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Original Research Article

Endocrinal assessment of chronic obstructive pulmonary disease patients as compared to control groups

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ABSTRACT

Background: Hormones also take part in respiratory control via peripheral chemo receptors or by their local effects on the lungs and the airways. In chronic obstructive pulmonary disease patients, respiratory muscles are required to work efficiently than normal individuals to establish a sufficient respiration. Changes in serum hormone levels of COPD patients adversely affect functioning of respiratory muscles. Objective of the study was to assess endocrinal profile in COPD patient with comparable control groups.
Methods: A Hospital based Case control study conducted at Department of Pulmonary Medicine, Late B.R.K.M Government Medical College, Jagdalpur, Chhattisgarh, India during July 2016 to January 2017. Study included 75 diagnosed cases of COPD in which moderate, severe, very severe COPD was 25 in each of this group (per GOLD 's guideline) and compared to age matched 25 healthy control.
Results: In this study serum growth hormone and serum testosterone showed significant difference between COPD cases and control group and fair significant difference in serum FSH between COPD cases and control groups. There was no significant correlation between serum growth hormone, serum testosterone and serum FSH with COPD grading. There was no statistically difference observed in serum LH (p=0.425) level between COPD cases and control groups. Present study showed there was statistically difference in FT3, FT4 and TSH level between COPD cases and control groups. There was significant negative correlation between FT4 levels between COPD grading. But no correlation seen between COPD grading and control with respect to serum FT3 and TSH level.
Conclusions: Endocrinal assessment in present study showed significant decrease in serum growth hormone and serum testosterone in COPD patients, which are anabolic hormones. Early detection and correction of such an anabolic hormonal abnormality may prevent skeletal and diaphragmatic muscle weakness, and improve respiratory drive of COPD patients.

Keywords: COPD, Endocrinal assessment, Growth hormone

INTRODUCTION

Hormones also take part in respiratory control via peripheral chemo receptors or by their local effects on the lungs and the airways. In chronic obstructive pulmonary disease patients, respiratory muscles are required to work efficiently than normal individuals to establish a sufficient respiration. Changes in serum hormone levels of COPD patients adversely affect functioning of respiratory muscles.

However, decrease effort capacity in COPD patients affecting their quality of life. And this cannot be solely explained by single organ dysfunction. Several studies

advocate that dysfunction of peripheral muscles is caused by dyspnoea and markedly decrease effort capacity.[1]

Central to the somatotropic axis are growth hormone (GH) and insulin-like growth factor (IGF)-I. Advanced age, malnutrition, inactivity and administration of glucocorticoids are associated with down regulation of the GH/IGF-I system.[2,3] Hence there is increase protein degradation and lead to muscle weakness which leads further detonations of disease. In men and women, the gonadal axis is a complex network of hormones that includes testosterone, an important anabolic hormone.[4]

In men, the main production site of androgens is the testicle, in women, the adrenals and the ovaries. Secretion is stimulated by luteinizing hormone (LH), one of the pituitary gonadotropins.[4] In both men and women, testosterone is responsible for libido, sexual hair and anabolic functions that affect muscle and bone.[5] Thus in patients with COPD testosterone supplementation can increase leg muscle mass and vastus lateralis mRNA for slow/b-myosin heavy chain. These anabolic responses are accompanied by increases in vastus lateralis IGF-I protein and myogenin mRNA.[6]

The adrenal glands produce a vast array of hormones with protean metabolic effects; among these are cortisol, DHEA and its metabolite, DHEAS, the most abundant steroid present in the blood. Reduced levels of DHEA and DHEAS and high cortisol/DHEA or cortisol/DHEAS ratios are thought to create an imbalance between protein synthesis and degradation favoring catabolism over anabolism.[2]

METHODS

It was a Hospital based Case control study conducted at Department of Pulmonary Medicine, Late B.R.K.M Government Medical College, Jagdalpur, Chhattisgarh, India during July 2016 to January 2017 for six month. Study includes 75 diagnosed cases of COPD in which moderate, severe, very severe COPD was 25 in each of this group (according to GOLD's guideline) and compared to age matched 25 healthy control.

This study was approved by the Institutional Review Board, Late B.R.K.M Government Medical College, Jagdalpur, Chhattisgarh, India

Inclusion criteria

- Diagnosed cases and newly diagnosed cases of COPD willing to participate were included in the present study
- Age 18-75 years.

