

Clinical benefits of aspirin desensitization in patients with nonsteroidal anti-inflammatory drug exacerbated respiratory disease are not related to urinary eicosanoid release and are accompanied with decreased urine creatinine

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ABSTRACT

Background: Treatment with acetylsalicylic acid (ASA) after desensitization may be a therapeutic option in patients with nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NERD). The mechanisms that lead to improvement in rhinosinusitis and asthma symptoms remain unknown.

Aim: To attribute the documented clinical effects of ASA treatment of chronic rhinosinusitis and/or asthma to the release of eicosanoid metabolites in urine.

Methods: Fourteen patients with NERD were successfully desensitized, and, eventually, eight patients were treated with 650 mg of ASA daily for 3 months. In addition to clinical assessments, nuclear magnetic resonance imaging and smell test were performed before and after treatment with ASA. Venous blood and urine were collected before desensitization and after 1 and 3 months of treatment. The levels of urinary leukotrienes (LT) (cysteinyl LT and LTE₄) and tetranor PGDM (metabolite of prostaglandin D₂) were measured by enzyme-linked immunosorbent assay.

Results: Treatment with ASA after desensitization alleviated symptoms of rhinosinusitis, improved nasal patency (mean, 50% decrease in peak nasal inspiratory flow) and sense of smell (fourfold increase in smell test score) in as early as 4 weeks. Clinical improvements were not accompanied by any change in sinonasal mucosa thickness as assessed with nuclear magnetic resonance. Urinary cysteinyl LTs, LTE₄, and prostaglandin D₂ metabolite remained relatively stable during ASA treatment and did not correlate with clinical improvements. Desensitization was associated with a progressive decrease of urinary creatinine.

Conclusion: Clinical improvement in rhinosinusitis and/or asthma after ASA desensitization was not related to concentrations of urinary eicosanoid metabolites. A decrease of urinary creatinine requires further study to determine the renal safety of long-term treatment with ASA after desensitization.

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Nonsteroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (NERD) is a clinical syndrome characterized by severe, chronic eosinophilic inflammation that affects the upper and lower airways.^{1–5} The clinical symptoms of rhinosinusitis and bronchial asthma can be exacerbated by ingestion of

aspirin (acetylsalicylic acid) (ASA) or other NSAIDs. A history of NSAID hypersensitivity is a risk factor for severe chronic asthma^{6–9} and is associated with near-fatal asthma phenotype.¹⁰ Most patients with NERD experience severe chronic symptoms of rhinosinusitis, which are very often further complicated by nasal polyps.^{7,8,11} Patients with NERD have a significantly higher occurrence of nasal polyps and their computed tomography (CT) scores are much worse compared with patients tolerant to ASA and NSAIDs.⁹ Moreover, the results of surgical treatment of patients with NERD are worse compared with those patients who tolerate ASA and NSAIDs.^{12,13} One of the therapeutic options proposed for patients with NERD is chronic treatment with ASA after desensitization,^{1,14–16} which not only improves clinical symptoms of rhinosinusitis but also decreases the recurrence of nasal polyps and improves asthma control (decreasing the need for inhaled or oral

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glucocorticosteroids, asthma exacerbation rates, and asthma emergency visits and hospitalizations).^{17–19}

The beneficial effect of ASA after desensitization on nasal symptoms and nasal patency has been documented in several studies,^{14,17,18} but only one study attempted to assess the objective improvement of the sense of smell or sinonasal inflammation and hypertrophy by objective sinus imaging.²⁰ The mechanisms that lead to the improvement of nasal and bronchial symptoms after ASA desensitization remains unclear, although they have been associated with changes in eicosanoid release or, more recently, with suppression of cytokine and/or interferon production.^{21,22} Reduction of inflammatory cells that express receptor type 1 for cysteinyl LTs (CLT),²³ decreased LT production²⁴ and decreased levels of thromboxane-B2 and LTB4 in monocytes,²⁵ have also been reported in parallel with ASA treatment. Although baseline urinary metabolites of LTs are increased in patients with NERD^{26,27} and their production is up-regulated after ASA challenge,^{24,26} measurements of eicosanoid metabolites in urine after desensitization yielded variable results.^{20,28} Furthermore, the association of changes in urinary arachidonic acid metabolites with clinical improvement has not been well documented.

