Acta Med Kinki Univ Vol. 36, No. 2 53-61, 2011

The association between anxiety and a decline in saliva cortisol during interview stress in adult patients with asthma

Ryuta Haraguchi, Katsuyuki Tomita,[1] Nanase Watatani,[1] Shu Imbe,[1] Ryuji Satoh,[1] Yasushi Makino,[1] Osamu Nisiyama,[1] Hiroyuki Sano,[1] Hirokazu Nakajima[1] and Yuji Tohda[1]

Department of Respiratory Medicine, Higashiosaka City General Hospital, 3-4-5 Nishi-Iwata, Higashiosaka, Japan

[1]*Department of Respiratory Medicine and Allergology, Kinki University Faculty of Medicine, Osakasayama, Osaka 589-8511, Japan*

Abstract

The relationship between anxiety and asthma is currently being intensively studied. It has been demonstrated that there is reduced responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis to psychosocial stress in an animal model of asthma. Our objectives were to identify the associations between anxiety and the decline of saliva cortisol during stress in adult patients with asthma. Saliva cortisol was sampled before and up to 30 min following stress induced by interviews in 30 adult patients with asthma, excluding known psychiatric patients. Anxiety was measured using the anxiety subscale of the Hospital Anxiety and Depression (HAD) scale. For interview stress, patients also completed the Asthma Control Test (ACT), the State/Trait Anxiety Inventory (STAI) for anxiety rating, and the 2006 questionnaire edited in a guideline for the diagnosis and treatment of psychosomatic diseases for diagnosing psychosomatic illness as asthma. The saliva cortisol levels were quantified by enzyme immunoassay. Clinically relevant anxiety (HADS score of ≥ 8) was indicated in 9 patients (30%) and depression in 4 (13%). Five patients (16.7%) had clinically significant state-anxiety scores of >52, and seven patients (23.3%) had clinically significant trait-anxiety scores of >55. Eight patients (26.7%) had been diagnosed as having psychosomatic asthma. The characteristics were similar between patients with and without anxiety, with the exception of age ($P<0.01$) and ACT score ($P<0.01$). The changes in the ratio [(after stress-before stress)/before stress] of saliva cortisol were lower in patients with anxiety than in those without anxiety (-0.3 ± 0.9 vs. 0.1 ± 1.9, $P<0.05$). In asthmatic patients with anxiety, there was a smaller interview stress-induced deterioration of saliva cortisol, which was consistent with reduced HPA axis activity.

Key words: anxiety, asthma, cortisol, saliva, stress

Introduction

Psychological disturbances such as anxiety or depression are important features of asthma, because many patients with chronic disorders are generally at risk for mental disorders. These mental disorders are associated with poor asthma outcomes such as worse asthma control and impaired health status,[1] frequent utilization of emergency and hospital admissions,[2] more asthma symptoms,[3,4] higher dosing of corticosteroids,[5] medication non-adherence,[6] a worsening of chronic inflammation,[5] or even death.[6] In a systemic review, an overall meta-analysis exhibit-

Received January 20, 2011; Accepted May 23, 2011

ed a positive association between psychosocial factors and future atopic disorders, including asthma.[7] Severe stressful events, both on their own and in conjunction with high chronic stress, significantly increased the risk of new asthma attacks over the coming few weeks in children who already had asthma.[8,9]

Anxiety is likely to be a problem for many patients with asthma. Anxiety was associated with worse subjective asthma outcomes and increased use of medication and/or healthcare services, but with decreased airway inflammation, and was not associated with lung function.[10] Stress and anxiety can actually make asthma symptoms worse. Feldman et al.[11] found in a sample of 85 adult patients with asthma that 65% had a psychiatric disorder, and the criteria for mood disorders and anxiety disorders were met by 51% and 45% of their patients, respectively. In general, numerous researchers have found that patients with asthma have elevated levels of anxiety disorders,[12,13] in particular panic disorder and depression.[14] Mrazek et al.[15] hypothesized that the stress of having a chronic illness increases the likelihood of the development of anxiety and depression symptoms.

