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ORIGINAL ARTICLE

Long-Term Therapy with Corticosteroids in Nasal Polyposis: A Bone Metabolism Assessment

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Abstract Chronic rhinosinusitis associated with nasal polyposis (RSCwNP) affects 4% of the general population. As chronic condition, it requires chronic pharmacological treatment, whereas the surgical approach becomes necessary in obstructive and/or complicated cases. Intranasal and systemic corticosteroids (CS) represent the "Gold Standard" treatment for RSCwNP. The present study aimed to evaluate the side effects of prednisone in a group of patients with RSCwNP treated with long-term CS. In particular, attention was focused on bone disorders (osteopenia and osteoporosis) and prospective fracture risk increase. Forty patients (26 females, mean age 55.70 ± 14.03 years) affected by RSCwNP have been enrolled. Control group included 40 healthy subjects (17 females, mean age 56.37 ± 13.03 years). Nasal endoscopy, skin prick tests, nasal cytology, and bone densitometry were evaluated in all subjects. The likelihood of impaired bone metabolism (osteopenia or osteoporosis) was superimposable in both groups. Within RSCwNP group, no parameter was statistically significant in predicting a metabolism alteration.

Keywords Chronic rhinosinusitis · Nose-sinus polyposis · Corticosteroids · Densitometry · Osteoporosis

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Introduction

Chronic rhinosinusitis associated with nasal polyposis (RSCwNP) affects 4% of the world's population [1–3]. Pathogenesis is partially known [4]. Being a chronic condition, it requires a chronic pharmacological treatment [5]; a surgical approach becomes necessary in obstructive and/or complicated cases the [6]. Recently, it has been evidenced that RSCwNP can be divided into different phenotypes according to a Clinical-Cytological Grading (GCC) [7]. Due to this classification, it is actually possible to carry out targeted medical treatment [8] as recently promised by scientific societies in several medical fields. This has been defined as "Precision Medicine" [9].

Intranasal and systemic corticosteroids (CS) represent the "Gold Standard" treatment for RSCwNP [10]. The last twenty-year literature has reported unexpected effects in predisposed people or in patients exposed to long-term treatments. Beyond well-known side effects (arterial hypertension, diabetes, gastric ulcer, glaucoma, etc.) [11], modification in bone metabolism has been discovered. Patients can present bone disorders (osteopenia and osteoporosis) and prospective fracture risk increase [12]. The present study aimed to evaluate these side effects in a group of patients with RSCwNP treated with long-term CS schedules.

Materials and methods

Forty patients (26 females, mean age 55.70 ± 14.03 years) affected by RSCwNP have been enrolled. Inclusion criteria were documented RSCwNP diagnosis and long-term CS treatment. Exclusion criteria were comorbidities, including

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hypertension, diabetes, gastric ulcers, cataracts, glaucoma, bone fractures.

Control group included 40 healthy subjects (17 females, mean age 56.37 ± 13.03 years).

Nasal endoscopy, skin prick tests, nasal cytology, and bone densitometry were evaluated in all subjects.

Nasal Endoscopy

Nasal endoscopy was carried out by a 3.4 mm diameter flexible fiberscope (Vision-Sciences® ENT-2000). Nasal polyposis (NP) endoscopic classification proposed by Meltzer [13] was adopted (stage 0: no polyps visualized, open middle meatus; stage 1: small polyps noted in the middle meatus; stage 2: middle meatus completely filled with polyps; stage 3: polyps extending out of the middle meatus but above the inferior turbinate; stage 4: massive nasal polyposis filling the entire nasal cavity and sphenoethmoid region).

Skin Prick Test

It was performed using a panel of the most common aeroallergens (Stallergenes, Milan, Italy) according to the recommendations of the European Academy of Allergy and Clinical Immunology: house dust mite, grass mix, Parietaria, olive, cypress, mugwort, alternaria, ragweed, cat and dog dander [14].

Nasal Cytology

This procedure was performed by scraping the middle part of the inferior turbinate with a Rhino-Probe® device (Arlington Scientific). The sample was smeared on a slide, air-dried, then stained with the May-Grünwald Giemsa preparation. The type and cell number were examined using microscopy (Nikon® E600). Cell types were identified, and intracellular components were studied at 1000× in oil immersion. The mean number per 50 fields was calculated and reported. This noninvasive method allows to get representative samples of the nasal mucosa and its cellular components [15, 16].

