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Original Research Article

Impact of Pulmonary Rehabilitation on Serum Irisin Levels in Patients with COPD

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Abstract:

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the most common causes of disease burden both globally and in India it needs more emphasis than ever, the third leading cause of death in India and globally. There is a need for more diagnostic and therapeutic options. We studied Serum IRISIN in hope of finding a new biomarker for COPD. Serum IRISIN is a skeletal muscle protein associated with physical activity, the levels of which are increased in COPD patients after 8 weeks of pulmonary rehabilitation. There is no Indian data available on IRISIN in COPD patients.

Objective:

Primary objective of our study is to assess the level of serum IRISIN level in COPD before starting Pulmonary Rehabilitation and after 8 weeks of Pulmonary Rehabilitation.

Secondary objective is to study correlation between IRISIN and spirometry, 6 minute walk test, Clinical features, Dyspnea score and Quality of life.

Methodology: Cases were selected from OPD department of Pulmonary Medicine JSS Hospital Mysore. 80 subjects satisfying inclusion and exclusion criteria underwent PFT, 6MWT, SGRQ-C, CAT score, BODE index and ELISA for serum IRISIN levels. Statistical analysis included, Chi2 test/Fisher extract test, One, Independent t Test, Mann Whitney test, Pearson correlation test and spearman correlation test.

Results: The mean age of the study group was 62.4 ± 9.8. Male subjects in the study were 50 and female subjects were 30. There is a significant increase in IRISIN levels between COPD (control group, no pulmonary rehabilitation) and COPD (intervention group, with pulmonary rehabilitation) with significant p value <0.001.

Conclusion: IRISIN levels are significantly high in COPD patients with pulmonary rehabilitation compared to COPD patients without pulmonary rehabilitation as hypothesized. (p value <0.001). Serum IRISIN levels correlate well with quality of life suggesting IRISIN may also reflect changes in domains other than airflow limitation in COPD patients. There is no significant difference in serum IRISIN levels among male and female COPD patients, suggesting that levels of IRISIN are independent of age.

Keywords: IRISIN, COPD, Pulmonary.

Introduction

Chronic obstructive pulmonary disease consists of spectrum of obstructive airway diseases which at present is third leading cause of death in world wide. In India COPD contributes to half millions people death, which is more than the deaths caused by AIDS, Malaria and TB combined, COPD involves a number of cytokines and chemokine's which not only affect the lungs but involves the number of other organs and produces the systemic effects like hypertension, diabetes, depression, muscle wasting, cardiovascular diseases and osteoporosis,[1] therefore COPD represents an important public health challenge and is a major cause of chronic morbidity and mortality throughout the world.

According to WHO, COPD was the 6th major cause of death in 1990 and Is estimated to be the 3rd major cause by 2020. [2] As the global population ages, the burden of COPD Will increases in future. It continues to be an important cause of morbidity, mortality and health care costs worldwide. [3] However, it is known that low- and middle income countries already shoulder much of the burden of COPD with almost 90% of COPD deaths taking place in these countries. [4,5]

In this issue of Lung India, the joint ICS/NCCP (I) consensus guidelines for the diagnosis and management of COPD have been published [6,7] to facilitate the Indian practitioner in burden reduction, diagnosis and management of COPD. Globally, the COPD burden is projected to increase in future because of continuous exposure to COPD risk factors and aging of the population. [2]

Chronic Obstructive Pulmonary Diseases is defined by GOLD 2018 as a common preventable and treatable disease which is characterized by airflow limitation and persistent respiratory symptoms due to airway and alveolar abnormality resulting from significant exposure to noxious particles or gases. COPD may involve small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema destruction) causing the chronic airflow limitation that is characteristic of COPD. [1]

Risk factors: Tobacco smoking is major risk factor for COPD in India and globally. Second major risk factor in India and other developing countries is exposures to air pollution both indoor [1] and outdoor air pollution. [1] In rural India Indoor air pollution is a major problem mainly contributed by use of biomass fuel (wood, crops, cow-dung cake) for cooking. In the last decade, government policy such as providing subsidized or free LPG gas in rural areas has markedly improved the indoor air quality. However, there is still a large number of non-smoker COPD population caused by biomass smoke exposure, especially effecting women in rural India. In urban areas Outdoor air pollution contributed by industries and traffic is also major etiological factor. Other risk factors for COPD include- genetic factors such as severe hereditary deficiency of alpha-1 antitrypsin (AATD), poor lung growth and development.

