

Full Length Research Paper

Validation of a quality of life scale for asthmatic patients

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Exacerbations of asthma reduce the quality of life of people with asthma, and obesity increases the frequency and severity of such exacerbations. Method: The present study was a cross-sectional study. We designed, tested and validated a Likert-type scale to evaluate quality of life from clinical, epidemiological, and public health perspectives. The scale was built on the basis of four theoretical dimensions: physical fitness, clinical condition, emotional condition and economic impact. Results: The quality of life scale had a Cronbach α of 0.8395; one factor with nine variables explored the impact of treatment and medical costs on patients and their clinical condition and physical fitness. Several correlations with the quality of life score were statistically significant, including the frequency of inhaler use ($r=0.333$; $p=0.003$), the number of attacks in the last year ($r=-0.324$; $p=0.005$) and the thickness of the subcutaneous adipose panicle ($r=-0.376$; $p=0.003$). Two variables associated with obesity explained the scale scores: breathlessness and the number of exacerbations in the last year ($R^2=0.258$; $p=0.001$). Conclusion: We presented a valid, accurate scale that measures the economic impact and lack of control on the quality of life for persons with asthma. Anti-inflammatory alternatives and physical fitness programmes for obese or overweight asthmatic patients should be developed.

Keywords: Quality of life, obesity, asthma, reliability and validity, control.

INTRODUCTION

Asthma is associated with high medical costs and a reduction in quality of life (Neffen et al., 2005). Two factors that affect the quality of life of asthmatic patients and their families are the severity (Juel and Ulrick, 2012) and frequency of exacerbations, both of which increase with obesity (Farah and Salome, 2012).

Obesity doubles the probability of suffering more than one exacerbation per year (Tapia and Casas, 2009), and treatment response is reduced in overweight and obese asthmatic patients (Juel and Ulrick, 2012). A high body mass can even reduce the effect of inhaled corticosteroids (Sutherland et al., 2009), and the reduction

remains even after controlling for sex, atopy and smoking (Pisi et al., 2012). If asthma control is defined as the maximum reduction of the clinical expression of asthma (GEMA, 2009), being overweight or obese worsens asthma control (Gullón et al., 2013). These conditions call for re-evaluations and adjustments of the therapy of those patients (GINA, 2012). Quality of life can be nearly five times worse among obese asthmatic patients compared to non-obese controls, as asthmatic patients have less control of their asthma and have an increased probability of being hospitalised (Mosen et al., 2008), which increases the burden of the disease.

Obesity triggers vascular, metabolic and respiratory problems because of an accumulation of fat in the abdomen and neck. Obesity is a risk factor for obstructive sleep apnea and is associated with arterial hypertension,

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type II diabetes mellitus, dyslipidemia, heart disease and gastro-oesophageal reflux (Oliveira et al., 2011). When an asthmatic patient presents metabolic syndrome, the asthma severity increases even more (Adeyeye et al., 2012). In Mexico, four out of ten obese youths between 17 and 24 years of age suffer from metabolic syndrome (Murguía-Romero et al., 2012). In Mexico City almost thirty out of one hundred adults between 25 and 64 years of age suffer from metabolic syndrome (Schargrofsky et al., 2008). Obesity produces a low-intensity chronic inflammatory state (Shore and Johnston, 2006) that is associated with insulin resistance and non-alcoholic fatty liver disease (Duval et al., 2010); these conditions are known to contribute to a loss of asthma control and reduced quality of life. In the inflammatory process that is associated with obesity and adipocyte death, adipokines promote phagocytosis, chemotaxis and the production of proinflammatory cytokines (Farah and Salome, 2012; Ahmed et al., 2011). Adipokines activate surface markers and affect the adaptive immune response by modulating Th1 cytokine production (Dixon et al., 2010).

Obesity reduces the functional residual capacity (FRC) by reducing the elasticity of the walls of the thorax and lungs (O'Donnell et al., 2012). Both FRC and airflow affect airway resistance (RAW) and fibro-muscular lung tissue, which promotes respiratory tract constriction and can increase smooth muscle stiffness (Farah et al., 2011). Increases in body mass index (BMI) are associated with reductions in forced expiratory volume in one second (FEV_1) to a greater extent than with a reduction in forced vital capacity (FVC) or the expiratory reserve volume (ERV), which explains why obese patients develop restrictive respiratory problems with a high FEV_1/FVC ratio (Zammit et al., 2010).

