ORIGINAL ARTICLE

EFFECT OF INHALED GLUCOCORTICOIDS ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN MALE PATIENTS WITH OSTEOPOROSIS

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Abstract

The aim of this study was to assess the bone mineral density (BMD) and the clinical changes of male COPD (chronic obstructive pulmonary disease) patients treated with inhaled glucocorticoids for a long time. Eighty cases of COPD patients were selected and divided into osteoporosis group (OP group, 42 cases) and non-osteoporosis group (NOP group, 38 cases). The control group included 40 healthy males (NC group). Pulmonary function (PF) of COPD patients was tested. Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), bone mineral density (BMD), serum albumin (ALB), serum total protein (STP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (CREA), serum uric acid (SUA), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) of all subjects were evaluated. Bone mineral density was higher in the NC group, followed by NOP group and OP group ($p < 0.05$). There was a negative correlation between the accumulated dosages, the application time of inhaled glucocorticoids and BMD of L1 - L4 (lumber vertebra 1 - 4) ($p < 0.05$). Logistic regression model analysis showed that risk factors for male COPD patients to have osteoporosis include age, sunshine exposure duration < 2h/d, COPD course of the disease and application time of inhaled glucocorticoid while its protective factors are weighted, BMI and reduced accumulated dosages of glucocorticoids.

Rezumat

Scopul studiului a fost de a evalua densitatea minerală osoasă și modificările clinice după tratamentul prelungit cu glucocorticoizi inhalatori la pacienții de sex masculin cu bronhopneumopatie obstructivă cronică (BPOC). În studiu au fost incluși 80 de pacienți împărțiți în două grupuri: grupul cu osteoporoză (grup OP, 42 pacienți) și grupul fără osteoporoză (grup NOP, 38 pacienți). Grupul de control a fost format din 40 de pacienți de sex masculin, sănătoși (grup NC). Au fost evaluate funcția pulmonară (PF), indicele de masa corporală (BMI), presiunea sanguină sistolică (SBP), presiunea sanguină diastolică (DBP), densitatea minerală osoasă (BMD), albumina serică (ALB), proteinele serice totale (STP), alanin-aminotransferaza (ALT), aspartat-aminotransferaza (AST), ureea serică (BUN), creatinina (CREA), acidul uric seric (SUA), colesterolul total (TC), trigliceride (TG), colesterolul legat de lipoproteinele cu densitate mare (HDL-C) și colesterolul legat de lipoproteinele cu densitate mică (LDL-C) la toți subiecții incluși în studiu. Densitatea minerală osoasă a fost crescută la grupul NC, urmați de grupul NOP și grupul OP ($p < 0.05$). S-a înregistrat o corelație negativă între dozele totale, timpul de aplicare a glucocorticoizilor inhalatori și BMD la nivelul vertebrelor lombare L1-L4 ($p < 0.05$). Analiza prin model de regresie logistică a evidențiat ca factori de risc pentru osteoporoză la pacienții bărbați cu BPOC: vârsta, durata de expunere la soare < 2 ore/zi, evoluția BPOC și timpul de aplicare al glucocorticoizilor inhalatorii, iar ca factori protectori: greutatea, BMI și dozele mici acumulate de glucocorticoizi.

Keywords: glucocorticoid, chronic obstructive pulmonary disease (COPD), osteoporosis, bone mineral density (BMD)

Introduction

COPD is an airway obstruction disease [31], where glucocorticoid treatment is used as bronchodilator [5]. The association of comorbidities reveals the need for adjustment of therapy [27]. Inhaled corticosteroid therapy is more and more extensively applied to COPD treatment to prevent acute exacerbations because it can not only inhibit osteoblasts function, reduce osteogenesis and promote bone resorption but also it directly affects osteoblasts and inhibit osteogenesis, reduce intestinal calcium absorption and decrease calcium re-absorption from kidney tubules [2, 9, 30]. Osteoporosis is caused by restricted calcinosis, due to large amount of cortisol which stimulates decomposition of proteins, glycogen and bone matrix [18, 23].