Bone Densitometry

The bone mass density was calculated by means of dual-energy X-ray absorptiometry (DEXA) analysis (Hologic Inc EXPLORER QDR series-Mo 010-157, 35 Crosby Drive Bedford, MA, 01730 USA). DXA equipment was calibrated using a lumbar spine phantom and following the Hologic guidelines. The same operator (IC) performed all scans and analyses in order to ensure consistency. Participants were scanned in supine position, with their body and limbs fully extended and inside the limits set by the scan lines.

The BMD (g cm^{-2}) was measured in the head of the left femur with intra rotated hip and at the level of the first four lumbar vertebrae with hips flexed 90°. For hip and lumbar vertebra the BMD was used to calculate T-score and/or Z-score [17, 18]. Both T-scores and Z-scores are derived by comparison to a reference population on a standard deviation scale. T-score is bone density compared with what is normally expected in a healthy young adult of the same sex (normal is between + 1 and − 1; Osteopenia is between − 1 and − 2.5; Osteoporosis is ≤ − 2.5). The z-score is the number of standard deviations away from the average value of the reference group, consisting of people of the same age and gender. When the value is equal to or less than − 2, the definition is lower than the reference values.

Statistical Analysis

Continuous variables were expressed as M ± DS, categorical variables as percent (%). We have verified the Gaussian distribution of continuous variables. Comparison of groups was performed using Student's *t* test for independent samples for the continuous variables and using framework's test for categorical variables. A non-variated binomial logistic regression analysis was performed using as a dependent variable the presence of alterations in bone metabolism and as independent variables all the parameters studied. All significances were assumed for values of $p < 0.050$. All analyzes were carried out using the SPSS 20.0 software.

Results

No patient reported episodes of gastric ulcer and type 2 diabetes mellitus. Comparing patients with nasal polyposis (n = 40) with healthy group (n = 40), it emerged that the two populations were different in terms of bone metabolism parameter ($p = 0.971$), showing superimposable percentages for osteopenia (37.5% vs 40%) and normality (47.5% vs 45%) (Fig. 1). No differences were appreciated in terms of age, sex, and BMI (Table 1).

Patients with nasal polyps were subdivided by the Clinical-Cytological Grading (CCG) classification in mild (CCG = 1–3, n = 14), moderate (CCG = 4–6, n = 15) and severe (CCG ≥ 7, n = 11) as reported in Table 2. Treatment duration was similar ($p = 7.707$) among subgroups CCG = 1, CCG = 2 and CCG = 3 (85.42 ± 45.53 vs 74.40 ± 42.83 vs 70.45 ± 55.54 months). In addition, there was a significant difference concerning the nasal eosinophils: patients with more severe grading had more nasal eosinophilic infiltrate ($p = 0.001$). In contrast, no