The anxiety subscale of the Hospital Anxiety and Depression (HAD) scale is widely used to detect clinically significant anxiety among patients who attend outpatient medical clinics.[16,17] An association was observed between the reported respiratory symptoms and psychological status. When the psychological status was assessed by means of the HAD scale questionnaire, a significant correlation was found between anxiety and depression and the report of asthma-related symptoms, such as attacks of breathlessness after activity and awakening with attacks of breathlessness.[3]

It was demonstrated that there is reduced responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis to psychosocial stress in young and adult patients with atopic disorders.[18] In atopic adolescents, serum cortisol was attenuated in response to the stress of laboratory procedures, such as venous puncture for collecting blood.[19] On the other hand, the estimation of salivary free cortisol level is a useful and non-invasive screening method for evaluating the glucocorticoid function of the adrenal cortex in asthma patients.[20]

It is not known whether there is reduced responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis to psychosocial stress in adult patients with asthma. The aim of the present study was to measure the prevalence of anxiety in adult patients with asthma, using the questionnaire of the HAD scale, and to confirm the reduced responsiveness of the HPA axis to interview stress in adult patients with asthma who demonstrate co-morbid disease with anxiety.

Methods

Study Population

We recruited 30 consecutive outpatients with stable asthma. The entry criteria included : (1) meeting the definition of asthma by the American Thoracic Society (ATS)[21] ; (2) a significant postbronchodilator force expiratory volume in 1s (FEV_1) and/or FVC response of 200 mL after the inhalation of β_2-agonists (salbutamol 200 μg) or greater and 12% improvement from baseline ; (3) regular attendance and treatment for asthma over 6 months ; (4) a best ratio of FEV_1 to forced vital capacity of more than 0.7 when a subject had a smoking history (to exclude COPD) ; (5) no other co-morbidities likely to affect changes in any clinical parameters ; (6) no exacerbations over the preceding 4 weeks ; and (7) no changes in treatment within 4 weeks. All clinical measurements were evaluated on the same day. The present study was performed as part of our standard outpatient treatment and care. The study was approved by the local ethics committee, and participants gave informed consent.

Measurement of anxiety and administration of questionnaires

All patients underwent 30-min interview stress in order to determine their psychological status, anxiety rating, status of asthma control, presence of psychosomatic asthma, and adherence to inhaled corticosteroids. It was reported that level of serum cortisol were significantly increased in 8 of 11 subjects as "responders" after an interview stress.[22] The details of the interview and assessments are described below.

The psychological status was evaluated using the Japanese version of the Hospital Anxiety and Depression (HAD) scale,[16,23] which consists of 14 items, seven for anxiety and seven for depression. Anxiety was measured using the 7 items on the HAD scale's anxiety subscale (HAD-A). The anxiety scale score ranges from 0 to 21, with

higher scores reflecting more severe anxiety. The optimal cut-off point of 8/9 points to identify subjects with significant anxiety was recommended,[24] so anxiety was defined as a score of 8 or more on the HAD-A.

Asthma control was measured by the Asthma Control Test™ (ACT) score, which is a 5-item questionnaire that assesses the multidimensional perspectives of asthma control from activity limitation, shortness of breath, night symptoms, use of rescue medication and self-perception of asthma control, dichotomized into "well-controlled" (score$>$19) or "not well-controlled" (score$\leq$19).[25]

To measure the level of anxiety using a standardized measure, the State/Trait Anxiety Inventory (STAI)[26,27] was used. The instrument consists of two scales, with 20 questions in each scale: the State scale (STAI-S) measures the current level of anxiety experienced by the respondent, while the Trait scale (STAI-T) measures the respondent's general tendency to experience anxiety.

In order to diagnose psychosomatic illness as asthma, we evaluate patients using the 2006 questionnaire edited in a guideline for the diagnosis and treatment of psychosomatic diseases, which has been published only in Japanese.[28]

To assess the use of inhaled corticosteroids in children with persistent asthma, patients' adherence to these drugs and physicians' prescribing patterns were assessed using a novel drug adherence measure, the Proportion of Prescribed Days Covered (PPDC). The PPDC measure was defined as the total days' supply dispensed divided by the total days' supply prescribed. For each patient, we calculated the total number of prescriptions in the reference year.