Researches have shown that [7, 14] after treating COPD patients with inhaled glucocorticoids for a long time regularly, forced expiratory volume (FEV1)%, reflecting the severity of patients' pulmonary function, 6-min walking distance test for exercise tolerance and life quality score were improved and the acute attack frequencies were significantly reduced. Thus, glucocorticoids are suitable for relapsing and aggravating

COPD patients with clinical symptoms in medium, severe and extremely serious conditions of stable phases. Although glucocorticoids have a good clinical effect on COPD treatment, they reduce bone mass, destroy bone microstructure and cause metabolic diseases resulting in fracture when administered for long term [19, 21]. Glucocorticoid-induced osteoporosis is a common drug-induced disease, whose morbidity ranks first among secondary osteoporosis [11, 32]. The risk of osteoporosis is higher in male patients with metabolic syndrome due to sex steroid deficiency [26].

Materials and Methods

Patients

120 cases of male participants (age ≥ 60 years) were selected and divided into experimental group and control group. Prior selection, patients and their relatives were informed of possible risks during the trial. Informed consent signed by patients voluntarily was obtained. The study was approved by the Ethics committee of Tong Lu First People's Hospital China.

Experimental group (COPD group): 80 cases of COPD patients with medium and severe conditions hospitalized in the respiratory department of the clinic from February 2015 to November 2016, were selected. These patients had FEV1/FVC% < 70%. Patients in COPD group had been treated with inhaled glucocorticoids for more than 6 months. According to standard diagnostic method of osteoporosis, recommended by World Health Organization (WHO), patients were divided into two groups: Osteoporosis group (OP group), 42 patients; Non-osteoporosis group (NOP group), 38 patients. The control group (healthy males, NC group): 40 healthy male individuals admitted at the hospital for regular examination during the same period.

Exclusion criteria: patients with endocrine system disease, rheumatic immunologic disease, chronic liver and kidney disease, digestive system disease (small intestinal resection and gastrectomy), haematological system diseases (multiple myeloma, leukaemia and lymphoma), Duchenne muscular dystrophy, tumour-related bone disease, transplant operation, poor compliance and a long time immobilization and bed rest were excluded. Patients whose lumber vertebra was not suitable for bone mineral density densitometry and those who had been treated with glucocorticoids for other diseases were also excluded.

Patients general data

Basic characteristics of the participants were obtained: gender, age, height, weight, underlying disease, COPD course of disease, bone mineral density, history of glucocorticoid treatment, history of osteoporotic treatment, fracture history, chronic disease history, drug history, lifestyle (exercising way and time, dietary habit) and prophylactic medicine (taking calcium tablet regularly during glucocorticoid treatment, diphosphonate and vitamin D (VD)).

Clinical and biochemical indexes

Anthropometry: height, weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP).

Blood tests (Blood analyser, Beckman Coulter Ltd., USA): 10 mL of fasting venous whole blood were collected and there were determined: serum albumin (ALB) (Salting-out method, Type 722 spectrophotometer, Shanghai Jingke Industrial Co. Ltd., China), serum total protein (STP) Biuret reagent (Jining Hongming Chemical Reagent Co., Ltd., China), alanine aminotransferase (ALT), apartate aminotransferase (AST) (enzyme-coupled assay, Fully automatic clinical biochemical analyzer, Beckman Coulter Ltd., USA), blood urea nitrogen (BUN) (Velocity method, urea nitrogen test kit, Shanghai enzyme linked Biotechnology Co., Ltd., China), creatinine (CREA) (Sarcosine oxidase, creatine oxidase reagents, Beijing Lidman Biochemical Limited by Share Ltd., China) and serum uric acid (SUA) (phospho-tungstic acid deoxidizing method, Type 722 spectrophotometer, Shanghai Jingke Industrial Co. Ltd., China), phosphotungstic acid solution (Nantong Wanbang technology new material Co., Ltd., China), blood lipids (biochemical analyser was used, Nova Biomedical Corporation, USA): total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C).

