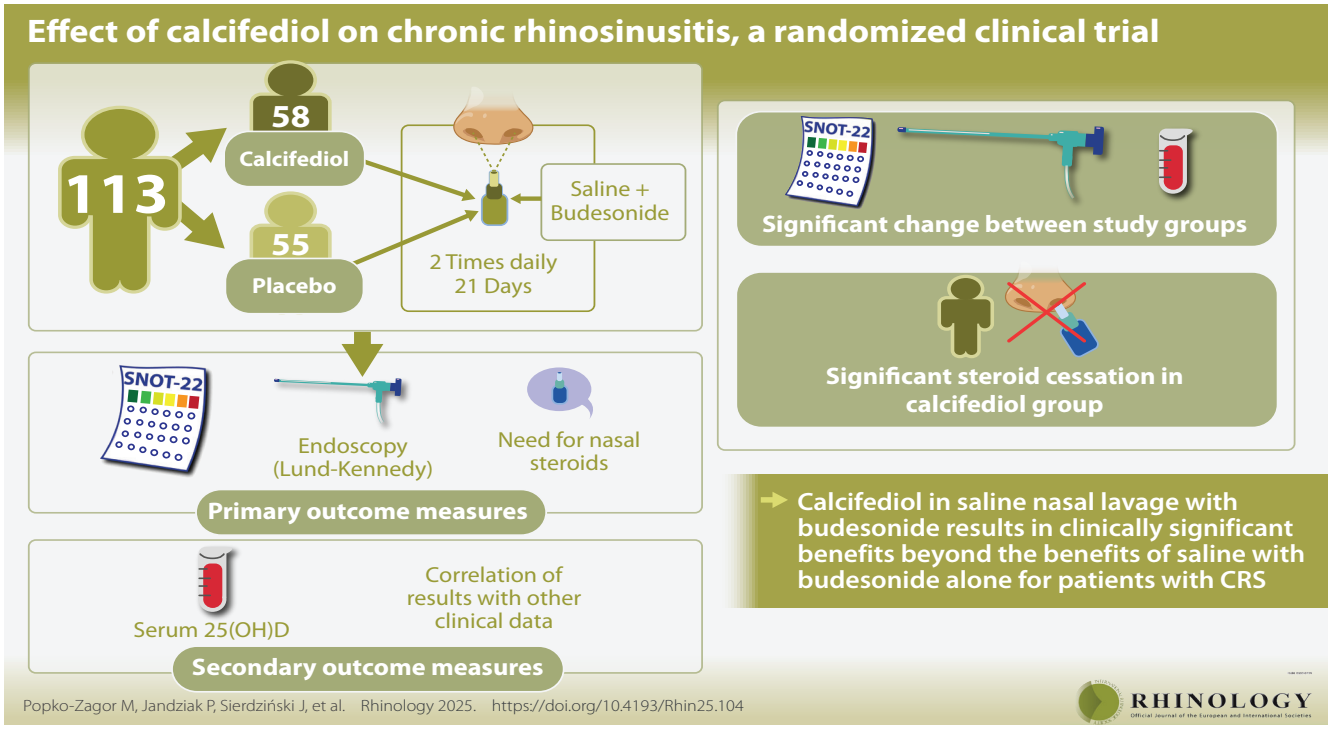

Abstract

Background: Recent studies suggest that intranasally administered vitamin D can be an effective treatment for patients with chronic rhinosinusitis (CRS). We performed a double-blind, placebo-controlled, randomized clinical trial to evaluate the effect of adding calcifediol to saline sinus irrigation with budesonide for patients with CRS.

Methods: A total of 113 adult patients with CRS were enrolled. Patients were randomized to either calcifediol (n = 58, 51%) or placebo (n = 55, 49%) lavage and were instructed to irrigate both nasal cavities twice daily for 21 days, with either calcifediol or placebo dissolved in a solution of saline with budesonide. The primary outcome measure was the change in Sino-Nasal Outcome Test (SNOT-22) scores, endoscopic examination scored by the Lund-Kennedy (L-K) grading system, and physician-reported response to treatment, as measured with decreased need for nasal steroids/cessation of nasal steroids in the calcifediol group compared with the placebo group. The secondary outcome measures included the change in serum 25(OH)D concentration and the correlation of results with other clinical data.

Results: 108 patients completed the trial. Significant changes in SNOT-22 score, L-K score and serum 25(OH)D were reported between the 2 study groups. A significant percentage of participants in the calcifediol group could cease nasal steroids.

Conclusion: Calcifediol in saline nasal lavage with budesonide results in clinically significant benefits beyond the benefits of saline with budesonide alone for patients with CRS.