The quality of life of asthmatic patients has been measured by exploring the impact of many features, including symptoms, pharmacological considerations, concerns, physical condition, social factors, academic achievement (Feng et al., 2011), emotional and communication problems (Vázquez et al., 2010), rescue inhaler use (Pinnock et al., 2012), differences in birth conditions and racial groups, environmental risks (McManus et al., 2012) and medical costs of health care access (Wade and Guo, 2010).

Considering the complexity of the relationship between asthma and obesity, we designed a quality of life scale based on the following characteristics: emotional and physical deterioration, alterations of family and social dynamics, medical costs and exacerbations that place the life of the patients at risk. As validity criteria, we evaluated the results from epidemiological, clinical and public health perspectives.

MATERIALS AND METHODS

With the objective of evaluating the relationship among asthma, obesity and quality of life, we initiated a cross-

sectional study in the asthma and metabolic syndrome clinics at the National Institute of Respiratory Diseases (INER) in March of 2010.

For the random selection of subjects, our sampling frame relied on hospitalization and external consultation usage records. The validation of the quality of life scale was conducted with the results from 76 asthmatic patients with a body mass index (BMI) range of 29.51 (15.98-45.49). Our study was designed in the context of overweight and obesity being serious public health problems in Mexico.

The exclusion criteria were: subjects who suffered from nasal polyps, chronic bronchitis, gastro-oesophageal reflux, chronic obstructive pulmonary disease or any other pulmonary disease and patients who had used oral corticosteroids in the previous six months or had inhaled corticosteroids in the previous two weeks. We included male and female asthmatic patients over 18 years of age, and the age range was 64 (18-82). We eliminated records with incomplete information.

Patients knew the objectives of the investigation and signed informed consent forms prior to the study. The following procedures were conducted: spirometry (Spirometer Dataspir 120C, Sibelmed Sibel SA Barcelona Spain), oximetry (Finger Pulse Oximeter 2.0D Trading Company China ISO 9001-2008) and anthropometry with standardised measurements (Body Composition Monitor HBF-500 OMROM Healthcare Latin America ; Body Caliper Skinfold, Caliper Co. Inc., Carson City, Nv USA).

The Likert-type quality of life scale contained 25 items with five response intervals between 'absolutely certain' and 'completely false'. The scale had four theoretical dimensions: clinical condition, physical fitness, emotional situation and economic impact. The scale was applied, validated, and it obtained a reliability score of 0.84. The first factorial axis had nine points, with factorial loads higher than 0.300. The factorial axis was identified with an orthogonal varimax rotation. Using the data on medical costs, anthropometric measures and clinical condition, we validated the scale using external criteria. We applied the modified asthma control questionnaire (ACQ-5) and explored co-morbidity and the use of medications.

We processed the data utilising the software SPSS (v.12). The analysis included Student's t tests, product-moment correlation coefficients of Pearson, factorial analyses, calculations of reliability by Cronbach α and Guttman split-half coefficients and a linear stepwise regression model.

RESULTS

A total of 76 asthmatic patients participated in the study. The sample was 77.6% female and 22.4% male. A total

Table 1. Use of medical services and reported events among overweight or obese and non obese patients.