Accumulative dosage of glucocorticoid

Inhaled glucocorticoid dosages were: salmeterol xinafoate/fluticasone propionate powder for inhalation (Glaxo Wellcome UK Limited, UK) specification: 50/500 μg, 1 inhalation/time and 2 times/day; budesonide/formoterol (Bright Future Pharmaceuticals Factory, Hong Kong, China) specification: 80/4.5 μg, 1 inhalation/time and 2 times/day; budesonide aerosol inhalation (Bright Future Pharmaceuticals Factory, Hong Kong, China) 1 mg/time, 2 - 3 times/day. We observed whether there were adverse reactions such as hyperglycaemia, gastrointestinal discomfort, hypertension and electrolyte disturbance during treatment.

Diagnostic criteria

COPD diagnostic criteria: cardinal symptoms were chronic cough, expectoration and/or dyspnoea and risk factors exposure history. Incomplete reversible airway limitation and pulmonary function (PF) test results were essential for COPD diagnosis. After inhaled bronchodilators, if forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) < 70%, it was considered as incomplete reversible airway limitation.

COPD disease phases: in acute exacerbation phase, cough, expectoration, hard breath and/or wheeze were aggravated in a short time, accompanied by increased purulent sputum quantity in purulence or mucopurulent

and fever. In stable phase, there might be symptoms such as cough, expectoration and hard breath.

Standards of osteoporotic diagnosis: lower levels of bone mineral density (BMD) compared to healthy adults of the same gender and the same race. DXA method was used to test bone mineral (BMD) of Lumbar Vertebra 1 - 4 (L1-4). It was identified as normal if the standard deviation was less than one. If the standard deviation was lowered by 1 - 2.5, it was identified as osteopenia. If its standard deviation was lowered by ≥ 2.5, it was identified as osteoporosis. If decreased levels of bone mass were followed by osteoporosis diagnosis and there were one or more fragility fractures histories, it was identified as severe osteoporosis.

Statistical method

Statistical software SPSS19.0 was used to analyse data. Data were assessed using chi-square test or Fisher's Exact Test and correlation analysis was performed using Spearman's rank correlation test. Interaction of multi-level factors and among factors was analysed using logistic regression analysis. $p < 0.05$ indicates statistically significant difference. Type I collagen of bovine origin was extracted by the currently.

Results and Discussion

Clinical data analysis

As portrayed in Table I, the three groups of experimental subjects, had no statistically significant difference in age, height, HDL-C, LDL-C, STP, ALT, AST, BUN, CREA and SUA ($p > 0.05$). However, SBP of NC group was lower than that of OP group and NOP group ($p < 0.05$). Weight, BMI and TC of OP group were lower than that of NC group and NOP group ($p < 0.05$). Weight, BMI and TC of OP group were also significantly reduced compared to NOP group ($p < 0.05$) while TG levels are higher compared to the NOP group ($p < 0.05$). Differences in other parameters were not statistically significant ($p > 0.05$).