The goals of the study were (1) to assess with objective parameters (smell test and magnetic resonance imaging [MRI]), the clinical efficacy of short-term treatment (up to 3 months) with oral ASA after desensitization in patients with NERD with intractable symptoms of rhinosinusitis despite optimal chronic rhinosinusitis (CRS) treatment; and (2) to attribute objectively documented clinical effects of ASA treatment to changes in the release of eicosanoid metabolites in urine. One novel and unexpected finding was a decrease in urine creatinine secretion during ASA treatment after desensitization, which prompted us to question the usefulness of creatinine as a correction factor during measurement of eicosanoids in urine after ASA desensitization.

Patients

Sixteen patients with NERD were included in the study (12 women and 4 men; mean $\pm$ standard error [SE] age, 44.3 ± 2.9 years). Patient characteristics are presented in Table 1. A positive history of hypersensitivity reaction to NSAIDs was confirmed in all the patients by positive challenge with inhaled lysine ASA or oral ASA provocation. Patients had current symptoms of CRS despite treatment with intranasal glucocorticosteroids (128–160 μ g of budesonide/day). One patient did not receive intranasal glucocorticosteroids due to an earlier documented adverse effect, hirsutism). All of the patients (except one) were on inhaled glucocorticosteroids (400–1600 μ g of budesonide/day,

Table 1 Characteristics of patients with NSAID-exacerbated respiratory disease

No. patients	16
No. men/women	4/12
Age, mean $\pm$ SE, y	44.3 ± 2.8
Asthma duration, mean $\pm$ SE, y	9.9 ± 2.1
Rhinosinusitis duration, mean $\pm$ SE, y	15 ± 2.9
Nasal polyp history, mean $\pm$ SE, y	9.2 ± 1.6
No. polypectomies, mean $\pm$ SE	2.9 ± 0.7
History of urticarial hives, no. of patients	8
Intranasal glucocorticosteroids, mean $\pm$ SE daily dose in μ g of budesonide	145 ± 16
Inhaled glucocorticosteroids, mean $\pm$ SE daily dose in μ g budesonide	700 ± 106
No. patients on montelukast, 10 mg daily	16

NSAID = nonsteroidal anti-inflammatory drug; SE = standard error.

mean $\pm$ SE dose of 700 ± 106 μ g of budesonide), and their asthma symptoms were well controlled. All the patients received 10 mg of montelukast per day and a long-acting β 2-agonist. The last dose of montelukast was taken in the evening before desensitization, long-acting β -agonists were withheld for 24 hours, and short-acting β -agonists were given 8 hours before the beginning of desensitization. The study was approved by the local ethical committee, and all the patients provided written consent.

Desensitization and Treatment with ASA

Desensitization was performed according to the La Jolla 2-day protocol,²⁹ with serial spirometry and peak nasal inspiratory measurement monitoring. In brief, after the threshold dose of ASA, each patient received increasing doses of ASA (15, 30, 45, 60, 100, 150, 325, and 650 mg of ASA) every 2.5 hours until at least a 20% fall in forced expiratory volume in 1 second was observed, accompanied by nonpulmonary symptoms. The dose was then repeated, and, if tolerated, the procedure was continued with consecutive doses until 650 mg was tolerated. After successful desensitization, the patients were then given 325 mg of ASA twice a day.

Clinical Assessment

The patients filled in the questionnaire that assessed their nasal symptom score (nasal congestion, rhinorrhea, postnasal drip, smell, sneezing, snoring, nasal bleeding, nasal itching, headaches, facial pain) and the Rhinosinusitis Quality of Life Questionnaire (by Juniper).³⁰ Peak nasal inspiratory flow (PNIF) was measured and the smell test using Sniffin' Sticks (Burghart Messtechnik, Wedel, Germany) was carried out before desensitization and then again at 1 month and at 3