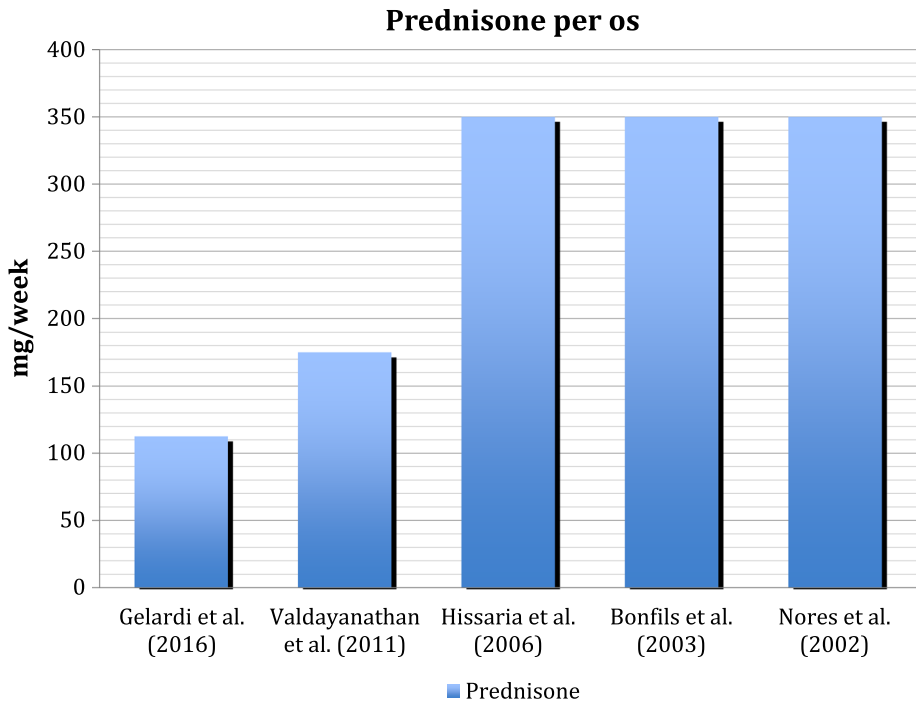

Fig. 1 Comparison of systemic corticosteroid weekly dosages in different RSCwNP studies

Table 1 Comparison of healthy group versus nasal polyposis group

	Healthy group (n = 40) M ± DS, n (%)	Nasal polyposis group (n = 40) M ± DS, n (%)	Statistical significance
Gender (m)	23 (57.5)	26 (65)	0.323
Age	56.37 ± 13.03	55.70 ± 14.03	0.824
Age division			0.968
18–35	3 (7.5)	3 (7.5)	
36–49	6 (15)	5 (12.5)	
50–60	14 (35)	16 (40.0)	
> 60	17 (42.5)	16 (40.0)	
BMI	25.73 ± 4.34	25.65 ± 4.17	0.929
Nasal eosinophils	0.01 ± 0.01	4.4 ± 2.6	0.023
Bone metabolism			0.971
Normal	18 (45)	19 (47.5)	
Osteopenia	16 (40)	15 (375)	
Osteoporosis	6 (15)	6 (15)	

Comparison of patients with nasal polyposis with healthy subjects showed overlapping percentages ($p = 0.971$) of osteoporosis (15% vs 15%), osteopenia (37.5% vs 40%) and normality (47.5% vs 45%)

other statistically significant difference was detected analyzing the remaining evaluated parameters, including alteration of bone metabolism ($p = 0.153$).

The likelihood of having impaired bone metabolism (osteopenia or osteoporosis) was verified individually for all predictors. Belonging to group of patients with polyps rather than healthy subjects did not increase the likelihood of being affected by osteoporosis or osteopenia (OR 0.904 [0.375–2.179], $p = 0.904$). Within polyposis group, no parameter was significantly predictive statistically for metabolism alteration (Fig. 2).

Discussion

The present study investigated clinical-diagnostic-therapeutic aspects of chronic rhinosinusitis with nasal polyposis (RSCwNP). This issue was considered fifteen years

Table 2 Comparison among groups with different severity disorders

	CCG 1–3 (n = 14) M ± DS, n (%)	CCG 4–6 (n = 15) M ± DS, n (%)	CCG ≥ 7 (n = 11) M ± DS, n (%)	Statistical significance
Gender (m)	10 (71.4)	10 (66.7)	3 (54.5)	0.670
Age	60.35 ± 14.49	50.13 ± 14.30	57.36 ± 11.33	0.131
Age division				0.312
18–35	1 (7.1)	2 (13.3)	0 (0.0)	
36–49	0 (0)	3 (20.0)	2 (18.2)	
50–60	5 (35.7)	7 (46.7)	4 (36.4)	
> 60	8 (57.1)	3 (20.0)	6 (45.5)	
BMI	26.98 ± 5.09	23.97 ± 2.32	26.25 ± 4.42	0.129
Care period (mounths)	85.42 ± 45.53	74.40 ± 42.83	70.45 ± 55.54	0.707
Allergy: yes	0 (0)	8 (53.3)	10 (90.9)	**0.000**
ASA sensitivity: yes	2 (14.3)	2 (13.3)	6 (54.5)	**0.029**
Asthma: yes	0 (0)	7 (46.7)	8 (72.7)	**0.001**
Nasal eosinophils	3.5 ± 1.9	4.4 ± 3.1	6.2 ± 4.0	**0.001**
Blood eosinophilia: yes	11 (78.6)	10 (66.7)	10 (90.9)	0.341
Blood neutrophilia: yes	7 (50.0)	7 (46.7)	6 (54.5)	0.924
Mast cells: yes	0 (0.0)	3 (20.0)	2 (18.2)	0.213
Hypertension: yes	0 (0.0)	2 (13.3)	1 (9.1)	0.385
Bone metabolism				0.153
Normal	10 (71.4)	5 (33.3)	4 (36.4)	
Osteopenia	4 (28.6)	7 (46.7)	4 (36.4)	
Osteoporosis	0 (0)	3 (20.0)	3 (27.3)	