Key words: calcifediol, chronic rhinosinusitis, randomized clinical trial

Introduction

Chronic rhinosinusitis (CRS) affects around 13 % of the population in the USA [1], and around 10.9% of the European population with major impact on the quality of life [2]. Despite a substantial burden on individuals, society and health economies, the treatment of CRS has had varying degree of success [2].

According to EPOS2020 both phenotyping and endotyping are used in management of patients with CRS [1]. Phenotyping consists of reporting patients' symptoms, the endoscopic view, and CT scan. Initially appropriate medical treatment with nasal corticosteroids, rinsing with saline, treating co-morbidities, smoking cessation, followed by systemic corticosteroids treatment and/or sinus surgery is applied. If the patient's symptoms of disease are uncontrolled despite appropriate medical treatment, the underlying pathophysiology of the CRS is addressed, i.e. endotyping is performed in order to differentiate between type 2 and non-type 2 disease in CRS. In type 2 disease there is the option to use aspirin desensitization (in patients with NSAID intolerance) or biologics [3, 4]. In non-type 2 disease long-term antibiotics or xylitol rinsing can be considered [5].

The pathophysiology of CRS is heterogeneous. Allergy, bacterial superantigens, biofilms, immunodeficiency, ciliary dyskinesia, osteitis, anatomical disorders, along with many different susceptibility genes, may contribute to the complex pathophysiology of CRS [1].

There is evidence that vitamin D influences CRS [6]. The reasons are that vitamin D receptors are abundantly present in paranasal sinuses and also in different tissues, nearly 3% of the human genome is regulated by a vitamin D-related pathway [6], and vitamin D exerts anti-inflammatory and antibacterial actions [7]. Vitamin D produced in the skin or acquired in diet is metabolized in the liver to 25-hydroxyvitamin D (25OHD) [8]. 25OHD is further metabolized in the kidneys or other tissues, e.g. sinunasal mucosa to its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D] [8,9]. 1,25(OH)2D plays an important role in mineralization of the skeleton and modulation of the immune system, a.o. exerting an anti-inflammatory effect [8,9].

The objective of the present study was to evaluate the effect of the addition of vitamin D to a large volume saline sinus irrigation with budesonide for patients with CRS in a double-blind, placebo-controlled, randomized clinical trial.

Materials and methods

Study design and participants

This study was a two-site, double-blinded, placebo-controlled, randomized clinical trial of patients with CRS. The trial was registered at EudraCT: 2019-003066-40. The diagram of study enrollment and participation is shown in Figure 1. Men and women 18 years or older with a diagnosis of CRS were recruited from the two medical centers (Bialystok and Warsaw, Poland) from March 4, 2022, to June 16, 2023. The study was approved by the Ethics Committee of Warsaw Medical University in Poland, no. KB 200/2018. All participants signed informed consent.

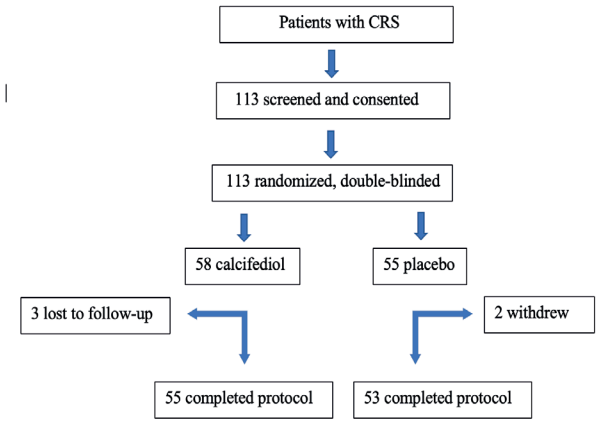

Figure 1. Diagram of study enrollment and participation.

Study participants were suffering from primary chronic rhinosinusitis, as documented by the recruiting physicians (M.Z. and E.P.), for 12 weeks or longer. Patients had 2 or more of the following symptoms consistent with CRS: mucopurulent drainage (anterior, posterior, or both), nasal obstruction, facial pain-pressure-fullness, and decreased sense of smell.

The following patients were excluded from the study: those with a history of cystic fibrosis (CF) and congenital mucociliary problems (e.g. primary ciliary dyskinesia (PCD)); antibiotic use in the 2 weeks prior to enrollment; previous sinus surgery; past/ongoing budesonide treatment for CRS; diagnosed with any malignancy in the 6 weeks prior to enrollment; identified oral vitamin D supplementation during the clinical trial; other reported nasal medicaments intake during the clinical trial; tuberculosis lung infection; and/or herpes infection. In addition, patients were excluded if they were pregnant, breastfeeding, or dependent on prolonged corticosteroid therapy for a comorbid condition.