Table I

Clinical data comparison of experimental subjects in three groups

Indexes	OP group	NOP group	NC group
Age (years old)	74.54 ± 6.36	72.13 ± 7.98	73.34 ± 8.55
Weight (Kg)	55.64 ± 9.23	67.99 ± 9.46	67.58 ± 7.93
Height (m)	1.65 ± 0.06	1.68 ± 0.05	1.67 ± 0.05
BMI (Kg/m^2)	20.11 ± 3.23	24.58 ± 3.12	24.12 ± 2.26
SBP (mmHg)	132.23 ± 11.26	133.11 ± 12.41	128.98 ± 6.12
DBP (mmHg)	73.32 ± 8.77	70.24 ± 7.16	74.93 ± 8.12
TC (mmol/L)	4.12 ± 0.58	4.51 ± 0.66	5.07 ± 0.80
TG (mmol/L)	1.25 ± 0.91	0.77 ± 0.21	1.20 ± 0.48
HDL-C (mmol/L)	1.17 ± 0.28	1.17 ± 0.30	1.23 ± 0.26
LDL-C (mmol/L)	2.76 ± 0.71	2.79 ± 0.70	2.78 ± 0.68
ALB (g/dL)	39.87 ± 7.55	39.82 ± 7.68	47.56 ± 1.60
STP (g/dL)	71.43 ± 5.90	72.51 ± 5.56	70.34 ± 6.87
ALT (UI/L)	29.08 ± 14.12	27.83 ± 13.66	27.72 ± 13.43
AST (UI/L)	24.25 ± 4.10	24.92 ± 3.43	24.41 ± 4.03
BUN (mmol/L)	5.14 ± 0.95	4.96 ± 0.87	5.05 ± 0.96
CREA (μmol/L)	86.01 ± 11.87	84.78 ± 9.88	85.63 ± 10.15
SUA (μmol/L)	320.62 ± 55.75	323.46 ± 49.33	338.02 ± 61.04

BMI = body mass index, SPB = systolic blood pressure, DBP = diastolic blood pressure, ALB = serum albumin, STP = serum total protein, ALT = alanine aminotransferase, AST = apartate aminotransferase, BUN = blood urea nitrogen, CREA = creatinine, SUA = serum uric acid, TC = total cholesterol, TG = triglyceride, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol

Correlation between the bone mineral density and the clinical data

The NC group. Bone mineral density in different parts of the body was correlated with clinical data, in patients of NC group (Table II). Height was positive correlated to bone mineral density of L1, Femoral Neck and Trochanter. Weight was positive correlated to bone mineral density of L1 - L4, L1, L2, L3, L4, Femoral Neck and Trochanter. BMI was positive correlated to bone mineral density of L1, L3, L4 and L1 - l4.

Table II

Correlation of bone mineral density with the clinical data of patients in NC group (r value)

Indexes	L1	L2	L3	L4	L1~L4	Femoral Neck	Trochanter
Age	0.062	0.163	0.155	0.212	0.143	0.134	0.166
Height	0.301 [a]	0.218	0.224	0.170	0.225	0.382 [b]	0.368 [a]
Weight	0.428 [b]	0.390 [b]	0.413 [b]	0.410 [b]	0.442 [b]	0.287 [a]	0.332 [a]
BMI	0.293 [a]	0.257	0.325 [a]	0.336 [a]	0.337 [a]	0.071	0.163
SBP	-0.106	-0.089	-0.085	0.012	-0.061	-0.120	0.104
DBP	0.033	-0.017	0.118	0.121	0.088	0.162	0.216

Indexes	L1	L2	L3	L4	L1~L4	Femoral Neck	Trochanter
TC	-0.136	-0.141	-0.045	-0.096	-0.113	-0.286	-0.223
TG	-0.106	-0.067	0.057	0.073	0.015	0.053	0.102
HDL-C	-0.079	-0.027	-0.024	-0.001	-0.039	-0.242	-0.213
LDL-C	-0.068	-0.133	-0.096	-0.068	-0.132	0.001	-0.086
ALB	0.167	0.079	0.168	0.182	0.168	0.096	0.094
STP	0.165	0.091	0.076	0.107	0.135	0.192	0.166
ALT	0.113	0.195	0.273	0.241	0.223	0.084	0.213
AST	0.247	0.283	0.312	0.228	0.280	0.057	0.227
BUN	0.041	0.046	0.019	0.044	0.034	0.081	-0.079
CREA	0.025	-0.058	-0.061	-0.058	-0.032	0.195	0.003
SUA	-0.077	-0.023	-0.054	-0.032	-0.066	-0.116	-0.205

a indicates $p < 0.05$, b indicates $p < 0.01$.

