

Sinonasal outcome under aspirin desensitization following functional endoscopic sinus surgery in patients with aspirin triad

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Abstract Recalcitrant forms of recurrent nasal polyposis are problematic for patients as for rhinosurgeons. In aspirin-sensitive patients, aspirin desensitization is supposed to prevent recurrence by targeting the metabolism of arachidonic acid. Aspirin-sensitive patients ($n = 65$) following aspirin desensitization after functional endoscopic sinus surgery (FESS) for recurrent nasal polyposis under daily intake of 500-mg aspirin were compared to a post-FESS group ($n = 81$) of aspirin-sensitive individuals using exclusively topical mometasone. Quality of life (QoL) scores including sinonasal, pulmonal and general QoL items as well as endoscopic endonasal examination findings were evaluated during the postoperative follow-up period. After a follow-up period of minimum 18 months, a significant improvement in nasal obstruction, rhinorrhea, post nasal drip, sense of smell, facial pain, sleep quality and further general QoL items in desensitized patients was found compared to aspirin-sensitive controls. Improvement in sinonasal symptoms was evident, whereas the severity of asthmatic symptoms showed no significant changes. Although the pathophysiology of aspirin sensitivity is still not fully understood and the therapy is not sufficiently investigated, aspirin desensitization seems to have a

positive effect on QoL scores concerning sinonasal symptoms and should be regarded as a possible postoperative treatment modality for recurrent nasal polyposis in aspirin-sensitive individuals.

Keywords Aspirin desensitization · Aspirin sensitivity · Aspirin triad · Asthma · Functional endoscopic sinus surgery · Quality of life · Recurrent nasal polyposis

Introduction

In aspirin-sensitive individuals, a persistent and therapy-refractory form of nasal polyposis prevails, mostly coexisting with more or less severe asthma that is referred to as “aspirin triad”, “Samter or Widal triad” or aspirin-exacerbated respiratory disease (AERD) [1]. The severity of upper airway involvement manifests itself in early and recalcitrant recurrences of nasal polyposis, yet within a few months after sinus surgery, causing a frustrating situation for the patient as well as for the surgeon [2–4]. The mechanism by which sinus disease exacerbates asthma is not clearly understood, however, effective treatment of upper airways may improve and help to stabilise lower-airway disease [5, 6]. Since Szczeklik et al. described an increased susceptibility of nasal polyp cells to the inhibitory action of aspirin in aspirin-sensitive patients [7], arachidonic metabolism abnormalities have been considered a distinctive feature of nasal polyps in this subpopulation of patients. A significantly lower production of PGE₂ by nasal polyps and nasal polyp epithelial cells as well as a decreased expression of COX-2 in nasal polyps in these patients were reported [8, 9]. As Awad et al. have suggested, functional endoscopic sinus surgery (FESS) in asthmatic patients with nasal polyps results in an

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improvement of sinonasal outcomes as well as asthma symptom scores. For aspirin-induced asthma, these effects are significantly more pronounced in aspirin-tolerant patients than in their aspirin-sensitive counterparts [10, 11].

To minimise the intrinsic mucosal inflammation and thus to prevent recurrences of nasal polyps as well as revision endoscopic procedures, postoperative medical treatment is essential. Present recommendations for postoperative management of chronic sinusitis with (CRSwNP) or without (CRS) nasal polyps in general consist in application of topical and systemic corticosteroids (exclusively or in combination), as well as long-term antibiotics [12]. For particularly reluctant forms of disease, e.g., in case the patient fails to respond, treatment regimens with methotrexate [13], topical amphotericin and antibiotic (gentamicin/mupirocin) irrigations [14, 15], surfactant irrigations [16] and in an *in vitro* study even manuka honey [17] have been reported.

In the subpopulation of CRSwNP patients presenting with AERD, aspirin desensitization with subsequent acetylsalicylic acid (ASA) therapy is supposed to have a positive impact on the course of the disease [18–20]. The sinonasal benefit is mostly assessed in reduction of nasal polyp formation in pre-existing polyposis. In this retrospective analysis, objective and subjective parameters were used to evaluate the sinonasal outcome after FESS in patients with aspirin triad. Particularly, potential differences in the subgroups of AERD patients with postoperative aspirin desensitization compared to aspirin-sensitive controls treated exclusively with topical mometasone were elucidated to rule out the effect of ASA treatment as a therapeutic modality on the postoperative course of the disease.

