Received: 27 October 2020 | Revised: 26 May 2020 | Accepted: 21 January 2021

DOI: 10.1111/crj.13336

ORIGINAL ARTICLE

WILEY

Association between insulin resistance and BMI with FEV_1 in non-hypoxemic COPD out-patients

Faisal Faiyaz Zuberi[1] | **Nimrah Bader**[2] | **Tazeen Rasheed**[3] | **Bader Faiyaz Zuberi**[3]

[1]Department of Pulmonology, Ojha Institute of Chest Disease, Dow University of Health Sciences, Karachi, Pakistan

[2]Department of Internal Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

[3]Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan

Correspondence
Faisal Faiyaz Zuberi, Department of Pulmonology, Ojha Institute of Chest Disease, Dow University of Health Sciences, A-112, Al-Habib Pride, CL-8/5, Civil Lines, Karachi, Pakistan.
Email: faisal@zuberi.net

Abstract

Objectives: This study was conducted to determine the impact of insulin resistance using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score and BMI in non-hypoxemic out-patients with COPD on FEV_1 using linear and polynomial regressions and to determine their correlation.

Methods: COPD patients of both genders were included after informed consent. Fasting blood sugar and serum insulin were done to calculate HOMA-IR, which were segregated into two groups of ≥ 3 and < 3 labeled insulin resistance present and absent, these were compared with BMI. Patients were segregated into GOLD Grade 1–4 per GOLD Guidelines and compared with HOMA-IR and BMI. Curve and linear regressions, multivariate and univariate analysis of HOMA-IR with BMI, FVC, and FEV_1 were done.

Results: A total of 273 subjects were inducted after informed consent. There was a linear correlation between HOMA-IR and BMI (r^2 0.498, $P < 0.001$) and nonlinear correlation between HOMA-IR and FEV1 (r^2 0. 617, $P < 0.001$) which showed little evidence of association above FEV1 > 60 predicted, but a clear negative association below that. Significant increase in HOMA-IR was seen from GOLD-2 to 3 and from GOLD-3 to 4 classes. The impact of HOMA-IR on FEV1 was 49.9% ($P < 0.001$) on FVC was 43.7%.

Conclusions: The results indicate that there is a high prevalence of IR in non-hypoxemic COPD. A nonlinear association is present between FEV1 and HOMA-IR which is most evident with FEV1 <60% predicted.

KEYWORDS

BMI, COPD, FEV_1, GOLD grade, insulin resistance

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a group of chronic inflammatory pulmonary disorders that are characterized by partially reversible airflow obstruction which are often secondary to significant exposure to noxious gases.[1] COPD is increasingly been regarded in the context of a "cardiopulmonary continuum"[2] and is associated with a 2- to 3-fold increased risk for cardiovascular diseases and type II diabetes mellitus (T2DM) and has higher frequency of blood eosinophilia in moderate to severe cases.[3,4] In a study by Mathers CD et al it was predicted that the prevalence of COPD and its resultant mortality would increase several folds by the year 2030.[5] COPD and obesity are widespread clinical conditions with significant impact on health in our society. It is likely, that prevalence of both these disorders will increase in future leading to increase burden on health resources of our country. Although

impact of both these disorders is well documented in epidemiological studies but the exact nature of their relation with Insulin Resistance (IR) is still unclear.[6,7] IR is related to many clinical diseases/states like diabetes, hypertension, and obesity and all these have great impact on health, morbidity, and all-cause mortality in population.[8,9] It is a common condition, present in about 10% of world's adult population,[10] and its prevalence is showing increasing trend due to sedentary lifestyles and increasing prevalence of obesity.[11] IR has an established role in many clinical disorders like polycystic ovaries,[12] cardiovascular mortality,[8] and end stage renal disease.[9]

Metabolic Syndrome (MetS) which was previously called Syndrome X, is a complex clinical disorder which is characterized by the presence of risk factors including excess abdominal obesity or body mass index (BMI) > 30 kg/m^2, elevated blood pressure, proatherogenic blood lipid profile, and impaired fasting blood glucose with or without insulin resistance.[13,14] Significant association between MetS and COPD has been documented by various studies[15-17] the prevalence of these disorders is expected to increase in future due to sedentary life style.[12] Obesity, COPD, and IR are related in complex interactions of genetic and environmental factors. These factors play an important role in initiating and propagating a low-grade systemic inflammatory response in all three conditions. COPD is characterized by persistent airflow obstruction and inflammation while extra-pulmonary manifestations and co-morbidities increase its severity. Despite all these facts, the evidence related to frequency of IR in COPD and its relation to BMI, is very scanty and is have not been reported from our area.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was developed to use in epidemiological studies and it is an alternative to glucose clamp. It is used as surrogate measure of IR in vivo and is comparable to glucose clamp in terms of precision and reproducibility and it requires only a single measurement of glucose and insulin in fasting.[18] Thus, it is a handy and easily available tool to measure insulin resistance.

