**Quality of Life and Inflammatory Markers in Mild Asthma***

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*Study objectives:* The aim of this study was to explore the relationship between quality of life and measures of asthma, such as lung function, reversibility to bronchodilation, exhaled nitric oxide (NO), and bronchial responsiveness to direct and indirect stimulus in patients with mild asthma in a primary care setting.

*Patients and measurements:* Seventy-seven asthmatic patients not treated with glucocorticosteroids completed the Asthma Quality of Life Questionnaire. Spirometry was performed before and after bronchodilation, and bronchial challenges with methacholine and eucapnic dry air hyperventilation were conducted on separate days. NO in exhaled air and serum IgE were also analyzed.

*Results:* We found no correlation between quality of life and any of the other parameters. There was a significant covariation between exhaled NO and bronchial responsiveness to methacholine and dry air, and also between FEV₁ (percentage of predicted) and reversibility to a bronchodilator. The levels of exhaled NO were higher in the asthmatic subjects with atopy than in the nonatopic asthmatics.

*Conclusions:* The measures used in our study do not reflect health-related quality of life in subjects with mild asthma. We conclude that in the clinical situation, quality of life and other measures of asthma provide complementary information. *(CHEST 2006; 129:624–631)*

**Key words:** airway inflammation; bronchial responsiveness; mild asthma; primary care; quality of life

**Abbreviations:** AQLQ = Asthma Quality of Life Questionnaire; ATS = American Thoracic Society; CI = confidence interval; DRS = dose-response slope; MID = minimal important difference; NO = nitric oxide; PC_{20} = provocative concentration of methacholine causing a 20% decrease in FEV₁; PD_{20} = provocative dose of methacholine causing a 20% fall in of FEV₁; ppb = parts per billion; VAS = visual analog scale

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Most patients with asthma are managed in the primary care setting, where the majority of patients have mild-to-moderate asthma.1,2 In a worldwide study,3 it was demonstrated that 59% of asthmatic patients in the United States and 63% in Western Europe had mild or intermittent disease. Consequently, people with mild disease constitute a large part of the asthmatic population yet remain a relatively unstudied group.

In clinical practice, the patients are normally monitored by registration of symptoms, spirometry, and peak expiratory flow measurements. Several studies2,4 have shown a weak correlation between lung function and changes in the well being and quality of life. In a previous asthma study2 examining quality of life in primary care, we found that the predominant difference between patients who experienced symptoms and those who did not was revealed in the environment domain of the quality-of-life questionnaire. This finding suggested that airway responsiveness to irritant stimuli may be more closely related to symptoms than to lung function as assessed by spirometry.
Asthma is considered to be caused by airway inflammation, which has been an important target for asthma therapy. In research, there has been great interest in monitoring biological markers in order to assess the inflammatory process. It would be extremely useful for clinicians to have reliable, objective methods on which to base clinical decisions. The discovery of new markers raises expectations of new tools for use in clinical practice. It has been claimed that outcomes such as markers of inflammation, bronchial responsiveness, reversibility to bronchodilators and lung function are able to reflect the clinical status of the asthmatic patient.

Although some authors have found a relationship between symptoms and the above-mentioned outcomes, the basis for such a claim does not seem to be fully justified. The aim of the present study was to investigate the relationship between quality of life, as assessed by the validated Asthma Quality of Life Questionnaire (AQLQ), and “objective” measures of asthma such as lung function, reversibility to a bronchodilator, bronchial responsiveness to a direct and an indirect stimulus, and nitric oxide (NO) in exhaled air.

**Materials and Methods**

**Subjects**

All patients with previous symptoms diagnosed as asthma by a general practitioner were invited to participate in the study. However, it was not possible to assess whether the diagnosis of asthma had been based on peak expiratory flow variability, a reversibility test, bronchial challenges, or on a seasonal variability of asthma symptoms. The patients visited one of four health-care centers in downtown Stockholm, Sweden, and were included in the study after having been identified in the primary care asthma register and then invited by the investigator. Thus, no subjects were included in connection with a consultation due to worsening of asthma symptoms.