Materials and methods

A retrospective chart review was performed of 146 adult aspirin-intolerant (AI) patients with recurrent nasal polyposis that were classified into two groups. An informed consent was signed by all patients. The data collection conformed to the privacy policy as determined by data security administrator at our institution and was approved by the Institutional Review Board at the University of Munich. Group I included 65 patients with AERD, who underwent aspirin desensitization with maintenance therapy of 500 mg of aspirin 4–6 weeks following FESS. Group II included 81 patients with AERD who were postoperatively observed (mainly patients with history of gastritis, ulcer, gastroesophageal reflux, patients with severe systemic disease and in case of planned or ongoing pregnancy). Two patients from group I and 39 patients from group II were excluded from the study due to lack of

sufficient postoperative data. A total of 105 patients (63 in group I = AI desensitized, 42 in group II = AI controls) were eligible for the 1 year follow-up and a total of 89 patients (56 in group I = AI desensitized, 33 in group II = AI controls) were eligible for the long-term data analysis in this study. The long-term follow-up was defined as the last-documented visit during the post-desensitization and post-FESS period, respectively, and was set at minimum 18 months (18–84 months, mean 35 months for AI-desensitized group and 18–72 months, mean 31 months for AI controls).

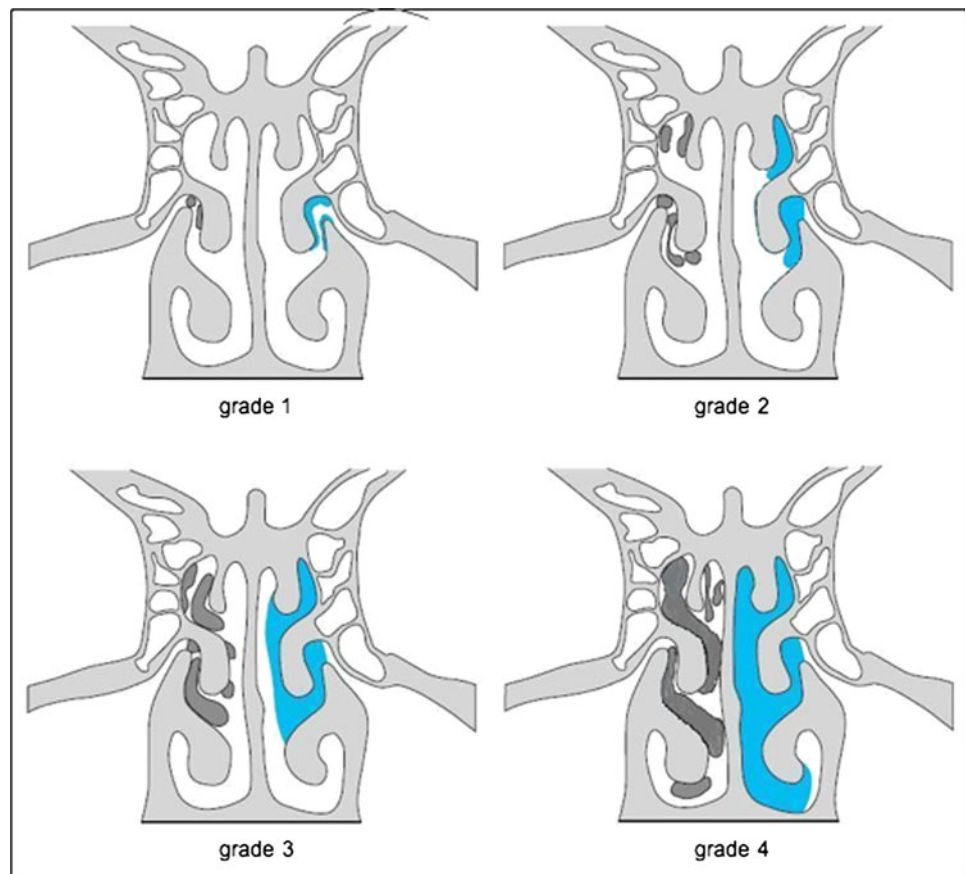
Inclusion criteria

Patients were selected using the following inclusion criteria.