Furthermore, the following clinical variables were assessed on the initial visit: age; sex; skin phototype according to Fitzpatrick scale [10]; comorbidities; body mass index (BMI); previous vitamin D supplementation 1000 IU/day (approx. 2 wks before the clinical trial); active smoking; nasal polyps; computed tomography (CT) Lund-Mackey scores, extension of the disease on CT (localized - unilateral, diffuse – bilateral). Severity of overall comorbidities was assessed with the Adult Comorbidity Evaluation-27 (ACE-27) grading system [11].

Interventions

All study participants received a 240 ml Irigasin Bottle Kit (Aflofarm), a 3-weeks supply of sodium chloride mixture. Participants were asked to use boiled and cooled down (to room temperature) tap water with the saline irrigation. Additionally, participants

received 42 capsules of budesonide (0.5 mg/capsule). After enrollment, a randomized block design, generated by the study randomizer (B.Z.), consecutively assigned participants to the treatment or placebo group. Participants in the treatment group received 3 bottles of calcifediol, while participants in the placebo group received 3 identical-appearing bottles of placebo= cholecalciferol. Each study bottle was assigned a number from 001 A, B, C to 130 A, B, C corresponding to the randomization schedule. The participants and all members of the study team except the study randomizer were blinded for the randomization assignment. Participants were instructed to dissolve 16 drops (8 drops for each nasal cavity) of the study drug into the Irigasin bottle along with the saline and one capsule of budesonide (0,5mg/ml), and to irrigate left and right nasal cavities with half of the contents of the nasal rinse twice daily for 21 days. All participants received verbal and written instructions on how to conduct the irrigation properly and were requested to administer the initial dose at the clinical trial site.

Additionally, on the first day of the clinical trial, before administration of the initial dose, and the next day after completion of the trial (22nd day, +2-3days), each patient underwent a laboratory test for serum 25OHD concentration. All study participants were informed to cease oral supplementation of vitamin D at least 2 weeks before the enrollment and not to expose themselves to the sun during the clinical trial. Those patients who were enrolled from June to August received additionally sun protecting factor 50.

On the first day of the clinical trial, before administration of the initial dose, women aged 18-49 consented to undergo a pregnancy test.

Doses of calcifediol

The calcifediol (25OHD) concentration was 150mcg/ml, 1 drop contained 5mcg calcifediol. The anti-inflammatory dose of 100nM calcifediol was established based on the report by Di Franco et al. [12]. 100nM calcifediol equal 40mcg calcifediol. Therefore 8 drops of calcifediol had to be administered to each nasal cavity. Thus, the total dose of calcifediol was 16 drops twice daily, i.e. 32 drops daily. 32 drops equal 160mcg calcifediol daily.

Placebo

Cholecalciferol was used as placebo. Cholecalciferol is converted in the liver by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D], i.e. calcifediol. There is no reported vitamin D-25-hydroxylase protein expression in sinunasal mucosa [8,9,12]. Therefore, cholecalciferol is biologically inactive in the sinunasal mucosa.

The cholecalciferol concentration was 500mcg/ml, i.e. 20 000 IU. 1 drop of cholecalciferol equals 500IU, 1mcg cholecalciferol equals 40 IU [13]. 8 drops of cholecalciferol equal 4000 IU to each nasal cavity, 16 drops of cholecalciferol for both nasal cavities equal 8000 IU twice daily. Thus, the total daily dose of cholecalciferol was 32 drops daily which equals 16000 IU (1 drop equals 500IU) [14].

Primary outcome measures

Patient-reported outcome measure

The primary outcome measure was the change, from pretreatment to posttreatment, in Sino-Nasal Outcome Test (SNOT-22) scores in the calcifediol group compared with the control group. The SNOT-22 is a validated, patient-reported out-come measure that captures the physical, functional, and emotional consequences of rhinosinusitis [14]. The SNOT-22 score is calculated as the sum of scores provided for each question and ranges from 0 to 110. All participants were asked to complete the SNOT-22 at baseline and on the 22nd day (+2-3days), after completion of 3 weeks treatment.

Physician-reported outcome measure

The objective change in sinus disease was assessed with endoscopic examination by the recruiting otolaryngologists (M.Z. and E.P.) at baseline and postintervention. The findings were recorded using the Lund-Kennedy grading system (L-K score) [15].

We investigated the effect of calcifediol/placebo on further CRS treatment after completion of the trial based on the EPOS 2020 criteria for current clinical control of CRS [2]. We assumed that partially controlled CRS justifies the reduction of nasal steroids and controlled CRS is a reason to cease nasal steroids on the follow-up on the 22nd day of the clinical trial.

The second follow-up was a consult by phone performed 7 days after the last doses of calcifediol/placebo. Thus, the total follow-up was 4 weeks which can be a limitation to our study.