Events	Classification of patients												TOTAL		
	Overweight or obese asthmatic patients						Non-overweight or obese asthmatic patients								
	F		M		T		F		M		T				
	N	%	N	%	N	%	N	%	N	%	N	%			
Emergency room care*	yes	17	22.4	6	7.9	23	30.3	5	6.6	1	1.3	6	7.9	29	38.2
	no	25	32.9	6	7.9	31	40.8	11	14.5	3	3.9	14	18.4	45	59.2
	missing	0	---	1	1.3	1	1.3	1	1.3	0	---	1	2.6	2	2.6
	total	42	55.3	13	17.1	55	72.4	17	22.4	4	5.3	23	27.6	76	100.0
Hospitalizations*	yes	10	13.1	4	5.3	14	18.4	2	2.6	1	1.3	3	3.9	17	22.4
	no	31	40.8	8	10.5	39	51.3	14	18.4	3	3.9	17	22.4	56	73.7
	missing	1	1.3	1	1.3	2	2.6	1	1.3	0	---	1	1.3	3	3.9
	total	42	55.3	13	17.1	55	72.4	17	22.4	4	5.3	21	27.6	76	100.0
Intensive Care Unit Admission**	yes	3	3.9	1	1.3	4	5.3	0	---	0	---	0	---	4	5.3
	no	38	50.0	11	14.5	49	64.5	16	21.0	4	5.3	20	26.3	69	90.8
	missing	1	1.3	1	1.3	2	2.6	1	1.3	0	---	1	1.3	3	3.9
	total	42	55.3	13	17.1	55	72.4	17	22.4	4	5.3	21	27.6	76	100.0
Intubated at least once**	yes	3	3.9	1	1.3	4	5.3	0	---	0	---	0	---	4	5.3
	no	38	50.0	11	14.5	49	64.5	16	21.0	4	5.3	20	26.3	69	90.8
	missing	1	1.3	1	1.3	2	2.6	1	1.3	0	---	1	1.3	3	3.9
	total	42	55.3	13	17.1	55	72.4	17	22.4	4	5.3	21	27.6	76	100.0

*In the previous year

** At the time of asthma development

of 72.4% of the patients were overweight or obese, and 31.6% suffered from metabolic syndrome. The average BMI was 28.8 (CI_{95%}: 27.6-30.1). Based on the hip-to-waist ratio, 73.7% of the patients were considered to be at a high coronary risk. A total of 58.8% of the patients perceived themselves as being exacerbation-free. The average age was 50.5 years (CI_{95%}: 46.8-54.3), and the average time of disease evolution was 14.8 years (CI_{95%}: 11.4-18.1).

On average, the patients reported having activity limitations every 15 days, breathlessness and arousals one or two times per week and the need for a rescue inhaler once per day. A total of 68.5% of the patients denied having been in contact with allergens or in situations associated with exacerbations in the previous four weeks. The average number of attacks in the previous year was 1.99 (SD: 4.54).

The average values from the respiratory function tests were FVC: 79.61 (CI_{95%}: 72.2-81.6, SD: 20.14); FEV₁: 73.2 (CI_{95%}: 68.5-78.0, SD: 20.6); and FEV₁/FVC: 89.9 (CI_{95%}: 86.2-93.6, SD: 15.7). The average oxygen saturation was 92.5% (CI_{95%}: 91.6-93.5, SD: 4.0).

Considering the data, the epidemiological profile describes a group of overweight and obese patients with moderate persistent uncontrolled asthma.

In comparing the groups, we found that 14.3% of non-obese patients and 25.5% of obese patients used a rescue inhaler two or more times per day. The prevalence of diabetes was 15.4% among thin asthmatic patients, 18.75% among overweight asthmatic patients and 25.0% among obese patients; the risk of diabetes was similar between overweight and obese patients.

The prevalence of systemic arterial hypertension was 28.2%, and we detected systolic hypertension in 32.8% of obese and overweight asthmatics and 15.0% of thin controls. The average systolic pressure values among obese asthmatics were significantly different than those of non-obese and overweight patients (p<0.001).

The risk of systemic arterial hypertension was 12.0 times higher among obese patients than among overweight patients (CI_{MH95%}: 2.56-64.4; p<0.001).

With respect to the functional tests, the FEV₁/FVC ratio and oxygen saturation values were significantly different among the groups (p=0.049 and p=0.032, respectively). However, the FVC and FEV₁ values were not statistically significant. The magnitude of neck circumference was negatively correlated with FEV₁ (r=-0.285; p=0.012).