1. Patient was diagnosed with recurrent nasal polyposis based on the history of at least one FESS procedure due to CRSwNP and the presence of nasal polyps of minimum grade II according to the Rasp polyp grading system [21] on the preoperative baseline examination.
2. Confirmatory evidence of mucosa pathology on CT scans supported endoscopic findings.
3. Aspirin sensitivity was determined by patients' history of severe lower and/or upper airway symptoms after aspirin or other NSAID intake.
4. Patient was diagnosed with asthma by a pulmonologist and received asthma therapy according to GINA criteria [22].
5. Postoperative follow-up of at least 18 months following surgery in our ORL-department was concluded.

Atopic status was defined as presence of positive *in vitro* allergy-screening test (Phadiatop) of regionally relevant aeroallergens and total IgE in serum method [23]. The decision for surgical intervention was made as patients symptoms were not improved after intensive medical treatment consisting of topical steroids, nasal saline irrigation, long-term antibiotics and/or short term (maximum 2 weeks) oral steroid bursts. Patients presenting with cystic fibrosis, Kartagener's syndrome, allergic fungal sinusitis, or immune suppression were excluded from the study. Asthma medication was used in all patients as prescribed by the pulmonologist consisting of inhaled bronchodilators and inhaled steroids. In both groups, no oral corticosteroids, theophylline or leukotriene modifying drugs were needed. FESS was performed on all patients under general anaesthesia. The procedure included polypectomy, uncinectomy, anterior ethmoidectomy and exploration of posterior ethmoid according to the criteria of the Messerklinger technique [24]. Determined by the extent of the affected mucosa, surgery was continued posteriorly with posterior ethmoidectomy, sphenoidectomy and

Fig. 1 Polyposis grading system according to Rasp as assessed by rigid endonasal endoscopy. Grade 0 (no polyps) not shown (illustration courtesy of G. Rasp, Salzburg, illustration modified)



opening of the frontal recess if these structures were involved. In case of extensively pneumatized concha bullosa, the lateral mucosa and bone were removed. In case of massive septal deviation, a septoplasty was performed. All patients were set on mometasone nasal spray (50 µg/2 puffs bid each side) and saline nasal irrigation at least 6 months prior to surgery. Methylprednisolone (starting with 32 mg per os on day 1 and 2; 16 mg on day 3 and 4; 8 mg on day 5 and 6) was used immediately pre- and postoperatively, respectively. Topical mometasone (50 µg/2 puffs bid each side) and saline nasal irrigation were continued as a constant medication during the follow-up period in both groups.

Four to six weeks following FESS aspirin desensitization with escalating doses of ASA beginning with 25 mg and incremental increasing at 50, 100, 150, 200, 300, 400 and 500 mg were administered orally under intensive care unit condition in the department of pulmonology. In case of volume/flow spirometry response and/or clinical respiratory symptoms in the patient, the threshold dose was repeatedly administered after recovery at minimum intervals of 3 h until no more response occurred. As soon as the patient tolerated 500-mg maintenance dose without adverse reaction for 24 h, he/she was discharged and continued to take 500-mg daily dose of ASA.

Demographic patient data were retrieved through chart review. Sinonasal symptoms were analysed using subjective and objective measures. Objectively, the extent of polypoid formation was determined according to Rasp polyp grading system using rigid endoscope (0°/4 mm, Karl Storz, Tuttlingen, Germany). Polyp recurrence was defined as grade 0 = no polyps; grade 1 = polyp growth in the roof of the ethmoid; grade 2 = polyp growth in the middle and upper meatus reaching no further than the lower part of middle turbinate; grade 3 = polyps exceeding the middle meatus; grade 4 = complete obstruction of nasal cavity [21] (see Fig. 1).