The secondary outcome measures

The laboratory test for serum 25OHD concentration was performed on the first day of the clinical trial, before administration of the initial dose, and the day after completion of the trial (22nd day, +2-3days). The laboratory in our trial estimated the normal range of the serum 25OHD concentration to be between 30 ng/ml and 50 ng/ml [8].

Collection of other clinical variables: age; sex; skin phototype according to Fitzpatrick scale [10]; comorbidities; body mass index (BMI); previous vitamin D supplementation 1000 IU/day (approx. 2 wks before the clinical trial); active smoking; nasal polyps; computed tomography (CT) Lund-Mackey scores, extension of the disease on CT (localized - unilateral, diffuse – bilateral).

Statistical analysis

The sample size was determined using a 2-sided α of 0.05, with 80% power. A total of 120 ± 10 participants was required to

Table 1. Comparison of clinical characteristics between the calcifediol vs. placebo treatment groups in patients with chronic rhinosinusitis [a].

Characteristics of patients, n=108	Calcifediol n=55 (51%)	Placebo n=53 (49%)	Statistical analysis	p-value
Age mean (SD)	45 (13,32)	46 (13,83)	t-test = 0,60	0,54
Sex				
Male	18 (17)	11 (10)	chi-square =1,96	0,16
Female	37 (34)	42 (39)		
Skin phototype [b]				
I	10 (9)	22 (20)	chi-square =18,84	**<0,001**
II	34 (32)	11 (10)		
III	11 (10)	20 (19)		
IV-VI	0	0		
Comorbidities [c]				
none	26 (24)	23 (22)	chi-square = 0,16	0,6
mild	29 (26)	30 (28)		
moderate, severe	0	0		
BMI (SD)	24,93 (3,98)	26,43 (5,84)	t-test = 1,57	0,119
Previous vitamin D supplementation 1000 IU/day (approx. 2 wks before the clinical trial)	19 (17)	25 (23)	chi-square = 2,24	0,1
Active smoking				
yes	10 (9)	5 (5)	chi-square = 1,73	0,18
no	45(42)	48(44)		
Nasal polyps				
yes	9 (8)	5 (5)	chi-square = 1,15	0,28
no	46 (42)	48 (45)		
CT Lund-Mackey scores, mean (SD)	10,15 (5,25)	10,43 (4,28)	t-test =0,31	0,755
Extension of the disease on CT				
localized - unilateral	0 (0)	2 (2)	chi-square = 2,11	0,14
diffuse - bilateral	55 (50)	51(48)		
SNOT-22 baseline, mean (SD)	48,04 (19,51)	41,79 (17,42)	t-test = -1,75	0,083
Endoscopic L-K score baseline, mean (SD)	9,56 (2,39)	8,08 (2,8)	t-test = -2,98	**0,004**
25(OH)D ng/ml baseline, mean (SD)	31,11 (14,86)	30,31 (17,98)	t-test = -0,25	0,800
SNOT-22 3 wks, mean (SD)	15 (5,94)	23 (14,4)	t-student = 3,47	**<0,0001**
			Anova, F-test = 20,62	**<0,0001**
Endoscopic L-K score 3 wks, mean (SD)	1,47 (1,45)	6 (2,13)	t-test = 12,95	**<0,001**
			Anova, F-test = 171,90	**<0,0001**
25(OH)D ng/ml 3 wks, mean (SD)	35,93 (17,14)	29,18 (12,16)	t-test = -2,35	**0,021**
			Anova, F-test = 14,213	**<0,0003**
CRS treatment after clinical trial [d]				
reduction of nasal steroids	14 (13)	48 (44,5)	chi-square = 46,79	**<0,001**
nasal steroids cessation	41(38)	5 (4,5)		
Adverse events related to				
large-volume irrigation	31 (28)	27 (25)		
steroids	1 (0,9)	3 (3)	chi-square = 1,41	0,7
vitamin D	0 (0)	0 (0)		

Abbreviations: SNOT-22 - Sino-Nasal Outcome Test, endoscopic L-K score – endoscopic Lund-Kennedy grading system, BMI - body mass index. [a] Unless otherwise indicated, data are reported as number (percentage) of study participants. [b] Skin phototype according to Fitzpatrick (FZ) scale: Type FZI white skin, always burns, never tans; Type FZII white skin, always burns, minimal tan; Type FZIII white skin, burns minimally, tans moderately and

compare SNOT-22 scores, L-K scores, serum 25OHD concentrations, and other clinical variables between the 2 treatment groups.

The statistical analysis was carried with SAS 9.4 software. In all cases, results were considered statistically significant at $p<0.05$. Basic descriptive statistics of the analysed groups and variables consisted of a t-test and Chi-square test. Subsequently, ANOVA was used to check for significant differences in particular variables (L-K score, SNOT-22, serum 25(OH)D, and other clinical data) in the time course between the calcifediol and placebo groups. A 95% confidence interval (CI) around the difference was calculated and used to assess for clinically significant differences between the treatment groups.

