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Risk Factors Associated with the Prolonged Usage of Inhaled Corticosteroids in Case of Asthma, COPD and ACOS Cases Compared with the Controls

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Abstract---The effect of Inhaled corticosteroid therapy may vary in COPD, ACOS and asthmatic cases. The influence of risk factors like age, BMI, stress BP and fracture history are adding to the adverse effects of inhaled corticosteroids. This study aims to assess the risk associated with the prolonged use of inhaled corticosteroids in case of Asthma, COPD, and ACOS compared with the controls. Reduced bone mineral density that leads to fracture risk and also to assess bone mineral density, vitamin D, and BMI. A total of 259 patients were involved in this cross-sectional study, 122 males and 137 females along with the controls. The study was conducted at the NRI Institute of Medical Sciences after getting the ethical committee clearance and received consent form from each subject along with their accompanied ones. 30 cases with serum micro RNA 146 compared with 10 controls. Cases were identified with osteoporosis and osteopenia in both females and males. The subjects who got low BMD also have low BMI. The major risk factors like age, BMI, occupational stress are not in our hands, only solution that, management by decreased usage of inhaled corticosteroids. That is only in certain COPD cases with the minority of patients in whom the treatment works better rather than the adverse effects. In asthma and ACOS cases life style changes with dietary management improves the situation.

Keywords---ACOS, asthma, COPD, inhaled corticosteroids, risk factors.

Introduction

Bronchodilators is recommended as the first-line therapy according to the national guidelines for the management of COPD. To decrease the sensitivity of the bronchial wall anti-inflammatory therapy with inhaled corticosteroids (ICS) may be added to long-acting β 2-agonists (LABAs) in patients with exacerbations and moderate-to-very severe COPD. The combination of ICS and LABA tends to be more effective compared to the individual drugs alone for the improvement of lung function and health status to reduce exacerbations (Nannini et al., 2007; Barrecheuren et al., 2016), and patients with asthma-COPD overlap syndrome (ACOS) can also be managed with the same combination (Miravittles et al., 2017; Crim et al., 2015). With the effect of ICS, patients with severe exacerbations especially in older patients (aged \geq 55 years) being linked with an increased risk of cataracts, pneumonia, as well as an increased prevalence of hoarse voice, skin bruising and oral candidiasis (Nieto et al., 2007).

ICS and LABA combination treatment considered as first-line therapy in cases with suspected ACOS and high blood eosinophil counts also (Agusti et al., 2013). After the assessment of the high-risk cases, ICS therapy may be considered as potential only in a minority of cases with COPD as indicated in real-life data. Besides, the rate at which ICS is being prescribed either as combination therapy or alone ranges from 42% to 86%, as reported regardless of COPD severity and exacerbation risk. The other major group that is vulnerable to ICS-related bone loss are middle-aged and older women who have airways disease (Lung Health Study Research Group, 2000). This high ICS usage significantly increases the risk of serious pneumonia, respiratory infections (Vestbo et al., 2014), and an early onset of dental problems.

As reported in a Spanish consensus in 2015, there was an agreement that patients with frequent exacerbations and those with ACOS phenotype should add ICS therapy to long-acting bronchodilators, and that it should not be included in LABA therapy to improve lung function (Reddel et al., 2017), also ICS withdrawal is possible in patients with stable COPD as agreed by the expert panel, although they did not reach a consensus on when, how, and in whom to discontinue ICS (Rubio et al., 2017).

Bone anatomy and osteoporosis

Bone tissue is continuously rebuilt by the formation and lost by resorption; bone loss occurs when the activity of osteoblasts formation rate of bone is less than the activity of osteoclast resorption rate. The bone mass is improved and modelled to form the final shape from birth to adulthood: bone mass reaches a peak (referred to as peak bone mass (PBM)) at puberty; subsequently, the loss of bone mass starts. PBM is largely determined by genetic factors, independent well being like nutritional intake, endocrinal regulation, sex, and physical fitness. The activities of the removal of older bone to replace new bone known as remodeling done by automatic body adjustment are often used in repairing microfractures and this helps to prevent bones from becoming hairline fractures, and this also helps to maintain a healthy and wealthy texture of an individual skeleton.

During remodelling, age advancement and menopause may result in an imbalance (absorption becomes lesser than resorption), thereby making fracture risk increase than the normal persons. It may also increase as the age advances decreased the amounts of bone mineral density along with less gastrointestinal absorption. Definite elements that cause an increase in resorption more than formation also induces bone loss thereby weakening the bone structure. Individual trabecular plates of bone are lost, leaving an architecturally weakened structure with significantly reduced mass; leading to an increased risk of fracture that is aggravated by other ageing-associated declines in functioning with the drug effect.