Subjectively, patient symptoms were assessed using a modified version of a pre-validated health related quality of life (QoL) questionnaire [25]. Severity of sinonasal (nasal obstruction, rhinorrhea, post nasal drip, sneezing, sense of smell, snoring, dry mouth, hoarse throat, facial pain), and asthmatic symptoms (shortness of breath, chest tightness, dyspnea, cough) as well as general QoL items (sleep disturbance, frustration, irritability, sadness, use of paper tissue) were rated by means of an interval scale with 1 = none; symptoms absent, 2 = mild; symptoms present but not annoying, 3 = symptoms present and annoying, 4 = severe; remarkable symptoms affecting daily life/activities. In addition, overall nasal and asthma condition

was rated using a visual analogue scale (VAS; 0 = no impairment, 10 = massive impairment). A minimum of 18 months of follow-up was required for inclusion in the study.

Statistical analysis was performed using Mann–Whitney *U* test for non-parametric data. A *p* value <0.05 was considered statistically significant.

Results

Baseline/preoperative parameters

Demographic characteristics

The demographic characteristics of both patient groups are represented in Table 1. Mean age in AI-desensitized group was 51 ± 11 years and in AI control group 50 ± 11 years. There were no significant differences in age, sex, and previous FESS rate between the groups. In 29 desensitized patients (44 %) and 34 controls (42 %), a positive atopic status was detected.

To fit the inclusion criteria of recurrent nasal polyposis, all patients underwent sinus surgery for at least the second time, e.g., the desensitization (group I = desensitized) or observation (group II = controls) was effected after minimum of two FESS-procedures.

Preoperative endoscopic findings

All patients were assessed endoscopically and via multiplanar CT-analysis concerning the extent of the disease. The preoperative endonasal endoscopic score according to Rasp polyp grading system showed massive polyp growth in both groups (AI desensitized mean 3.47 ± 0.11 vs. AI

controls 3.50 ± 0.06) showing no differences between groups (see Table 2).

Preoperative sinonasal and asthma scores, VAS and general QoL items

For a detailed disclosure of assessed symptoms (sinonasal and asthma domain, general QoL items) see Table 3. Except for facial pain that was more pronounced in the AI-desensitized group, there were no significant differences between groups in any of the items.

Compared to sinonasal symptoms, asthma symptoms were considerably less pronounced in both groups. Thus, the VAS score for sinonasal and asthma condition was more severe for the sinonasal domain compared to the asthma related symptoms.

Follow-up parameters

Endoscopic findings on follow-up

Sixty-three patients had completed 1 year of follow-up after aspirin desensitization on 500-mg daily intake. One patient discontinued ASA due to headache and one patient due to gastrointestinal irritation. These patients were not included in the final evaluation. No further side effects related to the ASA therapy were reported.

The data of 56 patients from the desensitized group were eligible for a long-term follow-up. The end point indicates the last documented contact of minimum 18 months, on average 35 ± 20 months (18–84 months) in the post-FESS and post-desensitization course. One patient discontinued ASA therapy after 20 months due to headache. Two patients discontinued ASA due to gastrointestinal irritation. Four patients were lost to follow up. Three desensitized patients had to stop ASA treatment for maximum 6 weeks due to surgery (no sinus surgery) and were postoperatively re-desensitized again. No patient underwent further sinus surgery.

Forty-two patients from the AI control group receiving exclusively topical mometasone for polyp control had completed 1 year of follow-up. In all patients, recurrent polyposis was observed. In the long-term follow-up (minimum 18 months, mean 31 ± 14 months), 33 patients were eligible. Seven patients underwent revision sinus surgery due to massive impairment of nasal patency and anosmia. Sixteen patients were using oral steroid bursts to improve sinonasal symptoms.

There were significantly less polyp recurrences in the AI-desensitized group compared to the AI control group on 1-year follow-up as well as on the long-term follow-up examination ($p < 0.001$, respectively). For mean values see Table 2.