Lung function studies

After they were clinically stable for at least two months, asthmatic patients were instructed to continue all of their medications, except to withhold inhaled long-acting β_2-agonists for 24 hr and inhaled albuterol sulfate for 6 hr prior to testing. Spirometry was performed using a CHESTAC-8800 (CHEST, Tokyo). Airway inflammation was determined by the fraction of exhaled nitric oxide (FeNO, in ppb) using an online collection apparatus using chemiluminescence (280A Nitric Oxide Analyzer; Sievers, Boulder, CO, USA) according to current guidelines.[29] Three samples were collected from each subject and the mean values were recorded.

Saliva cortisol level

Saliva cortisol samples were collected before and up to 30 min following stress with interviews in the morning. Saliva cortisol was analyzed by an enzyme immunoassay (EIA) (cortisol EIA kit; Cayman Chemical Company, Ann Arbor, MI, USA) with a CV of 4% for both within-day and between-day analyses. To reduce the limit of detection to 0.04 g/dl, the 1.0 μg/dl standard was diluted using the zero standard to the equivalents of 0.88, 0.75, 0.5, 0.25, 0.13, 0.06, and 0.03 μg/dl in order to achieve a calibration curve appropriate for saliva cortisol concentrations. Recent report was demonstrated that saliva cortisol response was attenuated in an independent manner with a kind of stressor in atopic adolescents; 50% decline by venous puncture for collecting blood and 22.3% decline by interview.[19] It was assessed as the changes in the ratio [(after stress-before stress)/before stress] of saliva cortisol.

The "responders" were defined to be those subjects whose had the changes in the ratio of less than -0.5.

Data analysis

Basic biometric and demographic variables were compared by the Mann-Whitney U test or χ^2-test for unpaired data. Wilcoxon's test was used for paired data. Spearman's rank correlation coefficients were calculated to determine the relationship between parameters, including saliva cortisol level of pre-stress, the changes in the ratio [post-stress-pre-stress)/pre-stress] of saliva cortisol, the HAD-A, the ACT score, the STAI-S, the STAI-T, and the psychosomatic sore. The results are expressed as the means$\pm$SD. Statistical analyses were performed using the SPSS statistical software program (SPSS ver. 16.0; SPSS Inc., Chicago, IL, USA). A p value<0.05 was considered significant.

Results

Patients

Thirty patients with mild to severe asthma were included in the analysis. The study population had a mean age of 60 years (Table 1). Fourteen patients (47%) had never been smokers, 10 (33%) were former smokers, and 6 (20%) were current smokers. Patients had a mean FEV_1 of 84.8%, and regarding the severity of FEV_1, 20 patients (67%) had mild impairment (more than 80% predicted), 7 (23%) had moderate (60-80%

Table 1 Characteristics of the study population (I).

Characteristics	All patients (N=30)	Patients without anxiety (N=21)	Patients with anxiety* (N=9)
Age (y), mean (SD)	60.3(14.1)	65.2(12.4)	52.9(15.4)
Female, n (%)	18(60)	12(57)	6¶(67)
Asthma duration (y), mean (SD)	16.6(14.2)	17.0(14.7)	15.6(13.7)
Smoker, n Never/past/current	14/10/6	9/8/4	5/2/2
%FEV_1, mean (SD)	84.8(20.1)	85.0(21.5)	84.4(17.7)
FeNO (ppb), mean (SD)	36.9(18.8)	34.7(17.8)	42.1(21.0)
ACT score, mean (SD)	22.0(4.0)	23.2(2.8)	19.1¶(4.9)
Inhaled corticosteroid dose† (μg), mean (SD)	540(321)	586(297)	433(367)
Adherence‡ (%), mean (SD)	87(22)	89(22)	83(24)

*Anxiety defined as scores of 8 or more on HAD scale anxiety subscale (HAD-A).
†Fluticasone equivalent.
‡To assess the use of inhaled corticosteroids, the Proportion of Prescribed Days Covered (PPDC) was measured as the total days' supply dispensed divided by the total days' supply prescribed.
¶$P<0.01$ compared with patients without anxiety for age, and ACT score.

predicted), and 3 (10%) had severe impairment (less than 60% predicted). The mean asthma control test (ACT) score was 22.0±4.0. When subjects with an ACT score of>19 were defined as having well-controlled asthma and those with a score of≤19 were defined as having not well-controlled asthma, 23.3% of treated asthmatics were not well-controlled (ACT score≤19). When we evaluated the patients' adherence to inhaled corticosteroids using the Proportion of Prescribed Days Covered (PPDC), the mean of the % adherence was shown to be 87%.