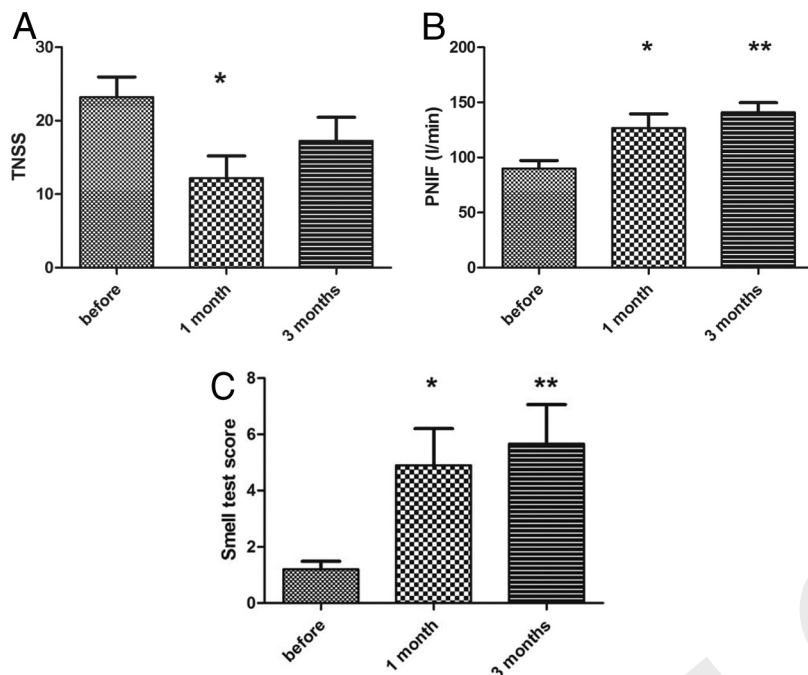


Figure 1. Effect of treatment with aspirin on (A) total nasal symptom score (TNSS) symptoms, (B) peak nasal inspiratory flow (PNIF), and (C) smell test score. All data are presented as mean $\pm$ standard error. * $p < 0.05$; ** $p < 0.01$, compared with before desensitization.

months of the study. Asthma Control Test and Asthma Quality of Life Questionnaire (Juniper)³¹ were analyzed. Forced expiratory volume in 1 second was measured by using a spirometer.

Sinus MRI

The sinus MRI was performed with Signa HDi (GE, Fairfield, CT), and two experienced radiologists (B. W. and A. R.) scored the extent of sinus disease by using the system by Lund and Mackay³² in a blinded fashion. In addition, the thickness of mucosa in maxillary sinuses was measured on the anterior, lateral, and medial walls (the mean thickness of these three walls is presented in the Results section).

Laboratory Evaluation

Urinary samples were collected to assess eicosanoid metabolites before desensitization, 1 month after desensitization, and at 3 months after desensitization. The level of urinary leukotriene (LT) E₄, CLT (LTC₄, LTD₄, LTE₄), and tetranor PGDM (metabolite of prostaglandin D₂) were measured by using an enzyme-linked immunosorbent assay kit (Cayman Chemical Co, Ann Arbor, MI). The complete blood cell count, aminotransferase concentration, and creatinine level in serum and in urine were monitored by using routine laboratory testing.

Statistical Analysis

The statistical evaluation was performed by STATISTICA 10 software (StatSoft, Tulsa, OK). Data are presented as mean $\pm$ SE. The following statistical methods were applied as appropriate and as indicated in the text:

Kruskal-Wallis statistics and the *post hoc* Dunn test analysis of variance.

RESULTS

Fourteen of 16 patients (87.5%) underwent successful desensitization and could tolerate 650 mg of ASA. In two patients, the desensitization procedure was not completed because, despite total resolution of respiratory symptoms with repeated "threshold" doses of ASA, the patients continued to have urticaria. In 8 of 14 patients, the 3-month treatment period with 650 mg of ASA was completed, whereas 6 patients dropped out of the study after 2 to 10 weeks of treatment. Three of these patients had gastrointestinal symptoms (gastric pain and dyspepsia) and one had bleeding from the lower gastrointestinal tract (presence of blood in the stool). One patient was withdrawn from the study after 3 weeks because of anxiety (which stopped after the cessation of ASA) and another was withdrawn after 1 month due to an increase in serum creatinine level above the normal value.

Clinical Evaluation

In the eight patients who received 650 mg of ASA daily for 3 months, a significant improvement in the mean total nasal symptom score (mean, 47% decrease), nasal congestion (mean, 50% decrease), and sneezing (mean, 62% decrease) was observed after 4 weeks of treatment. Although these symptom scores tended to be still lower from baseline after 3 months of treatment, the difference was not statistically significant (Fig. 1 A). Nasal patency assessed with PNIF significantly increased both after 1 month (mean, 48%

