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Nasal steroid use and osteitis development in chronic rhinosinusitis with nasal polyps

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Abstract

Objectives: Osteitis and tissue remodeling are inflammatory processes associated with the severity of chronic rhinosinusitis with nasal polyps (CRSwNP). Nasal steroids are the mainly recommended therapeutics in the treatment of the disease, and besides their beneficial effects, they may worsen osteitis via osteopenia. This study aimed to search for the coalescence of osteitis in CRSwNP and nasal steroid use (NSU).

Methods: A cross-sectional study was designed. Patients who underwent paranasal sinus computed tomography (PNSCT) imaging were queried, and the sino-nasal outcome test-22 (SNOT-22) was completed. Regular NSU was defined as a continued treatment for 2 months in the last 6 months. The cumulative period of NSU during the last 6 months was determined and classified as no use or, for 1 to 3 months, or more than 3 months. Lund-MacKay scores (LMS) and Global Osteitis Scores (GOS) were calculated for 10 sinuses via PNSCT.

Results: Sixty-two patients were included in the study. The mean GOS score was 5.7 ± 1.7 points higher in patients with regular NSU ($p = 0.002$, 95% *CI*: 9.2–2.2, *t*-test). LMS and SNOT-22 scores also were significantly higher for patients with regular NSU ($p = 0.036$ and < 0.001 consecutively). The mean GOS score showed a significant increase according to the cumulative period of NSU ($p < 0.001$, one-way ANOVA test). Similarly, LMS and SNOT-22 scores were also significantly associated with the duration of total NSU. GOS score showed a significant positive high correlation with LMS and SNOT-22 scores ($p < 0.001$, $r = 0.608$ and $r = 0.753$ consecutively).

Conclusions: This association found between the severity of GOS and NSU is probably due to the severity of the disease. However, it may question the value of the NSU effect in the development of osteitis. The presence of NSU should be investigated in future histopathological studies.

Level of evidence: IV

Keywords: Chronic rhinosinusitis, Nasal polyps, Nasal steroid, Osteitis, Bone remodeling, Global Osteitis Score

Background

Chronic rhinosinusitis with nasal polyps (CRSwNP) affects social and work-life quality and causes mental and physical dysfunction. The treatment of CRSwNP includes topical and systemic medicines such as antibiotics and corticosteroids; moreover, endoscopic sinus surgery (ESS) may be necessary for insufficient medical therapy for these patients [1]. Management of CRSwNP may vary according to the extent of the disease, the severity of the symptoms, the response to previous medical or surgical treatments, and comorbid diseases or conditions [2]. Topical nasal steroid use (NSU) is recommended as an important agent of medical treatment for chronic rhinosinusitis with polyps, and current meta-analyses demonstrate that it has beneficial effects on symptom control, polyp size, and polyp recurrence, with little evidence of significant adverse effects [3]. Also, the extent of the CRSwNP is related to the treatment option and symptom

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intensity, and objective evaluation can be made clinically [4], radiologically [5], or histopathologically [6–8].

The sino-nasal outcome test-22 (SNOT-22) is the most widely accepted questionnaire for an objective measurement of rhinological symptoms of the nasal mucosa and paranasal sinuses diseases [9]. Also, this questionnaire has been divided into four validated subscales representing categorical symptoms, including nasal, otologic/facial pain, sleep, and emotional function, and validity and reliability of SNOT-22 in the Turkish language have been previously confirmed [10].

Nasal steroids are the primary and frequently used drugs in the treatment of allergic or other rhinitis and chronic sinusitis [11–13]. The clinical effects of topical steroids increase the recruitment of inflammatory cells to the airway mucosa, selectively suppress local cytokine expression, inhibit mediator release, and support the normal mucosal structure [14]. Chronic inflammation of overlying sinus mucosa is accompanied by inflammatory changes on sinus bone, such as osteopathology, osteitis, neoosteogenesis, or osteopeni, and is also an established marker for severity and management of CRSwNP [6, 7, 15, 16]. Steroids may participate in the systemic circulation with nasal intranasal nebulization or spraying and make changes in the level of inflammatory cytokines, remodeling tissue markers [17, 18]. In addition, systemic steroid therapy or NSU may cause osteopenia/osteoporosis development in patients depending on dose and duration, but the effect of NSU on the sinus bones is unclear and was not discussed before [19]. The presence, severity, and extent of osteitis can be defined by a radiologist and an otolaryngologist in paranasal sinus computed tomography (PNSCT) images via loss of bone definition, hyperostosis, new bone formation, signal heterogeneity, or the thickness of sinus wall [20, 21] (Fig. 1). Histopathologically, osteitis can be defined as a process of neo-osteogenesis and bone remodeling through periosteal reaction and fibrosis, rather than bone inflammation [6, 22].