The current study was planned to determine the frequency of insulin resistance in non-hypoxemic patients with COPD and to determine its impact and correlation with BMI and FEV_1 in our population. The study will lead to first time documentation interaction of these four conditions in our area and will help to identify patients at risk. This will lead to better understanding and management of these disorders. IR leads to obesity and increases the risk of diabetes in future. Diagnosis of this condition will help in better management and overall reduction in risk factors. It will help to formulate better exercise and dietary plans in these patients.

2 | MATERIALS AND METHODS

2.1 | Operational definition

2.1.1 | COPD

COPD will be diagnosed with Spirometry as per GOLD guideline of post-bronchodilator $FEV_1/FVC < 0.70$.[19]

2.1.2 | Non-hypoxemia

Non-hypoxemia will be diagnosed if SpO_2 is ≥ 94% on pulse oximetry

2.1.3 | GOLD Grade

GOLD-1-Mild: $FEV_1 \geq 80\%$ predicted
GOLD-2-Moderate: $50\% \leq FEV_1 < 80\%$ predicted
GOLD-3-Severe: $30\% \leq FEV_1 < 50\%$ predicted
GOLD-4-Very Severe: $FEV_1 < 30\%$ predicted

2.1.4 | Insulin resistance

Insulin Resistance will be labeled if HOMA-IR score is ≥ 3.0.[18,20] HOMA-IR will be calculated with formula:

$$\text{HOMA} - \text{IR} = \textit{Fasting Glucose}\ (mg/dl) \times \textit{Fasting Insulin}/405$$

2.1.5 | Body mass index (BMI):

Body Mass Index will be calculated by the formula BMI = weight (kg)/height (m)^2. Asian BMI classification was used in this study.

Underweight: < 18.5 kg/m^2
Normal: 18.5–22.9 kg/m^2
Overweight: 23.0–27.5 kg/m^2
Obese: >27.5 kg/m^2

2.2 | Study design

Cross-section Observational Study

2.3 | Setting

Clinics of Ojha Institute of Chest Diseases and Dow Medical College & Ruth KM Pfau Civil Hospital Karachi, Pakistan.

2.4 | Sample size

Using reported frequency of 62%,[15] power of 95%, and alpha of 0.05; sample size was calculated as 228. Sample size calculation was done by PASS 2019 software.

2.5 | Inclusion criteria

Current smokers of both genders of age 25–70 years were included after informed consent. Patients presenting with symptoms suggestive of airway disease were evaluated in clinics for COPD. COPD was diagnosed as per operational criteria.

2.6 | Exclusion criteria

Patients with pulse oximetry SpO_2 of < 94% were excluded. Patients with pulmonary tuberculosis, pleural effusion, and heart failure and previously diagnosed cases of diabetes mellitus were excluded.

2.7 | Data collection procedure

Study has ethical approval from IRB of Dow University of Health Sciences vide its letter number IRB-1420/DUHS/Approval/2019 dated 04-11-2019. Pulse oximetry was done of all patients satisfying COPD criteria and those with oxygen saturations of ≥ 94% were included in study for further workup after informed consent. Demographics like age, gender, weight, and height were recorded. BMI calculations were done. Spirometry was done using Vitalograph Spirometer as per standard departmental protocol and FEV_1 values were recorded. An 8-hour fasting sample of blood was withdrawn for blood sugar and serum insulin were done on same sample for the calculation of Insulin Resistance Index (HOMA-IR). Insulin resistance was labeled if HOMA-IR score of ≥ 3.0.[18]