Materials and Methods

1. Source of Data: Patients with COPD attending the Department of Pulmonary Medicine, JSS HOSPITAL MYSURU meeting inclusion and exclusion criteria will be taken into study.
2. Duration of Study: From October 2016 to September 2018
3. Type of Study: Cohort study
    - Study site: JSS Medical College & Hospital, Mysore.
    - Study design: Cohort study.
    - Study period: This study has been carried out for a period of 2 years.

Method of collection of data:

Sample size: 80 COPD PATIENTS (40 in intervention group and 40 in control group) The study will be conducted over a period of 2 years at pulmonary medicine Department, JSS Hospital Mysuru, it includes COPD patients coming to JSS Hospital will be screened for inclusion and exclusion criteria after explaining them about the study, patients satisfying inclusion criteria will be included in the study after obtaining informed consent, patient serum will be collected and analyzed for serum IRISIN level in patients with COPD at baseline and after 8 weeks of pulmonary rehabilitation.

Inclusion criteria:

1. COPD Patients who are not on pulmonary rehabilitation program
2. Age >40 years of either gender
3. Able to undergo informed consent process
4. Able to perform the study related process

Exclusion criteria:

1. Subjects in acute exacerbation /too sick/require hospitalization for any illness.
2. Subjects with contraindication for any of the study related procedure like recent MI. Recent stroke, Eye surgery Recent pneumothorax, Stress incontinence, Hemoptysis, Deep vein thrombosis,
3. Patient not giving consent
4. Patient less than 18 years

Observation and Results

During the study period (OCTOBER 2016 - SEPTEMBER 2018)

A total of 80 patients with COPD who visited Pulmonology Department; of which all patients could perform Spirometry. 24 patients were excluded from the analysis for one of the following reasons: 8 patients did not give consent and 16 patients were not willing for pulmonary rehabilitation and regular follow up. Finally,68 patients (136 blood samples) were included for further analysis.

In this study following groups were included-

A total of 80 subjects were studied, whom include, 50 patients with COPD (Smoker COPD) and 30 subjects with COPD (biomass exposure/non smoker COPD).

Table 1: Age and gender distribution of study subjects

Age Category yrs	Gender					
	Female		Male		Total	
	Count	Column N %	Count	Column N %	Count	Column N %
<50	7	23.3%	1	2.0%	8	10.0%
51-60	11	36.7%	18	36.0%	29	36.3%
61-70	9	30.0%	21	42.0%	30	37.5%
>71	3	10.0%	10	20.0%	13	16.3%
Total	30	100.0%	50	100.0%	80	100.0%

Of the 80 patients 50 are male and 30 are females 80 patients with COPD, 50 were males and 30 were females. The social, demographic and clinical characteristics of study population are presented in tables. Majority of patients were farmers. All the patients were non hypertensive, non diabetic and no cardiac abnormalities.

50 smokers COPD are selected on the basis of number of pack years smoked (at least 10 pack years), presence of symptoms; confirmation by Spirometry.

30 Non smoker COPD are selected on the basis of biomass index (at least 10 years, 3hrs/day) presence of symptoms; confirmation by Spirometry

1) Among 80 patients, 40 patients selected randomly in each of the two group i.e intervention group and control group. baseline blood sample is collected to see the serum IRISIN levels.

The intervention group have been adviced and enrolled for pulmonary rehabilitation for 8 weeks and regular follow up every second week, blood sample collected at completion of 8 weeks of pulmonary rehabilitation.