CCG Clinical Cytological Grading

Bold values are significant

ago at the Center for Rhinology of the University Hospital in Bari (Italy). The research evidenced that RSC with and without polyposis was a multifactorial disorder [19],

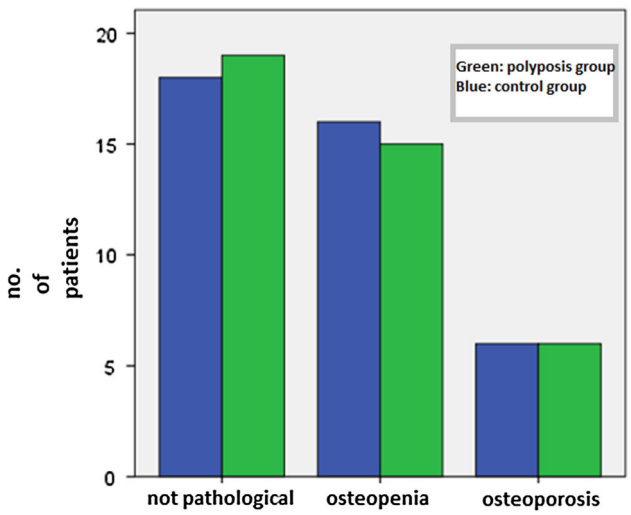

Fig. 2 Results of bone densitometry in terms of number of patients having no alteration in bone metabolism, osteopenia and osteoporosis. Comparison between nasal polyposis group (green) and healthy control group (blue)

characterized by various phenotypes: each of them could have a different therapeutic approach [20]. Over time, we evaluated in each patient possible comorbidity, including asthma, aspirin hyersensitivity, associated or not with specific inflammatory cell-type (i.e. neutrophil, eosinophil, mast cell, lymphocyte) [21]. The aims were to "phenotypize" the polyposis [7] and indicate a "targeted" therapeutic program for each different phenotype [8]. This concept has recently renamed "Precision Medicine" [9].

The ultimate goal is the control of symptoms (nasal obstruction, smell, reduction of surgical recurrences) and its complications (thrombophlebitis, abscesses, rhinoplasty syndrome, etc.), and also the prescription of medications and/or medical devices, in order to "calibrate" dosages avoiding risks associated with under-over-treatment.

Although our consciousness of using systemic CS doses far below those reported in the literature [22, 23], we investigated the possible long-term therapy CS side effects [11, 24, 25].

In literature, clear therapeutic references for the use of CS in nasal polyposis are missed. Although several therapeutic dosages has been reported, no time duration is clearly described. In fact, nasal polyposis is not a short-term or self-limiting disease. Densitometry modifications

