

C. Picado
R. Deulofeu
R. Lleonart
M. Agustí
E. Casals
L. Quintó
J. Mullol

Lipid and protein metabolism in asthma. Effects of diet and corticosteroid therapy

Authors' affiliations:

C. Picado, Servei de Pneumologia, Hospital Clinic, Departament de Medicina, Universitat de Barcelona

R. Deulofeu, E. Casals, Servei de Bioquímica Clínica, Hospital Clinic, Departament de Medicina, Universitat de Barcelona

R. Lleonart, M. Agustí, L. Quintó, J. Mullol, IDIBAPS, Hospital Clinic, Departament de Medicina, Universitat de Barcelona, Spain

Correspondence to:

César Picado
Servei de Pneumologia
Hospital Clinic
Villarroel 170
08036 Barcelona
Spain

Key words: asthma; corticosteroid; diet; lipid; metabolism; protein.

Background: Because little is known about the effects of asthma and asthma therapy on lipid and protein metabolism, we have investigated the characteristics of diet and plasma/serum levels of fat and protein in a group of asthma patients with various degrees of severity.

Methods: A case-control study was carried out on 118 asthma patients recruited from an outpatient clinic and 121 healthy subjects. Asthma severity was characterized in four groups according to clinical symptoms, lung-function tests, and therapy. Normal dietary intake was estimated from a food frequency questionnaire. Serum protein, albumin, and fatty acids were determined by standard methods.

Results: The dietary energy intake of the asthmatics was significantly lower than that of the controls. However, no differences in the body mass index were found between asthma patients and healthy subjects. There were no differences in serum/plasma levels in any of the measured biochemical parameters between healthy subjects and asthmatics. Plasma levels of protein and albumin were significantly lower in severely corticosteroid-dependent patients. There was a significant negative correlation between plasma protein ($r=0.36$, $P<0.05$) and plasma albumin levels ($r=0.43$, $P<0.01$) and the daily dose of oral corticosteroids. We did not find any differences in plasma levels of cholesterol, HDL-cholesterol, LDL-cholesterol, and fatty acids between cortico-dependent patients and those not receiving this therapy. No correlation was found between any biochemical parameters and the daily dose of inhaled corticosteroids.

Conclusions: Our results suggest that asthma induces a decrease in energy intake that does not result in a decreased body weight. Inhaled corticosteroids do not exert any metabolic

Date:

Accepted for publication 28 December 1998

To cite this article:

Picado C., Deulofeu R., Lleonart R., Agustí M., Casals E., Quintó L. & Mullol J. Lipid and protein metabolism in asthma. Effects of diet and corticosteroid therapy. *Allergy* 1999; **54**: 569–575.

Copyright © Munksgaard 1999

ISSN 0105-4538

effect, whereas severe asthma with regular oral corticosteroid therapy is associated with reduced plasma protein and albumin levels.

Inhaled corticosteroids are recommended as first-line therapy in asthma patients with persistent symptoms. Although systemic corticosteroids can cause changes in protein (1), lipid (2), and carbohydrate (1) metabolism and body composition (redistribution of fat), only a few studies have investigated the metabolic effects of corticosteroid therapy in asthma. Yavuz et al. (3) found that high doses of budesonide (1600 µg/day for 4 weeks) decreased serum cholesterol concentration and increased serum high-density lipoprotein (HDL)-cholesterol level. Turpeinen et al. (4) also found that 800 µg/day of budesonide for 4 weeks significantly increased serum HDL concentration. The treatment had no effects on serum total cholesterol and serum triglycerides. Budesonide also decreased insulin resistance and improved glucose tolerance, suggesting that asthma itself may lead to abnormalities in carbohydrate metabolism (4). Previous short-term studies have reported that inhaled corticosteroids decrease some metabolic bone parameters such as osteocalcin (5). Impaired growth in children treated with inhaled corticosteroids has also been detected in short-term studies by knemometry (6). However, long-term studies with inhaled corticosteroids failed to show any effect from this therapy on osteocalcin (7) and on growth (8). These findings suggest that although results from short-term studies reflect systemic effects, they do not necessarily predict long-term side-effects.