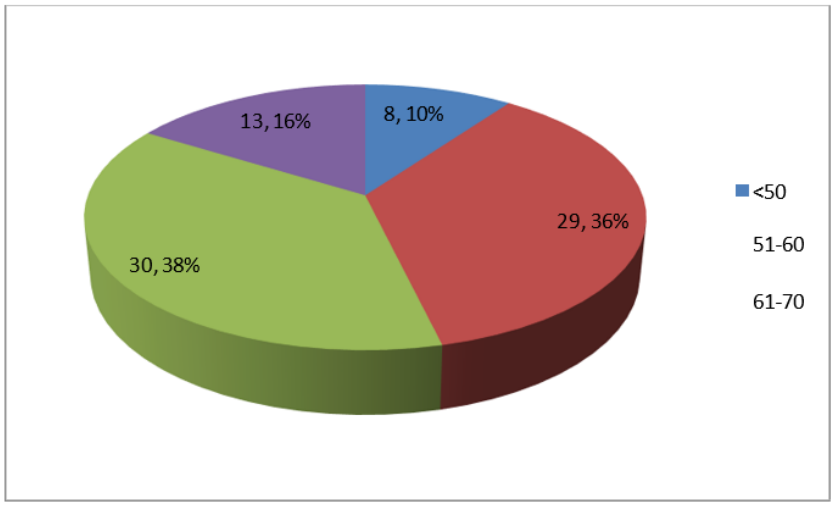

Figure 1: Age wise distribution of patients

Table 2: Gender distribution of study subjects

		Control		Intervention	
		Count	Column N %	Count	Column N %
Gender	Female	15	36.6	15	38.5
	Male	26	63.4	24	61.5

P=0.8, chi square test

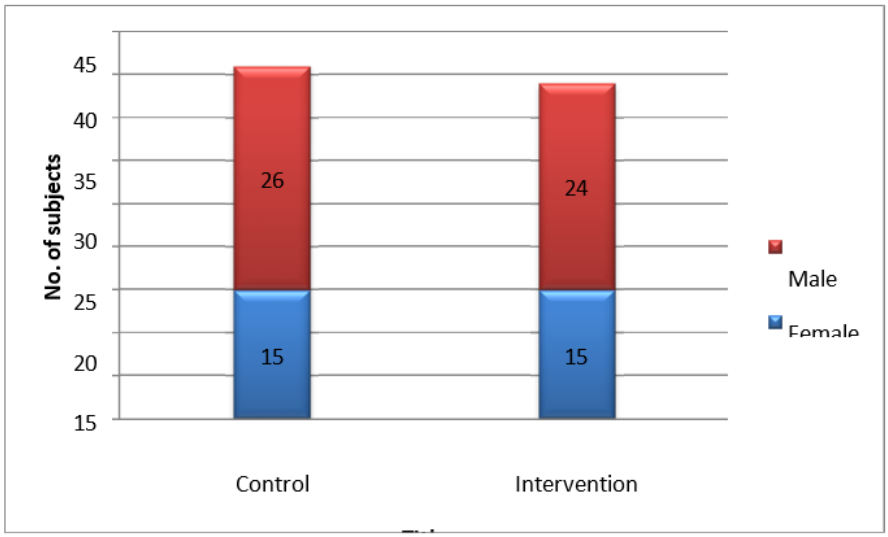

Figure 2: Gender wise distribution between control and intervention group

Table 3: Age distribution of study subjects between genders

	Gender					
	Female		**Male**		**Total**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age in years	58.4	10.6	64.9	8.5	62.4	9.8

Mean age in females is 58.4 with a SD of 10.6 Mean age in males is 64.9 with a SD of 8.5 Total mean is 62.4 with SD of 9.8.

Table 4: Smoking status distribution of study subjects

		Count	Column N %
SMOKER	Non Smoker	30	37.5%
	Smoker	50	62.5%
	Total	80	100.0%

Of the 80 subjects 30 are Non Smokers (Females with biomass exposure) 50 are Smokers (Males)

Our study had more males than females, which is probably due to more rate of smoking in males when compared to females.