Table 2 Clinical effectiveness of aspirin treatment

	Before Desensitization, mean (SE)	After 1 Month of Treatment, mean (SE)	After 3 Months of Treatment, mean (SE)
FEV ₁ (L)	2.9 ± 0.25	3.0 ± 0.3	2.9 ± 0.25
MEF25–75 (L)	2.9 ± 0.4	2.6 ± 0.4	2.4 ± 0.35
ACT score	22.3 ± 0.4	23.88 ± 0.5*	24.1 ± 0.6
AQLQ score	147.7 ± 11.3	166.9 ± 8.2	172.4 ± 10
RQLQ score	70.7 ± 10.5	34.22 ± 7.3*	40.13 ± 7.4
Smell test score	1.2 ± 0.3	4.9 ± 1.3*	5.7 ± 1.4**
Total nasal symptoms score	23.20 ± 2.7	12.20 ± 3**	16.8 ± 2.9
Nasal congestion score#	3.1 ± 0.3	1.4 ± 0.4*	2 ± 0.5
Nasal discharge score#	3 ± 0.4	1.7 ± 0.5	2.1 ± 0.4
Loss of smell score#	4.7 ± 0.2	2.7 ± 0.6*	3.4 ± 0.6
Sneezing score#	2.1 ± 0.4	0.5 ± 0.17*	1.3 ± 0.4

SE = standard error; FEV₁ = forced expiratory volume in 1 second; MEF25–75 = maximal expiratory flow 25–75; ACT = Asthma Control Test; AQLQ = Asthma Quality of Life Questionnaire; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

* $p < 0.05$.

** $p < 0.01$.

#Subjective score of 0–5 points.

of improvement) and after 3 months of treatment (mean, 50% of improvement) (Fig. 1 B).

The sense of smell assessed by patients' score improved already after 1 month of treatment, but, after 3 months, the mean score was not significantly lower from baseline (Table 2) However, when the sense of smell was assessed by a smell test, a dramatic improvement was observed both after 1 and 3 months of treatment (mean, fourfold increase at 3 months) (Fig. 1 C). The quality of life related to CRS symptoms assessed by the Rhinosinusitis Quality of Life Questionnaire score improved at 1 and 3 months, but the improvement was significant only after the first month of treatment (Table 2).

Sinus Nuclear Magnetic Resonance Score

Sinus nuclear MRI was performed before and after 3 months of ASA treatment in six patients. Neither the mean ± SE extensions of nasal and/or sinus mucosa hypertrophy assessed by the Lund-Mackay score, nor maxillary sinus thickness changed significantly after ASA treatment (16.29 ± 1.34 versus 15.29 ± 0.9 , and 21.43 ± 4 versus 22.3 ± 4.1 for total and maximal scores, respectively) (Fig. 2). Only in one patient was a dramatic resolution of hypertrophy seen in all sinuses and documented on nuclear MRIs; his total score decreased from 21 to 13 points, and his maxillary sinus score decreased from 34 to 5.5. Interestingly, he was the only patient not to receive both the nasal and the inhaled glucocorticosteroids during ASA treatment.

Effect on Asthma

Only slight improvement in the mean Asthma Control Test value was observed after 1 month of treatment with

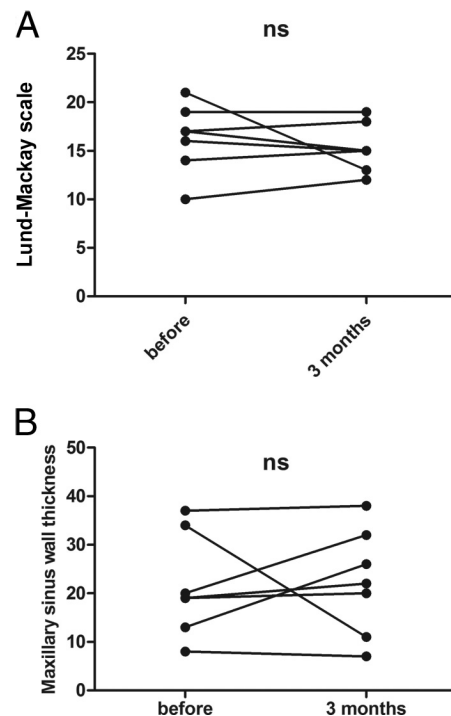


Figure 2. Individual magnetic resonance imaging scores before and after 3 months treatment with 650 mg of aspirin assessed by (A) the Lund-Mackay scale and (B) maxillary sinus hypertrophy score (sum of the thickness of mucosa in maxillary sinuses measured on anterior, lateral, and medial walls).