Results

A total of 108 patients were enrolled in the study between March 4, 2022, and June 5, 2023. Patients were randomized to either calcifediol (n = 58, 51%) or placebo (n = 55, 49%) nasal lavage. 113 patients completed the baseline assessments and started their assigned interventions. Three participants were lost for follow-up, 2 patients were withdrawn due to an acute infection during the follow-up visit. 108 patients completed the intervention and postintervention assessments (Figure 1).

The baseline characteristics of all participants are summarized in Table 1. A statistically significant difference was found in the percentage of participants with skin phototype II in the calcifediol group (n = 34, 32%) compared to other skin phototypes in both treatment groups ($p<0,001$). 29 (26%) patients in the calcifediol and 30 (28%) patients in the placebo group were suffering from different comorbidities in a mild degree according to the Adult Comorbidity Evaluation-27 (ACE-27) grading system. Six (5%) patients in the calcifediol group and 5 (4%) patients in the placebo group reported allergy, 2 (1%) patient in the calcifediol group, 4 (3%) patients in the placebo group reported asthma. Given these data we could not obtain statistically significant results in an additional subanalysis to see if there was a variable response among different endotypes.

Furthermore, there were 9 (8%) patients in the calcifediol and 5 (5%) in the placebo group who suffered from CRSwNP. Again, it was not significant data to conduct further diagnostics elaborating on patient's endotypes.

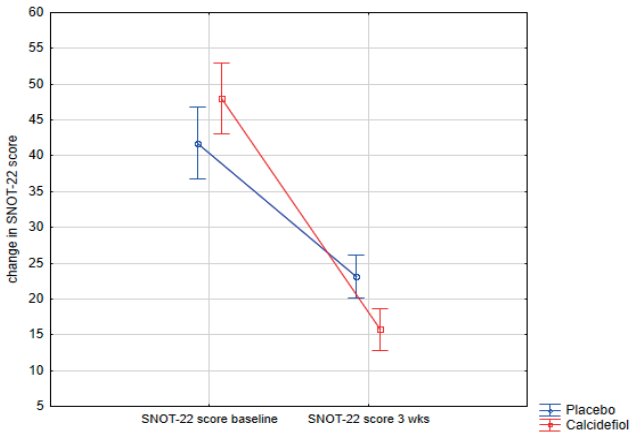

Figure 2. Comparison of change in SNOT-22 score between the calcifediol and placebo group (Anova, F-test=20,62, $p<0,0001$).

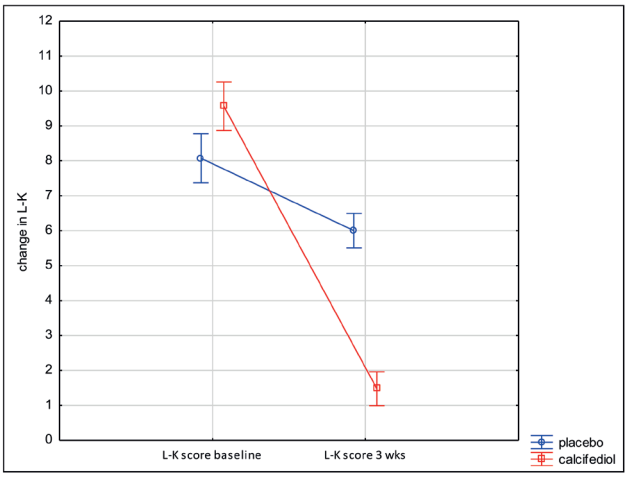

Figure 3. Comparison of change in L-K score between the calcifediol and placebo group (Anova, F-test=171,90, $p<0,0001$).

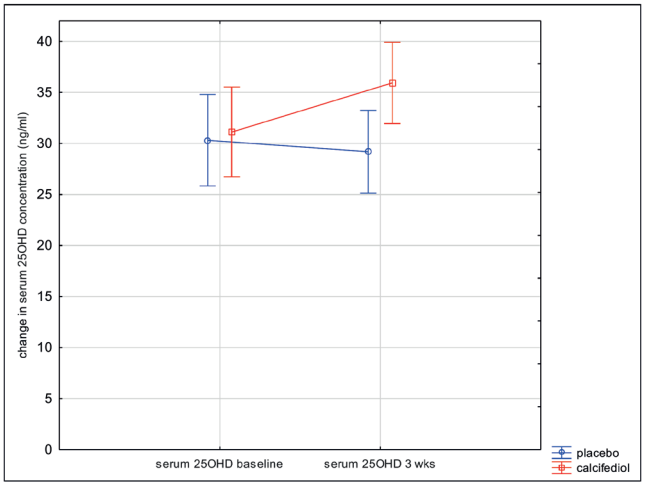

Figure 4. Comparison of change in the serum 25(OH)D concentration (ng/ml) between the calcifediol and placebo group (Anova, F-test=14,213, $p<0,0003$).