Table 1 Demographic characteristics of aspirin-sensitive patients with postoperative aspirin desensitization (AI desensitized) and without desensitization (AI controls) on the baseline visit

	AI desensitized (<i>n</i> = 65)		AI controls (<i>n</i> = 81)	
	<i>n</i>	%	<i>n</i>	%
Age				
<25	0	0	1	1
26–50	31	49	39	48
51+	32	51	41	51
Sex				
Male	27	43	34	42
Female	36	57	47	58
Previous FESS				
1–2	28	44	46	55
>2	35	56	35	45

Table 2 Endonasal endoscopic findings graded according to Rasp polyp grading system on preoperative (baseline), 1 year postoperative (1 year) and minimum 18 months postoperative (long term) visit in aspirin-sensitive patients with postoperative aspirin desensitization (AI desensitized) and without (AI controls) aspirin treatment

Endoscopy Rasp score	Baseline			1 year			Long term		
	<i>n</i>	Mean ± SD	<i>p</i>	<i>n</i>	Mean ± SD	<i>p</i>	<i>n</i>	Mean ± SD	<i>p</i>
AI desensitized	63	3.47 ± 0.11	0.903	56	1.00 ± 0.18	0.000*	51	1.47 ± 0.186	0.000*
AI controls	81	3.53 ± 0.06		42	3.13 ± 0.15		33	3.06 ± 0.175	

* Significant differences

Table 3 Baseline means of clinical assessment before surgery and during subsequent course in aspirin-sensitive patients without (AI controls) and with postoperative aspirin desensitization (AI desensitized)

Quality of life	AI desensitized						AI controls					
	Baseline		1 y		Long term		Baseline		1 y		Long term	
	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>
Sinonasal												
Nasal obstruction	3.20	65	1.71*	63	1.77*	56	3.24	81	2.70	42	2.58	33
Rhinorrhea	2.84	65	1.43*	61	2.00	56	2.66	81	2.56	40	2.35	33
Post nasal drip	2.90	65	1.81*	63	2.00*	56	2.84	81	2.59	42	2.58	32
Sneezing	2.50	65	1.76	60	1.96	56	2.21	80	2.04	40	1.93	30
Sense of smell	3.80	65	2.56*	63	2.94*	56	3.72	81	3.52	42	3.55	33
Snoring	2.53	65	1.71	61	2.00	55	2.58	79	2.00	39	2.03	30
Dry mouth	2.90	64	1.45*	61	1.56*	55	2.78	80	2.44	38	2.48	31
Hoarse throat	1.93	65	1.50	60	1.32	56	1.74	77	1.56	39	1.53	30
Facial pain	2.73	65	1.36*	63	1.54*	56	2.15	80	2.04	41	2.21	31
Pulmonal												
Short breath	2.32	62	1.83	60	1.87	53	2.20	75	2.04	39	1.97	29
Chest tightness	2.14	61	1.61	58	1.64	55	1.85	72	1.73	36	1.69	29
Dyspnea	2.10	64	1.66	59	1.50	55	1.73	77	1.54	36	1.45	29
Cough	2.25	64	1.66	59	1.57	55	2.41	78	1.96	37	1.86	29
General												
Sleep disturbance	2.87	65	1.53*	63	1.60*	55	2.72	81	2.48	41	2.43	33
Frustrated	2.69	62	1.83*	60	1.73*	54	2.62	77	2.41	39	2.40	32
Irritable	2.43	62	1.70	60	1.67*	54	2.37	76	2.15	39	2.30	30
Sad	2.50	60	1.60	60	1.43*	54	2.38	76	2.19	37	2.13	30
Tissue use	2.93	64	1.87*	62	2.16*	55	2.98	80	2.85	40	2.87	31

Mean base, preoperative assessment/baseline; 1 y, 1-year follow-up; long term, follow-up of minimum 18 months following surgery

* Significant differences (*p* < 0.05)

Sinonasal and asthma scores, VAS and general QoL items on follow-up

Sixty-three patients from the AI-desensitized group and 42 patients from the control group had completed 1 year of follow-up and were assessed concerning their health related QoL as described above. There were significant better symptom ratings in the AI-desensitized group compared to AI controls for following symptoms: nasal obstruction, rhinorrhea, post nasal drip, sense of smell, sleep

disturbance, dry mouth and use of paper tissue. For the long-term follow-up data of 56 patients from the AI-desensitized group and 33 patients from the control group were eligible. There were significant different symptom ratings for the following symptoms: nasal obstruction, rhinorrhea, post nasal drip, sense of smell, sleep disturbance, dry mouth and use of paper tissue. All differences showed better QoL ratings in the AI-desensitized group. For detailed disclosure of QoL assessment after 1 year and on the long-term follow-up, see Table 3.