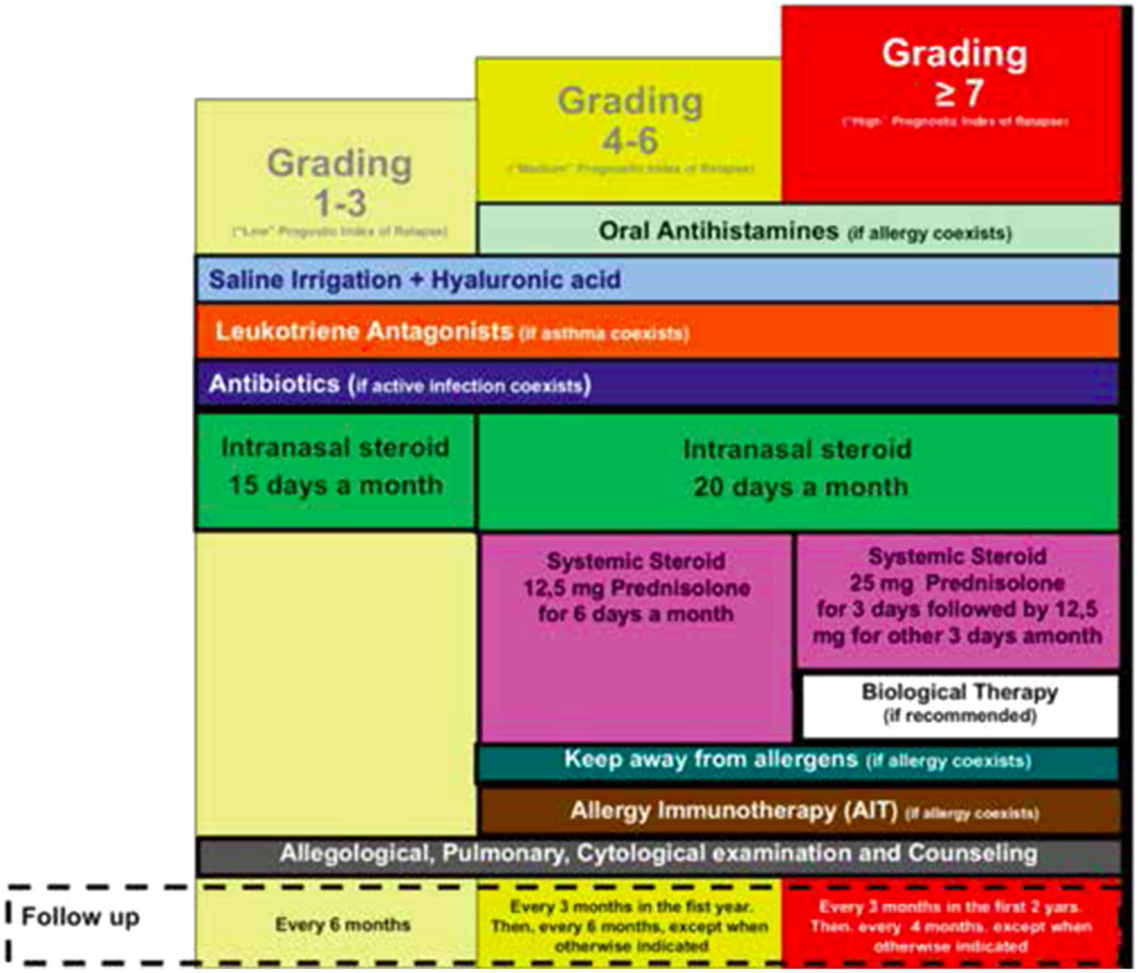

Fig. 3 Flow chart concerning modification of therapy according to clinical cytology grading in RSCwNP

of the bone after CS treatment for RSCwNP have never been referred in literature.

The current most interesting evidence was, for the first time, the total absence of statistically significant side effects in long-term treated patients with both intranasal and systemic CS. In fact, comparison of patients with nasal polyposis with healthy subjects showed overlapping percentages ($p = 0.971$) of osteoporosis (15% vs 15%), osteopenia (37.5% vs 40%) and normality (47.5% vs 45%) for treatment duration ranging from a minimum of 70.45 ± 55.54 to a maximum of 85.42 ± 45.53 months (Table 2). In addition, in subjects with mild GCC, the only treatment with topical corticosteroids (Mometasone Furoate) was referred for 15 days per month, both in subjects with mean/high CS, with the addition of systemic CS therapy (Fig. 3). No complications occurred after chronic treatment with CCS (hypertension, type 2 diabetes mellitus, gastric ulcer, cataracts and glaucoma). Therefore, in view of the "therapeutic" dosages indicated in a previous study [8], we have been able to foresee the actual safety of this treatment. According to our RSCwNP clinical-cytotoxicity adjustment protocol, the total corticosteroid dosage in patients with a higher grade of RSCwNP (also considering asthma) remained below 175 mg/week (Prednisone per os) as reported by Valdayanathan et al. [22].

The ENT specialist, treating patients with RSCwNP, should have reliable data on the actual safety of CS, in relation to a precise dosage, so can surely help the patient to control the disease, avoiding the "corticophobia" that promptly accompanies all subjects who, for various pathologies, resort to such drugs.