Table 1. Demographic data from patients and controls expressed as means $\pm$ SEM (range), *P* value. ANOVA adjusted for age and sex when necessary

	Asthma	Controls	<i>P</i>
<i>n</i>	118	121	
Sex (M/F)	48/70	45/76	NS
Age (years)	41.6 $\pm$ 1.4 (16–72)	38.8 $\pm$ 1.3 (17–74)	NS
Weight (kg)	65.8 $\pm$ 1.2 (40–101)	66.2 $\pm$ 1.3 (45–98)	NS
Height (cm)	164 $\pm$ 0.8 (146–186)	164.8 $\pm$ 1.0 (150–188)	NS
BMI (kg/m ²)	24.2 $\pm$ 0.4 (16.6–34.9)	24.3 $\pm$ 0.3 (18–36.8)	NS
BMI: body mass index; NS: nonsignificant.			

Besides its direct metabolic effects, asthma therapy might also have a potential impact on the characteristics of diet by increasing or decreasing appetite. Moreover, asthma treatment might also modify the characteristics of diet in relative terms by, for instance, increasing the intake of carbohydrates compared with fat or proteins.

There is little information about the long-term effects of inhaled and systemic oral corticosteroid therapy on lipid and protein metabolism in asthma. Moreover, to our knowledge, the effects of asthma by itself on food intake, body composition, and metabolism have not been studied so far. We have therefore investigated the effects of asthma and asthma therapy on the characteristics of diet and on plasma/serum levels of fat and protein.

Material and methods

Study subjects

A total of 150 consecutive asthmatic patients attending the outpatient clinic were asked to take part in the study. They all presented a history of intermittent wheezing, shortness of breath, and chest tightness; they all had a diagnosis of asthma and were taking asthma medication. The severity of the disease was characterized in four groups, by a method similar to the one proposed in the Global Initiative for Asthma (GINA) (9). The method was modified to include the characteristics of therapy in the classification of the severity of disease. The four groups were as follows: intermittent (group 1), mild persistent (group 2), moderate persistent (group 3), and severe (group 4). Group 1 contained patients who were on β -adrenergic agents on demand. Group 2 contained patients who regularly used β -adrenergic agents, with or without low doses of inhaled corticosteroids. Group 3 contained patients with a continuing history of episodic asthma, most of whom were on regular inhaled corticosteroid therapy, and group 4 contained patients with a current history of chronic, unremitting asthma requiring high doses of inhaled corticosteroids and regular oral corticosteroid therapy, or frequent short courses of oral corticosteroids.

A total of 150 healthy volunteers were selected as a control population from various sources, including neighbors of patients, families of the members of the staff, and the blood donor population.

Smokers and subjects who were on an exclusion diet or had received diet recommendations were excluded.

Table 2. Demographic data from asthmatic patients according to severity expressed as means $\pm$ SEM (range), *P* value, ANOVA

Severity	1	2	3	4	<i>P</i>
<i>n</i>	30	40	24	24	
Age (years)	29.5 $\pm$ 2.2 (16–63)	40.8 $\pm$ 2.2 (19–72)	47.2 $\pm$ 2.9 (19–67)	50.4 $\pm$ 2.3 (44–99)	<0.05*
Weight (kg)	63 $\pm$ 2.6 (44–99)	64.8 $\pm$ 2 (47–101)	65.9 $\pm$ 1.7 (48–79)	70.2 $\pm$ 3 (40–96)	NS
Height (cm)	165.8 $\pm$ 1.6 (150–182)	163.7 $\pm$ 1.6 (148–186)	161.7 $\pm$ 1.7 (146–180)	165 $\pm$ 1.9 (148–186)	NS
FEV ₁ (%)	86 $\pm$ 1.1 (80–93)	83 $\pm$ 1.01 (77–91)	74 $\pm$ 1.2 (62–86)	62 $\pm$ 2.1 (46–75)	<0.05*#
FVC (%)	91 $\pm$ 1.3 (82–101)	87 $\pm$ 0.9 (81–95)	84 $\pm$ 1.2 (75–94)	78 $\pm$ 1.9 (68–88)	<0.05*#
Atopy (%)	71	67	59	39	<0.05*#
BMI (kg/m ²)	22.6 $\pm$ 0.6 (17.1–30.5)	24.1 $\pm$ 0.5 (17.4–30.5)	25.2 $\pm$ 0.6 (18.9–28.9)	25.6 $\pm$ 0.9 (16.6–34.5)	NS