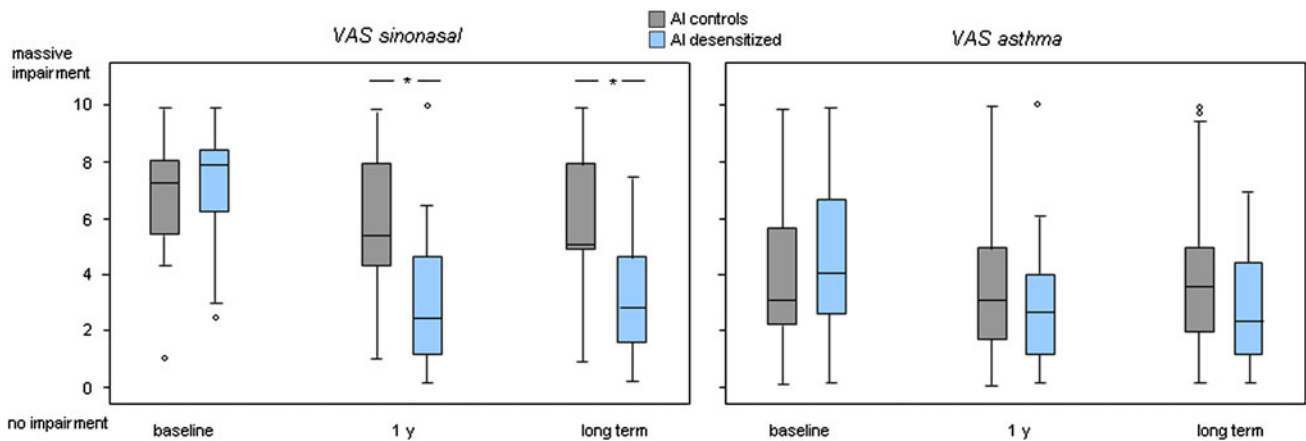


Fig. 2 VAS assessment preoperatively and on follow-up visits (1 year and long term, mean 31 months in AI control group, mean 35 months in AI-desensitized group) comparing the sinonasal (*left*)

and asthma condition (*right*) as assessed by means of VAS for AI-desensitized and AI control group, respectively. Significant differences ($p < 0.05$) are indicated with *asterisk*

Both groups were comparable concerning the VAS ratings for sinonasal and asthma condition on baseline visit (sinonasal condition $p = 0.11$, asthma condition $p = 0.25$). VAS ratings showed significant better results in overall sinonasal condition and no difference in the asthma condition for desensitized group compared to controls on the 1-year ($p < 0.001$ sinonasal, $p = 0.69$ asthma) as well as on the long-term follow-up ($p < 0.001$ sinonasal, $p = 0.46$ asthma), respectively (see Fig. 2).

VAS ratings assessing asthma condition were not as severe preoperatively as compared to sinonasal condition. In the course of the follow-up period, there was no improvement as compared to baseline or no differences between the groups were detectable.

Discussion

The presented data support the hypothesis that aspirin desensitization may be valuable in the treatment of sinonasal disease in patients with AERD. There is a general assumption in the previous literature that sinonasal disease in patients with AERD is more severe than in aspirin-tolerant patients. Beneficial effects of endoscopic surgery on the sinonasal outcome in patients with nasal polyps were shown in several studies. However, in aspirin intolerant patients, the postoperative positive effects were not or significantly less pronounced than in aspirin-tolerant asthmatics [10, 11, 26]. Because surgery does not directly affect the underlying inflammatory component of the disease, a postoperative treatment is also necessary. In our experience, which is consistent with numerous publications, aspirin desensitization should be considered as treatment in AERD patients with refractory CRSwNP requiring high-dose systemic steroid bursts and repeated

revision surgeries of the sinuses [18, 28]. In concordance with findings by Fergusson et al. [27], there is no “melting away”-effect of aspirin desensitization on preexisting nasal polyps in our experience. However, the better postoperative sinonasal long-term outcome observed in the desensitized group compared to patients those received the same conventional treatment but were not desensitized, may imply that long-term aspirin desensitization prevents or retards ongoing inflammatory process of the sinuses. As both patient groups were comparable concerning the parameters of disease activity as objectively and subjectively assessed, aspirin desensitization may have been responsible for the improved sinonasal outcome in desensitized individuals.