ASA ($p < 0.05$) but not after 3 months (Fig. 3 A). The lung function parameters and asthma-related quality of life were not affected by ASA treatment (Fig. 3, B and C). The doses of inhaled or intranasal corticosteroids and the anti-LT drug

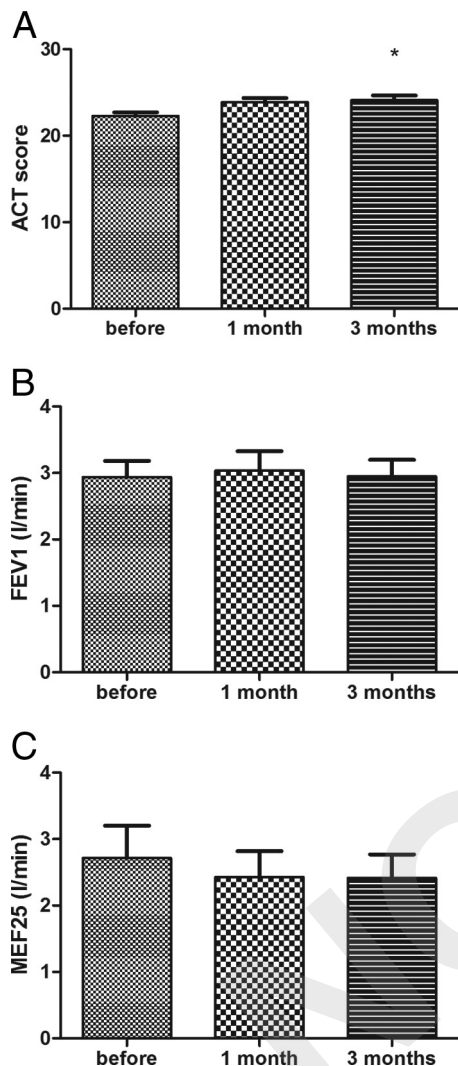


Figure 3. Effect of aspirin treatment on asthma control and spirometry. * $p < 0.05$, significantly different from baseline. (A) Asthma Control Test (ACT). (B) Forced expiratory volume in 1 second (FEV₁). (C) Maximal expiratory flow 25–75 % (MEF 25–75).

montelukast remained unchanged during the 3 months of observation.

Laboratory Safety Assessments

No significant changes in complete blood cell count (including platelet count) or liver function were observed during the 3 months of ASA treatment. However, the mean $\pm$ SE level of creatinine in urine decreased from 187 ± 32 mg/mL at baseline to 108 ± 37 mg/mL (statistically not significant) at month 1 (Fig. 4 A) and to 55 ± 7.8 mg/mL ($p < 0.05$) at month 3 of ASA treatment (Fig. 4 B). The level of creatinine at month 3 decreased in six patients. The decrease in the urine creatinine level in individual patients ranged from 4% to 92% after 3 months. With the exception of one patient who was withdrawn after the first month,

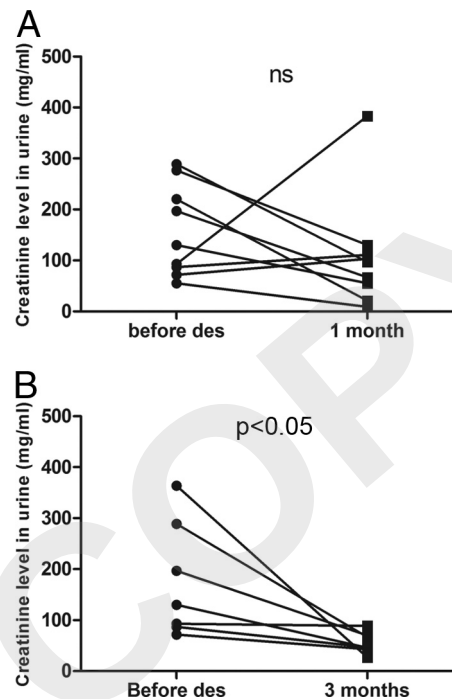


Figure 4. Changes in urinary creatinine levels in individual patients before and after treatment with aspirin. (A) Before and after 1 month of treatment. (B) Before and after 3 months of treatment.

no decrease in serum creatinine was noticed in individual patients and no significant change in the mean serum creatinine level was observed (baseline mean $\pm$ SE, 0.8 ± 0.03 mg/dL; 1-month mean $\pm$ SE, 0.86 ± 0.05 mg/dL; and 3-month mean $\pm$ SE, 0.76 ± 0.12 mg/dL).