Patients were included if they were 18 to 65 years of age and if they considered themselves to be free of symptoms, as assessed by a visual analog scale (VAS), and had not been treated with inhaled corticosteroids during the previous 3 months. Patients with other serious disorders, such as psychiatric disease, alcoholism, rheumatoid arthritis, cancer, or COPD, were excluded, as were pregnant women. In the asthma register, 578 patients were identified and contacted by mail. Only those with mild symptoms or only minor symptoms, were included in the study.

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One hundred fifty-three patients responded, of which 57 patients withdrew or did not fulfill the inclusion criteria as judged by a telephone interview. The remaining 96 patients were tested at the primary care center; of these, 19 patients did not fulfill the inclusion criteria or declined participation, leaving 77 patients for the study.

**Study Design**

At visit 1, all patients were asked to indicate asthma control on a VAS and to answer a standardized questionnaire regarding smoking habits and allergic symptoms. The questionnaire has previously been used in Sweden. The patients also answered a disease-specific quality-of-life questionnaire, the AQLQ. In addition, spirometry was performed before and after bronchodilatation. Exhaled NO was also analyzed, and blood samples for analysis of specific IgE were drawn from all participants.

Airway hyperresponsiveness was assessed by a bronchial methacholine challenge and eucapnic hyperventilation with dry air at two further visits in random order. All three visits took place within 10 days.

**Methods**

**Symptoms**: Patients indicated the severity of asthma symptoms on a 100-mm VAS, answering the question “Have you experienced any asthma symptoms or breathing difficulties during the past 2 weeks?” Each end of the scale indicated the range being considered from “no discomfort” (0) to “severe discomfort requiring hospitalization” (100). Only patients who indicated a point < 30 mm on the VAS, i.e., those who had experienced no symptoms or minor symptoms, were included in the study.

**Quality of Life**: The AQLQ devised by Juniper et al was used. The questionnaire has 32 items classified into four domains: activity limitations, symptoms, emotional function, and effects of environmental stimuli. Five of the 11 items in the activity domain were individualized. The patients were asked to indicate the extent to which they had experienced limitation on a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment at all. The minimal important difference (MID) indicates the smallest difference, in the score of a domain, that the patient perceives as beneficial. In the AQLQ, the definition of MID is 0.5.

**Lung Function**: FEV1 and FVC were measured using a spirometer (MicroLab 3300; Micro Medical Ltd., Rochester, Kent, UK) according to the standards of the American Thoracic Society (ATS). Reference values were by Hedenström et al. For reversibility tests, salbutamol (5.0 mg) and ipratropium bromide (0.5 mg) were mixed and inhaled using a jet nebulizer (Aiolos; Medicinsk Teknik AB; Karlstad, Sweden). Lung function was measured before and 20 min after inhalation of the bronchodilators. Significant reversibility was defined by an increase in FEV1 of 10% of the preinhalation value. This is in accordance with ATS guidelines, in which an increase in FEV1 of < 8% of preinhalation values is likely to be within measurement variability.

**Bronchial Responsiveness**: Bronchial responsiveness to methacholine was assessed by a provocation test using a wedge spirometer (Vitalograph; Buckingham, UK). Inhalation of the diluent was followed by inhalation of doubling concentrations of methacholine, starting at 0.5 mg/mL. The challenge was stopped when FEV1 had decreased by 20% compared to the value obtained after inhalation of the diluent, or after inhalation of the highest methacholine concentration (32 mg/mL). The results were expressed as the cumulative provocative dose of methacholine causing a 20% fall in FEV1 (PD20) or provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) and dose-response slope (DRS), i.e., the percentage decrease of FEV1 as a function of the cumulative methacholine dose, calculated by linear regression.

**Reference Values for Bronchial Hyperresponsiveness to Methacholine**: Reference values for bronchial responsiveness to methacholine have been defined in our laboratory. Reference values for PD20 and PC20 and the DRS were obtained in 203 healthy and 102 asthmatic subjects. Median (10th to 90th percentiles) PD20 was 2.15 mg (0.32 to 9.24 mg) in healthy subjects and 0.22 mg (0.06 to 1.12 mg) in subjects with asthma. To obtain the least possible overlap between normal and increased bronchial respon-
siveness, the cutoff level for bronchial hyperresponsiveness was defined as based on the distribution of log-PD20 for healthy and asthmatic subjects. The cutoff level was set at the point where the two distributions met (i.e., the point with the highest sensitivity as well as the highest specificity) and was found to be 0.6 mg, corresponding to the 15th percentile of the distribution of the healthy subjects (Fig 1). The corresponding PC20 was 1.5 mg/mL. The same analysis of the DRS revealed a median value of 8.85%/mg (1.04 to 66.6%/mg) in healthy subjects and 84.7%/mg (21.7 to 353%/mg) in asthmatic subjects with a cutoff level of 41.7%/mg, corresponding to the 85th percentile of the healthy subjects.