Exclusion criteria

- Patient using iodine containing drugs
- History of primary infertility
- COPD patient required mechanical ventilation.

Study protocol

This study was affiliated by Institutional Review Board, Late B.R.K.M Government Medical College, Jagdalpur, Chhattisgarh, India. After giving full explanation regarding the study, written consent was obtained from patients. Consent form included details of the study plan. An inclusion and exclusion criterion was applied on case and control. Then following evaluation was preformed

- Thyroid function test
- Growth hormone
- Luteinizing stimulating hormone
- Follicular stimulating hormone
- Testosterone

Sample collection and storage

The blood samples of about 5 to 10 ml taken from COPD patients in morning after overnight fasting. Blood samples of control group will be taken after overnight fasting. The samples will be left standing for one hour; Serum will be separated at 2500 rpm centrifugation and analyzed on fully automated analyzer randox (imola). Then it was subjected to endocrinal assessment.

Endocrinal assessment parameter

- Growth hormone
- Luteinizing hormone
- Follicular stimulating hormone
- Thyroid profile
- Testosterone

Statistical analysis

The data was entered in statistical software. Data was analyzed using student t-test. P value of less than 0.05 was considered as significant.

RESULTS

Above table shows that there was highly statistically significant difference found with respect to the mid arm circumference and mid-thigh circumference in the COPD cases and control group (p value<0.001) and fair significant was seen with respect to BMI between COPD cases and control group (p value 0.015). There was no statistically difference seen in respect with weight and height of cases and control groups.

With respect to hormonal level above Table suggest that there was highly statistically significant difference was seen in serum growth hormone level, serum testosterone level, serum free T3 level and serum free T4 level (p value <0.001) and fair statistically difference was seen with respect to TSH (p value 0.001) and FSH (p value

0.018) between COPD cases and control groups. There was no statistically significant difference with respect to serum LH (p value 0.425) between COPD cases and control group.

Table 1: General characteristics of COPD cases and controls.

Variable	Group	N	Mean	Standard deviation	P value
Height (in cm)	case	75	162.51	6.176	0.060
	control	25	159.84	5.699	
Weight (in kg)	case	75	44.92	8.547	0.100
	control	25	48.04	6.748	
BMI (kg/m2)	case	75	16.92	3.321	0.015
	control	25	18.75	2.736	
Mid arm circumference (in cm)	case	75	20.79	3.793	<0.001
	control	25	24.56	3.417	
Mid-thigh circumference (in cm)	case	75	33.59	4.691	<0.001
	control	25	40.76	4.816	

Table 2: Hormonal profile wise distribution of COPD cases and control.

Variables	Group	N	Mean	Standard deviation	P value
GH (ng/dl)	Cases	75	0.95	0.72	<0.001
	Control	25	1.81	0.51	
LH(mIU/ml)	Cases	75	5.48	3.02	0.425
	Control	25	3.81	3.09	
FSH (mIU/ml)	Cases	75	5.88	3.90	0.018
	Control	25	3.81	3.09	
Testosterone (ng/dl)	Cases	75	306.89	149.63	<0.001
	Control	25	600.27	210.38	
Free T 3 (pg/ml)	Cases	75	1.76	0.75	<0.001
	Control	25	3.32	0.59	
Free T 4 (ng/dl)	Cases	75	1.26	0.75	<0.001
	Control	25	1.73	0.45	
TSH (mIU/ml)	Cases	75	2.64	1.02	0.001
	Control	25	1.87	1.00	

Table 3: Comparison between different grades of COPD cases as regard to hormonal assessment of growth hormone.

Variable	COPD grade	N	Mean	SD	P Value	II vs. III	II vs. IV	III vs. IV
Growth hormone (ng/dl)	II	25	0.77	0.75	0.027	S	NS	NS
	III	25	1.26	0.72				
	IV	25	0.81	0.62				

Table 4: Comparison between different grades of COPD cases as regard to thyroid hormone levels.