Measurement of Urinary Eicosanoids

Because creatinine is produced and removed by the kidneys at a relatively constant rate, in most studies, urine creatinine has been used as the correction factor for expressing the concentrations of eicosanoids (as well as other proteins and/or mediators in urine.) When the concentration of eicosanoids in urine was expressed per milligram of urine creatinine, a marked increase in the amount of eicosanoids in urine was observed (Fig. 5, A–C). The mean level of urinary LTE₄ increased significantly after 1 month of ASA treatment ($p < 0.05$) (mean, 297% increase compared with baseline) and was still elevated at month 3 (mean, 216% increase), although it was not significant (Fig. 5 A). Urinary levels of PGDM (Fig. 5 B) and CLTs increased already at 1 month (mean, 191% increase and 130% increase, respectively) and were significantly higher after 3 months (mean, 236% increase and 270% increase, respectively) compared with baseline ($p < 0.05$) (Fig. 5 C).

Because it was observed in the majority of the patients that ASA treatment after desensitization was associated with a marked decreased in urinary creati-

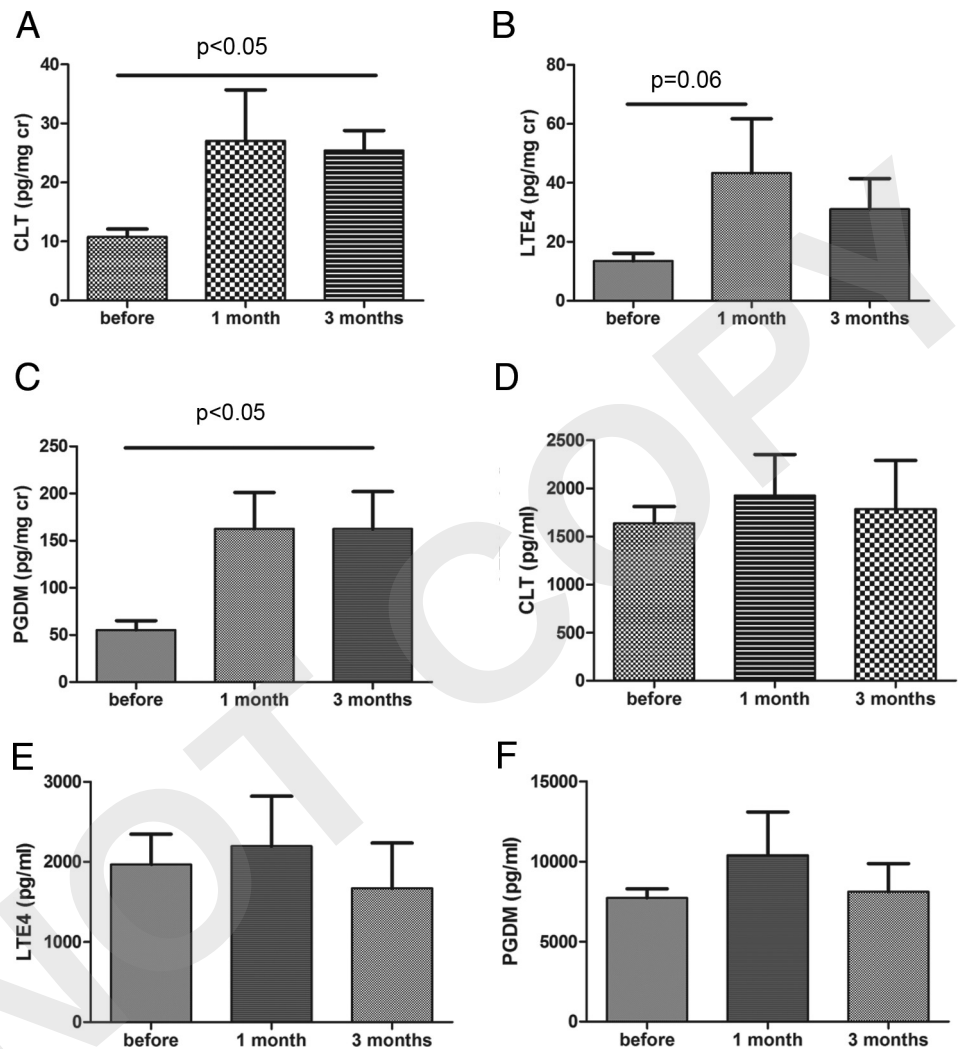


Figure 5. Cysteinyl leukotrienes, LTE4, and PGDM levels in urine before desensitization, and 1 month and 3 months after desensitization (mean $\pm$ standard error). (A–C) Eicosanoid concentrations are expressed as urine creatinine ratio. (D–F) Eicosanoid concentrations are expressed as raw data. CLT = cysteinyl leukotrienes; PGDM = prostalandin D2 metabolite.

nine, we expressed eicosanoid concentrations without correcting for urine creatinine. When data were presented without correction for the creatinine, mean concentrations of CLTs, prostaglandin D2 metabolite (PGM), and LTE4 did not change after ASA desensitization (Fig. 5 D, E, and F). There was no correlation between the changes in any of the clinical parameters of CRS or asthma after ASA desensitization and variations in measured eicosanoid metabolites concentrations in urine (regardless of how they were expressed).