Eucapnic Dry Air Provocation: Eucapnic hyperventilation was performed for 4 min with dry air containing 5% carbon dioxide at room temperature (Aiolos Asthma Test; Medicinsk Teknik AB). The target ventilation was 35 × FEV1 × 0.75, which was adjusted by the patient breathing through a balloon, and FEV1 was measured 1, 3, 5, 10, 15, and 20 min after hyperventilation. Then the maximal FEV1 decrease compared to the baseline, prehyperventilation value was recorded.17 Bronchial hyperresponsiveness to dry air hyperpnea was defined as a postchallenge fall in FEV1 > 10% compared with the prechallenge value.18

Exhaled NO: Exhaled NO was determined during a single-breath exhalation. The measurements were performed in accordance with recommendations from the ATS, with an exhalation flow rate of approximately 50 mL/s.19 To decrease contamination from the oral cavity, subjects were asked to rinse their mouths with water and sodium bicarbonate (10%) for 1 min prior to the measurement procedure.20 NO levels were measured by chemiluminescence following a reaction with ozone (NIOX; Aerocrine; Stockholm, Sweden). A NO concentration < 20 parts per billion (ppb) was considered normal.21

Atopy: The presence of allergies was evaluated by a questionnaire, and atopy was assessed by measurement of specific IgE antibodies in plasma (Phadiatop, Unicap; Pharmacia; Uppsala, Sweden). IgE values ≥ 0.35 kilounits of antibody per liter were considered normal.

Statistical Analysis

Results are presented as mean values with 95% confidence intervals (CIs) or median (25 to 75th percentiles) [bronchial methacholine responsiveness]. PD20 and DRS values were logarithmically transformed prior to statistical calculations. Comparisons were conducted by linear regression and by a Mann-Whitney U test. A p value < 0.05 was considered significant. Correction for multiple comparisons was performed using the Bonferroni method, when appropriate.

RESULTS

Seventy-seven patients were included in the study (Table 1). Results were based on the assumption that the symptoms of asthma (that had led to diagnosis of asthma by a physician), in combination with one positive test result (bronchial responsiveness, exhaled NO, reversibility test) were sufficient to confirm the diagnosis of asthma. All test results, including methacholine challenge, dry air challenge, levels of NO in exhaled air, and reversibility to bronchodilator drugs, were normal in 8 of the 77 subjects. Four of these patients had symptoms of asthma according to the asthma-specific questionnaire and an overall quality-of-life score < 5. We cannot exclude the possibility that these four patients had asthma, although we did not find any objective evidence for the asthma diagnosis. In the four remaining subjects with negative test results and high quality-of-life scores, the asthma diagnosis was probably erroneous.

Four patients declined blood sampling, leaving 73 patients for the final IgE analysis, of which the Phadiatop findings were positive in 53 patients and negative in 20 patients. Eleven of 53 atopic patients (21%) and 7 of 20 nonatopic patients (35%) were smokers. The mean age of the atopic patients was 35 years (range, 18 to 60 years), and the mean age of the nonatopic patients was 47 years (range, 23 to 63 years).

Symptoms and Quality of Life

According to the inclusion criteria, all the participating subjects had experienced no symptoms or only minor ones (0 to 30 mm on the VAS) during the 2 weeks prior to the study. Quality of life was

<table>
<thead>
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<th>Variable</th>
<th>Data</th>
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</thead>
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<tr>
<td>Patients, No.</td>
<td>77</td>
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<tr>
<td>Male/female gender, No.</td>
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<tr>
<td>Mean age (range), yr</td>
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<td>Mean FEV1 % of predicted (95% CI)</td>
<td>90.6 (87.8–93.5)</td>
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<tr>
<td>Mean reversibility test (95% CI), ΔFEV1 %</td>
<td>6.4 (5.1–7.6)</td>
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<tr>
<td>Smoking status, No. (%)</td>
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<tr>
<td>Smokers</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>38 (49)</td>
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Table 1—Patient Data
monitored in all 77 patients. The majority of patients were unable to specify activity limitation according to the five individualized questions. These questions therefore were not included in the assessment of activity limitation, which is based on only six questions. The mean quality-of-life scores for the whole group were as follows: activity limitation, 6.00; symptoms, 5.67; emotion, 5.92; environment, 5.49; and the quality-of-life overall score, 5.75.