gradually; Type FZIV light brown skin, burns minimally, tans well; Type FZV brown skin, rarely burns, tans deeply; Type FZVI dark brown/black skin, never burns, tans deeply [10]. [c] Severity of overall comorbidities was assessed with the Adult Comorbidity Evaluation-27 (ACE-27) grading system [11]. [d] CRS treatment after completion of the clinical trial, by means of physician-reported response to the treatment based on the EPOS 2020 criteria for current clinical control of CRS [2].

There was no significant difference in the mean (±SD) SNOT-22 score at initial visit (baseline) between the calcifediol group 48,04 (±19,51) and placebo 41,79 (±17,42) (p<0,083). A significant difference was found in endoscopic L-K baseline score between the calcifediol 9,56 (±2,39) and placebo group 8,08 (±2,8) (p<0,004). Mean (±SD) 25(OH)D ng/ml at initial visit (baseline) was 31,11 (±14,86) and 30,31 (±17,98) in the calcifediol and placebo group, respectively.
No significant differences were found between the treatment groups in the distribution of clinical characteristics, i.e. age and sex, comorbidities, BMI, previous vitamin D supplementation, active smoking, nasal polyps, CT Lund-Mackey scores, extension of the disease on the computed tomography scans, and serum 25OHD baseline concentration (ng/ml).

ANOVA was used to explore significant changes in SNOT-22 score, L-K score, and serum 25(OH)D concentration in the two study groups before intervention and 3 weeks after intervention (Figures 2-4). The interaction effect between the times of assessment and the treatment groups was statistically significant for all tested variables. The mean (±SD) value in SNOT-22 after intervention was 15 (±5,94) points for participants in the calcifediol group and 23 (±14,4) points for those in the placebo group (t-test=3,47, p<0,0001) with significant change as a result of interaction with time (Anova, F-test=20,62, p<0,0001) (Figure 2). The mean (SD) value in endoscopic L-K scores after intervention was 1,47 (±1,45) points for participants in the calcifediol group and 6 (±2,13) points for those in the placebo group (t-test=12,95, p<0,001) with significant change as a result of interaction with time (Anova, F-test=171,90, p<0,0001) (Figure 3). The mean (±SD) value in serum 25(OH)D concentration after intervention was 35,93 (±17,14) points for participants in the calcifediol group and 29,18 (±12,16) points for those in the placebo group (t-test=-2,35, p=0,021) with significant change as a result of interaction with time (Anova, F-test=14,213, p<0,0003) (Figure 4). The serum 25(OH)D concentration increased significantly in the calcifediol group after 3 weeks.
In the calcifediol group there was a significantly higher percentage of participants who could cease nasal steroids administration, n=41, 38% (p<0,001). In the placebo group there was a higher percentage of participants who could reduce nasal steroids n=48, 44,5% (p<0,001).

Adverse events during the therapy were analysed. Most reported adverse events were related to a large volume irrigation, i.e. ear pressure, ear pain, facial pressure, headache, and post nasal drip, n=31, 28% and n=27, 25% in the calcifediol and placebo group, respectively. There were adverse events related to nasal steroid use, i.e. nasal bleeding and irritation, hoarseness, weakness, stomach ache, nausea, n=1, 0,9% and n=3, 3% in the calcifediol and placebo group, respectively.

Discussion

In this double-blind, placebo-controlled, randomized clinical trial, we found that the addition of 160mcg calcifediol daily to saline sinus irrigation with budesonide for 3 weeks resulted in a significant improvement in the patient-reported outcome measure (SNOT-22) as well as the physician-reported outcome measurements of CRS (L-K score, reduction of nasal steroids/cessation of nasal steroids). The secondary outcome measure of serum 25(OH)D concentration indicated a significant elevation of serum 25(OH)D in the calcifediol group after 3 weeks of trial. Furthermore, we found that there was a significantly higher percentage of participants who could cease nasal steroids in the calcifediol group, and a higher percentage of participants who could reduce nasal steroids in the placebo group. This may be due to the fact that active vitamin D, produced in the sinunasal mucosa from calcifediol, augments the anti-inflammatory function of budesonide.