2.8 | Data analysis procedure

Mean ± SD of age, BMI, FEV_1, and HOMA-IR were calculated and compared with gender using independent samples *t*-test. Data from BMI were recoded into a new variable as per Asian BMI guidelines into underweight, normal, overweight, and obese categories. These categories were compared with gender using χ^2 test. HOMA-IR values were compared with BMI categories using one-way ANNOVA test with post hoc analysis. Values of FEV_1 were recoded into new variable as per GOLD Guidelines into GOLD Grade 1 to 4 and compared with gender by χ^2 test and with HOMA-IR values by one-way ANNOVA with post hoc test. Mean of HOMA-IR was tested with reported cut off value of 3.0 for presence of IR using one-sample *t*-test. Data were recoded into new variable for HOMA-IR values of ≥ 3 and < 3 to create groups with insulin resistance present and absent and were compared with BMI Groups using χ^2 test. Correlation between HOMA-IR, BMI, FVC, and FEV_1 was done using Pearson bivariate correlation test as a prerequisite for Multivariate analysis (MANOVA). All these variables correlated significantly as reported in Table 4 fulfilling its pre-condition. MANOVA was done using HOMA Groups as independent variable and BMI, FEV_1, and FVC as dependent variables. Linear and polynomial (quadratic) regressions were fitted to the relationship between HOMA-IR as dependent variable and FEV1 as the independent variable.

Significance was set at ≤ 0.05. SPSS version 26 was used for analysis.

3 | RESULTS

A total of 273 subjects fulfilling selection criteria was inducted after informed consent. Study was conducted during the period of 05 November to 04 May 2020 at outpatient clinics of Ojha Institute of Chest Diseases, Dow Medical College & Ruth KM Pfau Civil Hospital Karachi, Pakistan. These included 161 (59.0%) males and 112 (41.0%) females. Mean age of males was 60.1 ± 10.3 years that of females was 56.3 ± 9.5 years. Mean age was significantly higher in males on Student's *t*-test, $t(271) = 3.1$, $P = 0.002$. BMI was calculated from data of height and weight and no significant difference was found in BMI values among gender $t(207.9) = 0.118$, $P = 0.906$. No significant difference was present in FEV_1 values among gender on Student's *t*-test $t(217.9) = -549$, $P = 0.583$. Fasting glucose values in males were significantly higher as compared to females $t\ (225.5) = 3.6$, $p < .001$. Fasting insulin was significantly less in males $t(264.7) = -3.5$, $P = 0.001$. No statistical difference was found in HOMA-IR values among gender $t(271) = -0.64$, $P = 0.525$. Details are given in Table 1.

3.1 | BMI analysis

BMI Groups were calculated as per Asian Guidelines described in methods, the breakup showed that 56 (20.5%) were underweight, 124 (45.4%) were normal, 77 (28.2%) were overweight, and 16 (5.9%) were in obese group of BMI. On analysis with χ^2 test no significant difference was found in BMI Groups with gender. χ^2 ($df = 3$, N = 273) = 6.0; $P = 0.112$. Effect of BMI categories was studied on HOMA-IR scores by one-way ANNOVA test. It showed significant impact of BMI Groups on HOMA-IR scores, $F(1, 269) = 253.72$,

TABLE 1 Comparison of age, BMI, FEV1,FVC, fasting glucose, fasting insulin, and HOMA-IR with gender and statistical significance

	Gender				
	Male		Female		
	Mean	SD	Mean	SD	Sig.
Age	60.1	10.3	56.3	9.5	0.002
BMI	21.3	3.5	21.2	4.3	0.906
FEV_1	46.4	13.0	47.3	14.9	0.583
FVC	47.8	15.2	51.3	20.6	0.126
Fasting glucose	100.6	9.7	96.1	10.6	<0.001
Fasting insulin	12.5	1.9	13.2	1.5	0.001
HOMA-IR	3.1	.5	3.1	.5	0.525

$P < 0.001$. Post hoc multiple comparisons were done to see the significance among various BMI Categories. There was progressive increase in HOMA-IR scores from underweight to normal ($P < 0.001$), normal to overweight ($P < 0.001$), and overweight to obese ($P < 0.001$). Details are given in Table 2. There was strong positive correlation between HOMA-IR and BMI when tested with Pearson correlation test $r = 0.78$, n = 273, $P < 0.001$. This is also shown in scatter plot in Figure 1.

3.2 | FEV_1 analysis

Patients were segregated on basis of FEV_1 as per GOLD Grade. In GOLD-1(mild) there were 14 (5.1%), in GOLD-2 (moderate) there were 48 (17.6%), in GOLD-3 (severe) there were 203 (74.4%), and in GOLD-4 (very severe) there were 8 (2.9%) patients. There was no significant difference in GOLD Grade among gender. χ^2 ($df = 3$, N = 273) = 4.3; $P = 0.227$. Strong negative correlation existed between HOMA-IR and FEV_1 showing progressive decrease in HOMA-IR values as FEV_1 increases, $r = -0.707$, n = 273, $P < 0.001$. The R squared value for a linear regression between HOMA-IR and FEV1 was 0.498, but a quadratic equation had significantly better fit than the linear regression ($P < 0.01$), with a R squared value of 0.617. It can be seen in Figure 2 that the association between HOMA-IR and FEV1 was largely confined to patients with an FEV1 <60% predicted.

