CHANGES IN INSULIN LIKE GROWTH FACTOR 1, BONE MINERAL DENSITY AND MUSCLE MASS IN ELDERLY PATIENTS WITH COPD

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Abstract

Background: COPD is a highly prevalent systemic disease in the elderly population and it is considered as a major health problem in Egypt, However information on its prevalence, morbidity, and mortality is still lacking.COPD has a variety of extra-pulmonary manifestations and our study was conducted to determine the changes in insulin like growth factor-1, Bone mineral density and muscle mass in elderly people with COPD.

Material and Methods: case control study conducted on 90 elderly participants and they were classified into two groups:

Cases Group:
Forty five patients diagnosed to have COPD either mild or moderate.

Control Group:
Forty five healthy subjects, age and gender matched to cases recruited from the community
Both groups were subjected to detailed history taking and clinical examination, comprehensive geriatric assessment, spirometry , measurement of serum IGF-1, DXA scan to determine BMD and muscle mass.

Results: The study showed that elderly COPD patients had a lower level of IGF-1 (106.1) compared with control group (184.6) which is lower by 42%and a lower BMD in the cases group (1.15) compared to the control group (1.52) and also a lower muscle mass (47465) when compared to normal elderly(49400).

Conclusion: the study concluded that COPD patients had a lower mean level of IGF-1,BMD and Muscle mass than normal elderly

Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.(1)

Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD, However manyCountries suffer air pollution resulting from the burning of wood and other biomass fuels which have been also identified as a COPD risk factor.(1)

COPD is a major cause of morbidity and mortality worldwide and results in an economic and social burden that is both enormous and expected to increase(2)The Global Burden of Disease study projected that COPD, which was ranked the sixth cause of death in 1990, will become the third leading cause of death worldwide by 2020; and will be the fourth leading cause of death in 2030.This increased mortality is explained by the expanding epidemic of smoking, reduced mortality from other common causes of death and aging of the world population.(3)

In Egypt, although COPD is a rising significant health problem, data on its prevalence, morbidity, and mortality are still lacking and have to be estimated, a previous study estimated that it is present in 9.6% in high risk patients(4). Further studies are recommended to predict more accurate data as regard prevalence and complications of this disease that is associated with a high risk of disability and independence in Egyptian elderly population as Mannino and colleagues estimated age adjusted years with disability was 302 per 100000 (5).

Many of the important comorbidities have an increased incidence in COPD patients due to shared risk factors and may be thought of as systemic consequences of COPD, instead of being comorbidities as Osteoporosis, Sarcopenia, Depression and Fatigue.(6)
One of the mechanisms by which COPD causes these co morbidities is by influencing IGFs which circulates in blood as a low molecular weight peptide produced largely by hepatocytes under the influence of Growth Hormone and share homology with insulin and are potent mitogenic agents(7)(8).andhas been proposed as an index of healthy aging, due to the finding that it directly correlates with the leukocyte telomere length.(9)

Growth hormone provides stimulation of muscle growth and development by increasing levels of insulin-like growth factors (IGF). Increasing age, systemic corticosteroids commonly used to treat COPD exacerbations are known to down-regulate the growth hormone system(10)and that's whythe data that exist suggest that IGF-1 levels in stable COPD patients tend to be low consistent with the impression that the growth hormone axis is suppressed by chronic disease.(11)

The World Health Organization (WHO) defined osteoporosis as ''A disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.''(12)

Patients with osteoporosis are at an increased risk of fracture, particularly fragility fractures which are caused by injury that would be insufficient to break a normal bone. The impact of osteoporosis and osteoporosis-induced fractures in COPD patients is enormous.(13)

Various risk factors explaining the prevalence of osteoporosis in COPD patients include aging, smoking, physical inactivity, systemic inflammation, malnutrition, low body-mass index (BMI), hypo-gonadism, vitamin D deficiency, and the frequent use of corticosteroids.(14)

The most common type of osteoporosis-induced fracture is the vertebral compression fractures (VCFs) which are associated with back pain and kyphosis. Kyphosis can cause loss of height, resulting in impaired lung function. Every single VCF decreases the vital capacity by 9%, and the lung function impairment is most notable when kyphotic angle is more than 55°.(15)

Osteoporotic fractures in COPD may further decrease the mobility of the patients, thereby, predisposing them to the risk of deep venous thrombosis (DVT) and pulmonary embolism. Therefore, diagnosis and prevention of osteoporosis should be an important goal in the management of patients with COPD.(16)

Muscle wasting in COPD progresses gradually, but it is likely accelerated during acute disease exacerbations. Moreover weight loss prior to as well as during hospitalization for a COPD exacerbation is associated with an increased risk for impaired recovery and hospital readmission. (17)

In COPD, on a whole body level, increased protein turnover has been reported, Indirect evidence for increased muscle-protein degradation was shown in emphysematous and underweight COPD patients based on increased circulatory levels of methyl-histidine, a product of muscle protein breakdown.(18)

Materials and methods
Study Design
A case control study was conducted to determine the effect of COPD on IGF-1, Muscle mass, Bone mineral density.