In general, the quality-of-life scores were higher in the atopic subjects (overall score of 5.88) than in the nonatopic group (overall score of 5.42), implying a difference of 0.46, which is close to the MID. When atopic subjects were compared with nonatopic subjects, the MID was > 0.5 in the activity limitation (0.68) and environmental domains (0.74) but not in the symptom (0.41) and emotional (0.12) domains (Fig 2).

**Bronchial Responsiveness and Exhaled NO**

A bronchial methacholine challenge was performed on all 77 patients, of which 59 patients had a positive test result defined as PD20 ≤ 0.56 mg. Eucapnic hyperventilation challenges were performed on all 77 patients, and a postchallenge decrease in FEV1 > 10% was found in 24 patients. Eighteen patients showed positive reversibility to a bronchodilator (≥ 10% FEV1 increase following bronchodilation).

Due to technical problems, exhaled NO was not measured in 4 of the 77 patients. Thirty-seven subjects (approximately 50%) had elevated levels (≥ 20 ppb) of exhaled NO. Of the 73 subjects who performed both bronchial challenges and exhaled NO measurements, results of 8 subjects were negative in all three. The remaining 65 patients showed positive results in one or more tests (Fig 3). Of the eight patients with negative results to these three tests, none had a positive reversibility test.

**Relation Between Different Outcomes**

There was no significant correlation between quality of life (four domains and overall score) and any of the other parameters: exhaled NO, lung function, reversibility, or bronchial responsiveness to methacholine and dry air (Fig 4). The coefficient of correlation between the quality-of-life overall score and exhaled NO, lung function, reversibility to a bronchodilator, or bronchial responsiveness to methacholine and dry air were all between −0.07 and 0.13 with 95% CIs within the range of −0.3 to 0.3. The difference in the quality-of-life overall score between those with normal and abnormal bronchial responsiveness to methacholine and/or dry air, elevated NO in exhaled air, and reversibility > 10% of prebronchodilator FEV1 did not reach the MID (≥ 0.5) [Fig 5].

Patients with an increased level of exhaled NO ≥ 20 ppb (n = 37) had significantly higher quality-of-life scores in sections concerned with activity limitation (p = 0.04) and environment (p = 0.03). For the environment domain, this difference exceeded the MID (0.63). In general, patients who responded positively to dry air provocation (n = 22) had a somewhat lower quality of life than those...
showing normal responsiveness to dry air. This difference only reached the MID level for the emotion domain (0.66).

Levels of exhaled NO showed a significant correlation with bronchial responsiveness to methacholine ($r = 0.37; \ p < 0.002$) and dry air ($r = 0.47; \ p < 0.0001$). A weak, but significant correlation was also found between FEV$_1$ (percentage of predicted) and reversibility ($r = 0.44; \ p < 0.0001$). Otherwise, no significant correlations were found between the test results (Fig 6).

**Atopy**

The mean value of NO in exhaled air was 32.9 ppb (26.1 to 39.7 ppb) in the atopic patients and 21.0 ppb (10.8 to 31.2 ppb) in the nonatopic patients ($p = 0.01$). There was a tendency toward enhanced bronchial responsiveness to methacholine in the atopic subjects (PD$_{20}$, 0.16 mg; 0.07 to 0.40 mg) compared with nonatopic patients (PD$_{20}$, 0.26 mg; 0.15 to 0.78 mg; $p = 0.066$). Bronchial responsiveness to eucapnic hyperventilation was similar in atopic ($-9.3\%$; $-12.0$ to $-6.5\%$) and nonatopic ($-8.6\%$; $-11.5$ to $-5.8\%$) patients ($p = 0.53$).