*Group 1 vs 2, 3, 4.
#Groups 1, 2 vs 4. BMI: body mass index; NS: nonsignificant.

A total of 118 patients and 121 subjects met all the inclusion criteria and agreed to participate in the study. The subjects gave informed consent to the study, which was approved by the ethics committee of the institution.

The skin prick test was performed with common allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat, dog, grass pollen mixture, tree pollen mixture, *Parietaria judaica*, *Aspergillus fumigatus*, *Alternaria tenuis*, and cockroach) (Ifidesa-Arístegui, Bilbao, Spain). Histamine (10 mg/ml) and glycerol were used as positive and negative controls. A skin prick reaction was regarded as positive if the wheal size was >3 mm. Subjects were considered atopic if

they had a positive reaction to any of the allergens in the testing panel.

Food frequency questionnaire

All subjects completed a food frequency questionnaire (FFQ). We used a 150-item semiquantitative FFQ to assess normal dietary intake during the previous 6 months. A trained dietitian who was unaware of the subjects' characteristics administered the FFQ to all the subjects. Nutrient intake was computed from the reported frequency of consumption of each specified unit of food or beverage, and from published data on the nutrient content of the specified portions. To help the subjects to quantify food consumption, the dietitian used photographs showing servings with six progressive portions of the reported consumed foods.

Biochemical measures

A 100-ml sample of venous blood was taken. Total protein, albumin, and glucose were measured by standard laboratory methods. Fatty acids extracted from serum were measured by gas chromatography after methylation, with a fatty acid analysis column from Supelco (Teknokroma, Sant Cugat, Spain) in a Perkin-Elmer 8500 GC, according to a method described elsewhere (10).

Table 3. Daily nutrient intake of patients and controls, means $\pm$ SEM. ANOVA adjusted for sex and age

	Patients	Controls	<i>P</i>
<i>n</i>	118	121	
Total energy intake (kcal/day)	2363 $\pm$ 557	2591 $\pm$ 763	0.013
Carbohydrate (g/day)	265 $\pm$ 75	294 $\pm$ 91	0.013
Protein (g/day)	100 $\pm$ 24	108.5 $\pm$ 34	0.038
Fat (g/day)	30 $\pm$ 11.8	33.0 $\pm$ 13	0.022
Saturated fat (g/day)	30 $\pm$ 11.8	33.0 $\pm$ 13	NS
Monounsaturated fat (g/day)	47.8 $\pm$ 14	50.2 $\pm$ 17	NS
Polyunsaturated fat (g/day)	10.7 $\pm$ 1.2	11.2 $\pm$ 1.8	NS
Cholesterol (mg/day)	399 $\pm$ 14	437 $\pm$ 15	NS

NS: nonsignificant.

