INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Influence of Obesity on Control in Asthmatic Japanese Patients Defined by the Japanese Definition of Obesity

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Abstract

Background Despite the use of inhaled corticosteroid (ICS) becoming increasingly widespread, many problems related to asthma management still need to be addressed. One of them, obesity, has been reported to exert a harmful influence on asthma control. However, there have been few reports focusing not only on both obesity and its influence on Japanese asthma patients but also on the Japanese definition of obesity, as defined by the Japan Society for the Study of Obesity (JASSO).

Aims & Methods The aim of this study was to confirm the influence of obesity, as defined by the JASSO, on asthma management in Japanese asthmatic patients. Using data from the Niigata Asthma Treatment Study Group 2008 questionnaire survey, differences between the "normal" group (18.5 kg/m^2 ≦ BMI <25 kg/m^2) and the "obese" group (25 kg/m^2 ≦ BMI) were analyzed.

Results There was a significantly lower step 1 rate (19.4% v.s. 26.8%) and a higher proportion of patients using inhaled salmeterol (43.6% v.s. 35.8%) and leukotriene receptor antagonist (49.8% v.s. 40.8%) in the obese group relative to the normal group, although there were no significant differences in indicators of asthma control, including asthma control test scores.

Conclusion This study investigated influences of JASSO-defined obesity on asthma severity and management in a clinical setting in Japan. It is possible that there are strong interactions between asthma and obesity, such as obesity causing decreased ICS therapy efficacy and leukotriene (LT)-related inflammation, although further investigation is necessary.

Key words: bronchial asthma, obesity, inhaled corticosteroid, disease severity

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Introduction

The widespread use of inhaled corticosteroid (ICS) in the clinical setting has resulted in excellent asthma control (1, 2). However, asthma prevalence and mortality are significantly high, leading to an annual loss of 15 million disability-adjusted life-years, as estimated by The World Health Organization (3). The social and economic burden of asthma remains heavy and needs to be immediately addressed (4, 5), and therefore there is a need for improved asthma management.

There is an increasing body of literature suggesting interactions between obesity and asthma (6). Epidemiological studies have suggested that being overweight defined as a body mass index (BMI) of 25-29.9 kg/m^2 and obesity (BMI >30 kg/m^2) increases the incidence of asthma (7) and skew the prevalence of asthma toward a more difficult-to-control phenotype (8-11). However, the mechanisms by which obesity modifies asthma risk or phenotype remain unclear, as do the clinical implications of such interactions (12).

It is well known that not only asthma but also other common diseases, including coronary disease (13), hypertension (14), type II diabetes mellitus (15) and obstructive

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sleep apnea syndrome (16), are influenced by obesity. In analyses of studies on such relationships, obesity is usually defined as described above (BMI >30 kg/m^2). However, the influence of obesity on these common diseases can differ by ethnicity (17, 18). In the analysis of the influence of obesity on obesity-related diseases in the Asian population, it has been reported that obesity was defined not as BMI >30 kg/m^2 but as >25 kg/m^2 (19-22). The Japan Society for the Study of Obesity (JASSO) has also issued a definition of normal weight (18.5 kg/m^2 ≦ BMI <25 kg/m^2) and obesity (25 kg/m^2 ≦ BMI) in Japan. However, there have been few reports on the influence of obesity on the control and severity of asthma based on the JASSO definition.

The Niigata Asthma Treatment Study Group has been carrying out a regular questionnaire on problems related to asthma management since 1998. The subjects surveyed are adult bronchial asthma patients who visited medical institutions in Niigata Prefecture, and the attending physicians of these patients are included in the survey. On the basis of these surveys, we have reported the clinical characteristics of adult bronchial asthma patients (23), elderly bronchial asthma (24), near fatal asthma (25), perimenstrual asthma (26), asthma exacerbation factors (27), the selection of ICS (28), the relationship between smoking and gender in asthmatics (29), and changes in asthma management (1, 2). These surveys provide a clear picture of the state of asthma management in Japan. Using the data from the 2008 surveys, this study analyzed the influences of JASSO-defined obesity on the severity and the management of Japanese asthmatic patients.