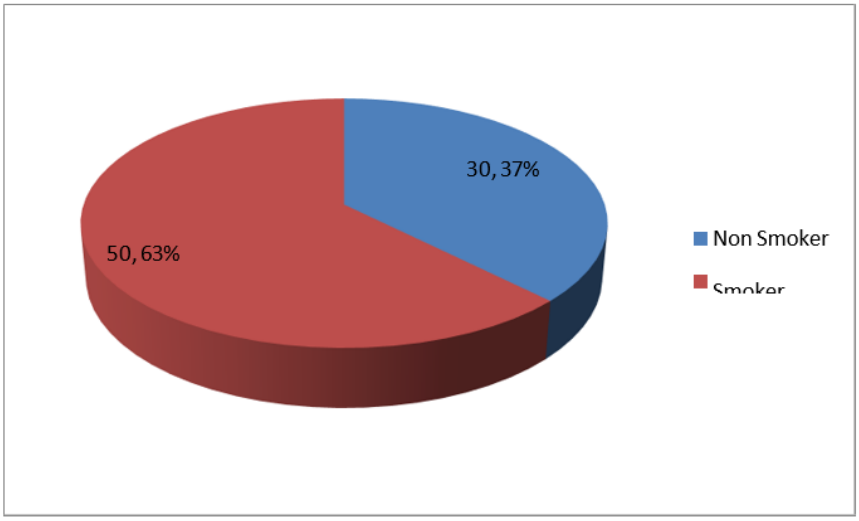

Figure 3: Distribution of study subjects i.e. smokers and non smokers

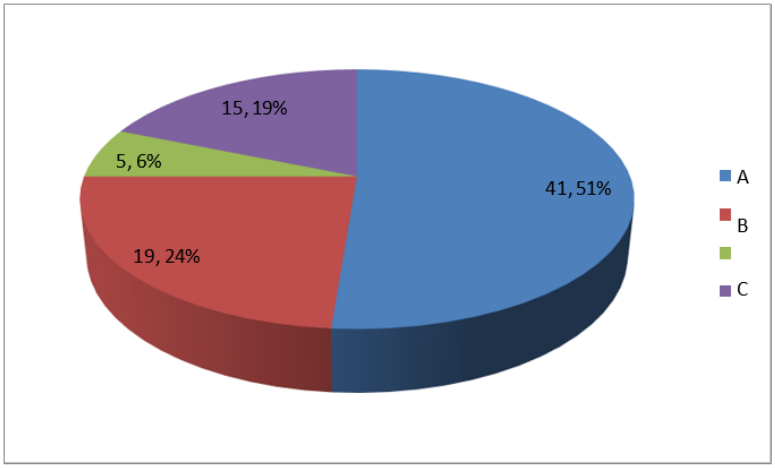

Figure 4: Distribution of study participants according to COPD assessment tool ABCD

A (Low risk, Less symptoms B (Low risk, More symptoms) C (High risk, Less symptoms) D (High risk, more symptoms).