Currently CRS management is based on both phenotyping, i.e. clinical features, and endotyping, i.e. type of inflammation. The preferred option advised by the EPOS2020 for treatment of primary CRS is appropriate medical therapy (AMT). AMT includes nasal steroids (drops/spray/rinses), saline rinses, patient's technique education, and considering oral steroids. If there is no improvement after 6-12 weeks additional work-up is recommended consisting of CT-scanning, skin prick tests, laboratory tests (e.g. elevated IgE, IL-5, eosinophilia, periostin) to differentiate between type 2 and non-type 2 inflammation, i.e. endotyping. Subsequently, the treatment is tailored depending on the type of inflammation. Endotyping may facilitate to predict the natural course of the disease and the prognosis in terms of recurrence after surgery and the response to different treatments, including nasal corticosteroids. It may also help to identify patients who need more extensive surgery, or plan more specific treatment, e.g. with biologics [16]. International guidelines, however, present conflicting evidence for including long-term antibiotics and oral steroids as part of AMT with regard to side-effects [17-19]. The appropriate moment for surgery for CRS is also controversial [19].

Identifying inflammatory patterns in CRS by endotyping became important since clinical phenotypes do not provide full insight into the underlying cellular and molecular pathophysiologic mechanisms of CRS [20]. It is recognized that CRS may reflect a dysfunctional innate and adaptive immune system or "endotypes" that can serve as targets for therapy.

There is substantial literature that shows that vitamin D acts as a modulator of adaptive and innate immunity locally within the respiratory epithelium [8], where the vitamin D receptors and its enzymes where detected [9]. Stokes et al. included seven, four prospective and three retrospective studies, with a total of 539

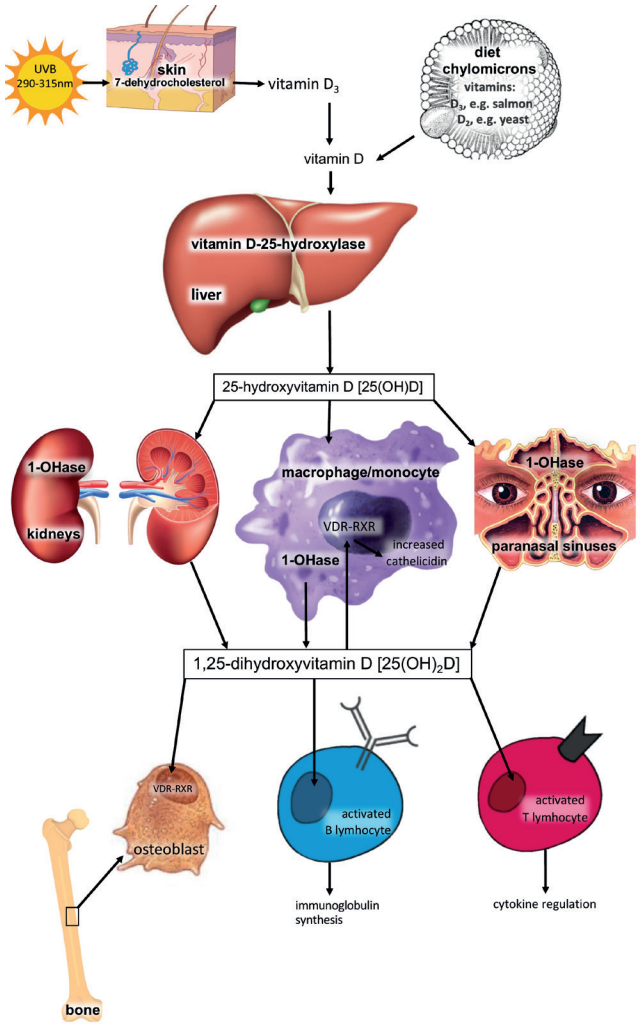

Figure 5. Aspects of vitamin D metabolism. Vitamin D from the skin and the diet is transported to the liver, where it is converted to 25-hydroxyvitamin D [25(OH)D]. This biologically inactive form of vitamin D is converted in the kidneys, or tissues such as sinunasal mucosa, macrophages/monocytes by 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to the biologically active form 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1,25(OH)2D plays an important role in the mineralization of the skeleton through the receptor in osteoblasts [the vitamin D receptor–retinoic acid x-receptor complex (VDR-RXR)]. Besides its skeletal function, 1,25(OH)2D increases the expression of cathelicidin in the nucleus of macrophages/monocytes and thereby promotes innate immunity, 1,25(OH)2D produced in macrophages/monocytes or in the epithelium of sinunasal mucosa acts locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis [8].

patients, in a systematic review on the role of vitamin D in CRS [21]. Significantly lower vitamin D levels were reported in the polypoid phenotypes of CRS compared with controls. Low vitamin D levels were associated with an increased degree of inflammation. The available evidence indicates that there is a significant relationship between low vitamin D level and polypoid CRS phenotypes [21].