Prevalence of anxiety

To determine the patients' psychological status, the 14-item HAD scale[30] was used, which is ideally suited for clinical settings because items avoid any reference to physical symptoms. Seven questions relate to anxiety and seven to depression, with total scores for both subscales in the range of 0-21. For all patients, the anxiety and depression HADS scores were a mean of 5.1±3.7 and 4.3±3.8, respectively. For categorized scores, a value of 7 or less was interpreted as non-clinical, 8-10 as indicating possible clinical relevance, and values of 11 or higher as indicating important relevance.[16] We define anxiety as scores of 8 or higher on the HAD-A. For the HAD-A questionnaire, 9 patients (30%) had clinically-relevant anxiety (8 or higher), and 3 patients (10%) had significant levels (11 or higher) of anxiety. On the other hand, for the HAD scale depression subscale (HAD-D), 4 patients (13%) had clinically-relevant depression (8 or higher), and one patient (3%) had a significant level (11 or higher) of depression. Only one patient had an overlap of clinically-relevant anxiety and depression.

For all patients, the rate of state anxiety determined by the STAI-S was 39.3±10.7 ; trait anxiety (STAI-T) was a mean of 43.4±13.6. We determined that STAI-S scores>50 indicated clinically significant state-anxiety and STAI-T scores>54 indicated clinically significant trait anxiety.[31] Five patients (16.7%) had clinically significant state anxiety, and seven patients (23.3%) had clinically significant trait anxiety. Four of nine patients with anxiety (8 or higher of HAD-A) and one of 21 patients without anxiety showed clinically significant state anxiety (χ^2 test, $P<0.01$). On the other hand, five of nine patients with anxiety and two of 21 patients without anxiety showed clinically significant trait anxiety (χ^2 test, $P<0.01$).

Psychosomatic asthma was diagnosed as psychosomatic scores≥23 on the questionnaire based on the Japan guidelines.[28] Eight patients (26.7%) were diagnosed as having psychosomatic asthma. Five of nine patients with anxiety (8 or higher of HAD-A) and three of 21 patients without anxiety showed clinically psychosomatic asthma (χ^2 test, $P<0.01$).

Effects of stress on saliva cortisol

Compared to patients without anxiety, those with anxiety were younger (age : 65.2±12.4 yr vs. 52.9±15.4 yr, $P<0.01$) and had lower control asthma (ACT score : 23.2±2.8 vs. 19.1±4.9, $P<0.01$). A total of 55.5% of patients with anxiety did not have not well-controlled asthma (ACT

Table 2 Characteristics of the study population (II).

Characteristics	All patients (N=30)	Patients without anxiety (N=21)	Patients with anxiety* (N=9)
STAI-S*, mean (SD)	39.3(10.7)	35.7(10.5)	47.6¶(5.5)
STAI-T†, mean (SD)	43.4(13.6)	38.5(9.7)	54.9¶(14.9)
Psychosomatic sore‡, mean (SD)	16.5(8.1)	14.0(7.4)	22.4¶(6.5)

*STAI-S : the State/Trait Anxiety Inventory-State scale for measuring the current level of anxiety experienced by the respondent.

†STAI-T : the State/Trait Anxiety Inventory-Trait scale for measuring the respondent's general tendency to experience anxiety.

‡Psychosomatic sore was evaluated using the 2006 questionnaire edited in a guideline for the diagnosis and treatment of psychosomatic diseases.

¶$P<0.01$ compared with patients without anxiety for STAI-S, STAI-T, and Psychosomatic sore.

score≤19). Patients with anxiety had significantly higher scores of STAI-S, STAI-T, and psychosomatic score than those without anxiety (Table 2).