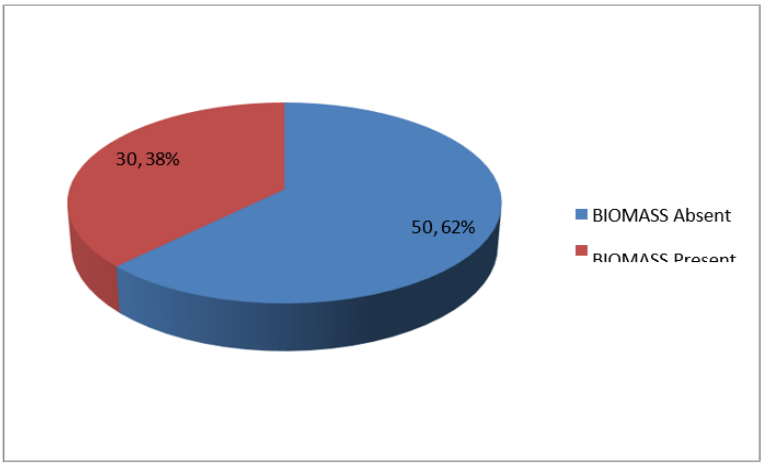

Figure 5: Distribution of study participants according to biomass exposure

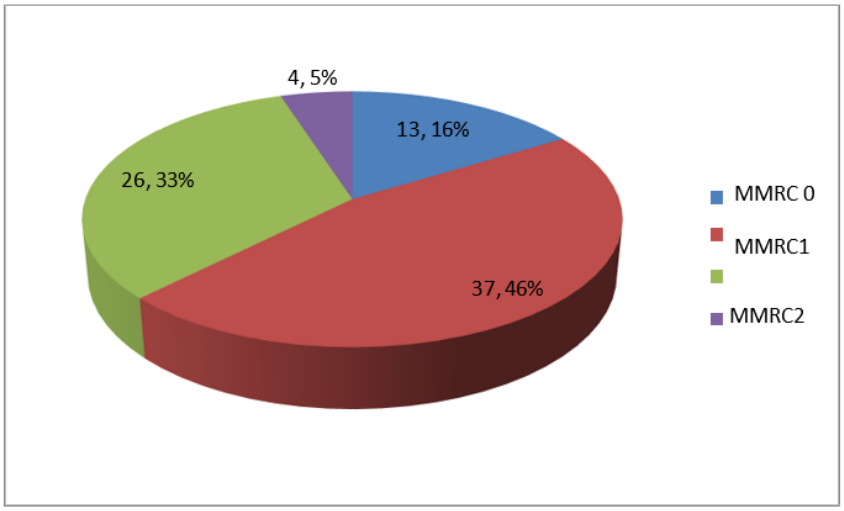

Figure 6: MMRC Grading among study population

This infers that out of 80 subjects there was grade 0 dyspnea in 13, grade 1 in 37, grade 2 in 26 and grade 3 in 4 patients.

Table 5: Comparison of MMRC grades between control and intervention group

		Control		Intervention	
		Count	Column N %	Count	Column N %
MMRC	0.00	5	12.5%	8	20.0%
	1.00	25	62.5%	12	30.0%
	2.00	9	22.5%	17	42.5%
	3.00	1	2.5%	3	7.5%

P=0.03, chi square test, no statistical significant between MMRC of control and intervention group.

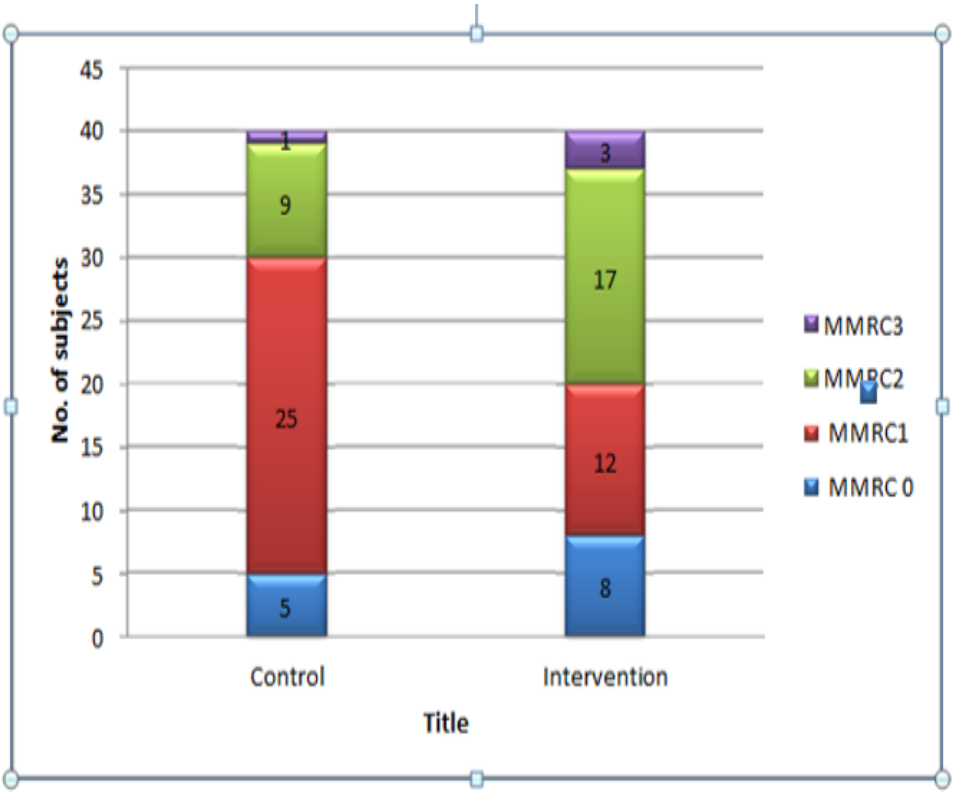

Figure 7: Comparison of MMRC grades between control and intervention group

Table 6: Comparison of Age distribution between control and intervention group

		Group			
		Control		Intervention	
		Count	Column N %	Count	Column N %
Age Category yrs	<50	4	9.8%	4	10.3%
	51-60	11	26.8%	18	46.2%
	61-70	17	41.5%	13	33.3%
	>71	9	22.0%	4	10.3%

P=0.2, chi square test, there is no significant difference between ages of control and intervention group

Table 7: Comparison of smoking status distribution between control and intervention group

		Group			
		Control		Intervention	
		Count	Column N %	Count	Column N %
Smoker	Non Smoker	15	36.6%	15	38.5%
	Smoker	26	63.4%	24	61.5%

P=0.8, chi square test, no significant difference between smoking status in control and intervention group.