Materials and Methods

Participation in this study was open to all medical institutions in Niigata Prefecture if they intended to join the Niigata Asthma Treatment Study Group. This study was performed with the approval of the Ethics Committee at the School of Medicine of Niigata University in Niigata Prefecture, Japan, or at the relevant participating institution, in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki). The study involved 28 large hospitals (200 beds or more), 14 small hospitals (less than 200 beds), and 62 clinics (no beds). A total of 5,260 questionnaires were prepared, and 3,146 responses were received (response rate: 59.8%). Table 1 shows the contents of the questionnaire (originally in Japanese). The questionnaire study was performed over 2 months from September to October 2008. Subjects were adult patients (aged 16 years and more) with bronchial asthma who regularly visited the participating institutions for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves. Therefore, individual patients were expected to understand technical terms such as “attack” or “unconsciousness” in the questionnaire (Table 1). In addition to this questionnaire, an asthma control test (ACT), which has been validated as a clinical indicator of asthma control (30, 31) was separately carried out at the same time. To evaluate problems in asthma management and treatment related to normal activity levels, the questionnaires also asked patients about their satisfaction in daily life. The subjects answered by choosing 1 of 5 answers as shown in Table 1.

In addition to monitoring the completion of the questionnaire by the patients, physicians were asked to supply details on the current treatment, primary control medication, the type of asthma (atopic or nonatopic) in accordance with the elevation in serum total IgE or detection of a specific IgE for allergens, and the severity of asthma in accordance with the Japanese Society of Allergology guidelines for the diagnosis and management of bronchial asthma. The definition of the severity of asthma used was essentially the same as that used by the Global Initiative for Asthma.

The representative results for continuous variables were expressed as arithmetic means and standard deviations. Intergroup differences in terms of continuous variables were evaluated using the Kruskal-Wallis test and Wilcoxon’s rank sum test with the Bonferroni correction. A Chi-square test with the Bonferroni correction was also used to assess the significance of differences in proportions among groups. All statistical analyses were performed with the statistical software StatView 5.0 PowerPC version (SAS Institute Inc., Cary, NC, USA). For all statistical analyses, a p-value <0.05 was considered to be significant.

Results

Patient background

Patient backgrounds are summarized in Table 2. Of the asthmatic patients who answered the questionnaire, 1,464 were classified as being in the normal group (18.5 kg/m^2 ≦ BMI <25 kg/m^2) and 660 were classified as being in the obese group (25 kg/m^2 ≦ BMI). The BMI values and ages of the obese group were significantly higher (28.1+/-4.0 kg/m^2, 57.4+/-16.6 years old) than those of the normal group (22.7+/-1.8 kg/m^2, 55.1+/-17.4 years old). There was no significant difference in gender between the normal and obese group. In asthma severity, the proportion of step 1 patients in the obese group was significantly lower (19.4%) than that in the normal group (26.8%). There were no significant differences in disease duration, disease type, smoking status and the proportion who used peak flow meters between the normal and obese groups.

Asthma control and symptoms

The ACT scores and the rate of asthma attacks, peak flow values, the rate of asthma-related symptoms in morning and at night, and the rate of sleep disturbances during the two weeks prior to answering the survey are shown in Table 3-a. There were no significant differences in these indicators between the normal and obese groups. There were no significant differences between the normal and obese groups in

Table 1. Questionnaires Administered to Asthmatic Patients in This Study (the Original was in Japanese.)