The most common chronic metabolic bone disease is known as Osteoporosis –this is related to various factors including menopause and ageing -, which is characterized by increased bone fragility. Although it can be found in all gender, age groups, races of (white race) women and older people. With an ageing population and longer life span, osteoporosis is increasingly becoming a global epidemic. Recently, it was found that more than 200 million people are suffering from osteoporosis. The International Osteoporosis Foundation revealed that 1 in 5 men and 1 out of 3 women over the age of 50 years will experience osteoporotic fractures in their lifetime. Each fracture is a sign of another impending one.

There are no clinical manifestations of Osteoporosis until there is a fracture. In men, in particular, Fractures cause psychological disability; that can also lead to decreased quality of life and even may cause mortality. Moreover, reduced quality of life is one of the results of osteoporosis an adjusted life span of increased disability-, and a big financial burden to the health insurance systems of countries that are responsible for the care of such patients. Osteoporosis can be prevented with an early diagnosis of this disease by assessing the bone mineral density and with early treatment before fractures occur. Therefore, an awareness campaign for doctors is necessary and will facilitate the awareness of the normal populace, to help prevent this epidemic.

Various factors are associated with the increased risk of osteoporosis-related fractures. Among these factors are sex steroid deficiency and related ageing, also the use of glucocorticoids (which cause the decrease of bone formation and bone loss), disruption of microarchitectural integrity and reduced bone quality. When the bone is weakened and the weakened bone become overloaded as a result of certain daily chores or often by falls, then Fractures occurs (Ernst et al., 2015).

Not until the patient experiences a fracture, Osteoporosis will remain a silent disease. Any fracture experienced recently at any major skeletal site, such as the proximal femur (hip), vertebrae (spine), shoulder in an adult older than 50 years with or without trauma, or distal forearm (wrist), should be referred for the diagnosis of osteoporosis and such needs further urgent assessment that involves the diagnosis and treatment. These Fractures may cause disability, chronic pain, and death. 15–20% is associated with Hip fractures and this has increased mortality rate within 1 year, mortality rate is higher in men than in women, risk of future fractures is increased by a 2.5-fold. Approximately 20–50% of hip fracture patients require long-term nursing home care and suffer from decreased

quality of life, social isolation, depression, mania and loss of self-esteem (Riggs et al., 1982).

Review of literature

Fragility fractures are fractures that occur following minor trauma or spontaneously (e.g., fall from a standing height or less)—individuals with osteoporotic experience this a lot. During daily chores, Vertebral fractures might occur without any trauma or fall, and these are the predictors of future fracture risk: the probability is fivefold for subsequent vertebral fractures and twofold to threefold for fractures at other sites (Kanis et al., 2004). Vertebral compression causes loss of height and this is usually the first complaint by the patient.

Sex, Low body mass index (≤ 19 kg/m²), Age, and stress are clinical risk factors used for the assessment of fracture probability also previous fragility fractures, particularly of the wrist and spine, hip, including morphometric vertebral fracture, are included as risk fractures. Parental history of hip fracture, smoking, Rheumatoid arthritis, including Current glucocorticoid treatment (any dose, by mouth for three months or more) Alcohol intake of three or more units daily, Prolonged immobility, Untreated hypogonadism in men and women, Organ transplantation, Chronic obstructive pulmonary disease. Chronic liver disease Hyperthyroidism, Gastrointestinal disease, and Type I diabetes are secondary causes of osteoporosis.

Twenty-two million women and 5.5 million men were estimated to have osteoporosis; and 3.5 million new fragility fractures were sustained, comprising 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures) (Hernlund et al., 2013). Due to the presence of multiple fractures, frequent falling is more evident; this abnormality can be detected by increased occiput-to-wall distance caused by dorsal kyphosis (dowager's hump). The determination of historical height loss (difference between the current height and peak height at an age of 20 years) of 1.5 inches (4 cm) or more and prospective height loss (difference between the current height and a previously documented height measurement) of 0.8 inches (2 cm) or more is important to notice to take preventive measures. Secondary heart problems and restrictive lung diseases may occur as a result of multiple vertebral and thoracic fractures. Volumes between the ribs to the pelvis may be decreased by several Lumbar fractures, this may alter abdominal anatomy, crowded internal organs (particularly the gastrointestinal system, causing gastrointestinal complaints such as premature satiety, reduced appetite, abdominal pain, constipation, and distention); further, back pain (acute and chronic), due to prolonged disability, poor self-image, social isolation, depression, and positional restriction are the other problems created by compression fractures in addition to increased mortality leads morbidity (Melton et al., 2013).