Subjects
90 Elderly individuals above age of sixty years were involved in our study both males and females and were divided into two groups

Cases Group
Forty five patients diagnosed to have COPD either mild or moderate.

Control Group
Forty five healthy subjects, age and gender matched to cases recruited from the community

Inclusion Criteria: Age above 60 years.

Exclusion criteria:
- Any patient refusing to participate in the study
- Any patient on systemic corticosteroids or inhaled steroids >=3years
- Patients with COPD in exacerbation
- Patients with FEV1 <=50% indicating severe COPD
- Patients with conditions altering IGF :

    1. Acromegally
    2. Dwarfism
    3. Liver cell failure
    4. End stage renal disease
    5. Diabetes mellitus

Methods
Each patient gave an oral consent then underwent:

(1) Comprehensive geriatric assessment:
- Detailed history taking: including personal history, demographic data, past medical history.
- Detailed clinical examination.
- Screening for dementia: using the Arabic version (El-Okl et al., 2002) of the mini-mental state examination (MMSE) (Folstein et al., 1975).
- Screening for depression: Using Geriatric depression scale 15 items (GDS-15) (Sheikh and Yesavage, 1986) and an Arabic version of the test was applied and validated by (Shehata et al., 1998).
- Functional assessment: using Activities of daily living (ADL) (Katz et al., 1963) and Instrumental activities of daily living (IADL) (Lawton and Brody, 1969).

(2) Respiratory function tests: using Spirometry (Flow screen spirometry, VIASYS, Model 2007)

(3) Assessment of Bone mineral density and muscle mass by (Dual energy X-Ray absorptiometry) DXA:
- DXA measurements were made using a total-body scanner (Lunar iDXA; GE Healthcare, Madison, WI), Scan analysis was performed using GE Encore 11.10 software.

(4)Laboratory measurement:

- From each patient, a sample of venous blood was collected by venipuncture of a peripheral vein. Serum was separated by centrifugation then it was stored, in a small vial, frozen at -20º C until assayed, using Access automated biochemistry analyzer.

It was done by using DRG IGF-1 600 ELISA Kit.

Results

Table 1 : Difference between both groups as regard Age, Gender, Smoking ,cognition and function

Gender	Groups						Chi-Square	
	Cases		Control		Total			
	N	%	N	%	N	%	X^2	P-value
Male	41	91.11	41	91.11	82	91.11	0.000	1.000
Female	4	8.89	4	8.89	8	8.89		
Total	45	100.00	45	100.00	90	100.00		
Smoking habit								
Smoker	21	46.67	0	0.00	21	23.33	65.378	<0.001*
Ex-smoker	21	46.67	4	8.89	25	27.78		
Non-smoker	3	6.67	41	91.11	44	48.89		
Total	45	100.00	45	100.00	90	100.00		
Activities of daily living								
Independent	44	97.78	45	100.00	89	98.89	1.011	0.315
Assisted	1	2.22	0	0.00	1	1.11		
Total	45	100.00	45	100.00	90	100.00		
Instrumental activities of daily living								
Independent	44	97.78	45	100.00	89	98.89	1.011	0.315
Assisted	1	2.22	0	0.00	1	1.11		
Total	45	100.00	45	100.00	90	100.00		

Age	Groups						T-Test	
	Cases			Control			t	P-value
Range	60	-	72	61	-	73	-0.533	0.595
Mean ±SD	64.489	±	3.992	64.867	±	2.581		
MMSE*								
Range	25	-	30	26	-	29	-0.166	0.869
Mean ±SD	27.400	±	1.543	27.444	±	0.918		
GDS**								
Range	1	-	4	2	-	4	-0.146	0.885
Mean ±SD	2.756	±	0.883	2.778	±	0.517		

*MMSE : Mini-mental status examination
**GDS : Geriatric Depression scale

Table 2: Difference between both groups as regard airflow limitation and its degree, BMD ,muscle mass and IGF-1.