**DISCUSSION**

In the present study, we found no correlation between quality of life as assessed by the AQLQ and parameters such as lung function, reversibility to a bronchodilator, bronchial hyperresponsiveness to a direct and an indirect stimulus, and exhaled NO in steroid-free subjects with mild asthma. Patients were included according to three criteria: asthma diagnosed by a physician, mild disease according to a VAS ($<30$ mm), and no treatment with steroids (inhaled or oral) during the last 3 months prior to the study. In Swedish primary care units, the diagnosis of asthma is normally based on the presence of asthma symptoms and lung function measurement. FEV$_1$/FVC was only $70\%$ in two of the patients, and one of these patients (aged 41 years) had never smoked, which would suggest that we have not included more than one possible patient with COPD. As our intention was to study a population of patients with mild asthma seen at primary care centers, we did not exclude smokers or ex-smokers as long as they had no clear indications of COPD.

The aim of the present study was to look at the relationship between quality-of-life assessments and markers of asthma in patients with mild disease. We did not find any covariation between these objective parameters and quality-of-life scores. Previously, no clear relationship has been found between the recommended markers of asthma inflammation and current symptoms in children with varying severities of asthma. Inflammatory markers of asthma were found to be elevated after 5 years (range, 1 to 12 years).
From previous studies, it is apparent that most asthmatic patients visiting a primary care unit have mild disease. Therefore, we have reason to believe that the findings in the present study reflect the situation at the majority of primary care units. In a previous study of adult asthma patients identified by the screening of households, daytime symptoms of at least once a week were reported by half of the patients. This would suggest that approximately half of the patients had symptoms more seldom than 

Only one patient had an overall quality-of-life score of 7.0, 75% had an overall score < 6.4%, and 25% had an overall score < 5.3. Despite the rather small range of quality-of-life scores, it should still be possible to find correlations between quality of life and objective measures. To fully elucidate such a relationship in asthmatic patients, a study of patients with all degrees of severity must be conducted. Thus, the objective measures used in our study do not seem to reflect the health-related quality of life of the asthma patients, and we do not consider these markers of asthma to be of great importance in guiding the treatment of patients with mild disease. It is, however, important to emphasize that the present study was not designed to evaluate the use of asthma for monitoring disease progress and guiding treatment.

Contradictory to our results, there are studies in which a relationship between symptoms and inflammatory variables has been demonstrated. Grönke et al found a negative correlation between quality-of-life scores and levels of exhaled NO, as well as sputum eosinophils in 10 subjects with severe asthma who were studied for 18 months. In another study of 26 patients with severe asthma, the levels of exhaled NO correlated closely with symptoms and the use of a rescue β-agonist but not with lung function. Tsujino et al found a correlation between levels of exhaled NO and symptom scores in 32 asthmatic subjects not treated with steroids. In the present study of patients with mild asthma, we found higher quality-of-life scores in asthmatic subjects with high levels of exhaled NO, and that atopic subjects had higher levels of NO than nonatopics. The most likely explanation of these differences is that the atopic subjects with higher NO levels were younger (35 years vs 47 years), and there were fewer smokers (21% vs 35%) than those with lower NO values. Our results may therefore reflect that younger nonsmokers have higher quality-of-life scores than older smokers, and consequently that the level of exhaled NO does not predict disease status in these patients with mild asthma. This finding further emphasizes that asthma treatment should probably not be guided by levels of exhaled NO in patients with mild disease.

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every week. In a study by Ställberg et al., 59% of the asthmatic patients in primary care only experienced symptoms “sometimes” and 26% were almost free of symptoms. These studies clearly indicate that a substantial number of the asthmatic patients in primary care have mild disease. Thus, the aim of the present trial was to focus on this group of patients with mild asthma, a group of patients that has not previously been studied extensively.

In conclusion, we have not been able to demonstrate a relationship between quality of life and tests that are commonly used when diagnosing and monitoring asthma in a group of patients with mild disease. However, we were able to demonstrate a fairly close correlation between the levels of exhaled NO and bronchial hyperresponsiveness. We found that most patients with asthma diagnosed in the primary care setting have a positive bronchial methacholine challenge finding, whereas the results of other tests such as eucapnic dry air hyperventilation, exhaled NO levels, reversibility to a bronchodilator, and lung function were found to be within the normal range in a large number of patients.

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