Table 8: Comparison of PFT between control and intervention group

	Group				P
	Control		Intervention		
	Mean	SD	Mean	SD	
FVC PREDICTED	2.60	0.59	2.62	0.63	0.9
PRE FVC test	1.75	0.46	1.72	0.62	0.8
Pre FVC percent	69.08	18.06	66.55	21.75	0.6
Post FVC test	1.99	0.51	1.94	0.66	0.7
Post FVC percent	78.55	21.49	75.35	23.85	0.5
FEV1 pred	2.10	0.48	2.15	0.51	0.6
Pre FEV1 test	0.99	0.28	0.97	0.41	0.7
Pre FEV1 percent	49.10	15.49	46.10	17.10	0.4
Post FEV1 test	1.14	0.29	1.13	0.49	0.9
Post FEV1 percent	56.63	18.31	53.70	21.17	0.5
FEVFVC ratio pred	0.81	0.02	0.81	0.02	0.4
Pre-FEVFVC ratio-test	0.57	0.08	0.56	0.08	0.6
Pre FEVFVC ratio percent	70.23	9.89	68.53	9.77	0.4
Post FEVFVC-ratio test	0.58	0.07	0.57	0.09	0.7
Post FEVFVC ratio percent	71.40	8.55	69.95	11.36	0.5

Independent t test, no significant difference between PFT in control and intervention group.

Table 9: Comparison of PFT between control and intervention group

	Group						P
	Control			Intervention			
	Median	Q1	Q3	Median	Q1	Q3	
FVC change percent	11.00	5.50	22.00	12.00	5.00	21.50	0.9
FEV1 change percent	11.00	6.00	26.00	15.00	6.00	25.50	0.9
Percentage Change	1.50	-1.50	7.00	2.00	-2.00	7.50	0.9

Mann Whitney test, no statistical significance between PFT in control and intervention group.

Table 10: Comparison of BODE index between control and intervention group

		Group			
		Control		Intervention	
		Count	Column N %	Count	Column N %
BODE INDEX	0.00	6	15.0%	4	10.0%
	1.00	10	25.0%	8	20.0%
	2.00	12	30.0%	8	20.0%
	3.00	6	15.0%	6	15.0%
	4.00	5	12.5%	6	15.0%
	5.00	1	2.5%	4	10.0%
	6.00	0	.0%	3	7.5%
	7.00	0	.0%	1	2.5%

P=0.4, chi square test, no significance difference between bode index in control and intervention group.

Table 11: Comparison of environmental factors between control and intervention group

	Group						P
	Control			Intervention			
	Median	Q1	Q3	Median	Q1	Q3	
BIOMASS_INDEX	0.00	0.00	75.00	0.00	0.00	60.00	0.7
CAT SCORE	11.00	8.00	12.00	11.00	8.50	14.50	1
PACK YEAR	26.00	0.00	31.00	25.50	0.00	30.00	0.3

Mann- Whitney test – no significant difference between control and intervention group.

Table 12: Comparison of signs and symptom scores between control and intervention group

	Group						P
	Control			Intervention			
	Median	Q1	Q3	Median	Q1	Q3	
Pred 6MWT DISTANCE	528.47	497.69	564.00	533.40	483.77	568.65	0.6
6MWT DISTANCE WALKED	448.00	406.00	478.00	430.00	390.50	466.00	0.4
6MWD PERCENT	87.00	80.00	90.00	82.00	76.00	90.00	0.08
SYMPTOMS	114.65	44.20	143.30	131.85	88.50	229.30	0.02
ACTIVITY	75.70	0.00	75.70	75.70	0.00	169.20	0.09
IMPACT	76.10	75.10	155.20	76.10	75.10	250.40	0.1
TOTAL SGRQ-C SCORE	239.30	106.30	367.60	292.90	174.70	533.95	0.048
SGRQ-C PERCENT	7.36	3.31	11.42	9.15	5.45	16.67	0.03

Mann Whitney test:

No statistical significance is there between symptoms and total SGRQ-C score in control and intervention group.