Table 4. Daily nutrient intake of asthmatic patients according to severity. Means $\pm$ SEM. ANOVA adjusted for sex and age

<i>n</i>	Severity				<i>P</i>
	1 (30)	2 (40)	3 (24)	4 (24)	
Total energy intake (kcal/day)	2648 $\pm$ 410	2278 $\pm$ 483	2259 $\pm$ 648	2284 $\pm$ 644	0.03 1 vs 2, 3, 4
Carbohydrates (g/day)	308 $\pm$ 75	254 $\pm$ 58	245 $\pm$ 82	243 $\pm$ 77	0.02 1 vs 2, 3, 4
Proteins (g/day)	107 $\pm$ 20	94.9 $\pm$ 18	96.6 $\pm$ 26	103.7 $\pm$ 32	NS
Fat (g/day)	109.8 $\pm$ 25	97.2 $\pm$ 26	96.7 $\pm$ 33	97.5 $\pm$ 36	NS
Saturated fat (g/day)	32.8 $\pm$ 10.8	28 $\pm$ 9.9	29.3 $\pm$ 12	32.3 $\pm$ 15	NS
Monounsaturated fat (g/day)	49.7 $\pm$ 11.9	49.4 $\pm$ 14	45.5 $\pm$ 17	45.6 $\pm$ 16	NS
Polyunsaturated fat (g/day)	11.8 $\pm$ 5.2	10.4 $\pm$ 5	9.5 $\pm$ 6	10 $\pm$ 5	NS
Cholesterol (mg/day)	445 $\pm$ 160	405 $\pm$ 109	415 $\pm$ 196	465 $\pm$ 243	NS
NS: nonsignificant.					

Statistics

Dietary intake of triacylglycerol and serum concentrations of some fatty acids were skewed; therefore, a logarithmic transformation was applied to the data before formal analysis. However, summary statistics are reported in the original scale in the text and tables. Correlation between dietary and serum levels was tested by simple Pearson correlation analyses. Means of dietary intake and biochemical measures were compared between patients and controls and between the four groups of patients by an ANOVA model, adjusting for age, sex, and corticosteroid therapy (inhaled and systemic). Results were considered statistically significant if the observed, two-sided significance level (*P* value) was not greater than 0.05. Values in the text and

tables are means $\pm$ SEM. Statistical analysis was carried out with SPSS statistical software.

Results

Demographic and clinical characteristics

Demographic characteristics were similar in patients with asthma and control subjects (Table 1). No significant differences were detected in the body mass index (BMI) (body weight in kg/height in m²) between asthmatics and healthy subjects (Table 1). The distribution of patients as regards severity is shown in Table 2. Patients from group 1 were significantly younger than those with moderate (groups 2 and 3) and severe asthma (group 4).

In group 1, there were no patients on inhaled corticosteroids. In group 2, 22 out of 40 patients were on inhaled corticosteroids (180 $\pm$ 100 mg/day, range 0–400 for 11 $\pm$ 19 months). Seventeen out of 24 patients in group 3 were on inhaled corticosteroid therapy (380 $\pm$ 260 mg/day, range 0–800 for 10 $\pm$ 15 months), and 19 out of 24 patients in group 4 were on this therapy (1060 $\pm$ 380 mg/day, range 800–2000, for 9 $\pm$ 16 months). The mean dose of inhaled corticosteroids was significantly higher in groups 3 (*P* < 0.05) and 4 (*P* = 0.03) than group 2. The difference between groups 3 and 4 was also significantly different (*P* < 0.05).

Patients from group 4 had a significantly lower FEV₁ and FVC than those from groups 1 and 2 (Table 2).

Table 5. Biochemical values in patients and controls. Results are presented as means $\pm$ SEM. ANOVA adjusted for sex and age

	Patients	Controls	<i>P</i>
<i>n</i>	118	121	
Glucose (mg/dl)	93 $\pm$ 13	94 $\pm$ 9	NS
Cholesterol (mg/dl)	214 $\pm$ 47	208 $\pm$ 43	NS
HDL-cholesterol (mg/dl)	60 $\pm$ 18	59 $\pm$ 15	NS
LDL-cholesterol (mg/dl)	137 $\pm$ 41	132 $\pm$ 38	NS
Triacylglycerol (mg/dl)	80 $\pm$ 18	77 $\pm$ 15	NS
Free fatty acids (mg/dl)	611 $\pm$ 275	586 $\pm$ 303	NS
Total proteins (g/l)	72 $\pm$ 4	72 $\pm$ 4	NS
Albumin (g/l)	44.3 $\pm$ 3.3	44.6 $\pm$ 3.4	NS
NS: nonsignificant.			