Saliva was collected in 30-min intervals before and after the interviews. Figure 1 shows the changes in saliva cortisol levels during interview stress in patients with and without anxiety. The level of saliva cortisol at baseline was similar in the two groups, with a mean of 5.7±7.3 μg/ml for patients with anxiety and 6.3±5.6 μg/ml for those without anxiety. A decrease in saliva cortisol levels was observed following the stress protocol in patients with anxiety compared with those without anxiety (1.2±0.9 μg/ml vs. 4.3±6.7 μg/ml, $P<0.05$). There was a significant change in saliva cortisol levels during interview stress in adult asthmatic patients with anxiety ($P<0.05$), but not without anxiety (Figure 1). The changes in the ratio [(after stress-before stress)/before stress] of saliva cortisol were shown to be lower in patients with anxiety than in those without anxiety (−0.3±0.9 vs. 0.1±1.9, $P<0.05$). Seven of nine patients (78%) with anxiety showed the "responders", who demonstrated half or more decline of saliva cortisol during the interview stress, on the other hand, 10 of 21 (47%) patients without anxiety.

Relationship between parameters

As presented in Table 3, the saliva cortisol level of pre-stress had significant correlation with the ACT score (rho=0.33) ; inverse correlation with the changes of the saliva cortisol (rho=−0.34), were also noted. The ACT score was correlated inversely with the HAD-A score (rho=−0.49), the STAI-S score (rho=−0.41), and the SATI-T score (rho=−0.35). A positive correlation was observed between the HAD-A

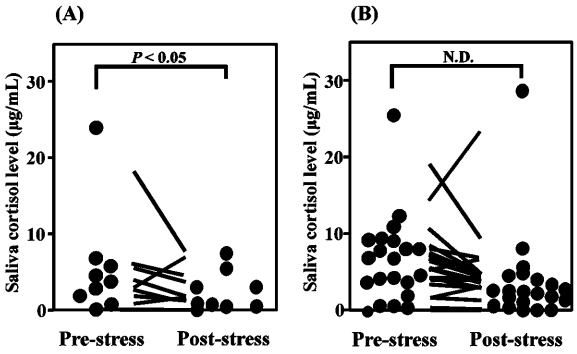

Fig. 1 Changes in saliva cortisol levels during interview stress in adult asthmatic patients with (n=9) (A) and without anxiety (n=21) (B).
N.D. ; not difference.

score and correlated positively with the STAI-S score (rho=0.68) and STAI-T score (rho=0.74), respectively. And also the score of psychosomatic illness was correlated with the saliva cortisol level of pre-stress (rho=−0.31), the HAD-A score (rho=0.76), the STAI-S score (rho=0.44), and the STAI-T score (rho=0.68), respectively. The ratio [(after stress-before stress)/before stress] of saliva cortisol showed no significant correlations with psychological parameters.

Discussion

We demonstrated that in adult patients, with maintenance therapies consisting of inhaled corticosteroids, the psychological status as evaluated by the HADS was associated with reduced HPA axis activity. To our knowledge, this is the first study to demonstrate a decline in saliva cortisol in asthma patients with anxiety following a 30-min interview stress protocol.

In this study, we found that 9 (30%) patients

Table 3 Relationship between parameters.

	Cortisol level of pre-stress, rho *P*	δ, rho *P*	HAD-A, rho *P*	HAD-D, rho *P*	ACT score, rho *P*	STAI-S, rho *P*	STAI-T, rho *P*	Psycho-somatic sore, rho *P*
Cortisol level of pre-stress	1.00							
δ*	−0.34 0.04	1.00						
HAD-A†	−0.21 0.24	0.05 0.79	1.00					
HAD-D‡	−0.02 0.92	0.08 0.66	0.43 0.02	1.00				
ACT score¶	0.33 0.04	−0.13 0.50	−0.49 0.01	−0.24 0.20	1.00			
STAI-S**	−0.11 0.55	−0.11 0.55	0.68 0.001	0.70 0.0002	−0.41 0.003	1.00		
STAI-T††	−0.15 0.42	0.12 0.53	0.74 0.001	0.66 0.0004	−0.35 0.04	0.75 0.001	1.00	
Psychosomatic sore‡	−0.31 0.04	0.09 0.64	0.76 0.001	0.22 0.25	−0.33 0.08	0.44 0.02	0.68 0.001	1.00

*δ : the changes in the ratio [post-stress-pre-stress)/pre-stress] of saliva cortisol.
†HAD-A : the Hospital Anxiety and Depression scale anxiety subscale for measuring anxiety.
‡HAD-D : the Hospital Anxiety and Depression scale depression subscale for measuring depression.
¶ACT score : the Asthma Control Test™ score for measuring asthma control.
**STAI-S : the State/Trait Anxiety Inventory-State scale for measuring the current level of anxiety experienced by the respondent.
††STAI-T : the State/Trait Anxiety Inventory-Trait scale for measuring the respondent's general tendency to experience anxiety.
‡‡Psychosomatic sore was evaluated using the 2006 questionnaire edited in a guideline for the diagnosis and treatment of psychosomatic diseases.
A p value < 0.05 was considered significant.