DISCUSSION

Beneficial effects of ASA after desensitization have been documented in several studies, including randomized double-blind placebo-controlled trials, and confirmed in meta-analyses.^{11,14,19,33–35} Although our study included a relatively small number of patients, we were able to demonstrate that, in the majority of those who had intractable sinonasal symptoms, moderate daily doses of ASA led to dramatic symptom

improvements. It took only 4 weeks for the severity of nasal symptoms to be decreased by half and the rhinosinusitis-related quality of life to be improved significantly. The subjective improvement in nasal patency was confirmed by a mean 51% increase in PNIF. It is worth noting that these improvements were observed in patients who had already been treated unsuccessfully with intranasal corticosteroids and anti-LTs. When observing such rapid improvement after 4 weeks of ASA, along with symptomatic improvements having already been reported previously,³⁵ this seemed to indicate that the majority of patients may expect some benefits at the early stages of treatment with ASA. Interestingly, no further symptomatic improvement in nasal symptoms was observed after 12 weeks of treatment, although symptom scores and objective measurements (e.g., PNIF) tended to still be lower than those from baseline. However, the most dramatic improvement was observed in the sense of smell, which subjectively improved within the first 3–5 days of treatment and was significantly better at 1

month and at 3 months of treatment when assessed with the smell test.

Although subjective improvements in sense of smell during ASA desensitization have been reported previously,²⁰ this is the first study, to our knowledge, in which improvement in smell perception was objectively documented with the smell test. Hyposmia or olfactory loss are typical features of CRS with nasal polyposis and have often been particularly associated with NERD.³⁶ The pathomechanisms of loss of smell associated with CRS and with nasal polyposis have been related either to the presence of nasal obstruction, which may impede the arrival of odorants to the receptors within olfactory epithelium, or to local inflammation that results in the impairment of olfactory neuroepithelium olfaction by affecting the transmission of synaptic impulses or by the destruction or damage of olfactory receptors.^{37,38} Improved nasal patency, which was concomitant with an improved sense of smell, may explain the beneficial effect of ASA on smell perception in our patients. However, the more direct effect of desensitization on the inflammatory component of loss of smell cannot be excluded.

We believe this study to be the first of its kind to use MRI to assess the effect of ASA desensitization on the mucosal hypertrophy in nasal passages and in sinuses. Even though CT is considered to be the criterion standard in the diagnosis of CRS, MRIs may be particularly useful in the evaluation of soft-tissue masses within the paranasal sinuses and the nasal cavity.³⁹ MRIs, in contrast to CTs, allow for repeated measurements without the potential risk associated with exposure to radiation. On MRIs, when using the Lund-Mackay scale, no change in the thickness of nasal mucosa either in nasal passages or in sinuses was observed in five of six patients. The lack of improvement in sinonasal mucosal hypertrophy, despite the prominent clinical improvement of symptoms, is difficult to explain. Desensitization in our patients was not performed as it is recommended just after sinus surgery, and patients had massive mucosal hypertrophy.⁴⁰

We, therefore, can speculate that ASA treatment after desensitization is not capable of reversing existing mucosal hypertrophy but only affects inflammation and mucosal edema or prevents regrowing of nasal polyps and delay their recurrence.^{18,41} It is also possible that the duration of treatment was too short to affect mucosal hypertrophy.¹⁷ However, Swierczynska-Krepa *et al.*,²⁰ who assessed sinonasal hypertrophy by CT did not find any significant improvement in CT scores after 6 months of treatment with ASA. Interestingly, one patient, who, due to earlier diagnosed hirsutism, did not receive nasal or inhaled glucocorticosteroids, yet a dramatic resolution of mucosal thickness in all sinuses on MRIs was documented during ASA treatment. It is tempting to speculate that some patients may be par-

ticularly responsive to ASA desensitization due to their unknown intrinsic characteristics.