FEV1*/FVC**	Groups			T-TEST	
	Cases		Control	T	P-Value
Range	0.55 - 0.69		0.75 - 0.89	-24.094	<0.001*
Mean ±SD	0.646 ± 0.033		0.818 ± 0.035		
FEV1					
Range	60 - 89		80 - 90	-6.190	<0.001*
Mean ±SD	78.289 ± 6.604		84.822±2.552		
BMD					
Range	0.88 - 1.81		1.22 - 1.96	-8.81	<0.001*
Mean ±SD	1.153 ± 0.166		1.52 ± 0.231		
Muscle mass					
Range	39000 - 56515		43566 - 55677	-3.277	0.002*
Mean ±SD	47465.02 ± 3346.293		49400.311 ± 2120.17		
IGF-1***					
Range	75 - 206		99 - 250	-10.745	<0.001*
Mean ±SD	106.178 ± 31.922		184.600 ± 37.122		

*FEV1: Forced Expiratory Volume in the first second,** FVC: Forced Vital Capacity, BMD: Bone Mineral Density
***IGF-1: Insulin Growth Factor-1

Our study included 90 patients with 82 patients were males representing 91% of all subjects and 8 patients were females representing 8%.they were matched between the two groups with 41 male and 4 females in each group, Our results showed also that there is no statistical significant difference between both groups as regard the age with a mean of 64.5 approximately.

As regard smoking habit there was a significant statistical difference between both groups, The case group had 21 subjects who were currently smoking representing 46.6% of the case group and 21 subjects who were Ex-smokers representing 46.6% and 3 cases were non-smokers representing 6.8%, On the other hand the control group had no subjects who were currently smokers and 4 subjects who were Ex-smokers (8.9%) and 41 subjects non-smokers (91.1%).

Concerning comprehensive geriatric assessment There was no significant statistical difference between both groups as regard MMSE,GDS, ADL and IADL.

Our study revealed that the case group had a lower BMD with a mean value (1.153) compared with the control group (1.52), Also it revealed the case group had a lower muscle mass with a mean value (47465) as compared with the control group (49400) and a lower mean value of IGF-1(106) s compared with the control group(184).

Discussion
The current study was conducted to determine the effect of COPD on Insulin growth factor 1, muscle mass and bone mineral density. The study included 90 elderly patients divided into 2 groups, The Cases group including 45 elderly patients(males and females) diagnosed with mild or moderate COPD and The Control group including age and gender matched 45 elderly individuals as control group.

Both groups were matched for age and gender, the present study showed no statistical difference between both study groups as regard, functional status and cognition but it showed that the case group had a higher smoking history with

more affection with chronic bronchitis and this approves with the fact that smoking is linked with COPD and it is responsible for 8 out of 10 deaths from COPD.(19)

As regard the cases group 21 patients were smokers and 21 were ex-smokers while only 3 cases had no previous history of smoking and all of the cases were diagnosed by spirometry having FVC/FEV1< 0.7.On the other hand the control group had 4 participants who were ex-smokers and no other participants were smokers.

By comparing both study groups it was found that the cases group had lower levels of IGF-1 than the control group and this agrees with Gupta and colleagues who conducted a study on 146 male COPD patients and 79 age matched healthy individuals and found that stable COPD patients had a lower level of IGF-1 than healthy individual.(20)

Our study revealed also that the cases group had a lower BMD than the control group,Silva and colleagues evaluated the BMD of clinically stable COPD patients by DEXA scan, osteoporosis and osteopenia were reported in 42% of patients and this agrees with our results.(21)

As regard the muscle mass it was found that the cases group had lower values than the control group and this agrees withRoig and colleagues who conducted a study to compare measures of muscle strength and muscle mass between 21 patient with COPD and 21 healthy subjects using computerized tomography, People with COPD showed lower cross-sectional area of thigh muscles denoting lower muscle mass and strength.(22)

Conclusion
COPD is a chronic health problem affecting the elderly population and has a variety of extra-pulmonary complications. It suppresses the growth hormone regulation system evidenced by low level of IGF-1 in COPD patients than control group, it also lowers the BMD by several ways unrelated to steroids and also lower the muscle mass and contributes to sarcopenia.All patients with COPD are at a great risk of osteoporosis and sarcopenia and accurate assessment of BMD and muscle mass using DEXA scan is mandatory throughout the disease for all patients.Larger studies are needed to ascertain the pathology and mechanisms of sarcopenia, osteoporosis and fatigue in elderly patients with COPD which will facilitate early recognition and intervention

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