had anxiety scores of 8 or more, suggestive of a clinical anxiety state, and 3 (10%) patients had significant levels (values of 11 or higher) of anxiety. In the present study, we observed that fewer patients at baseline had significant levels of anxiety than has been reported in other studies. This may be due to several factors. First, the psychological status can differ according to the patient populations included in residential areas, e.g. inner city vs. suburban.[32] In two studies,[33,34] approximately 10% of the patients had anxiety, which is similar to our study ; however, in another study,[32] the findings were 30% and 9%, respectively, for these regions. Second, in our study, all patients had been stably treated for more than 6 months for their asthma based on the guidelines, therefore, any psychological problems due to asthma instability should have been suppressed.

It was previously reported that assessing the psychological status is recommended, as it is seemingly related to many poor asthma outcomes.[1–6] In this study, anxiety in asthmatic patients was shown to be associated with the control of asthma, but not adherence to inhaled corticosteroids and airflow limitation.

The key finding of this study was that asthmatic patients with anxiety had decreased saliva cortisol after a 30-min interview stress test. In the saliva, approximately 67% of the cortisol is unbound. There is generally a good correlation between cortisol measurements in the saliva and

serum.[35] In general, activation of the HPA axis by glucocorticoid release is a characteristic feature of the acute response to stress.[36] Our findings contradict those of Ritz and colleagues[37] who found that a stress protocol induced increases in cortisol levels with increased FeNO levels in asthmatic patients. It was reported that anxiety disorders were linked to hypothalamic-pituitary-adrenal (HPA) axis activity, and a significantly higher awakening response of salivary cortisol levels in patients with anxiety disorders.[38] On the other hand, our result was in concordance with Wamboldt and colleagues[19] who demonstrated that patients with atopic disorders have an attenuated cortisol response to laboratory stress. In an animal model, chronic stress induced dysfunction in the HPA axis, and attenuation of HPA axis responsiveness in response to chronic stressor was linked to higher levels of pro-inflammatory and anti-inflammatory cytokines and, further, to increased inflammation.[39] Our analyses might support the hypothesis advocated by Buske-Kirschbaum[40] that dysregulation by chronic inflammatory processes with prolonged secretion of proinflammatory cytokines, or chronic stress due to social problems, could facilitate the dysfunction of the HPA axis in response to stress. There is a close correlation between anxiety and a poor asthma. Patients with poorly controlled asthma were more anxious and/or more depressed.[41,42] Our result might link between the conditions (Table 2). We speculated that chronic stress may induce hyporesponsiveness of the hypothalamus-pituitary-adrenal axis, resulting in reduced cortisol secretion, followed to poorer control of asthma symptoms with eosinohilic inflammation in the airway. It was reported that α7 nicotinic acetylcholine receptor (CHRNA7) modulates immune activation by suppressing production of proinflammatory cytokines in peripheral immune cells. Polymorphisms in the CHRNA7 promoter were associated with lower cortisol levels after a small laboratory stress, due to dampen the cholinergic response, leading to an increase in allergic inflammation.[43] So in our hypothesis, polymorphisms in some genes might contribute to have a low response of HPA axis after a 30-min interview stress test in asthmatic patients with anxiety.

One of the limitations of this study was the number of subjects in each study group. Thirty subjects were recruited, so a risk of type-2 error was possible, however, some features were significantly different between the two groups. Another consideration is that we did not use a standardized laboratory stressor (Trier Social Stress Test ; TSST).[44] This consists of a 5-min speech preparation, 5-min speech delivery in front of an "expert" audience of two evaluators and the experimenter, and a 5-min mental arithmetic problem with serial subtractions under evaluation by the "experts". A sensitivity of stress is depend on persons, however our result demonstrated that approximately 80% of patients with anxiety showed the responders with 50% or more decline of saliva cortisol during the interview stress. Future studies will be required to validate our interview stress test in a larger number of patients with asthma.