The prevalence of atopy defined according to the results of the prick test was significantly higher in groups 1 (71%) and 2 (67%) than in group 4 (39%) (Table 2).

There were no differences in BMI among the four groups of asthmatics (Table 2). Only patients from group 4 (18/24) were on regular oral corticosteroid therapy (mean 11.5 mg/day, range 5–20 mg/day for 14 ± 28 months) or were receiving frequent short courses of oral steroids.

Food frequency questionnaire

The daily nutrient intakes are given by asthma and control groups in Table 3. Total energy intake and the percentage of energy derived from carbohydrate, fat, and protein were significantly lower in asthmatics than in the control group. No differences in the percentages of saturated fat and polyunsaturated fat were seen between patients and healthy subjects.

There were differences in the eating pattern among the four groups of asthmatics (Table 4). Total energy intake and the percentage of energy derived from carbohydrate were significantly higher in group 1 than in the remaining three groups. No differences in the characteristics of diet were found between atopic and nonatopic subjects after adjusting for age and sex.

Biochemical measures

There were no differences in serum levels in any of the biochemical measures between healthy subjects and asthmatics (Tables 5 and 6). Plasma levels of protein and albumin were significantly lower in the most severe group, composed of corticosteroid-dependent patients (Table 7). There was a significant and negative correlation between plasma protein ($r=0.36$, $P<0.05$) and plasma albumin levels ($r=0.43$, $P<0.01$) and the daily dose of oral corticosteroids. No correlation was found between any biochemical measure and the daily dose of inhaled corticosteroids.

No differences in any biochemical measure were detected between atopic and nonatopic subjects.

No correlation were found between dietary values and biochemical measures of fat and protein.

Discussion

We investigated differences in dietary nutrient and biochemical measures between asthmatics and nonasthmatics. The dietary method most appropriate for measuring usual dietary intake is the FFQ. FFQs have been widely used and

have been found to relate well to more detailed methods of dietary evaluation (11).

The present analysis suggests that patients with asthma have different patterns of food intake from healthy controls. By this method, we found that total energy intake and the percentage of energy from carbohydrates, fat, and protein were significantly lower in asthmatic subjects than non-asthmatic ones. However, this lower energy intake was not reflected in a lower BMI in the asthmatic population.

Patients with less severe asthma (intermittent asthma) have a pattern of energy intake similar to that of the healthy population. In the remaining three groups, energy intake was significantly lower. The type of asthma therapy, such as inhaled and oral corticosteroids, did not exert any significant influence on the characteristics of dietary intake. This finding suggests that the lower energy intake detected in asthma patients is directly related to the disease rather than to the influence of therapy. It is not clear why moderate to severe asthma patients, independently of the characteristics of their treatment, ingest and apparently consume less caloric energy.

Although we have no convincing explanation of our findings, it is possible to hypothesize that these variable results might reflect different reporting biases toward food intake between asthmatics and nonasthmatics. However, we are not aware of any study in patients with asthma which shows any alterations in perception that may account for our findings.

Table 6. Biochemical values in patients and controls. Results are presented as means $\pm$ SEM. ANOVA adjusted for sex and age