The COPD group. Bone mineral density of different parts of body in patients with COPD was correlated to their clinical data, as shown in Table III. For example, there is a negative correlation between age and bone mineral density of Femoral Neck and Trochanter, while there is a positive correlation between weight, BMI and TC and bone mineral density of L1, L2, L3, L4, L1 - L4, Femoral Neck and Trochanter ($p < 0.05$).

Table III

Correlation of bone mineral density with the clinical data of patients in COPD group (r value)

Indexes	L1	L2	L3	L4	L1~L4	Femoral Neck	Trochanter
Age	-0.096	-0.142	-0.131	-0.021	-0.123	-0.302 [b]	-0.243 [a]
Height	0.051	0.064	0.108	0.094	0.075	-0.021	0.159
Weight	0.624 [b]	0.621 [b]	0.661 [b]	0.685 [b]	0.652 [b]	0.342 [b]	0.442 [b]
BMI	0.637 [b]	0.613 [b]	0.612 [b]	0.641 [b]	0.641 [b]	0.341 [b]	0.373 [b]
SBP	-0.122	-0.146	-0.109	-0.220 [a]	-0.191	-0.063	-0.125
DBP	-0.254	-0.224	-0.263	-0.286	-0.256	-0.105	-0.193
TC	0.202	0.213	0.270	0.262	0.247	0.231	0.184
TG	-0.204	-0.235	-0.152	-0.201	-0.228	-0.151	-0.082
HDL-C	-0.035	-0.013	0.053	0.043	0.013	0.043	0.157
LDL-C	0.023	0.008	-0.034	-0.062	-0.016	-0.021	-0.040
ALB	0.074	0.034	0.028	0.013	0.024	0.008	-0.022
STP	0.073	0.115	0.071	0.036	0.085	0.010	0.001
ALT	-0.075	-0.059	-0.029	-0.052	-0.063	-0.006	-0.002
AST	0.101	0.093	0.054	0.108	0.102	-0.092	-0.027
BUN	-0.134	-0.108	-0.112	-0.083	-0.163	0.032	0.008
CREA	-0.056	-0.060	-0.087	-0.059	-0.089	-0.008	0.109
SUA	0.013	-0.008	0.036	-0.007	0.034	0.056	0.083

a indicates $p < 0.05$, b indicates $p < 0.01$.

Table IV

Bone mineral density comparison among OP group, NOP group and NC group

	L1	L2	L3	L4	L1~L4	Femoral Neck	Trochanter
OP group	0.68 ± 0.07	0.74 ± 0.06	0.82 ± 0.07	0.89 ± 0.09	0.77 ± 0.07	0.69 ± 0.07	0.64 ± 0.11
NOP group	0.96 ± 0.14	1.06 ± 0.16	1.12 ± 0.17	1.14 ± 0.21	1.06 ± 0.17	0.82 ± 0.14	0.70 ± 0.07
NC group	0.98 ± 0.15	1.08 ± 0.17	1.16 ± 0.18	1.18 ± 0.17	1.10 ± 0.17	0.89 ± 0.13	0.83 ± 0.13
p value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Bone mineral density among OP group, NOP group and NC group. One-way analysis of variance for OP, NOP and NC groups showed heterogeneity of variance (Table IV). The non-parametric test result was $p < 0.05$. The DXA test results of bone mineral density levels were as follows: NC group > NOP group > OP group ($p < 0.05$).

Glucocorticoids administration. There was no correlation between clinical data, glucocorticoid's application time and accumulative dosages in patients with COPD ($p > 0.05$) (Table V).