The effect of glucocorticoids on bone metabolism is based on direct mechanism (stimulation of bone re-absorption by osteoclasts, inhibition of proliferation and differentiation of osteoblasts with reduction of neonatal bone deposition, increase of osteoblast apoptosis and osteocytes) and indirect mechanism (altered calcium metabolism with reduced intestinal absorption, increased kidney excretion, reduced secretion of androgens and estrogens, inhibition of hypophysis secretion of gonadotropins). These effects would occur within the first 6–12 months of therapy [12, 26]. In this "case–control"

study, we analyzed patients treated with inhaled and/or systemic corticosteroid from a minimum of 12 months up to a maximum of 17 years. We were sure to have covered the complete temporal gap concerning the pharmacological activity of CS on bone metabolism. In terms of dosages, we can therefore underline a substantial absence of significant metabolic disorders, as indicated by the results of bone densitometry, considering the lack of fracture reported by patients in the past medical history, during therapy.

Interestingly, in the group of subjects without alteration in bone metabolism, it was noticed that polyps were superior to control group, although the value was not statistically significant. Paradoxically, it should indicate that low CS doses could have a "protective" role on bone metabolism. This aspect is definitely not new in literature. Other molecules have also shown, when administered at low doses, a protective role against specific equipment and/or pathologies [27, 28]. Other studies have been able to clarify the mechanism behind bone protection. In addition to the above factors, the underlying disease for which glucocorticoid therapy is given may also have a role in bone loss. Many of these diseases are associated with chronic inflammation, sometimes with superimposed episodes of acute inflammation. Pro-inflammatory cytokines stimulate bone resorption, thus resulting in bone loss. Glucocorticoids suppress inflammation and, therefore, may have indirect beneficial effects on bone that attenuate their adverse effects [12].

The current study has shown that belonging to the group of patients with polyps did not increase the likelihood of being affected by osteoporosis or osteopenia (OR 0.904 [0.375–2.179], $p = 0.904$). Within polyposis patients, no parameter was predictively statistically significant for alterations in bone metabolism.

According to international literature, the fracture risk assessment was made using the FRAX score [29, 30]. It was positive for only one female, over 60 aged (osteoporosis found in 6 patients). So, the CS pathological effects are dose-dependent [31].

Really, other factors may adversely affect bone metabolism, sometimes unreasonable, such as diet (low calcium intake, vitamin D, etc.), solar exposure, genetic background, and physical activity [26, 30]. An appropriate counseling, that deepen all aspects of information and management of patients with RSCwNP, is mandatory for both physician and patient [32, 33].

Conclusions

In conclusion, corticosteroids, both topical and systemic, represent the "Gold Standard" of RSCwNP's therapy. This condition will not be modified until new therapeutic approaches will prove to be more effective, evaluating same cost and toxicity levels [34, 35]. Medical Treatments Safe, guided by phenotype, today represents the true best-known innovation therapy named "Precision Medicine".