	Patients	Controls	P
<i>n</i>	118	121	
Myristic (C-14) %	0.9 ± 15	0.9 ± 0.14	NS
Palmitic (C-16) %	25.0 ± 2.2	24.0 ± 2.1	NS
Palmitoleic (C-16:1) %	1.9 ± 0.14	1.8 ± 0.15	NS
Stearic (C-18) %	8.4 ± 0.6	8.6 ± 0.7	NS
Oleic (C-18:1) %	20.4 ± 3.6	20.6 ± 3.5	NS
Linoleic (C-18:2) %	29.0 ± 5	30.0 ± 5	NS
Dihomo- γ -linoleic (C-18:3, ω 6) %	0.4 ± 0.2	0.4 ± 0.2	NS
Linoleic (C-18:3, ω 3) %	0.4 ± 0.1	0.4 ± 0.2	NS
Eicosatrienoic (C-20:3) %	1.6 ± 0.4	1.6 ± 0.4	NS
Arachidonic (C-20:4) %	7.2 ± 1.8	6.9 ± 1.6	NS
Eicosapentaenoic (C-20:5) %	0.8 ± 0.2	0.7 ± 0.23	NS
Docosapentaenoic (C-22:5) %	0.4 ± 0.2	0.4 ± 0.1	NS
Docosahexaenoic (C-22:6) %	2.2 ± 0.8	2.0 ± 0.8	NS
NS: nonsignificant.			

Table 7. Biochemical values in patients and controls. Means $\pm$ SEM. ANOVA adjusted for sex and age

n	Severity				P
	1 30	2 40	3 24	4 24	
Glucose (mg/dl)	93 $\pm$ 8.7	96 $\pm$ 16	92 $\pm$ 15	91 $\pm$ 11	NS
Cholesterol (mg/dl)	197 $\pm$ 43	219 $\pm$ 42	212 $\pm$ 52	233 $\pm$ 53	NS
HDL-cholesterol (mg/dl)	59 $\pm$ 19	62 $\pm$ 18	56 $\pm$ 18	60 $\pm$ 19	NS
LDL-cholesterol (mg/dl)	121 $\pm$ 40	140 $\pm$ 35	138 $\pm$ 39	153 $\pm$ 48	NS
Triacylglycerol (mg/dl)	87 $\pm$ 47	82 $\pm$ 35	90 $\pm$ 33	102 $\pm$ 47	NS
Free fatty acids (mg/dl)	645 $\pm$ 335	567 $\pm$ 225	596 $\pm$ 331	658 $\pm$ 202	NS
Total proteins (g/l)	73 $\pm$ 3	73 $\pm$ 3	72 $\pm$ 5	68 $\pm$ 4	0.003*
Albumin (g/l)	45 $\pm$ 2	45 $\pm$ 3	44 $\pm$ 2	41 $\pm$ 2	0.001*

NS: nonsignificant.

It might also be possible that the lower energy intake, which is not reflected in a lower BMI, results from a reduction in energy consumption. These patients may be less active than healthy subjects; thus, the energy requirements for their daily activities may be less than for the normal subjects. Several studies have demonstrated that, as a group, asthma patients are physically unfit (12, 13). Although the mechanism of poor fitness in asthma is probably complex, it is conceivable that withdrawal from physical activity is responsible for loss of fitness. We did not find any differences in energy intake between moderate (groups 2 and 3) and severe asthmatics (group 4). However, physical unfitness affects patients with moderate and severe asthma to a similar degree, and limitations in exercise performance do not correlate with either the percent predicted FEV₁ or responsiveness to methacholine (13).

In this study, we found no evidence of any association of asthma with either dietary intake or biochemical measures of fat and protein.

Although it has been demonstrated that corticosteroids have some effects on fat, we did not find any differences in plasma levels of cholesterol, HDL-cholesterol, LDL-cholesterol, and fatty acids between cortico-dependent patients and those not receiving this therapy. However, the metabolic effects of corticosteroids have been described with daily doses of 20 mg

or higher of prednisone or equivalent (2, 14), a higher dose than that given to our patients.

Systemic corticosteroid therapy seems to have an effect on protein metabolism, as may be deduced from the significant negative correlation that was found between plasma protein and albumin levels and the daily dose of oral corticosteroids. Exogenous corticosteroids reduce protein formation by both increasing protein breakdown and reducing protein synthesis (15, 16). However, a direct effect of the disease on protein metabolism, independently of corticosteroid therapy, cannot be completely excluded.