Age: years old Gender: male / female
Question 1
When were you first diagnosed as having bronchial asthma? Year: Month: Day:
Question 2
1) select which of the following applies to you:
(I do not smoke, I am an ex-smoker, I currently smoke)
2) If you are an ex-smoker, please answer following
At what age did you start smoking ? The age you started:
At what age did you stop smoking ? The age you stopped:
How many cigarettes did you smoke per day? Cigarettes/day (mean):
Did you stop smoking due to your asthma? Yes or No:
3) If you currently smoke, please answer the following:
How old were you when started smoking? The age you started:
How many cigarettes did you smoke per day? Cigarettes/day (mean):
Question 3
1) Do you use a peak-flow meter? (Yes/No)
2) What was your average peak flow rate using your meter during the last 2 weeks?
morning: night:
Question 4 Select one answer for each the following questions:
1) How often did you have asthma attacks during the last 12 months?
(frequent attacks, seasonal attacks, or few attacks)
2) How often did you have asthma attacks during the last 2 weeks?
(5-7/week, 3-4/week, 1-2/week, or none)
3) How severe were your asthma attacks during the last 2 weeks?
(impossible to move, impossible to lie down, possible to lie down, strider, dyspnea upon exertion)
4) Have you ever been hospitalized due to asthma?
(yes/no)
5) Have you ever been taken by ambulance or visite an emergency room due to an atacck ?
(yes/no)
6) Have you ever been placed on a respirator due to an asthma attack?
(yes/no)
7) Have you ever been unconscious due to an asthma attack?
(yes/no)
8) Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicine?
9) Have you been absent from work or school due to an asthma attack?
(yes/no)
Question 5
How bad was your asthma during the last 2 weeks?
(very good, fairly good, mediocre, slightly bad, or bad)
Question 6
Describe your symptoms during the last 2 weeks:
1) in the morning
(cough, sputa, chest tightness, stridor, dyspnea, or no symptoms)
2) at night
(cough, sputa, chest tightness, stridor, dyspnea, or no symptoms)
3) sleep disturbance
(sometimes cannot fall asleep due to dyspnea, cannot to have a good sleep due to dyspnea, waking up in the night due to chest tightness, or none)
Question 7
Do you feel satisfied with your daily life?
(very satisfied, fairly satisfied, mediocre, slightly dissatisfied, or dissatisfied)

Table 2. Patient Background

	Normal group	Obese group
BMI (mean+/-SD: kg/m^2)	21.7+/-1.8	28.1+/-4.0***
Age (mean+/-SD: year)	55.1+/-17.4	57.4+/-16.6
Gender: male/female (%)	45.4/ 53.6	42.8/ 57.2
Duration (mean+/-SD: year)	14.0+/-13.5	14.6+/-14.2
Type: atopic/nonatopic (%)	69.8/ 24.4	65.0/ 28.6
Severity: Step1/ 2/ 3/ 4 (%)	26.8/ 28.3/ 25.8/ 4.7	19.1**/ 28.9/ 29.1/ 6.2
Smoking status: Non/ Ex/ Cu (%)	50.2/ 31.1/ 15.7	53.2/28.2/16.5
PEF use rate (%)	26.3	28.3

**: $p<0.01$, ***: $p<0.001$ *v.s.* normal group, Non: non-smoker, Ex: ex-smoker, Cu: current smoker, PEF: peak flow meter

Table 3-a. ACT, Incidence of Asthma Attacks, Percentages of Predicted Peak Flow Values, Asthma-related Symptoms and Sleep Disturbances during the Two Weeks Prior to Answering the Questionnaire

	Normal group	Obesity group
ACT Median (IQR)	23 (20-25)	23 (20-24)
Asthma attacks rate(%)	22.5	23.5
PEFV (morning mean+/-SD)	376+/-115	398+/-113
PEFV (night mean+/-SD)	383+/-116	404+/-112
ARS in morning rate (%)	41.7	43.9
ARS in night rate (%)	29.8	27.0
sleep disturbance rate (%)	13.7	13.8

PEFV: peak flow value, ARS: asthma-related symptoms

Table 3-b. Asthma Attacks and Asthma-related Work Absences during the One Year Period Prior to Answering the Questionnaire

