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Inhaled Corticosteroids and Bone Density in Chemical Warfare Patients with Pulmonary Complications

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ABSTRACT

Background: *The most effective treatment in chemical warfare victims (CWV) suffering from severe long-term obstructive pulmonary disease is inhaled corticosteroids (ICS) and long acting beta-2 agonists. Study results on adverse effects of ICS on bone were conflicting. In the present study, we evaluated the effect of ICS on bone mineral density (BMD) of CWV and possible effects of chemical warfare agents on BMD.*

Materials and Methods: *Thirty-five CWVs entered this study. Demographic and spirometric data (including staging of severity of lung disease) and BMD results as shown by z-score and t- score measured in lumbar and femoral regions were evaluated in this group of patients. In comparison, 75 normal subjects as controls were included in this study and their BMD results were compared with those of the case group.*

Results: *The mean age in CWVs was 41.40 ± 7.74 years, which showed no significant difference with that of the control group. According to spirometric data, CWVs had obstructive lung disease. BMD in lumbar and femoral regions in the case group was 1.14 ± 0.14 and 0.93 ± 0.13 g/cm^2 respectively, which showed no significant difference with that of the control group. Regression analysis showed that BMD in the femoral region was correlated with forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) and t-score in lumbar region was correlated with FEV1. BMD in the femoral region decreased as the severity of bronchial obstruction increased (0.99 ± 1.07 g/cm^2 in mild form to 0.75 ±0.27 in severe form; F= 3.91, P=0.03) but in the lumbar region BMD had no significant correlation with severity of bronchial obstruction.*

Conclusion: *BMD did not decrease during long-term therapy with ICS in CWVs. Severity of bronchial obstruction can be an important risk factor.* ***(Tanaffos 2007; 6(4): 25-30)***

Keywords: *Chemical warfare, Sulfur mustard gas, Bone mineral density, Inhaled corticosteroids, Beclomethasone, Fluticasone*

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INTRODUCTION

Chemical warfare agents such as sulfur mustard gas can cause late complications in organs such as lungs, peripheral nerves, skin, and eyes (1,2). The most common pulmonary complications of chemical warfare agents are obstructive lung diseases such as bronchiolitis obliterans, chronic obstructive pulmonary disease (COPD) and asthma (3, 4). For the time-being, these disorders are usually treated with high-dose inhaled corticosteroids (ICS) and long acting beta-2 agonists.

ICS are absorbed into the systemic circulation via the lungs, and therefore they can cause a dose-related reduction in bone mineral density (BMD) (5). In some studies a dose-related increase in fractures in subjects taking ICS was demonstrated (6). But in another study, no adverse effect on BMD or vertebral fractures with conventional dosage of ICS was reported (7). Considering the high dose and long-term use of ICS in chemical warfare victims (CWV), the fact that most of them are middle age, and lack of knowledge regarding the effect of chemical warfare agents on BMD, it seemed prudent to evaluate the effect of ICS on BMD in these subjects.

MATERIALS AND METHODS

BMD of 35 CWVs (the mean age ± SD 41.40±7.74 years) was measured. All of them had a history of exposure to chemical warfare agents and experienced skin symptoms after exposure. These subjects were suffering from obstructive lung diseases such as asthma or bronchiolitis obliterans and were treated with ICS (beclomethasone dipropionate or fluticasone dipropionate) 300-1000 µg/day for 3-15 years. The drugs were used regularly as a fix daily program for years and a spacer was recommended for all cases. Additional drugs like short or long-acting inhaled beta-2 agonists such as salbutamol or salmetrol were also used.

The control group comprised 75 normal subjects and their body mass index (BMI), age and sex were matched with those of the case group (mean age ± SD 43.41± 6.94 years). The controls were not suffering from any disease and used no drugs. All the case and control subjects were male nonsmokers that had not used any systemic steroids or drugs that may affect bone mineral metabolism such as calcium, vitamin D supplements or anticonvulsive drugs.

The experiments were approved by the Ethical Committee of Mashhad University of Medical Sciences and each subject gave informed consent.

Technique and protocol

Variables evaluated in this study consisted of demographic data, physical exam, spirometry data and BMD. Spirometry was performed by a calibrated spirometer (Fukuda Sangio ST-90), and main variables measured consisted of forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC. Severity of obstructive lung disease was classified according to the American Thoracic Society recommendations as mild (FEV1=60-80% predicted), moderate (FEV1=40-59% predicted) and severe (FEV1< 40% predicted) (8). Type and dosage of ICS were recorded and considered for evaluation in the case group. Daily steroid dosage was classified according to the Global Initiative for Asthma guidelines (9).

BMD was measured by a dual energy x-ray absorptimetry instrument (DPX-Ig, Lunar- USA) and was calibrated daily. Measurements were performed at L2 – L4 regions of the lumbar spine and neck region of the femoral bone. BMD (g/cm^2), Z-score and t-score were determined for both sites.