Some other factors that increase osteoporosis, and fracture risk are independent of bone mineral density (BMD) (Melton et al., 2013), a low body mass index (BMI) 3 months (ever) (Kanis et al., 2004), - age of the patient (Siminoski et al., 2006), - There is a close-dependent relationship between alcohol intake and fracture risk.

Taking 3 or more units of alcohol daily is associated with fracture risk (Kanis et al., 2007), - Rheumatoid arthritis increases fracture risk independently of BMD, as well as the use of glucocorticoids (Kanis et al., 2005), - Falls are an important risk factor for osteoporotic fractures.

WHO definitions of osteoporosis based on BMD²². Classification of Bone Mineral Density of T Score is Normal Within 1 SD of the mean level for a young adult reference population, T score at -1.0 and above is Low bone mass (Osteopenia), Between 1 and 2.5 SD is below that of the mean level for a young adult, T score between -1.0 and -2.5 adult reference population Osteoporosis 2.5 or more below that of the mean level for a young adult T score at or below -2.5 reference population Severe or established 2.5 or more below that of the mean level for a young adult reference T score at or below -2.5 with one or osteoporosis population with fractures.

Fracture Risk Assessment Tool Model (FRAX)

Fractures stand to be the most important health consequence of osteoporosis. In recent times, they have developed an algorithm to predict the risk of fracture in individuals that incorporate significant predictors of fracture risk in addition to BMD. Estimating the 10-year risk of a major osteoporotic fracture (i.e., fracture of the hip, vertebra (clinical), forearm, or proximal humerus) is possible with algorithms that integrate the weight of clinical risk fractures for fracture risk with or without information on the BMD being developed. They can be used to compute the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm, or humerus). Clinical risk factors used in FRAX are as follows: Probabilities have been computed for several countries.

A vertebral fracture is consistent with the diagnosis of osteoporosis, even in the absence of a bone density diagnosis; it is an indication for pharmacological treatment with osteoporosis medication to reduce subsequent fracture risk. Unrecognized vertebral fractures may change the diagnostic classification, alter future fracture risk calculations, and affect treatment decisions. Regardless of BMD, age, and other clinical risk factors, radiographically confirmed vertebral fractures are a sign of impaired bone quality and strength and a strong predictor of new vertebral and other fractures.

Vertebral imaging (Vertebral fracture assessment)

Asymptomatic vertebral fractures are very common in older patients necessitating vertebral imaging, which can be performed using a lateral thoracic and lumbar spine X-ray or lateral Vertebral Fracture Assessment (VFA) available on most DXA machines; this can be performed at the time of BMD assessment. Lateral spine imaging using conventional radiography or densitometric VFA is indicated when the T-score ≤ -1.0 at the spine, total hip, femoral neck, and other sites is present. Subjects with asthma and asthma overlapped chronic obstructive lung disease, there is no secondary osteoporosis and still, there was a reduction of bone mineral density in relation with 10% and 30% of low BMI was observed in respective cases.

Material and Methods

Subjects were selected from the pulmonology department OP, they were provided with informed consent, and also they were assured of confidentiality. The guidelines in Helsinki's declaration was used for conducting this study. Inclusion criteria: persons with stable asthma, COPD and ACOS cases suggested by the pulmonologist. Exclusion criteria: those who are bedridden, having complicated diseases like pneumonia, TB, HIV and other known disturbances with other viscera.

A total number of 257 patients was used for this study, of the 259 subjects 122 were males which accounted for 47.1%, while 137 are women accounting for 52.9%. Subjects were grouped into six as follows; C-COPD, C-A, C-ACOS. IC-COPD IC-AIC-ACOS, and also grouped into three categories namely; Normal, Osteopenia, Osteoporosis. The demographic data collected include: PSS score, fracture history, sex, age, weight, height, medications in use, allergies if any, smoking and alcohol intake, BP, and diabetes entered in the data collection sheet of each subject

Calculated BMI - Body Mass Index was in kilogramme divided by squared height meter (weight in kg/height in m²). The non-invasive method was used to measure Bone Mineral Density, Ultrasound densitometry (QUS – 2 Calcaneal Ultra sonometer; Hanson Medical Systems, Inc., Orlando, FL) was used to measure the bone mineral density of the calcaneus. miR-146a were assayed using Taqman miRNA assays (Life Technologies) according to the manufacturer's protocol.