	Normal group	Obese group
AA: frequent/seasonal/few (%)	129/500/681 (8.8/ 31.1/ 46.5)	70/213/323 (10.6/32.3/48.9)
ARWA rate (%)	8.6	9.1

AA: asthma attacks, ARWA: asthma-related work or school absences

Table 4. Drug/Medication

	Normal group	Obese group
ICS use rate (%)	87.0	88.0
ICS doses (mean+/-SD:μg/day calculated as FP)	317+/-178	326+/-158
LTRA use rate (%)	40.8	49.8 ***
OCS use rate (%)	4.8	4.5
OCS dose (mean+/-SD: mg/day: calculated as PSL)	6.4+/-4.2	6.2+/-3.8
SML use rate (%)	35.8	43.6 ***
p-TBL use:rate (%)	8.5	8.0
OSRT use:rate (%)	41.4	43.3

***: $p<0.01$ *v.s.*normal group, ICS: inhaled corticosteroid, LTRA: leukotriene receptor antagonist, OCS: oral corticosteroid, PSL: prednisolone, SML: salmeterol, p-TBL: tulobuterol patches, OSRT: oral sustained-released theophylline

terms of their asthma attacks during the one-year period prior to answering the survey and the rate of asthma-related work absences (Table 3-b).

Drugs/Medications

In terms of medications (Table 4), a significantly higher proportion of subjects in the obese group (48.8% and 43.6%) used leukotriene receptor antagonists (LTRA) and salmeterol (SML) relative to the normal group (40.8% and 35.8%). There was no significant difference between the normal and obese groups in terms of the proportion of subjects using ICS and oral corticosteroids (OCS), or in their doses. There were no significant differences in the use of tulobuterol patches (p-TUB) and oral sustained-released theophylline (OSRT) between the normal and obese groups.

Satisfaction in daily life

There was no significant difference in satisfaction with daily life between the normal and obese groups (Table 5).

Hospitalization, ambulance use or emergency department (ED) visits, attacks with unconsciousness, respirator management and asthma attacks induced by an anti-imflammatory agent (aspirin intolerant asthma, AIA)

Table 6 shows the rates of hospitalization, ambulance use or emergency ED visits, attacks involving unconsciousness, respirator management and AIA attacks. There were no significant differences in these rates between the normal and obese groups.

Discussion

The aim of this study was to investigate the influence of obesity on asthma control and management in an actual clinical setting in Japan. It was necessary to carry out this study in Japan (19-22) due to the difference in the definition of obesity by ethnicity, particularly between the traditional definition and the Asian definition. The JASSO-defined

Table 5. Satifaction in Daily Life

	Very satisfied/Fairly satisfied/Mediocre/Slightly dissatisfied/Dissatisfied (%)
Normal group	289/ 866/ 175/ 105/ 23 (19.6/ 59.2/ 12.9/ 7.2/ 1.6)
Obese group	120/ 397/ 83/4 5/ 9 (18.2/ 60.2/ 12.6/ 6.8/ 1.4)

Table 6. Hospitalization, Ambulance Use or ED Visits, Attacks with Unconsciousness, Respirator Management and AIA Attacks

	Normal group	Obese group
Hospitalization rate (%)	34.8	33.2
Ambulance use or ED visits rate (%)	32.0	29.1
Attacks with unconsciousness rate (%)	6.6	4.5
Respirator management rate (%)	5.7	5.3
AIA attacks rate (%)	7.1	7.1

ED: emergency department, AIA: aspirin intolerant asthma

obese group (25 kg/m^2 ≦ BMI) was compared with the normal group (18.5 kg/m^2 ≦ BMI <25 kg/m^2), and the results clearly indicated a relationship between obesity and asthma. There was a lower proportion of step 1 patients in the obese group than in the normal group (Table 2), indicating that obesity exerted a harmful influence on disease severity. There were few changes in the control of asthma between the two groups, because there were no differences in the ATC scores and other indicators of asthma control, as shown in Table 3-a, 3-b, 5 and 6, although the pulmonary function test data, one of the important factors in analyzing asthma severity, was lacking in this study. However, there were obvious differences between the normal and obese groups in terms of drugs/medications (Table 4), not in ICS use but with the use of other medications, such as SML and LTRA. These findings suggested that more medications were required in the obese group than in the normal group for the same level of asthma control. In this study, it is clear that obesity had an influence on asthma patients.