Statistical analysis

Sample size was calculated according to 5% alpha error, 80% power and 2/1 ratio of control to case group (35 CWVs and 75 control subjects). The mean values for age, spirometric data and BMD were quoted as arithmetic mean and standard deviation

(SD). The mean BMD values of CWV were expressed as Z- score deviation from the control subjects' means. For the comparison of values of spirometric data and BMD between normal and chemical war victims the unpaired t-test was used. Analysis of variance was used to test differences between the CWV severity groups. The correlation between BMD and dosage of ICS was evaluated by the Pearson correlation coefficient ($P<0.05$ was considered significant).

RESULTS

General data

Thirty-five CWVs with a mean age of 41.40±7.74 years and a mean BMI of 27.29±4.83 were enrolled in this study. The control group comprised 75 subjects with a mean age of 43.41±6.94 years and a mean BMI of 28.05 ± 3.88, that showed no significant differences with the case group (t= -1.38, P=0.17 and t= -0.871, P=0.386 respectively).

Spirometry results

Spirometry data in CWVs showed low FVC (3.05±0.58 L) and FEV1 (2.32±0.57 L) in comparison to their predicted value. The mean FEV1/FVC was 69.23±9.33 which is in favor of an obstructive pattern. Staging of severity of bronchial obstruction and steroid usage was available in 27 subjects with CWV and is shown in Table 1.

Table 1. Frequency of different stages of bronchial obstruction in CWVs

	Stage of obstruction	Steroid usage
Mild	14 (40%)	11 (31%)
Moderate	11 (31%)	21 (60%)
Severe	2 (5.7%)	2 (5.7%)

Bone mineral density results

Descriptive data of BMD and t-score in cases and controls are shown in Table 2. Comparison of BMD and t-score in lumbar and femoral regions between the case and control groups showed no significant differences (Table 2).

Table 2. Comparison of mean of BMD and t score in CWV and the control group

	BMD lumbar (g/cm²)	Z score lumbar	T score Lumbar	BMD Femoral (g/cm²)	Z score femoral	T score femoral
CWV	1.14±0.14	-0.56±1.03	-0.66±1.12	0.93±0.13	-0.63±0.73	-0.90±0.96
Control	1.08±0.13	-0.85±1	-1.09±1.05	0.98±0.13	-0.32±0.84	-0.66±0.96
Two tailed t test	1.94	1.3	1.88	1.66	-1.8	-1.25
P value	0.054	0.18	0.062	0.099	0.07	0.227

BMD in the femoral region decreased as the severity of bronchial obstruction increased, but in lumbar region BMD had no significant correlation with the severity of bronchial obstruction (Table 3).

Table 3. BMD (g/cm²) and t score in patients with different stages of severity of bronchial obstruction

	Stage of obstruction	Mean ± SD	F statistics	P value
BMD lumbar	Mild	1.13 ± 0.17	0.932	0.40
	Moderate	1.16 ± 0.12		
	Severe	1.01 ± 0.08		
Z score lumbar	Mild	-0.78 ± 1.17	2.25	0.12
	Moderate	-0.13 ± 0.93		
	Severe	-1.6 ± 0.21		
T score lumbar	Mild	-0.59 ± 1.31	1.14	0.33
	Moderate	-0.56 ±1.04		
	Severe	-1.90 ± 0.70		
BMD femoral	Mild	0.99 ± 1.07	3.91	0.033
	Moderate	0.91 ± 0.11		
	Severe	0.75 ±0.27		
Z score femoral	Mild	-0.37 ± 0.69	3.69	0.04
	Moderate	-0.62 ± 0.60		
	Severe	-1.8 ± 1.27		
T score femoral	Mild	-0.54 ± 0.90	3.23	0.057
	Moderate	-1.02 ± 0.85		
	Severe	-2.25 ± 1.62		

Decrement in FEV1 had significant correlation with decrement of t score in lumbar and femoral regions (Figure 1) and FVC correlated with t-score of the femoral region (Table 4 and Figure 2).

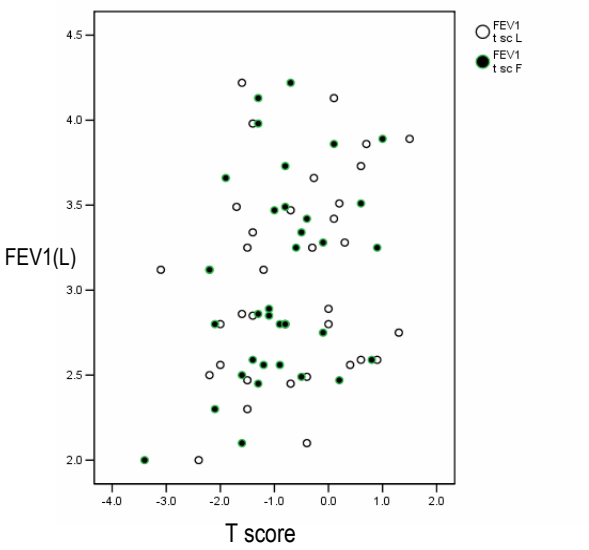

Figure 1. Correlation between FEV1 and t-score in lumbar and femoral region.