Statistical methodology

Discrete variables were analyzed with the Chi-square test and presented as percentages, shown in table 1. Continuous variables were analyzed by ANOVA and presented as means \pm SD. Relationships between the variables were assessed with Kruskal-Wallis Test. A P-value of 0.05 was considered significant. All statistical analyses were performed using SPSS version 16.0.

Results

Collected data from the subjects were compared with controls (those who are not on any medication related to airways). Both the qualitative and quantitative variables got significant P values. Each group means and standard deviations of sex, age, bone mineral density, and body mass index and other variables were compiled and displayed in table 2.

Table 1
Chi-square association table of BMD showing the values

s.no	Category	C-COPD	C-A	C-ACOS	IC-COPD	IC-A	IC-ACOS
1	Normal	5.5	7.8	6.5	0	0	0
2	Osteopenia	5.1	4.6	5.1	13.4	6.9	13.8
3	Osteoporosis	0	0	0	12.9	9.3	9.2

All collected data were analyzed and divided into 6 groups. Compared with those who are known with a specific disease without using medications at present, with stable health, taking good food with wealthy background came for the journal check-up. Bone mineral density was measured and recorded T- scores were divided into 3 categories. Group 1 controlled COPD percentage of optimum BMD T-score 5.5, osteopenia 5.1, osteoporosis 0. Group 2 controlled asthmatic percentage of optimum BMD T- score 7.8, osteopenia 4.6, osteoporosis 0. Group 3 controlled percentage of asthma overlapped chronic obstructive pulmonary disease optimum BMD 6.5, osteopenia 5.1, osteoporosis 0. Group 4 chronic obstructive lung disease using inhaled corticosteroid optimum BMD T-score 0, osteopenia 13.4, osteoporosis 12.9. Group 5 inhaled corticosteroids with asthma optimum T-score 0, osteopenia 6.9, osteoporosis 9.3. Group 6 inhaled corticosteroids with asthma overlapped chronic obstructive pulmonary disease optimum T- score 0, 13.8, osteoporosis 9.2. The people with good awareness regarding this disease background have taken precautions like avoiding allergic foods, smoking, alcohol intake, and other aggravating factors with lifestyle modifications without using any medication to maintain their good health even though they had a problem with respiration.

Table 2
Risk factors in inhalation of corticosteroids

S.No.	Variable	Category	c-copd	c-A	c-copd+A	ic-copd	ic-A	ic-copd+A	Statistics
1	Gender	Male	12	15	18	22	28	26	$\chi^2 = 10.305$ P = 0.067
		Female	11	12	7	35	42	29	
2	Age	<40	6	19	8	14	28	26	$\chi^2 = 19.844$ P < 0.001
		>41	17	7	16	39	34	28	
3	BMI	<25	8	5	7	39	51	39	$\chi^2 = 39.046$ P < 0.001
		>26	13	21	16	18	18	18	
4	Smoking	Yes	17	12	20	32	41	34	$\chi^2 = 7.920$ P = 0.161
		No	6	3	5	25	29	21	
5	Allergy	Yes	4	7	10	31	37	32	$\chi^2 = 17.213$ P = 0.004
		No	19	20	15	26	43	23	
6	Fracture History	Yes	2	5	3	38	63	39	$\chi^2 = 97.115$ P < 0.001
		No	21	22	22	19	7	16	
7	Diabetes	Yes	15	17	17	36	49	37	$\chi^2 = 0.880$ P = 0.972
		No	8	10	8	21	21	18	
8	Hypertension	Yes	21	24	7	24	42	55	$\chi^2 = 40.317$ P < 0.001
		No	2	5	24	33	52	47	
9	stress	yes	18	21	22	23	52	42	
		No	5	6	3	34	18	23	
n = 257			23	27	25	57	70	55	

Table 3
Comparative effect of MiRNA 146 expression of control, asthma and chronic obstructive pulmonary disease (COPD)

Variable	Category	Control	Asthma	COPD	Statistical analysis
MiRNA Expression	Mean	1.520	1.614	2.667	F = 30.882
	SD	0.239	0.253	0.615	P < 0.001

Gender	Male	4	8	10	$\chi^2 = 1.751$
	Female	6	7	5	$P = 0.417$
Age	< 40 years	2	3	3	$\chi^2 = 0$
	> 40 years	8	12	12	$P = 1$

n – Control = 10; Asthma = 15; COPD = 15.