No significant differences in asthma score was observed during the follow-up period, which may be explained by the already low asthma symptom score on the baseline visit. This is also reflected in the asthma medication applied in both patient groups which did not exceed inhaled bronchodilators and inhaled steroids. None of the patients was on oral steroids, leukotriene-modifying drugs or theophylline. Generally speaking, the asthma disease in the investigated groups seemed to be mild and is not in line with numerous publications describing a severe, difficult to control asthma in AERD individuals with correspondingly detectable positive effect of aspirin desensitization therapy on asthma parameters [29–31]. The patients presented in our ORL department seemed more severely affected by their sinonasal symptoms than by asthma, which may have led to a bias in assessing AERD as a primarily sinus affecting disease.

Typically, patients with aspirin triad suffer from difficult to severe attacks of asthma within 30–90 min after ingesting ASA or other NSAIDs, usually accompanied by nasal symptoms (rhinorrhea and/or nasal congestion) [32].

Although it can be confirmed by oral, inhaled, nasal or intravenous placebo-controlled challenge tests with increasing doses of aspirin [33–36], AERD remains a clinical diagnosis made on clinical presentation of the triad components with adult onset asthma, aspirin sensitivity and nasal polyps. Thus in this study, the diagnosis of the disease was based on positive history of aspirin sensitivity, which is the hallmark of this syndrome and is considered as a significant and reliable indicator of the syndrome [37].

To determine a stage of the disease and evaluate therapeutic effects, objective parameters are required besides subjective assessment via QoL questionnaires. We used Rasp polyp grading system for its easy availability and convenience as it is our practice to rely on endoscopic examination and patients symptoms on follow-up visits. Widely used Lund–Mackay-score for CT features was not used in this study, particularly to prevent the patient exposure to radiation from widespread use of CT scans for which a potential carcinogenetic effect has been reported recently [38]. Indication for this imaging was reserved exclusively for cases with acute complications or for planning of revision surgery and not for follow-up purposes. Interestingly, no relationship was found between CT-scan findings and patient perception of sinonasal symptoms as extensively shown by Stewart et al. [39]. In a comparison of sinus surgery outcomes in aspirin-sensitive and aspirin-tolerant patients, Awad et al. [10] also found a discrepancy between objective and subjective outcomes as assessed by Lund–Mackay-score and five-level-scale of patients' symptoms measurement. Objective measurement of nasal obstruction, which is a crucial parameter in sinonasal assessment is usually performed via anterior rhinomanometry and used also in AERD patients as an objective criterion [40]. However, anterior rhinomanometry as an objective method for nasal patency assessment is controversial as it strongly depends on the person performing the measurements. Subjective assessment of nasal obstruction provides important information about how the patient senses the severity of the symptoms. The lack of correlation of subjective scores of nasal obstruction with objective measures of nasal obstruction have partly led to the conclusion that objective measures such as rhinomanometry may be of limited clinical value [41].

The appropriate maintenance dose of ASA remains a controversial issue. A wide range of investigated doses from 100- to 1,300-mg daily per os as well endonasal administration of ASA showed significant improvement of rhinosinusitis symptoms [42–45]. In this work, a dose of 500-mg ASA daily was administered as we dispose of broad experience with this dosage at our institution and only very low drop-out rate due to side effects was observed.

Conclusion

In the present work, the improved outcome of objective and subjective parameters of sinonasal disease on long-term follow-up (nasal endoscopy findings as well as symptoms like nasal obstruction, sense of smell, post nasal drip) indicate the better disease control in the aspirin-desensitized group as compared to aspirin-sensitive counterparts treated exclusively by topical mometasone and is presumed to reflect the effect of aspirin-desensitization therapy. Aspirin desensitization should be considered as valuable post-FESS treatment modality in AERD individuals.

Conflict of interest The authors declare that there is no conflict of interest.

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