In summary, this study shows that asthma induces a decrease in energy intake that does not result in a decreased body weight. This finding suggests that there is a reduction in energy expenditure in asthma, perhaps due to a disease-induced limitation of physical activity. Inhaled corticosteroids do not exert any metabolic effect, whereas regular oral corticosteroid therapy is negatively correlated to plasma protein and albumin levels.

Acknowledgments This study was supported by grants from Fundació Catalana de Pneumologia (FUCAP), Fondo de Investigaciones Sanitarias (FIS-92/698 and 94/337), Sociedad Española de Neumología (SEPAR), and CIRIT (GRQ-9108). J.M. was supported in part by a grant from Ministerio de Educación y Ciencia (Spain).

References

1. Steel R. Influences of corticosteroids on protein and carbohydrate metabolism. In: Knobil E, Sawyer WH, editors. *Handbook of physiology*. Vol. 4. *Endocrinology. The pituitary gland and its neuroendocrine control*. Washington, DC: American Physiological Society, 1974:135-167.
2. El-Shaboury AH, Haynes TM. Hyperlipidaemia in asthmatic patients receiving long-term steroid therapy. *BMJ* 1973;2:85-86.
3. Yavuz O, Turktas I, Cevik C. The effect of high-dose inhaled budesonide on lipid profile in asthmatic patients. *Gen Pharmacol* 1996;27:89-90.

4. Turpeinen M, Sorva R, Juntunen-Backman K. Changes in carbohydrate and lipid metabolism in children with asthma inhaling budesonide. *J Allergy Clin Immunol* 1991;**88**:384–389.
5. Pow EM, Prummel MF, Oosting H, Roos CM, Endert E. Beclomethasone inhalation decreases serum osteocalcin concentrations. *BMJ* 1991;**302**:627–628.
6. Wolthers O, Pedersen S. Growth in asthmatic children during treatment with budesonide. *Pediatrics* 1992;**91**:517–518.
7. Kerstjens HAM, Postma DS, van Doormaal JJ, et al. Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in patients with airway obstruction. *Thorax* 1994;**49**:652–656.
8. Merkus PJ, van Essen Zandvliet EE, Duiverman EJ, van Houwelingen HC, Kerrebijn KF, Quanjer PH. Long-term effect of inhaled corticosteroids on growth rate in adolescents with asthma. *Pediatrics* 1993;**91**:1121–1126.
9. Global Initiative for Asthma. *Global strategy for asthma management and prevention*. NHLBI/WHO work-shop. National Institutes of Health, National Heart, Lung, and Blood Institute, 1995; Publication no. 95–3659, :1–176.
10. Morrison WR, Smith LM. Preparation of fatty acid methyl-esters and dimethylacetals from lipids with boron fluoride-methanol. *J Lipid Res* 1964;**5**:600–608.
11. Willett WC *Nutritional epidemiology*. New York: Oxford University Press, 1990.
12. Clark CJ, Cochrane LM. Assessment of work performance in asthma for determination of cardiorespiratory fitness and training capacity. *Thorax* 1988;**43**:745–749.
13. Garfinkel SK, Kesten S, Chapman KR, et al. Physiologic and nonphysiologic determinants of aerobic fitness in mild to moderate asthma. *Am Rev Respir Dis* 1992;**142**:741–747.
14. Blum RL. Computer-assisted design of studies using routine clinical data: analyzing the association of prednisone and cholesterol. *Ann Intern Med* 1986;**104**:858–868.
15. Rooyackers OE, Nair KS. Hormonal regulation of human muscle protein metabolism. *Annu Rev Nutr* 1997;**17**:457–485.
16. Fernandez-Gonzalez AL, Marzo F, Tosar A, Fruhbeck G, Santidrian S. Effect of anabolic agents on muscle protein metabolism in growing rats treated with glucocorticoids: a short review. *Rev Esp Fisiol* 1989;**45**(Suppl):61–63.