TABLE 2 ANNOVA post hoc analysis of BMI categories with HOMA-IR with significance

	Groups	Mean ± SD	Mean diff.	Sig.
1.	Underweight	2.59 ± 0.31	−0.42	<0.001
	Normal	3.01 ± 0.38		
2.	Normal	3.01 ± 0.38	−0.43	<0.001
	Overweight	3.44 ± 0.30		
3.	Overweight	3.44 ± 0.30	−0.53	<0.001
	Obese	3.99 ± 0.10		

3.3 | FVC analysis

Strong negative correlation existed between HOMA-IR and FEV_1 showing progressive decrease in HOMA-IR values as FEV_1 increases, $r = -0.731$, n = 273, $P < 0.001$. Mean FVC ± SD values according to GOLD Grade were as under:

GOLD-1: 97.3 ± 6.3
GOLD-2: 71.8 ± 12.1
GOLD-3: 41.3 ± 4.9
GOLD-4: 30.0 ± 0.0

3.4 | HOMA-IR analysis with GOLD grade

Comparison of HOMA-IR scores with GOLD Grade was done with ANNOVA showing significant difference in HOMA-IR scores in GOLD Grade, F (1, 269) = 95.70, $P < 0.001$ (Figure 3). Post hoc multiple comparison to see the difference of HOMA-IR scores with GOLD Grade. There was progressive increase in HOMA-IR scores. Increase in GOLD-1 to GOLD-2 was not significant ($P = 0.202$), but all the rest were very significant; GOLD-2 to GOLD-3 ($P < 0.001$) and GOLD-3 to GOLD-4 ($P < 0.001$).

3.5 | Insulin resistance

HOMA-IR value of ≥ 3.0 is defined as insulin resistance, using this cut off value mean HOMA-IR values were assessed in our study subjects of those with values ≥ 3.0 and those with values < 3.0 using one-Sample t-test which showed significant difference t (272) = 3.44, $P = 0.001$. Patients were segregated into two groups based on cut off 3.0 into patients with insulin resistance (IR) present and IR absent and were analyzed with BMI Groups by χ^2 test. Significant increase in frequencies of IR was seen in patients with higher BMI, χ^2 ($df = 3$, N = 273) = 106.14, $P < 0.001$. Details are given in Table 3.

3.6 | Multivariate analysis (MANOVA)

Multivariate analysis was performed using HOMA-IR Group as independent variable (Fixed Factor) and BMI, FEV1, FVC as dependent variables. However, prior to conducting the MANOVA, a series of Pearson correlations were performed between all the dependent variables to test the MANOVA assumption that the dependent variables should be correlated with each other in the moderate range. As detailed in Table