We also noted differences among the groups with regard to the use of health services and other events related to exacerbations (Table1). The average score on the quality

Table 2. Factorial analysis and rotated component matrix
Factor 1

Item	Factor loading	Dimension
1. The cost of medication prevents me from consistently following treatment.	0.766	Economic impact
2. The limitation of my activities is associated with my breathing difficulties.	0.675	Clinical condition
3. I have lost some physical abilities in the last year because of my asthma.	0.644	Physical fitness
4. My economic situation is affected by my medical costs.	0.643	Economic impact
5. My work performance is low because of my health problems.	0.629	Clinical condition

Table 3. Regression model and variables associated with the quality of life scores

Model	Non-standardised coefficient		T	Sig	CI _{95%}	
	B	Std error			LI	UL
Constant	61.492	6.324	10.441	0.000	52.507	77.553
Breathing difficulties	5.198	1.672	3.109	0.003	1.836	8.559
Exacerbations in the last year	-1.109	0.468	-2.368	0.022	-2.051	-0.167

a. Dependent variable: quality of life scale scores

of life scale was 78.56 (CI_{95%}: 74.11-83.01). Out of 125 possible points, the minimum score was 39, and the maximum was 117. The 75th percentile was 98.0, and the 95th percentile was 109.3 points. The correlation between the quality of life score and the frequency of rescue inhaler use was positive ($r=0.333$; $p=0.003$), but quality of life was negatively correlated with the number of exacerbations in the previous year ($r=-0.324$; $p=0.005$) and the thickness of the adipose panicle ($r=-0.376$; $p=0.003$). On the contrary, the correlation between the ACQ-5 scores and the frequency of rescue inhaler use was positive ($r=0.445$; $p<0.001$).

The reliability of the complete scale obtained a Cronbach coefficient of 0.8395. The principal factorial axis accumulated 66.9% of the variance and a total of 6.156 eigenvalues with eight components. Using an orthogonal rotation Varimax, we identified the first factor with nine variables that explored the impact of pharmacological treatment, medical costs and a patient's clinical condition and physical fitness on quality of life (Table 2).

The four remaining items, including emotional stress,

thoracic oppression, adinamia and aging, obtained factorial loads of less than 0.600. The internal consistency was evaluated with a split-halves correlation (0.6939) and Guttman coefficient (0.7937).

Using a regression model, we found that breathlessness and exacerbations in the previous year were the best fit for predicting the quality of life scores ($R^2=0.258$; $p=0.001$).

DISCUSSION

This quality of life scale is valid and reliable, as indicated by the magnitude of α of Cronbach coefficient, which was higher than those in other studies (Feng et al., 2011). We showed that medical care and the cost of treatment affects the quality of life of the patients. This pattern is chiefly due to the fragile economic situation of the population that uses services for asthma treatment, which we verified with institutional records. In the last twelve years, the cost of outpatient care at INER has

increased by 307.7% after being deflated to the American dollar, which is an increase of 6.5 times the reported national inflation during the same period. Curiously, our patients claimed to be clinically stable and denied having been in contact with triggering factors. In other words, patients lacked knowledge about their clinical condition, which is a situation that has been described by Neffen et al. (2005).

The average FVC and FEV₁ were lower than normal, and we found a high FEV₁/FVC relationship that was even higher among obese patients. FVC was lower than the value reported by Zammit et al. (2010). Airway resistance, measured by FEV₁, did not show significant differences among the groups, but given the average BMI of 28.6, the effect may have been underestimated. According to the parameters in the Spanish Guide for the Management of Asthma (GEMA) and from the Global Initiative for Asthma (GINA), the presence of more than three clinical parameters, the average FEV₁ value and the annual average number of exacerbations are used to create an epidemiological profile of uncontrolled asthma. The regression model explained approximately 26% of the variation in the quality of life scores, and the variables respiratory difficulty from airflow limitation and lack of asthma control have been associated with obesity (Farah and Salome, 2012). In addition to the respiratory difficulties associated with asthma, a component of haemodynamic origin may have also been involved.

The association between obesity and metabolic syndrome and a lack of asthma control has already been documented (Adeyeye et al., 2012; Pisi et al., 2012), but the prevalence of metabolic syndrome in our study was higher than those calculated by Murguía-Romero (2012) and Schargrotsky (2008).