No significant difference between 6MWT, activity, impact in control and intervention group.

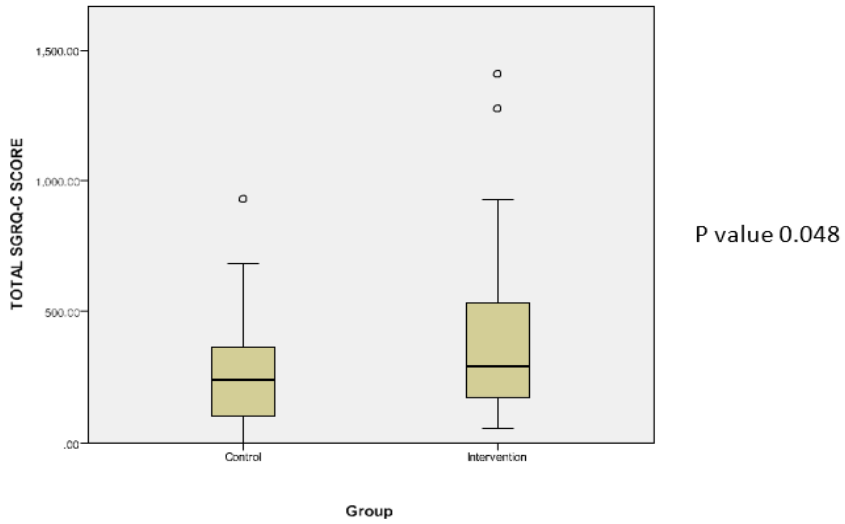

Figure 8: Comparison of total SGRQ-C score between control and intervention group

Total score is high in intervention group

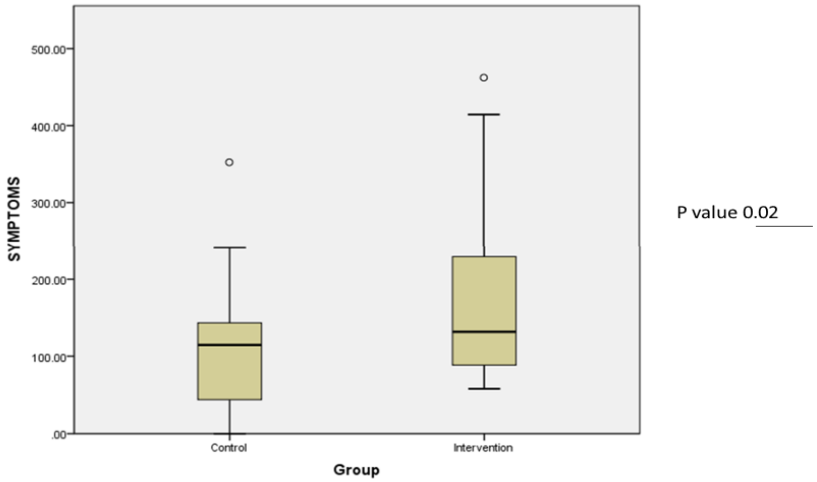

Figure 9: Statistically significance is there between symptoms in control and intervention group

Discussion

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of disease burden both globally and in India it needs more emphasis than ever. COPD is predicted to be one among the most common killer diseases affecting a large number of individuals by the year 2020. A continuous search for newer approaches to screen the smokers who are more probable to develop COPD has to be done by using biomarkers or advanced tests. An assistive or an alternative diagnostic test is required, as the diagnosis of COPD mainly relies on Pulmonary Function Test. There is also a need of test that can assesses the rate of disease progression and the prognosis of the disease. A better understanding of this complex lung disease at molecular level is required to develop new drugs or disease modifying agents that can add to the current treatment or may as well replace the current therapy.