Table V

Correlation between clinical data, glucocorticoid's application time and accumulative dosages (r value)

Indexes	Accumulative dosages (mg)	Application time (month)	Indexes	Accumulative dosages (mg)	Application time (month)
Age	-0.034	-0.032	ALB	0.036	0.048
BMI	-0.172	-0.175	STP	0.096	0.097
SBP	0.068	0.072	ALT	0.024	0.023
DBP	0.028	0.030	AST	0.075	0.080
TC	-0.020	-0.028	BUN	0.072	0.072
TG	0.096	0.109	CREA	0.118	0.119
HDL-C	0.121	0.133	SUA	-0.030	-0.036
LDL-C	0.053	0.055			

The total dosage of inhaled glucocorticoids of patients was between 180 - 1440 mg and the average value was 423 ± 285.41 mg. The average value of OP group was 562.34 ± 402.33 mg while in NOP group was 375.28 ± 231.59 mg, as shown in Table VI.

Accumulative dosages and application time of inhaled glucocorticoid were higher in OP group compared to the NOP group ($p < 0.01$).

Table VI

Comparison between glucocorticoid dosage of OP group and NOP group

	OP group	NOP group	p value
Glucocorticoid accumulative dosages (mg)	562.34 ± 402.33	375.28 ± 231.59	< 0.01
Glucocorticoid application time (month)	18.97 ± 11.54	12.58 ± 7.96	< 0.01

Glucocorticoid accumulative dosages and application time were negatively correlated to the bone mineral density of L4 and L1 - L4. These differences were statistically significant ($p < 0.05$) with the bone mineral density of L4 as the most significant ($p < 0.01$) (Table VII).

Table VII

Correlation between bone mineral density and glucocorticoids usage (r value)

	L1	L2	L3	L4	L1 - L4	Femoral Neck	Trochanter
Glucocorticoid accumulative dosages (mg)	-0.153	-0.178	-0.188	-0.252 [b]	-0.192 [a]	0.009	-0.002
Glucocorticoid application time (month)	-0.160	-0.186	-0.193	-0.263 [b]	-0.200 [a]	-0.002	-0.009

a indicates $p < 0.05$, b indicates $p < 0.01$.

Non-conditional logistic regression for risk factors of osteoporosis

Tables VIII and IX show that risk factors include age, sunshine exposure duration < 2h/d, COPD course of disease and application time of glucocorticoids, among which the most significant is the sunshine exposure duration < 2h/d ($p = 0.017$).

Glucocorticoid treatment increases osteoporosis. Protective factors for COPD patients with osteoporosis are weight, BMI and reduced accumulative dosage of glucocorticoids.

Table VIII

Possible risk factors of osteoporosis

Factors	Variable name	Notes
Age	x1	60 - 90 = 1, 70 - 79 = 2, > 80 = 3
BMI	x2	≤ 22 = 1, > 22 = 2
Smoking	x3	No = 0, Yes = 1
Daily sunshine duration (h)	x4	< 2 = 0, > 2 = 1
Long-term oxygen depletion	x5	No = 0, Yes = 1
Lung function impairment	x6	No = 0, Yes = 1
Treatment with inhaled glucocorticoid	x7	No = 0, Yes = 1
Long term calcium supplement, VitD	x8	No = 0, Yes = 1
COPD course of disease (years)	x9	< 5 = 1, 5 – 10 = 2, > 10 = 3
Osteoporosis	x10	No = 0, Yes = 1

Table IX

Results of non-conditional logistic regression analysis for risk factors of osteoporosis

Risk factors	B	S.E	Wald	df	p	Exp (B)	95.0% C.I. for Exp (B)	
							Lower	Upper
Age	0.058	0.035	2.612	1	0.107	1.062	0.986	1.138
Weight	-0.110	0.035	11.186	1	0.001	0.893	0.836	0.954
Sunshine duration < 2h/d	1.305	0.544	5.670	1	0.012	3.690	1.258	10.820
BMI	-2.032	1.176	3.000	1	0.087	0.132	0.011	1.304
COPD course of disease (years)	0.286	0.162	3.063	1	0.075	1.334	0.964	1.839
Accumulative dosage of glucocorticoid (mg)	-0.375	669.835	0.000	1	1.000	0.682	0.000	
Application time of glucocorticoid (month)	11.267	20097.055	0.000	1	1.000	83565.253	0.000	
Constant	1.202	3.434	0.123	1	0.718	3.318		

OR = odds ratio; OR > 1 = risk factor; OR < 1 = protective factor.