However, the mechanism of the influence of obesity on asthma in this study remains unknown. It has been reported that obesity may cause bronchial inflammation via activation of inflammatory cells and adipose tissue (32, 33), and may also exacerbate bronchial reactivity via modulation of lung function (34), resulting in a phenotype change to one that is more difficult to control. The difference in disease severity, the step 1 rate, expresses the severity of the disease, because there are few maintenance medications for asthma control that are commonly given to asthmatic patients classified as step (1). The differences in the proportion of patients using LTRA and SML can have implications other than those related to disease severity. It has recently been reported that the response of inflammatory cells derived from obese asthmatic patients to corticosteroid treatment was attenuated compared with that of those from non-obese asthmatic patients (9), indicating another important mechanism related to this problem. The decreased efficacy of corticosteroid treatment indicates that obesity may shift the dose-response curve of ICS to the right. This is consistent with our results, in that there was a higher proportion of patients using LTRA and SML in the obese group. It has been reported that leukotriene (LT) plays an important role in the aggravation of asthma amongst obese patients. These reports state that a greater amount of inflammation associated with LT was observed in asthmatic patients with higher BMIs (35), and the response to LT was maintained in the obese asthma patients relative to those who were not obese, but the response of ICS was not maintained (36). In addition to ICS efficacy, LT inflammation may also be associated with the influence of obesity on asthma, although there was no evidence that such inflammation existed in this study.

In summary, we attempted to elucidate the association of obesity with asthma control by comparing questionnaire survey data from normal and obese asthmatic patients in terms of their asthma characteristics and management. It was found that a higher proportion of patients used SML and LTRA in JASSO-defined obese patients and that they had lower step 1 rates. This study investigated the relationship between obesity and asthma in a clinical setting in Japan, and found that obesity may play a significant role in influencing the severity of asthma, decreased ICS efficacy, and LT-related inflammation, although further investigation will be necessary.

The authors state that they have no Conflict of Interest (COI).

References

1. Hasegawa T, Suzuki E, Terada M, et al. Improvement of asthma management in actual practice consistent with prevalence of anti-inflammatory agents: based on Questionnaire Surveys in Niigata Prefecture, Japan from 1998 to 2002. Allergol Int **54**: 555-563, 2005.
2. Hasegawa T, Suzuki E, Muramatsu Y, et al. Questionnaire-based analysis of the current level of asthma control and management in Niigata Prefecture, Japan: changes from 1998 to 2000. Allergol Int **53**: 135-144, 2004.

3. Masoli M, Fabian D, Holt S, Beasley R. Global initiative for asthma (GINA) program. The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy **59**: 469-478, 2004.

4. Lai CK, De Guia TS, Kim YY, et al. Asthma insights and reality in Asia-Pacific steering committee. asthma control in the Asia-Pacific region: the asthma insights and reality in Asia-Pacific study. J Allergy Clin Immunol **111**: 263-268, 2003.

5. Weiss KB, Sullivan SD. The economic costs of asthma: a review and conceptual model. Pharmacoeconomics **41**: 14-30, 1993.

6. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med **174**: 112-119, 2006.

7. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med **175**: 661-666, 2007.

8. Dolan CM, Fraher KE, Bleecker ER, et al. Design and baseline characteristics of the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol **92**: 32-39, 2004.

9. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med **178**: 682-687, 2008.

10. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med **101**: 2240-2247, 2007.

11. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J **27**: 495-503, 2006.