Finally, we noted that approximately 30% of patients with asthma had some anxiety, and these patients had deteriorations in saliva cortisol following interview stress. Patients with anxiety were demonstrated to have a tendency toward uncontrolled asthma, in spite of high adherence to inhaled corticosteroids. Unraveling these mechanisms and employing this understanding in clinical practice requires exploration in further studies.

Conflict of Interest Statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgments

We thank Ms. Yoshiko Ito for help in preparing the study and the cortisol analysis, and Ms. Mami Ueno and Ms. Naoko Yamashita for assistance during the data collection.

References

1. Lavoie KL, Cartier A, Labrecque M, Bacon SL, Lemière C, Malo JL, Lacoste G, Barone S, Verrier P, Ditto B (2005) Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? Respir Med 99 : 1249-1257
2. ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH (2001) Psychopathology in patients with severe asthma is associated with increased health care utilization. Am J Respir Crit Care Med 163 : 1093-1096
3. Janson C, Bjornsson E, Hetta J, Boman G (1994)

Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med 149 : 930–934
4. Bonala SB, Pina D, Silverman BA, Amara S, Bassett CW, Schneider AT (2003) Asthma severity, psychiatric morbidity, and quality of life : correlation with inhaled corticosteroid dose. J Asthma 40 : 691–699
5. Bender BG (2006) Risk taking, depression, adherence, and symptom control in adolescents and young adults with asthma. Am J Respir Crit Care Med 173 : 953–957
6. Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF (1985) Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. J Am Med Assoc 254 : 1193–1198
7. Chida Y, Hamer M, Steptoe A (2008) A bidirectional relationship between psychosocial factors and atopic disorders : a systematic review and meta-analysis. Psychosom Med 70 : 102–116
8. Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, Oja H (2000) The role of acute and chronic stress in asthma attacks in children. Lancet 356 : 982–987
9. Sandberg S, Järvenpää S, Penttinen A, Paton JY, McCann DC (2004) Asthma exacerbations in children immediately following stressful life events : a Cox's hierarchical regression. Thorax 59 : 1046–1051
10. Fernandes L, Fonseca J, Martins S, Delgado L, Pereira AC, Vaz M, Branco G (2010) Association of anxiety with asthma : subjective and objective outcome measures. Psychosomatics 51 : 39–46
11. Feldman JM, Siddique MI, Morales E, Kaminski B, Lu S-E, Lehrer PM (2005) Psychiatric disorder and asthma outcomes among high-risk inner-city patients. Psychosom Med 67 : 989–996
12. Ritz T, Thöns M, Fahrenberg S, Dahme B (2005) Airway, respiration, and respiratory sinus arrhythmia during picture viewing. Psychophysiology 42 : 568–578
13. Goodwin RD (2003) Asthma and anxiety disorder. Adv Psychosom Med 24 : 51–71
14. Zielinski TA, Brown ES (2003) Depression in patients with asthma. In : Brown ES, editor. Asthma : social and psychological factors and psychosomatic syndromes. Basel : Karger. Adv Psychosom Med 24 : 42–50
15. Mrazek DA (2003) Psychiatric symptoms in patients with asthma : causality, comorbidity, or genetic etiology. Child Adolesc Psychiatr Clin N Am 12 : 459–471
16. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67 : 361–370
17. Mykletun A, Stordal E, Dahl AA (2001) Hospital Anxiety and Depression (HAD) scale : factor structure, item analyses and internal consistency in a large population. Br J Psychiatry 179 : 540–544
18. Buske-Kirschbaum A, von Auer K, Krieger S, Weis S, Rauh W, Hellhammer D (2003) Blunted cortisol responses to psychosocial stress in asthmatic children : a general feature of atopic disease? Psychosom Med 65 : 806–810
19. Wamboldt MZ, Laudenslager M, Wamboldt FS, Kelsay K, Hewitt J (2003) Adolescents with atopic disorders have an attenuated cortisol response to laboratory stress. J Allergy Clin Immunol 111 : 509–514
20. Kos-Kudla B, Buntner B, Marek B, Ostrowska Z, Swietochowska E (1996) Serum, salivary and urinary cortisol level in the evaluation of adrenocortical function in-patients with bronchial asthma. Endocr Regul 30 : 201–206
21. Eliasson O, Degraff ACJr (1985) The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. Influence of clinical diagnosis, spirometric, and anthropometric variables. Am Rev Respir Dis 132 : 858–864
22. Abplanalp JM, Livingston L, Rose RM, Sandwisch D (1977) Cortisol and growth hormone responses to psychological stress during the menstrual cycle. Psychosom Med 39 : 158–177
23. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M (2007) Longitudinal deteriorations in patient reported outcomes in patients with COPD. Respir Med 101 : 146–153
24. Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52 : 69–77
25. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TE (2004) Development of the asthma control test : a survey for assessing asthma control. J Allergy Clin Immunol 113 : 59–65
26. Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the State Trait Anxiety Inventory. Palo Alto, CA : Consulting Psychologists Press
27. Sesti A (2000) State Trait Anxiety Inventory (STAI) in medication clinical trials. Qual Life Newsletter 25 : 15–16
28. Komaki M, Kubo C, Fukushi M, ed. (2006) A guideline for the diagnosis and treatment of psychosomatic diseases 2006. Kyowakikaku, Tokyo (in Japanese)
29. American Thoracic Society ; European Respiratory Society (2005) ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 171 : 912–930
30. Herrmann C, Buss U, Snaith RP (1985) HADS-D Hospital Anxiety and Depression Scale-Deutsche version. Ein Fragebogen zur Erfassung von Angst und Depression in der somatischen Medizin [HADS-D Hospital Anxiety and Depression Scale-German version. A survey for the assessment of anxiety and depression in somatic medicine], Verlag Hans Huber, Bern, Switzerland