Table 4. Correlation between spirometry parameters and BMD parameters evaluated by Pearson correlation coefficient

	BMD lumbar (g/cm²)	Z score lumbar	T score Lumbar	BMD Femoral (g/cm²)	Z score femoral	T score femoral
FEV1	r=0.274 P=0.117	r=0.125 P=0.481	r=0.353 P=0.041	r=0.424 P=0.013	r=0.418 P=0.014	r=0.398 P=0.020
FVC	r=0.156 P=0.371	r=0.077 P=0.656	r=0.225 P=0.194	r=0.307 P=0.073	r=0.391 P=0.020	r=0.334 P=0.050
FEV1/FVC	r=0.316 P=0.068	r=0.179 P=0.311	r=0.345 P=0.045	r=0.370 P=0.031	r=0.293 P=0.092	r=0.198 P=0.263

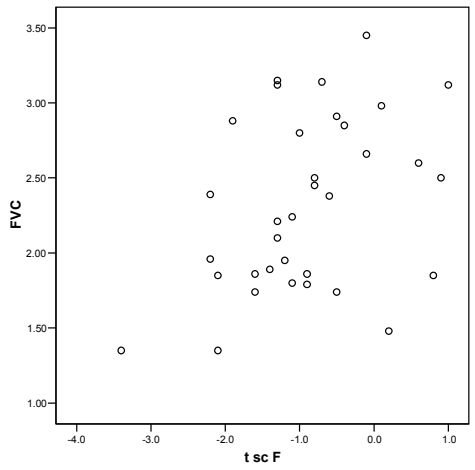

Figure 2. Correlation between FEV and t-score of the femoral region.

This finding may be related to increasing dosage of ICS; therefore, correlation between BMD, Z, t-score and ICS dosage was evaluated which showed significant correlations between steroid usage and BMD and Z score in the femoral region but not in t score (Table 5).

Table 5. Correlation between steroid dosage and BMD in lumbar and femoral regions of CWV

	BMD Lumbar	Z Score Lumbar	T Score Lumbar	BMD femoral	Z Score femoral	T score femoral
Correlation coefficient (Spearman Rho)	0.140	0.087	0.132	0.352	0.452	0.269
P value	0.41	0.63	0.46	0.04	0.00	0.13

DISCUSSION

Inhaled corticosteroids play a key role in treatment of asthma. Inhalation permits effective delivery of corticosteroid in high concentration to target sites within the lung while minimizing systemic exposure. Consequently, the safety profile of ICS is markedly better than that of oral corticosteroid therapy. However, ICSs are absorbed from the lungs into the systemic circulation; they can have systemic adverse effects, such as suppression of the hypothalamic-pituitary-adrenal axis and increased risk of bruising (10). Some studies showed that ICS caused a dose-related reduction in BMD (11) and increase hip fracture (12). On the contrary, other studies showed that ICS did not decrease BMD if used in mild to moderate dosage for long periods of time (13, 14). Returning to normal physical activity by these drugs may play an essential role in inhibiting further BMD loss (15). ICS also can acutely decrease growth velocity in children, an effect that fortunately appears to be temporary and may have no effect on final adult height (6). It seems that beclomethasone has more influence on BMD than fluticasone (16). Duration of ICS usage is also

an important issue and using ICS for more than 6 months is considered to cause more BMD loss than shorter periods (17).

This study was conducted on CWVs suffering from prolonged obstructive lung disease such as bronchiolitis obliterans, asthma, bronchiectasis and chronic bronchitis. To control this process, ICS is the best treatment enabling them to be free of symptoms and relatively active. Fluticasone had the best results but previously they were treated with beclomethasone. Treatment with these drugs should be continued for years with varying dosage. Results of this study showed that ICS did not affect BMD in lumbar and femoral regions (Table 2). No fracture in the femoral region was reported in the case group despite exposure to chemical agents. In femoral region, BMD showed correlation with steroid dosage and also correlation between femoral BMD and Z score was detected (Table 4). According to Tables 2 and 3, as the severity of obstruction increased or FEV1 and FVC fell, BMD in the femoral region decreased (Figures 2 and 3). Therefore, increasing the severity of disease should be considered a major risk factor. Severity of obstruction my affect BMD in two ways, first by increasing the steroid dosage and second by inhibiting physical activity. Good control of inflammatory process in patients leads to lower ICS dosage (most of our patients used steroid in the mild to moderate dosage, Table1), and helps them have good activity. By implementing these strategies, BMD is maintained in an acceptable range making replacement therapy for bone mineral loss unreasonable.

Long-term therapy with ICS in CWVs does not lead to significant bone mineral loss, but severe obstruction may be considered a risk factor.

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