In this study, the relationship between the radiologically staging osteitis stage and NSU pattern was investigated.

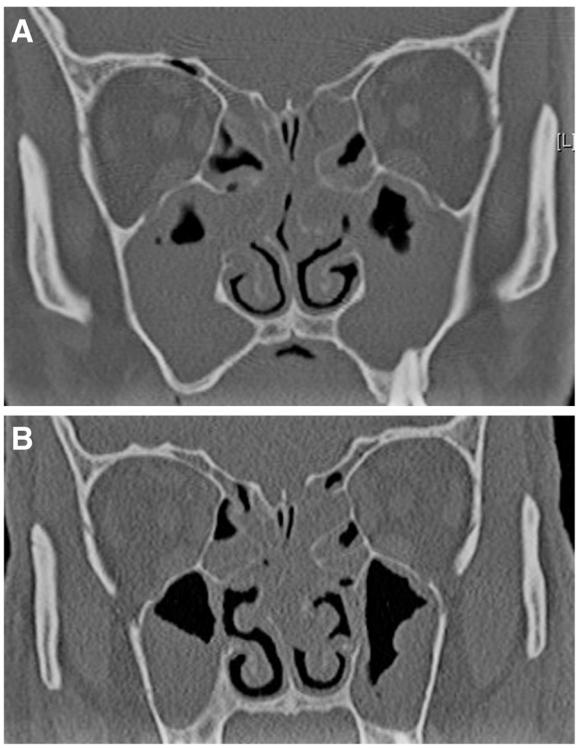

Fig. 1 Two consecutive PNSCT images in coronal sections. **A** Taken in May 2019, partial and mild demineralization areas with osteopenia are seen in the ethmoid cell walls. **B** PNSCT section taken 15 months later in September 2020 and crossing approximately the same level of ethmoid cells. The patient has been using 3 courses of irregular nasal steroids in this 15-month period. This slice of PNSCT was interpreted as a slight increase in osteitis

Methods

A cross-sectional study was designed at the second referral state hospital between October 2018 and March 2020. CRSwNP diagnosis is based on 12 weeks of continuous sinonasal symptoms and bilateral polyps in addition to positive findings for sinusitis on paranasal sinus computed tomography (PNSCT) scan as per guidelines outlined in the European Position Paper on Rhinosinusitis and Nasal Polyps [23]. Output parameters were evaluated based on the time the PNCST was received. Verbal and written informed consent was obtained from all the patients. Then, participants underwent PNSCT imaging according to complete medical indication and constant. Then, the volunteers were queried, and the SNOT-22 was completed by the patients. All subscales of the questionnaire (min. score: 0, max. score: 120) were completed. Regular NSU was defined as having received treatment for 2 successive months in the last 6 months. In addition, the cumulative period of NSU during the last 6 months was determined and classified as no use or, for 1 to 3 months, or more than 3 months. Only NSU with spraying form was accepted for study (mometason furoat, 0.05% spray, 1×400 μg). Verbal information about NSU courses from patients was compared with medical records, and participants presenting insecure data were excluded from the analysis.

Patients with other topical or systemic medical therapies for CRSwNP and previous nasal surgery were excluded from the study. Patients younger than 18 years old and patients with psychiatric or neurological diseases, the habit of smoking, previous trauma, surgery or radiotherapy in the head and neck region, and chronic

rhinosinusitis without nasal polyposis were also excluded from the study.

Lund-MacKay scores (LMS) were added for both sides to obtain a single score (min: 0, max: 24) [5]. Global Osteitis Scoring Scale (GOS) was calculated for 10 sinuses (right and left frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid; min: 0, max: 40) [20]. The study was reported according to the STROBE guidelines [24].

The results were compared between groups according to the NSU pattern with *t*-test or one-way ANOVA test. SPSS 22.0 program (IBM Corp., Armonk, NY, USA) was used for statistics.

Results

Sixty-two patients were included in the study. Forty-three (69.4%) of the patients were males, and 19 (30.6%) were females. The mean age was 43.0 ± 15.9 years. Overall summary of the findings is given in Table 1.