31. Bieling PJ, Antony MM, Swinson RP (1998) The State-Trait Anxiety Inventory, Trait version : structure and content re-examined. Behav Res Ther 36 : 777–788
32. Rimington LD, Davies DH, Lowe D, Pearson MG (2001) Relationship between anxiety, depression, and morbidity in adult asthma patients. Thorax 56 : 266–271
33. Kullowatz A, Kanniess F, Dahme B, Magnussen H, Ritz T (2007) Association of depression and anxiety with health care use and quality of life in asthma patients. Respir Med 101 : 638–644
34. Janson C, Bjornsson E, Hetta J, Boman G (1994) Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Me 149 : 930–934
35. Aardal E, Holm A-C (1995) Cortisol in saliva-reference ranges and relation to cortisol in serum. Eur J Clin Chem Clin Biochem 33 : 927–932
36. Sapolsky RM, Romero LM, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 21 : 55–89
37. Ritz T, Ayala ES, Trueba AF, Vance CD, Auchus RJ (2010) Acute stress-induced increases in exhaled nitric oxide in asthma and their association with endogenous cortisol. Am J Respir Crit Care Med 183 : 26–30
38. Vreeburg SA, Zitman FG, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Hoogendijk WJ, Smit JH, Penninx BW (2010) Salivary cortisol levels in persons with and without different anxiety disorders. Psychosom Med 72 : 340–347
39. Reber SO, Birkeneder L, Veenema AH, Obermeier F, Falk W, Straub RH, Neumann I (2007) Adrenal insufficiency and colonic inflammation after a novel chronic psychosocial stress paradigm in mice : implications and mechanisms. Endocrinology 148 : 670–682
40. Buske-Kirschbaum A (2009) Cortisol responses to stress in allergic children : interaction with the immune response. Neuroimmunomodulation 16 : 325–332
41. Di Marco F, Verga M, Santus P, Giovannelli F, Busatto P, Neri M, Girbino G, Bonini S, Centanni S (2010) Close correlation between anxiety, depression, and asthma control. Respir Med 104 : 22–28
42. Martínez-Rivera C, Vennera MD, Cañete C, Bardagí S, Picado C (2011) Psychological profile of patients with bronchial asthma and functional dyspnea : A comparison with a non-asthmatic population and impact on the disease. Arch Bronconeumol 47 : 73–78
43. Sinkus ML, Wamboldt MZ, Barton A, Fingerlin TE, Laudenslager ML, Leonard S (2010) The α7 nicotinic acetylcholine receptor and the acute stress response : Maternal genotype determines offspring phenotype. Physiol Behav
44. Kirschbaum C, Pirke KM, Hellhammer DH (1993) The 'Trier Social Stress Test'-a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28 : 76–81