In our study, the prevalence of arterial hypertension was higher than the 29.1% found by Adeyeye (2012) in patients with asthma, and our finding exceeded the prevalence in the Mexican population between 24 and 65 years of age (Schargrotsky, 2008). Obesity-associated hypertension produces diastolic heart failure, pulmonary congestion, bronchial oedema and high systemic levels of endothelin-1, which results in a bronchial-constriction effect (Shore, 2008). For these reasons, evaluations of excess risk and quantifications of attributable risks associated with corticosteroids, including inhaled corticosteroids, are needed. Anti-inflammatory alternatives for obese and overweight asthmatics should be developed.

While the correlation between the neck circumference and FEV₁ was negative, which is consistent with Zammit (2010) and Pisi (2012), the phenotypic component of obesity that most affects the quality of life of asthmatic patients is the thickness of the adipose panicle, given the negative correlation value with the quality of life score. This finding also demonstrates lack of physical fitness of

the patients, which can indirectly suggest the source of cytokines which perpetuate the low-intensity inflammatory state that negatively affects asthma control. In addition, the prolonged use of corticosteroids is associated with the tendency toward centripetal obesity.

The lack of respiratory and physical rehabilitation of asthmatic obese patients should be questioned in terms of the involvement of adipose tissue remodeling and adipocyte death in the liberation of proinflammatory cytokines (Lee et al., 2010). Moreover, visceral obesity that results from adipocyte hypertrophy and hyperplasia is associated with the periodic use of glucocorticoids (Ahmed et al., 2011). These findings should encourage the development of anti-inflammatory alternatives for obese asthmatic patients.

REFERENCES

- Adeyeye OO, Ogbera AO, Ogunleye OO, Brodie-Mens AT, Abolarinwa FF, Bamisile R, Onadecko BO (2012). Understanding Asthma and the Metabolic Syndrome: A Nigerian Report. *Int. Arch. Med.* 5(1):20.
- Ahmad F, Soelaiman IN, Ramli ESM, Hooi TM, Suhaimi FH (2011). Histomorphometric Changes in the Perirenal Adipocytes of Adrenalectomized Rats Treated with Dexamethasone. *Clinics* 66(5):849-853.
- Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, Celedon JC, Shore SA (2010). An Official American Thoracic Society Workshop Report: Obesity and Asthma. *Am. Thorac. J.* 7(5):325-335.
- Duval C, Thissen U, Keshtkar S, Accart B, Stienstra R, Boekschoten MV, Roskams T, Kersten S, Muller M (2010). Adipose Tissue Dysfunction Signals Progression of Hepatic Steatosis Towards Nonalcoholic Steatohepatitis in C57BL/6 mice. *Diabetes* 59(12):3181-91.
- Farah CS, Kermode JA, Downie SR, Brown NJ, Hardaker KM, Berend N, King GG, Salome CM (2011). Obesity is a Determinant of Asthma Control Independent of Inflammation and Lung Mechanics. *Chest* 140(3):659-66.
- Farah CS, Salome CM (2012). Asthma and Obesity: A Known Association but Unknown Mechanism. *Respirology* 17(3):412-21.
- Feng L, Zhang Y, Chen R, Hao Y (2011). The Chinese Version of the Pediatric Quality of Life InventoryTM (PedsQLTM) 3.0 Asthma Module: Reliability and Validity. *Health Qual. Life Out.* 9(1):64.
- Gullón JA, Rodríguez C, García JM, Alvarez F, Villanueva MA, Castaño G (2013). Asthma Control and Obesity: A Solid Link. *Med. Clin.* 140(3):110-2.
- Juel CT, Ulrik CS (2012). Obesity and Asthma: Impact on Severity, Asthma Control and Response to Therapy.