The mean GOS score was 5.7 ± 1.7 points higher in patients with regular NSU, and this difference was significant ($p = 0.002$, 95% *CI*: 9.2–2.2, *t*-test). LMS and SNOT-22 scores also were significantly higher for patients with regular NSU ($p = 0.036$ and < 0.001 consecutively, Table 2). In addition, the mean GOS scores showed a significant increase according to the cumulative period of NSU ($p < 0.001$, one-way ANOVA test). Similarly, LMS and SNOT-22 scores were also significantly associated with duration of total NSU (Table 3). Additionally, GOS, LMS, and SNOT-22 scores were not affected by gender ($p = 0.770$, 0.428, 0.620, *t*-test, respectively).

According to the multivariate analysis, GOS, LMS, and SNOT-22 scores were not statistically affected by regular steroid use ($p = 0.470$, 0.454, 0.907, respectively). However, the cumulative period of NSU was detected as a significant indicator for GOS, LMS, and SNOT-22 scores ($p < 0.001$).

GOS scores showed a significant positive high correlation with LMS and SNOT-22 scores ($p < 0.001$, $r = 0.608$, and $r = 0.753$ consecutively). No significant correlation was found between age and GOS scores ($p = 0.464$, $r = 0.10$).

Table 1 Summary of the findings

		n	%
Gender	Male	43	69.35
	Female	19	30.65
Regular nasal steroid use	No	27	43.55
	Yes	35	56.45
Cumulative period of NSU	0	21	33.87
	1–3 months	30	48.39
	> 3 months	11	17.74
		m	SD
Age		43.02	15.94
SNOT-22 score		69.05	26.84
Lund-Mackay score total		16.03	4.34
GOS score		20.02	7.75

GOS Global Osteitis Scale, *NSU* nasal steroid use

Table 2 Mean and standard (m + SD) deviations of outcome parameters according to regular nasal steroid use (NSU)

	Regular NSU				
	No, *n* = 27		Yes, *n* = 35		
	m	SD	m	SD	*p*
Age	50.89	14.09	36.94	14.73	< 0.001
GOS score	16.78	5.39	22.51	8.41	0.002
Lund-Mackay score total	14.78	3.37	17.00	4.79	0.036
SNOT-22 score	55.67	23.23	79.37	25.06	< 0.001

GOS Global Osteitis Scale

Discussion

It can be predicted that the need for nasal steroids increases with the severity of CRSwNP disease and symptoms. In this study, it was also desired to draw attention to whether the nasal steroid use contributed to the inflammation and osteitis in the sinus bone structures. Pathogenesis and epidemiology of osteitis in chronic rhinosinusitis (CRS) include clinical and biological such as previous sinus surgery, the severity of rhinosinusitis, the inflammatory pattern of rhinosinusitis, and biofilm formation [15]. Current reviews suggest a process of neo-osteogenesis and bone remodeling, rather than bone infection or inflammation for osteitis in primary CRS [15, 25]. Kuhar et al. [26] examined inflammatory parameters in 99 patients with CRSwNP and CRS without nasal polyp (CRSsNP), and they did not detect a significant effect of systemic or topical steroid use on histopathological parameters. These parameters include more than items such as degree of inflammation, basement membrane thickening, and fibrosis, but there is no parameter associated with bone remodeling. However, the number of patients with the use of any steroids was not given in this study, and the effect of steroid use on the inflammatory process on nasal mucosa or osteitis was not discussed comprehensively. Also, the dose, duration, and molecule of corticosteroids were not mentioned [26].

Zhang et al. [17] compared the efficacy of systemic and topical steroid administration (nasal inhalation or spray, budesonide) over a short period of 2 weeks via clinical and histopathological in a prospective controlled study. They reported that budesonide aqueous nasal spray did

Table 3 Mean and standard (m + SD) deviations of outcome parameters according to cumulative period of nasal steroid use (NSU)

	Cumulative period of NSU						
	0, $n=21$		1–3 months, $n=30$		> 3 months, $n=11$		
	m	SD	Mean	SD	m	SD	*p*
Age	47.57	13.86	42.90	17.57	34.64	12.25	0.091
GOS score	14.43	4.85	20.00	5.80	30.73	5.48	< 0.001*
Lund-Mackay score total	13.95	3.60	15.67	3.80	21.00	3.26	< 0.001
SNOT-22 score	47.95	20.84	71.27	20.73	103.27	6.54	< 0.001