References

1. Fokkens WJ, Lund VJ et al (2012) European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl 23:1–298
2. Johansson L, Akerlund A et al (2003) Prevalence of nasal polyps in adults: the Skovdepopulation-based study. Ann Otol Rhinol Laryngol. 112:625–629
3. Larsen K, Tos M et al (2002) The estimated incidence of symptomatic nasal polyps. Acta Otolaryngol 122(2):179–182
4. DeMarcantonio MA, Han JK (2011) Nasal polyps: pathogenesis and treatment implications. Otolaryngol Clin N Am. 44(3):685–695
5. Saleh K (2014) Evaluation on quality of life in patients with nasal polyposis managed with optimal medical therapy. Allergy Rhinol 5:e2–e8
6. Rimmer J, Fokkens W, Chong LY, Hopkins C (2014) Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev 2014(12):CD006991
7. Gelardi M et al (2009) Nasal-sinus polyposis: clinical-cytological grading and prognastic index of relapse. J Biol Regul Homeost Agents 23:133–140
8. Gelardi M et al (2017) Non-surgical management of chronic rhinosinusitis with nasal polyps based on clinical-cytological grading: a precision medicine-based approach. Acta Otorhinolaryngol Ital 37(1):38–45
9. Passalacqua G, Canonica GW (2015) AIT (allergen immunotherapy): a model for the "precision medicine". Clin Mol Allergy 8:13–24
10. Alobid I, Mullol J (2012) Role of medical therapy in the management of nasal polyps. Curr Allergy Asthma Rep 12:144–153
11. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG (2017) Prevention and management of glucocortcoid-induced side effects: a comprehensive review. A review of glucocorticoid pharmacology and bone health. J Am Acad Dermatol 76(1):1–9
12. Compston J (2010) Management of glucocorticoid-induced osteoporosis. Nat Rev Rheumatol 6:82–88
13. Meltzer EO, Hamilos DL, Hadley JA et al (2006) Rhinosinusitis: developing guidance for clinical trials. Rhinosinusitis Initiative. J Allergy Clin Immunol 118(5 Suppl):S17–S61
14. Bousquet J, Heinzerling L, Bachert C et al (2012) Practical guide to skin prick tests in allergy to aeroallergens. Allergy 67:18–24
15. Gelardi M, Iannuzzi L, Quaranta N, Landi M, Passalacqua G (2016) Nasal cytology: practical aspects and clinical relevance. Clin Exp Allergy 46(6):785–792
16. Gelardi M (2012) Atlas of nasal cytology, 2nd edn. Edi Ermes, Milan
17. Bazzocchi A, Ponti F, Albisinni U, Battista G, Guglielmi G (2016) DXA: techinical aspects and application. Eur J Radiol 85(8):1481–1492
18. Kling JM, Clarke B, Sandhu NP (2014) Osteoporosis prevention, screening, and treatment: a review. J Women's Health 23(7):563–572
19. Larsen PL, Tos M (1991) Origin of nasal polyps. Laryngoscope 101:305–312
20. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, Schleimer RP, Ledford D (2013) Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document

of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 131(6):1479–1490
21. Gelardi M, Russo C, Fiorella ML, Fiorella R, Ciprandi G (2010) Inflammatory cell types in nasal polyps. Cytopathology 21(3):201–203
22. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B (2011) Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. Ann Intern Med 154(5):293–302
23. Brittany BE, Lal D (2013) Oral steroid therapy in chronic rhinosinusitis with and without nasal polyposis. Curr Allergy Asthma Rep 13(2):236–243
24. Van Staa T, Hgm Leufkens, Abenhaim L, Zhang B, Cooper C (2001) Use of oral corticosteroids and risk of fractures. J Bone Miner Res 16(3):581–588
25. Etminan M, Sadatsafavi M, Ganjizadeh Zavareh S, Takkouche B, FitzGerald JM (2008) Inhaled corticosteroids and the risk of fractures in older adults: a systematic review and meta-analysis. Drug Saf 31(5):409–414
26. Linee Guida per la Diagnosi, Prevenzione e Terapia dell'Osteoporosi. Società italiana dell' Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro (2015)
27. Hamada T et al (2017) Aspirin use and colorectal cancer survival according to tumor CD274 (programmed cell death 1 ligand 1) expression status. J Clin Oncol 13:JCO2O16707547
28. Drew DA et al (2017) ASPirin Intervention for the REDuction of colorectal cancer risk (ASPIRED): a study protocol for randomized controlled trial. Trials 18(1):50
29. Hanson L (2013) Use of the Frax screening tool to assess fracture risk in a long term care facility. Consult Pharm 28(7):426–431
30. Sozen T, Ozisik L, Basaran NC (2017) An overview and management of osteoporosis. Eur J Rheumatol 4(1):46–56
31. Dalle Carbonare L et al (2001) Comparison of trabecular bone microarchitecture and remodeling in glucocorticoid-induced and postmenopausal osteoporosis. J Bone Miner Res 16:97–103
32. Gelardi M, De Candia N, Quaranta N, Russo C, Pecoraro P, Mancini M, Luperto P, Lombardo G, Macchi A, Bocciolini C, Ciofal A, De Corso E, Ciprandi G (2016) The relevance of counseling in pts with nasal polyps. *Acta Otorhinolaryngol Ital* 98:23–28
33. Contrera KJ, Ishii LE, Setzen G et al (2015) Accountable care organizations and otolaryngology. Otolaryngol Head Neck Surg 153:170–174
34. Gandhi NA et al (2016) Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov 15(1):35–50
35. Penn R, Mikula S (2007) The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. Am J Rhinol 21:428–432