Discussion

Long-term ICS use may also be associated with an increased risk of bone fractures in patients with COPD (Janson et al., 2013). A meta-analysis of RCTs and observational studies indicated a significant (27%) increase in the risk of fractures with fluticasone or budesonide therapy (Loke et al., 2011). Osteoporosis and COPD are also strongly correlated due to common lifestyle risk factors (eg physical inactivity, poor diet, and smoking), COPD-associated inflammation, and vitamin D deficiency. Other adverse effects associated with the use of ICS include an increased risk of new-onset diabetes or diabetes progression due to decreased secretion from endocrine system cataracts and tuberculosis. In a database cohort study of patients with respiratory disease, ICS therapy was associated with a 34% increase both in the risk of new-onset diabetes and in the risk of diabetes progression (Rossi et al., 2014).

Patients should be individually assessed by the pulmonologists, to determine whether or not ICS therapy should be discontinued, with the risk of ICS-related adverse effects being taken into consideration. This recommendation is supported by evidence from the WISDOM and FLAME studies, in which patients with moderate, severe, or very severe COPD and a history of exacerbations showed no increase in the annual rate of exacerbations after discontinuation of ICS and ongoing dual bronchodilator therapy.

In the FLAME study, the rate of pneumonia was lower with LABA and LAMA than ICS combination with LABA therapy and a post hoc analysis indicated that the lower rate of exacerbations with LABA/LAMA was independent of blood eosinophil levels. Although the risk of exacerbations may be increased in patients with FEV1 < 50% and exacerbations in the previous year, as well as patients with ACOS without exacerbations, ICS withdrawal needs to be considered in these patients, particularly those with an increased risk of serious ICS-related adverse effects. Following ICS withdrawal, these patients should be maintained on dual bronchodilator therapy and closely followed for exacerbations. Method of ICS withdrawal Based on clinical evidence, ICS therapy may be discontinued abruptly, rather than with gradual dose reduction. In the INSTEAD, FLAME, OPTIMO³¹, CRYSTAL, and DACCORD studies, ICS therapy was withdrawn abruptly with no apparent increase in exacerbations or loss of lung function (Rossi et al., 2014). WISDOM was the only study in which the ICS dose was decreased in a stepwise fashion. Although ICS withdrawal was associated with a significant decrease in FEV1 in this study, the decline in lung function was only observed after complete ICS discontinuation at 18 weeks and was not progressive. This suggests that the effect of ICS withdrawal on lung function (if any) only occurs after complete discontinuation, and there is no need to taper the dose in most patients. It should be noted that the LABA used in this study was salmeterol, which has low intrinsic efficacy and a well-known tolerance in terms

of reduction of effect over time. Particular care should be exercised in high-risk patients with frequent exacerbations or poor lung function receiving high doses of ICS, and routine follow-up of patients after ICS withdrawal is recommended. The decision to withdraw or continue ICS is based on the following:

- In patients with COPD, FEV1 > 50% and no previous exacerbations, the benefits of ICS withdrawal exceed risks and ICS must be withdrawn;
- In patients with ACOS and exacerbations in the previous year, the risks associated with ICS withdrawal exceed the benefits and ICS should not be withdrawn;
- Patients with FEV1 > 50% and exacerbations in the previous year and patients with FEV1 < 50% without exacerbations have an intermediate level of risk associated with ICS withdrawal. The risk of exacerbations after ICS discontinuation is low, but dual bronchodilator therapy should be maintained to make sure that the risk of exacerbations does not increase;
- Patients with FEV1 < 50% and exacerbations in the previous year, together with patients with ACOS without exacerbations, may have an increased risk of exacerbations after ICS withdrawal. Discontinuation should be considered only in patients with a significant risk of serious ICS-related adverse effects. In these patients, ICS withdrawal may still be possible provided that dual bronchodilator therapy is maintained, but close follow-up is essential.

Conclusion

There was a strong interrelation between decreased BMI and the long-term usage of inhaled corticosteroids in the case of asthma and asthma overlapped with chronic obstructive pulmonary disease. Whereas in COPD, there is an option that withdrawal of medication can be benefitted. In the case of asthma and ACOS case, regular monitoring of stress levels and BMD may be beneficial or simply without leaving the skeletal care and disease burden, which may add the adverse effect of inhaled corticosteroids. Health care practitioners should advise the monitoring of regulate BMD after the regular use of inhaled corticosteroids more than 3 years duration. After doing the statistical analysis, when we give supplements of vitamin D, calcium also may not improve the condition. So Prevention is better than cure. Detection of serum Micro RNA 146 explains the diseased or infectious status of a person. It may acts a prognostic and to assess the drug resistance especially in COPD cases. As a result stoppage of inhaled corticosteroid and alternative therapies may help to prevent to fall of bone mineral density along with the disease state.

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