Serum IRISIN have been emerging as an important biomarker in COPD. Available literature about serum IRISIN levels in COPD suggests that serum IRISIN levels are markedly elevated in COPD patients those who are on pulmonary rehabilitation for 8-10 weeks, so it can be used as a biomarker for assessing the progression of COPD and may have a prognostic value and therefore needs further studies.

Serum IRISIN is chosen as a biomarker as it is relatively stable and can be preserved for 6 months at 4 degree C oraliquot and store at -20 degree C for long term. It is important that any putative biomarker is stable when assessed over a short period. This was evaluated in a subset of 80 individuals who were COPD patients including male and females.

Serum levels reflect the capacity of the skeletal muscle cells to produce IRISIN in response to exercise. IRISIN that is secreted by the skeletal muscle in response to exercise is permeable and is actively transmitted into the circulation.

IRISIN helps in improving weight loss by inducing PGC-1alpha which is induced in muscle by exercise and stimulates many of the best known beneficial effects of exercise in muscle, mitochondrial biogenesis, angiogenesis and fiber type switching. [8]

One of the uses of IRISIN is balance blood sugar and fight diabetes via AMP- activated kinase (AMPK) pathway to mediate glucose uptake and fatty acid oxidation, lower HbA1c, plays an important role in regulation of maternal and fetal glucose hemostasis. [8]

IRISIN is anti-inflammatory, and antioxidant, can alleviates inflammation of macrophages (shifting then towards m2 state) and reduces level of IL-6, TNF-alpha, MIP-1alpha, MIP-1 beta and protect against endothelial injury and ameliorated atherosclerosis by inhibition of oxidative stress. [8]

More research work is needed to identify and assess blood and sputum biomarkers against disease progression and outcomes in COPD. Upcoming approaches to studying gene-environment interaction that has impact on disease pathogenesis and progression in COPD are providing promising leads for novel biomarkers. These include (I) sampling exhaled breath condensate for protein markers; (II) characterizing responses of the lung to inhaled air pollutants; (III) applying knowledge of the lung microbiome to COPD phenotypes; and (IV) determining the significance of biomarkers of ageing such as telomere attrition. Tackling methodological challenges in sampling and quality control, will enable potent and newer biomarkers to be developed and applied to optimise personalised medicine in patients with COPD. [9]

Blood biomarkers are more preferred as there are well-established procedures for procurement and processing of samples and standardization of measurements. In COPD, the most widely studied blood biomarker has been CRP. Although it performs well in large cohorts, clinical application is limited owing to the poor specificity of the measurement. Any inflammatory or infectious insults whether or not they are linked with COPD can modify CRP levels over time. [10]

As per recent global burden of disease 2017 published in Lancet, COPD is second leading cause of death morbidity in India. Due to lack of circulating predictive biomarkers of severity of disease, it has been challenge to manage the pharmacotherapy in patients with COPD. A growing body of evidence from Western world suggest that circulating serum IRISIN levels is reliable marker of skeletal muscle in patients of COPD whom undergoing pulmonary rehabilitation. Whether this association between circulating serum IRISIN levels and lung function decline in exist in Indian COPD population has not been investigated. To best of our knowledge based on the literature survey, this is a first study in Indian population to show that impact of pulmonary rehabilitation on serum IRISIN levels in COPD patients.

Secondly, we also investigated whether this association holds true among variables i.e. 6MWT, PFT, BOLD SCORE, GOLD, MMRC, SGRQC., Did not found any significant association with all other variables. Together, these results support existing hypothesis that circulating increased serum IRISIN levels is a novel biomarker in patients with COPD on pulmonary rehabilitation.

Conclusion

IRISIN levels are significantly high in COPD patients with pulmonary rehabilitation compared to COPD patients without pulmonary rehabilitation as hypothesized. (p value <0.001). Serum IRISIN levels correlate well with quality of life suggesting IRISIN may also reflect changes in domains other than airflow limitation in COPD patients. There is no significant difference in serum IRISIN levels among male and female COPD patients, suggesting that levels of IRISIN are independent of age. There is no significant difference in serum IRISIN levels among smokers and non smoker patients.FEV1 is significantly lower in patient with decrease serum IRISIN level before pulmonary rehabilitation (p value 0.003).FVC is significantly lower in patient with decrease serum IRISIN level before pulmonary rehabilitation (p value 0.005).

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