12. Weiss ST, Shore S. Obesity and asthma: directions for research. Am J Respir Crit Care Med **169**: 963-968, 2004.

13. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Arterioscler Thromb Vasc Biol **26**: 968-976, 2006.

14. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol **52**: 1749-1757, 2008.

15. Hill MJ, Metcalfe D, McTernan PG. Obesity and diabetes: lipids, 'nowhere to run to'. Clin Sci (Lond) **116**: 113-123, 2009.

16. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc **5**: 136-143, 2008.

17. Fernâdez JR, Allison DB. Understanding racial differences in obesity and metabolic syndrome traits. Nutr Rev **61**: 316-319, 2003.

18. Lee S, Kuk JL, Hannon TS, Arslanian SA. Race and gender differences in the relationships between anthropometrics and abdominal fat in youth. Obesity (Silver Spring) **16**: 1066-1071, 2008.

19. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. Int J Obes (Lond) **35**: 167-187, 2011.

20. Li G, Chen X, Jang Y, et al. Obesity, coronary heart disease risk factors and diabetes in Chinese: an approach to the criteria of obesity in the Chinese population. Obes Rev **3**: 167-172, 2002.

21. Moon OR, Kim NS, Jang SM, Yoon TH, Kim SO. The relationship between body mass index and the prevalence of obesity-related diseases based on the 1995 National Health Interview Survey in Korea. Obes Rev **3**: 191-199, 2002.

22. Deurenberg-Yap M, Chew SK, Lin VF, et al. Relationships between indices of obesity and its co-morbidities in multi-ethnic Singapore. Int J Obes Relat Metab Disord **25**: 1554-1562, 2001.

23. Suzuki E, Hasegawa T, Koya T, et al. Questionnaire-based analysis of current status of adult bronchial asthma in Niigata Prefecture: comparison with the Asthma Guideline. Acta Medica Biologica **50**: 135-143, 2002.

24. Suzuki E, Hasegawa T, Koya T, et al. Questionnaire-based characterization of bronchial asthma in elderly: analysis in Niigata Prefecture, Japan. Allergol Int **51**: 241-248, 2002.

25. Yoshimine F, Hasegawa T, Suzuki E, et al. Contribution of aspirin intolerant asthma to near fatal asthma based on questionnaire surveys in Niigata Prefecture, Japan. Respirology **10**: 477-484, 2005.

26. Suzuki K, Hasegawa T, Sakagami T, et al. Analysis of perimenstrual asthma based on questionnaire surveys in Japan. Allergol Int **56**: 249-255, 2007.

27. Koyanagi K, Koya T, Sasagawa M, et al. An analysis of factors that exacerbate asthma, based on a Japanese questionnaire. Allergol Int **58**: 519-527, 2009.

28. Ota K, Hasegawa T, Koya T, et al. Analysis of inhaled corticosteroid selection in patients with bronchial asthma using a questionnaire survey: Effects of age, gender, and disease severity. Allergol Int **58**: 365-371, 2009.

29. Satoh H, Hasegawa T, Suzuki E, et al. Gender differences in susceptibility of asthma to active smoking: questionnaire based analysis in the Niigata Prefecture, Japan. Allergol Int **54**: 401-410, 2005.

30. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol **113**: 59-65, 2004.

31. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol **117**: 549-556, 2006.

32. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol **115**: 911-919, 2005.

33. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest **112**: 1785-1788, 2003.

34. Fredberg JJ, Inouye DS, Mijailovich SM, Butler JP. Perturbed equilibrium of myosin binding in airway smooth muscle and its implications in bronchospasm. Am J Respir Crit Care Med **159**: 959-967, 1999.

35. Giouleka P, Papatheodorou G, Lyberopoulos P, et al. Body mass index is associated with leukotriene inflammation in asthmatics. Eur J Clin Invest **41**: 30-38, 2011.

36. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J **27**: 495-503, 2006.