COPD and osteoporosis are two common diseases and osteoporosis is one of the extra-pulmonary manifestations of COPD patients [24]. In patients with COPD that require long-term glucocorticoid treatment, osteoporosis may occur and the risk of fractures is high [15]. Previous studies [8, 16] suggest that inhaled glucocorticoid dosage is small. After being inhaled, the effective concentration (EC) is formed in the airway, part of which is decomposed by enzymes after entering pulmonary alveoli. Thus, it is safe and effective to treat COPD patients of stable phase in medium and severe conditions with glucocorticoids. However, some researchers [1, 17] found that bone metabolism would be abnormal if inhaled glucocorticoid is administered for a long time. After being treated with bronchodilators, COPD patients in acute exacerbation phase should take glucocorticoids orally or intravenous drip glucocorticoids and the dosage should be adjusted according to the clinical effect.

Relapsing and aggravating patients with clinical symptoms of COPD stable phase, whose FEV1 < 50%, are comparatively more suitable to treatment with regular inhaled glucocorticoids for a long time. Following this approach, acute exacerbation frequency can be lowered and life quality can be improved [8]. Treatment effect of inhaled glucocorticoid combined with β2 receptor stimulants is better than administered alone [13]. Up to date, there are two combined preparations: fluticasone-salmeterol and budesonide-formoterol [3, 12], which are used in this study. Among them, fluticasone propionate is a medium effective glucocorticoid that inhibits the activity of phosphatase A2 in inflammatory cells, such as neutrophils. In that way, the anti-inflammatory properties are combined with the reduction in bronchial hyper-responsiveness (BHR) and glandular secretion [6, 20, 25]. The treatment with budesonide and formoterol has local anti-inflammatory properties thus inhibiting immuno-reactions, lower anti-body synthesis and inhibits bronchus contracting substance synthesis and release. Thus, contraction of smooth muscle is relieved [22, 29].

The experiment results show that accumulative dosages of glucocorticoid and its application time is negatively related to bone mineral density of L4 and L1 - L4 ($p < 0.05$), with the bone mineral density of L4 being more significant ($p < 0.01$). Researchers found that [4, 28] local bone mineral density is related to fracture risk in corresponding areas. Besides, lumber vertebra bone mineral density is an essential indicator of vertebral fracture risk caused by osteoporosis, which is in accordance with our results. Current findings showed that the bone mineral density of patients in OP group and NOP group is markedly lowered compared to the NC group. Therefore, male COPD patients are at a higher risk for osteoporosis compared to the patients in the control group, thus their bone mineral density should be considered with caution and early intervention should be opted where needed, in order to prevent osteoporotic fracture.

Conclusions

Osteoporosis is regarded as dependent variable for COPD, while clinical data (height, weight and sunshine duration) are regarded as independent variable. The logistic regression analysis result indicated that risk factors of COPD patients to develop osteoporosis are related to age, sunshine duration < 2 h, course of disease and application time of glucocorticoids. However, appropriate weight, BMI and reduced accumulative dosage of glucocorticoid can help COPD patients to prevent osteoporosis. Osteoporosis is caused by many factors but male COPD patients with relatively long course of disease, pulmonary ventilation dysfunction and inflammatory factors are more likely to have osteoporosis [10]. Bone metabolism of male COPD patients is influenced by several factors. Possible threshold values of bone metabolism reaction to inhaled glucocorticoid and the role of genetic background should be addressed in future studies.

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