	GOLD stage	N	Mean	SD	P Value	II vs. III	II vs. IV	III vs. IV
FT3 (pg/ml	II	25	1.77	0.55	0.99	NS	NS	NS
	III	25	1.77	0.80				
	IV	25	1.75	0.89				
FT4 (ng/dl)	II	25	1.32	0.36	0.01	NS	S	NS
	III	25	1.39	0.42				
	IV	25	1.07	0.40				
TSH (m IU/ml)	II	25	2.82	0.89	0.52	NS	NS	NS
	III	25	2.49	1.12				
	IV	25	2.61	1.06				

Above table suggests that there was significant difference seen within the COPD grading (p value of 0.02) and significance was seen between moderate to Severe COPD group. There was no significant difference between the moderate COPD and very severe COPD group and severe COPD and very severe COPD group with respect to growth hormone. Above Table 4 shows that thyroid hormonal profile was statistically significant difference with serum free T 4 level (p value of 0.01). Serum free T 3 level (p value 0.99) and TSH level (p value 0.52) are not significant within the COPD grading. In free T 4 level there was significant difference between moderate to very severe COPD grade and rest of grades of COPD are not significant with free T_4 level.

Table 5: Comparison between different grades of COPD cases as regard to hormonal assessment of gonadotropins and testosterone.

Variable	GOLD stage	N	Mean	SD	P Value
LH(mIU/ml)	II	25	5.51	3.10	
	III	25	5.17	3.11	0.796
	IV	25	5.75	2.95	
FSH(mIU/ml)	II	25	5.51	4.17	
	III	25	6.00	4.18	0.839
	IV	25	6.14	3.44	
Testosterone(ng/dl)	II	25	305.75	145.13	
	III	25	293.39	163.01	0.805
	IV	25	321.52	144.87	

The above table represents that there was no statistically significant difference seen with respect to LH level (p value 0.796), FSH level (p value 0.839) and serum testosterone level (p value of 0.805) when compare between the COPD grading.

DISCUSSION

In present study, there is statistically significant decrease in growth hormone in COPD case and control group (p value 0.001). It was observed from the results of the current study that mean of growth hormone (GH) in patients with COPD was 0.95±0.72 ng/ml in cases group as compared to 1.81±0.51ng/ml in control group. So, there is significant decrease in GH in COPD patient as compared to control group. But no significant changes were seen within the severities of disease.

Similar results were observed in a recent study by Xu Zs et al, they studied about the changes of Ghrelin, growth hormone, growth releasing hormone and their clinical significance in patients with COPD. They found plasma GH was lower in the underweight patients than in the normal weight patients and in the controls (4.12±0.83, 5.17±0.72, and 6.49±1.13 microgram/ dl respectively). GRH was lower in the underweight patients and in control (20.43±4.41, 23.47±3.97, 27.48±10.06 ng/dl respectively].[7]

Similar to our results Kythreotis P et al also reported lower IGF -1 level in COPD patients on day 1 of exacerbation with respect to healthy control groups. Compared to its concentration in the healthy subject's plasma IGF was significantly lower in COPD patients on Day 1 of the exacerbation and remained lower on Day 15, p value <0.001 and p value <0.001 respectively. Growth hormone mediates its major metabolic effects predominantly through IGF-1. The growth hormone axis is suppressed in chronic diseases and this may partly explain the low IGF-1 levels.[8]

Inconsistent to our results by Debigare et al demonstrated an increase in circulating GH and IGF- 1 in COPD patients, physiological stress like chronic hypoxia and broncho constriction could possibly induce an increase in GH.[2,9]

Growth hormone provides stimulation for muscle growth and development. In addition to increasing age, systemic corticosteroids are known to down regulate the growth hormone level. Decreased level is thought to be related with suppressed GH axis. Circulating insulin like growth factor-1 level can be used as marker of growth hormone action because IGF-1 has longer half-life than GH and its concentration integrates the pulsatile release of GH, but not done because of unavailability in present study.

In a study by Coskun F et al, circulating IGF-1 levels were decreased in stable COPD patients compared with healthy controls and were related to severity of disease.[10] In a study by Schuetz P et al reported that long periods of systemic steroid therapy may influence circulating IGF-1 level by suppressing the growth hormone IGF axis.[11]

A significant difference is seen in testosterone between COPD cases and control groups. But there is no significant difference in LH, FSH level between COPD cases and control groups. In our study testosterone level

in COPD cases 306.89±149.67 ng/dl, in control group is 600.27±210.38 ng/dl (p value of <0.001) which was highly significant. LH level are 5.48±3.02 and 4.91±3.20 and for FSH level it is 5.88±3.90 and 3.81±3.09 mIU/ml for cases and control groups. But there is not statistically much difference between the severities of disease. There was no statistical correlation between testosterone and COPD severity grading.