GOS Global Osteitis Scale, *NSU* nasal steroid use

According to the post hoc Bonferroni test, there was no significant difference in GOS scores between patients without NSU and those with a total NSU for 1–3 months

* indicates the *p*-value for GOS score

not alter the level of any of these cytokines, compared to pretreatment values (except IL-10). They also found that budesonide aqueous nasal spray did not changed nasal polyp tissue level of any of remodeling markers matrix metalloproteinases (MMP-2 and 9), tissue inhibitors of metalloproteinases (TIMP-1 and 2), and collagen and albumin [17]. As stated in the literature, the 2-week nasal steroid treatment regimen in the treatment of CRSwNP is quite short, and this period usually exceeds 12 weeks [13].

Snidvongs et al. [22] demonstrated that CRS patients had osteoblastic activity together with woven bone formation. They reported that periosteal reaction (77.3%), partial fibrosis (90.9%), extensive fibrosis (4.5%), and neo-osteogenesis (77.3%) in bony samples. Specimen was obtained from patients who underwent ESS after failed medical therapy and no use of oral corticosteroid 4 weeks prior to surgery. Also, they found a significant correlation between tissue eosinophilia and the presence of neo-osteogenesis [22]. Wu et al. [27] confirmed that the BMP signaling pathway altered and highly associated with osteitis in nasal polyp tissue compared the normal control mucosa samples. They showed a downregulation of BMP7 and BMP9 with their receptors and enhancers, which are mediating the reduction in pro-osteoblastic activity in CRSwNP [27]. Long-term steroid treatment causes rapid bone loss, fractures, and osteonecrosis by a low mineral deposition and bone formation rate, through apoptosis and autophagy of bone cells. However, most of the studies examined the systemic use of corticosteroids [28]. Wang and Guo showed that BMP7 activity through BMPR2 receptor provides the protective effect against dexamethasone-induced apoptosis in primary osteocytes culture [29]. In addition, glucocorticoid-induced osteoporosis or bone tissue changes involve very different molecular and genetic pathways [28, 30, 31]. In a patient with CRSwNP, the method of administration of steroid therapy (systemic, topical), duration, and the molecule, together with the patient's response to this treatment, complicates the examination of relation between osteitis development and more steroid use.

The mean GOS scores were detected significantly higher in patients with regular NSU, in this study, and there was no significant difference in GOS scores between patients without NSU and those with a total NSU for 1–3 months. But, patients with a NSU more than 3 months had a significant high GOS score than other two group. Consistent with the literature, there is a clear relationship between NSU and the development of osteitis. Again, as shown in the literature, the extent of disease (LMS) and symptom severity (SNOT-22) were significantly correlated with GOS. Osteitis development has a significant association with CRSwSP severity and recurrence [32]. Therefore, regular and long-term use of NSU is an expected situation in a patient with CRSwSP prominent osteitis. This hypothesis is more appropriate than the view that "the development of osteitis is due to the use of NSU." Conducting a controlled clinical and histopathological study with a group of patients with CRSwNP who had never received corticosteroid therapy will clarify this discussion, if it is possible. The small sample size, narrow sampling period, retrospective data for nasal steroid use history, and lack of histopathological examination are the most important limitations of this study. On the other hand, this study poses an important question in order to reveal the chicken-egg problem on this subject and to shed light on future studies.

Conclusion

There is a tendency to develop osteitis with CRSwSP, and it is possible that this tendency may have made the bones of the paranasal sinuses vulnerable to the osteodegenerative effects of steroid use. So, it may be possible together to use longer-term nasal steroids due to the severity of osteitis (correlate with severity of CRSwNP) or to detect more severe osteitis due to nasal steroid use.

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Authors' contributions
Conceptualization, SŞ and Aİ. Data curation, SŞ and Aİ. Formal analysis, SŞ and Aİ. Funding acquisition, none. Investigation, SŞ and Aİ. Methodology, Aİ. Project administration, none. Resources, SŞ and Aİ. Software, SŞ and Aİ. Supervision, SŞ and Aİ. Validation, SŞ and Aİ. Visualization, none. Roles/writing — original draft, SŞ and Aİ. Writing — review and editing, SŞ and Aİ. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to ethical reasons but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. (Approval date: 02/12/2021, Number: 59763225-915.01-01-1174, Mardin Provincial Health Directorate). Verbal and written informed consent was obtained from all the patients.

Consent for publication
N/A

Competing interests
The authors declare that they have no competing interests.

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