Of great interest is the role that vitamin D can play in many chronic illnesses, including cancers, autoimmune diseases, infectious diseases, and cardiovascular disease [22-26]. The discovery that most tissues and cells in the body have the enzymatic possibilities to convert calcifediol to its biologically active form, i.e. 1,25-dihydroxyvitamin D [1,25(OH)2D], provided new insights into the function of this vitamin.

The biosynthesis of Vitamin D is well described in the literature. During exposure to solar ultraviolet B (UVB) radiation 7-dehydrocholesterol in the skin is converted to vitamin D3. From dietary sources vitamin D2 (ergocalciferol from yeast) and vitamin D3 (cholecalciferol from animal origin, e.g. salmon) are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D2 differs from D3 in having an additional -CH3 group. Both vitamins are represented in this article by vitamin D. In the circulation vitamin D is transported to the liver, where it is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D, calcifediol]. This form of vitamin D is biologically inactive and must be converted in the kidneys, or tissues such as sinunasal mucosa, macrophages/monocytes by 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to the biologically active form 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol]. 1,25(OH)2D is recognized by its receptor in osteoblasts [the vitamin D receptor–retinoic acid x-receptor complex (VDR-RXR)] and plays an important role in the mineralization of the skeleton. Besides its skeletal function, 1,25(OH)2D travels to the nucleus of macrophages/monocytes, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and thus inducing the destruction of infectious agents. Furthermore, it is likely that 1,25(OH)2D produced in macrophages/monocytes or in the epithelium of sinunasal mucosa acts locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis [8]. Figure 5 shows aspects of vitamin D metabolism.

Brain, prostate, breast, colon, sinunasal mucosa, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D [8,9]. 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis [8]. It decreases cellular proliferation of both normal cells and cancer cells [27]. An example of practical application is the use of 1,25-dihydroxyvitamin D3 and its active analogues for the treatment of psoriasis [28]. 1,25-Dihydroxyvitamin D is also an immunomodulator. Monocytes and macrophages exposed to a lipopolysaccharide or to

Mycobacterium tuberculosis up-regulate the vitamin D receptor and the 25-hydroxyvitamin D-1α-hydroxylase gene expression. Increased production of 1,25-dihydroxyvitamin D3 results in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents [29]. 1,25-dihydroxyvitamin D3 inhibits renin synthesis [30] increases insulin production [31] and increases myocardial contractility [26]. The results of a recent study by Bakhshaee et al. [32] demonstrate that patients who received vitamin D supplementation showed more improvement after endoscopic sinus surgery in terms of VAS, LK, and SNOT-22 scores, compared to the placebo group.

The assumption that vitamin D may be a drug for chronic rhinosinusitis appears to be justified. There are several advantages of the nasal route of vitamin D administration as shown in our study. The nasal vitamin D delivery was used to treat the sinunasal mucosa inflammation locally and access the venous circulation systemically to avoid parenteral administration. This means that vitamin D was beneficial both on a local and systemic level. The method of delivery in a large volume saline lavage is a simple process that leads to high patient compliance. Calcifediol is not a water-soluble vitamin. However, mixing calcifediol in a large volume irrigation and immediate irrigation increase the rate of distribution of particles evenly throughout the solvent and sinuses. Additionally, vitamin D is inexpensive and has both high patient acceptance and a high benefit-to-risk margin. Though the evidence regarding adding vitamin D to a large volume saline irrigation with budesonide is promising, more studies are needed to establish the vitamin D benefit when administered in other forms such as nasal spray in a fat-soluble solution.

Conclusion

In the present trial, we observed a clinically significant benefit of adding calcifediol to saline sinus irrigation with budesonide for chronic rhinosinusitis in patients who had not had previous sinus surgery. These results are promising and suggest that a large number of patients with primary CRS would benefit from nasal therapy with calcifediol.

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Trial registration

EudraCT: 2019-003066-40.

Abbreviations

25-hydroxyvitamin D [25OHD] – calcifediol; 1,25-dihydroxyvitamin D [1,25(OH)2D] – calcitriol; Vitamin D – vitamin D2 and vitamin D3; 1-OHase - 25-hydroxyvitamin D-1α-hydroxylase; VDR-RXR - vitamin D receptor–retinoic acid x-receptor complex; SNOT-22 – sinonasal outcome test 22; VAS – visual analogue scale; CRS – chronic rhinosinusitis; CRSwNP – chronic rhinosinusitis with nasal polyps; EPOS – European position paper on rhinosinusitis; L-K- Lund-Kennedy grading system; BMI - body mass index.

Authorship contribution

Conceived and designed the clinical trial: MPZ, PJ. Conducted the clinical trial: MPZ, Analyzed the data: MPZ, JS, ES, NR. Wrote the paper: MPZ. Revised the manuscript: MPZ, PJ, ES, NR.

Conflict of interest

The authors declare no conflict of interest.

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