Regarding sex hormones, normally when testosterone level is decreased, a negative feedback of sex hormones on the hypothalamic-pituitary axis is lost and secretion of gonadotropins, LH and FSH increase. In males, testosterone is secreted mainly by gonads. Testosterone synthesis in leydig cell is controlled by LH from hypophysis. FSH can also stimulate testosterone secretion by inducing Leydig-cell maturation. Present result of sex hormones alternation may be due to several mechanisms including hypoxemia, obesity, glucocorticoid therapy, atrophy of leydig cells and increase cytokines concentration.[12]

Our result was consistent with Akbas T et al who reported reduced testosterone level in COPD patient and explained their result by the presence of low grade systemic inflammation in stable COPD patients and there is high level of pro-inflammatory cytokines like IL-6, TNF alpha, and CRP in stable COPD patients and these cytokines cause hormone alternation.[13]

Present finding was also consistent with Van Vliet et al, their cross-sectional study showed significant low levels of testosterone in COPD patients but inconsistent with LH and FSH level in COPD cases as compared to control groups. However, in present study hypogonadal patients had circulating FSH and LH concentrations above the upper limit of normal. In present study hypogonadal patient with testosterone level below <300 ng/dl showed LH and FSH level above the lower limit of normal. Considering the role of LH and FSH in the biosynthesis of testosterone, hypergonadism represents compensatory mechanism of the hypothalamic-pituitary axis to correct for the low circulating testosterone in patients with COPD.[14]

Our results are like study of Laghi et al who found that severity of lung disease didn't predict the hormonal abnormality making chronic lung disease unlikely cause of hypogonadism.[15] Daabis et al observed that hypogonadism is highly prevalent in clinically stable COPD patients and is particularly related to the severity of the airway obstruction.[16] Other study done by Amany shaker et al found that statistically highly significant decrease in testosterone level in severe and very severe COPD but not statistically significant between mild and moderate one also not statistically significant as regards to LH and FSH levels, which is similar to our observations but in present study it does not show any significant change and required further evaluation by increasing sample size to detect of change in severity.[17]

Most of the previous studies do not have age matched control group. In our present study, we compared the circulating levels of gonadal hormones of COPD patients and age matched control group who are also smokers but normal spirometry finding, even then we find a significant decrease in testosterone levels of COPD patients.

Accumulating data indicate that testosterone levels are low in COPD. The findings of most study are consistent with our results. But mechanism of these alternations is unclear, but it has been speculated that hypoxia, disease severity, smoking, corticosteroid therapy, and chronic illness contribute to low testosterone levels. One of the suggested underlying factors for hypogonadism is hypoxemia; which is present in a portion of COPD population.

Thyroid hormone enhances mitochondrial oxidation and thus augments metabolic rate. This effect on metabolic rate is probably responsible for association between thyroid hormone and respiratory drive. Several characteristics alternation is possibly due to increased thyroid hormone imbalance. In present study there is a highly significant difference seen between thyroid hormone between COPD cases and control group more with FT3 (1.76±0.75, 3.32±0.59 pg/ml respectively) and FT4 (1.26±0.41, 1.73±0.45 ng/dl respectively) (p value <0.001) than with TSH level (2.64±1.02, 1.87±1.00 micro IU/ml respectively) (p value 0.001). FT4 value is significant lower (p =0.01) in COPD patients with severe and very severe obstruction as compare to patients with moderate to severe obstruction. However no significant difference was observed between moderate to severe and severe to very severe and moderate to very severe obstruction in levels of FT3 and TSH levels in COPD cases and control groups. There was a fair negative correlation between COPD grading and FT4.

Present results are consistent with Karadag F et al who found that total T3 and free T3 are lower in the COPD patient group than the control and the difference was more with free T3. Besides, there is difference between FT3, FT4 and TSH level in COPD and control groups in our study. But doesn't show significant decrease in thyroid hormone with severity of disease. As Karadag F et al observed a significant decrease in FT3 level between moderate to severe obstructive COPD groups.[18] In agreement to our results, a recent study by Amira Shoukry et al and Dimopoulou et al also observed similar findings.[19,20]

CONCLUSION

Endocrinal assessment in present study showed significant decrease in serum growth hormone and serum testosterone in COPD patients, which are anabolic hormones and significant decrease in free T3 and free T4. Hence early detection and correction of such an anabolic hormonal abnormality may prevent skeletal and

diaphragmatic muscle weakness, and improve respiratory drive of COPD patients.

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