- Resp. Care. Advance online publication. doi: 10.4187/respcare.02202.
- Lee M-J, Wu Y, Fried SK (2010). Adipose Tissue Remodeling in Pathophysiology of Obesity. *Curr. Opin. Clin. Nutr. Metab. Care.* 13(4):371-6.
- McManus BM, Robert S, Albanese A, Sadek-Badawi M, Palta M. (2012) Racial Disparities in Health-Related Quality of Life in a Cohort of Very Low Birth-Weight 2 and 3 Year Olds With and Without Asthma. *J. Epidemiol. Commun. H.* 66(7):579-85.
- Mosen DM, Schatz M, Magid DJ, Camargo CA Jr (2008). The Relationship Between Obesity and Asthma Severity and Control in Adults. *J. Allergy Clin. Immunol.* 122(3):507-11.
- Murguía-Romero M, Jiménez-flores R, Villalobos-Molina R, Méndez-Cruz AR (2012). Estimating the Geographical Distribution of the Prevalence of the Metabolic Syndrome in Young Mexicans. *Geosp. Health Sep.* 6(3):S43-S50.
- National Institutes of Health Global Initiative for Asthma (GINA) (2002). *Global Strategy for Asthma Management and Prevention: A Pocket Guide for Physicians and Nurses.* National Institutes of Health, Bethesda, MD
- Neffen H, Fritscher C, Cuevas Schacht F, Levy G, Chiarella P, Soriano JB, Mechali D (2005). Asthma Control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) Survey. *Rev. Panam. Salud Publ.* 17(3):191-7.
- O'Donnell DE, O'Donnell CDJ, Webb KA, Guenette JA (2012). Respiratory Consequences of Mild-to-Moderate Obesity: Impact on Exercise Performance in Health and in Chronic Obstructive Pulmonary Disease. *Pulm. Med.* 2012:818925.
- Oliveira LVF, Aguiar IC, Hirata RP, Newton FJ, Reis IS, Sampiao LMM, Oliveira C, Carvalho PTC, Filho FSSL, Giannasi L, Pinto LA, Malheiros CA, Freitas WR (2011). Sleep Study, Respiratory Mechanics, Chemosensitive Response and Quality of Life in Morbidly Obese Patients Undergoing Bariatric Surgery: A Prospective, Randomized, Controlled Trial. *BMC Surgery* 11:28.
- Pinnock H, Burton C, Campbell S, Gruffydd-Jones K, Hannon K, Hoskins G, Lester H, Price D (2012). Clinical Implications of the Royal College of Physicians Three Questions in Routine Asthma Care: A Real-Life Validation Study. *Prim. Care Respir. J.* Pisi R, Aiello M, Tzani P, Marangio E, Olivieri D, Pisi G, Chetta A (2012). Overweight is Associated with Airflow Obstruction and Poor Disease Control but not with Exhaled Nitric Oxide Change in an Asthmatic Population. *Respiration* 84(5):416-22.
- Schargrodsky H, Hernández-Hernández R, Champagne BM, Silva H, Vinueza R, Silva Ayçaguer LC, Touboul PJ, Boissonet CP, Escobedo J, Pellegrini F, Macchia A, Wilson E (2008). CARMELA: Assessment of Cardiovascular Risk in Seven Latin American Cities. *Am. J. Med.* 121(1):58-65.
- Shore SA, Johnston RA (2006). Obesity and Asthma. *Pharmacol. Ther.* 110(1):83-102.
- Shore SA, (2008). Obesity and Asthma: Possible Mechanisms. *Asthma & Immunol.* doi: 10-1016.
- Spanish Guide for the Management of Asthma (GEMA) (2009). Retrieved from www.gemasma.com, accessed January 2013.
- Sutherland ER, Lehman EB, Teodorecu M, Wrchler ME (2009). Body Mass Index and Phenotype in Subjects with Mild-to-Moderate Persistent Asthma. *J. Allergy Clin. Immunol.* 123(6):1328-34.
- Tapia Díaz AM, Casas Medina GA (2009). Medical costs and burden of disease in asthmatic patients from the National Institute of Respiratory Diseases. *Rev. Inst. Nal. Enf. Resp. Mex.* 22(3):182-9.
- Vazquez I, Sáñez E, González-Freire B, Romero-Frais E, Blanco-Aparicio M, Vere-Hernando H (2010). The Role of Alexithymia in Quality of Life and Health Care Use in Asthma. *J. Asthma* 47(7):797-804.
- Wade TJ, Guo JJ (2010). Linking Improvements in Health-Related Quality of Life to Reductions in Medicaid Cost Among Students Who Use School-Based Health Centers. *Am. J. Pub. Health* 100(9):1611-16.
- Zammit C, Liddicoat H, Moonsie I, Makker H (2010). Obesity and Respiratory Diseases. *Int. J. Gen. Med.* 3:335-43.