We did not expect spectacular improvement in asthma symptoms after desensitization because our patients had moderate asthma, which was well controlled on optimal doses of inhaled steroids and anti-LTs. Accordingly, no change in asthma-related symptom scores, respiratory function, or asthma-related quality of life was noticed throughout the study. Surprisingly, despite near-to-optimal asthma control, the mean Asthma Control Test significantly increased at 4 weeks of treatment and was still high at 3 months. Our study was consistent with previous observations that, in patients with NERD, ASA desensitization results only in a modest improvement of asthma, whereas the alleviation in nasal symptoms is remarkable.¹⁴

An unexpected and, to our knowledge, previously unreported observation was the significant decrease in urinary creatinine levels noticed as soon as 4 weeks but further progresses after 12 weeks of treatment with ASA. These decreases in urine creatinine were not accompanied by any changes in serum creatinine (with the exception of one patient who was withdrawn after 4 weeks of treatment), which indicated that renal function was not significantly affected. The negative impact of NSAIDs (both cyclooxygenase-1 and cyclooxygenase-2 inhibitors) on renal function has been described earlier, and renal adverse effects are reported in 1–5% of patients treated with NSAIDs.^{42–45} The effects of ASA or other NSAIDs on renal function have been explained by inhibition of prostaglandin E2 production, which is critical for maintaining renal blood flow and renal filtration.⁴⁶ Because patients with NERD seem to be more susceptible to cyclooxygenase inhibition with NSAIDs, the potential effect of these drugs on renal function in these subjects may be even more pronounced.⁴⁷ Further studies are required to assess the significance of our findings for renal safety of ASA treatment in desensitized patients with NERD.

Eicosanoids (LTs and prostaglandins) have been implicated in the pathogenesis of chronic inflammation in patients with NERD, and elevated levels of arachidonic acid metabolites in urine have been documented.^{48–51} To get some insight into the relationship between the objectively assessed clinical effects of ASA and changes in arachidonic acid metabolism in desensitized patients, urinary levels of CLTs (LTC4, LTD4, LTE4) and the major LT metabolite LTE4 in urine were measured. In addition to the concentration of stable metabolite of prostaglandin D2 (tetranor PGDM), which is potentially related to mast cell activation and tissue inflammation, was measured as well. Because creatinine is produced and removed by the kidneys at a relatively constant rate, in most studies, urine creatinine has been used as the correction factor for expressing the concen-

trations of eicosanoids (as well as other proteins and/or mediators in urine).

When the concentrations of arachidonic metabolites were expressed as the creatinine ratio, the mean levels of CLTs and LTE₄ at 12 weeks and PGDM concentration at 8 weeks of treatment were significantly increased from pretreatment values. However, analysis of raw value data revealed that an increase in the eicosanoid-to-creatinine ratio after ASA was clearly driven by decreased concentrations of urinary creatinine and not by a real increase in metabolite concentrations. We did not find any correlation between changes in clinical and objective parameters of CRS and asthma after desensitization, and urinary levels of eicosanoids, regardless of the method of calculation used, which indicated that eicosanoid levels in urine do not reflect the pathomechanism of successful desensitization. Earlier studies, which measured AA metabolites in urine of patients with NERD and which expressed values as creatinine ratio did not observe any significant changes in urinary levels of LTE₄ after ASA desensitization.^{20,24} In recent study by Cahil *et al.*,²⁸ the urinary levels of PGDM decreased after 2 months of ASA treatment; however, the urinary levels were expressed as a creatinine ratio, and changes in raw prostaglandin metabolite levels have not been reported.

We are aware of several limitations of the study: a relatively low number of patients kept on ASA for a designated period of time, the duration of treatment was much shorter than in other studies, and only moderate doses of ASA were used. Although one cannot exclude that a longer duration of treatment would result in a more-enhanced anti-inflammatory effect, we did not observe any tendency for further improvement in clinical symptoms or objective parameters after 12 weeks compared with that observed after 4 weeks.

CONCLUSION

Despite these limitations, our study demonstrated that treatment with moderate doses of ASA (600 mg/daily) after desensitization rapidly alleviated symptoms of rhinosinusitis and improved the objective measurements (nasal patency and sense of smell), but it was not associated with a decrease in sinonasal mucosal hypertrophy after assessment with MRI. Furthermore, urinary CLTs, LTE₄, and prostaglandin D metabolite remain relatively stable during ASA treatment and do not correlate with any clinical improvements. Desensitization was associated with a progressive decrease of urinary creatinine, which requires further study to determine the renal safety of desensitization and also puts into question the rationale for expressing measurements of urinary mediators as a creatinine ratio after ASA desensitization.

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