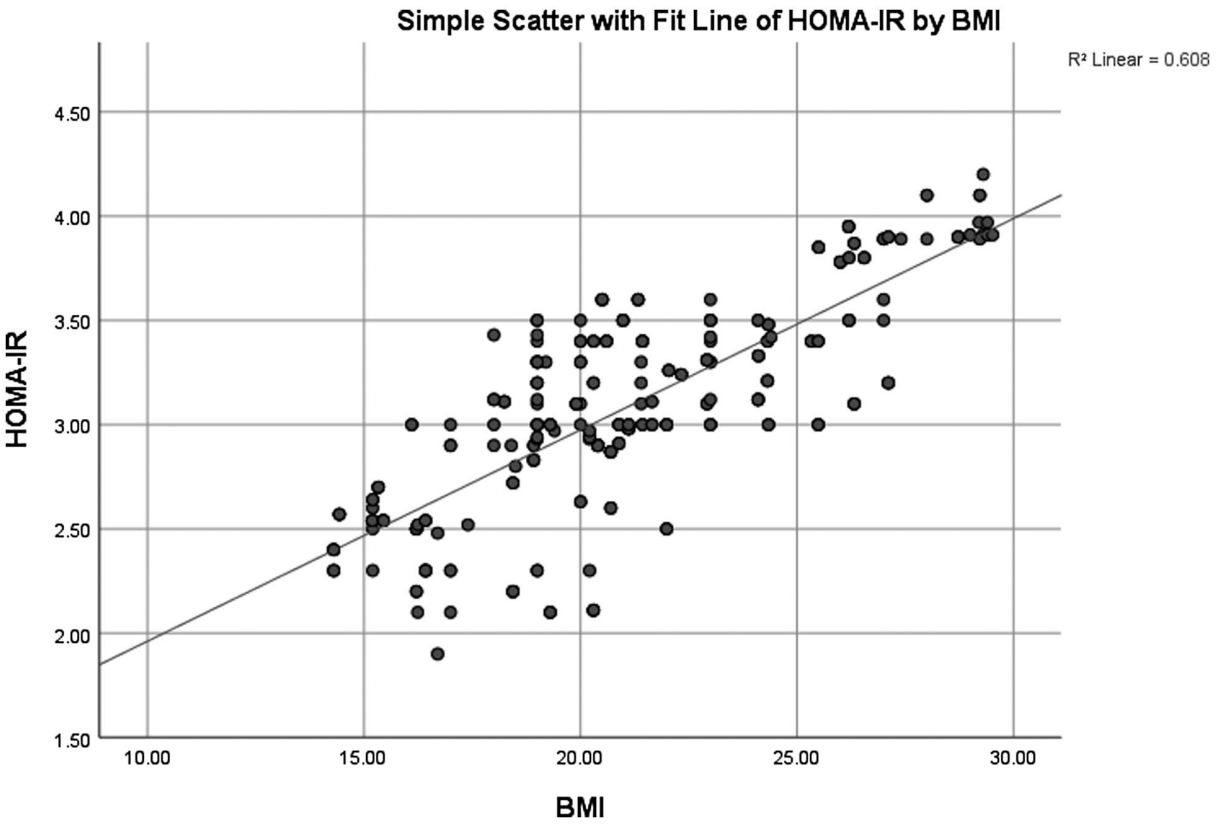

FIGURE 1 Scatter plot of HOMA-IR with BMI

4 all dependent variables correlated significantly ($P < 0.001$) suggesting the appropriateness of a MANOVA testing.

A one-way multivariate analysis of variance (MANOVA) was conducted to test the hypothesis that there would be one or more mean differences between HOMA-IR status (present and absent) and BMI, FEV1, and FCV. There was statistically significant difference in BMI, FEV1, and FVC based on HOMA-IR status F (3, 269) = 78.2, $P < 0.001$, Wilk's Lambda = .534, partial $\eta^2 = 0.466$.

A univariate ANOVA analysis was subsequently done on all dependent variables keeping alpha = 0.025. HOMA-IR had significant effect on all three studied dependent variables, BMI [$F(1, 271) = 183.21$, $P < 0.001$, partial $\eta^2 = 0.403$], FEV1 [$F(1, 271) = 190.06$, $P < 0.001$, partial $\eta^2 = 0.412$], and FVC [$F(1, 271) = 210.558$, $P < 0.001$, partial $\eta^2 = 0.437$]. Post hoc analysis was not performed as HOMA-IR had fewer than three groups.

4 | DISCUSSION

We in this study have documented significant association between HOMA-IR and BMI with FEV_1. We also documented high frequency of IR in non-hypoxemic COPD out-patients and have also documented that HOMA-IR negatively correlates with FEV_1. We also report negative correlation of HOMA-IR with FEV_1. Thus, an association between HOMA-IR and FEV_1 is documented. Patients of COPD with IR are at greater risk of poor lung function. Findings similar to our study were also reported by Lee YB et al in Korean population in which they also presented similar data of negative correlation of HOMA-IR with FEV_1.[21] A small study from Pakistan also showed higher values of HOMA-IR scores in COPD patients as compared to controls but they did not check for any correlation and cause/effect relationship between HOMA-IR and FEV_1 variables.[22]

It has been reported earlier that systemic inflammation due to diabetes and insulin resistance could lead to deterioration in lung function.[23-25] Insulin resistance and obesity are associated with systemic inflammation.[26,27] In our study the association of insulin resistance and FEV_1 was strongest in $FEV_1 < 50$, this could be due to greater systemic inflammation present in severe insulin resistance.

Our study showed non-significant increase in HOMA-IR between GOLD-1 and GOLD-2 but significant increase in HOMA-IR values between GOLD-2 and GOLD-3 and further significant increase between GOLD-3 and GOLD-4. This shows IR occurs more significantly in higher GOLD Grade. These are important finding reported by our study. IR has been reported to play a part in impairment of pulmonary function in COPD patients that could affect the COPD outcomes.[28] IR correlates with MetS which has its own set of complications, presence of IR in COPD patients will put them at risk of these complications.[9,29,30] It has

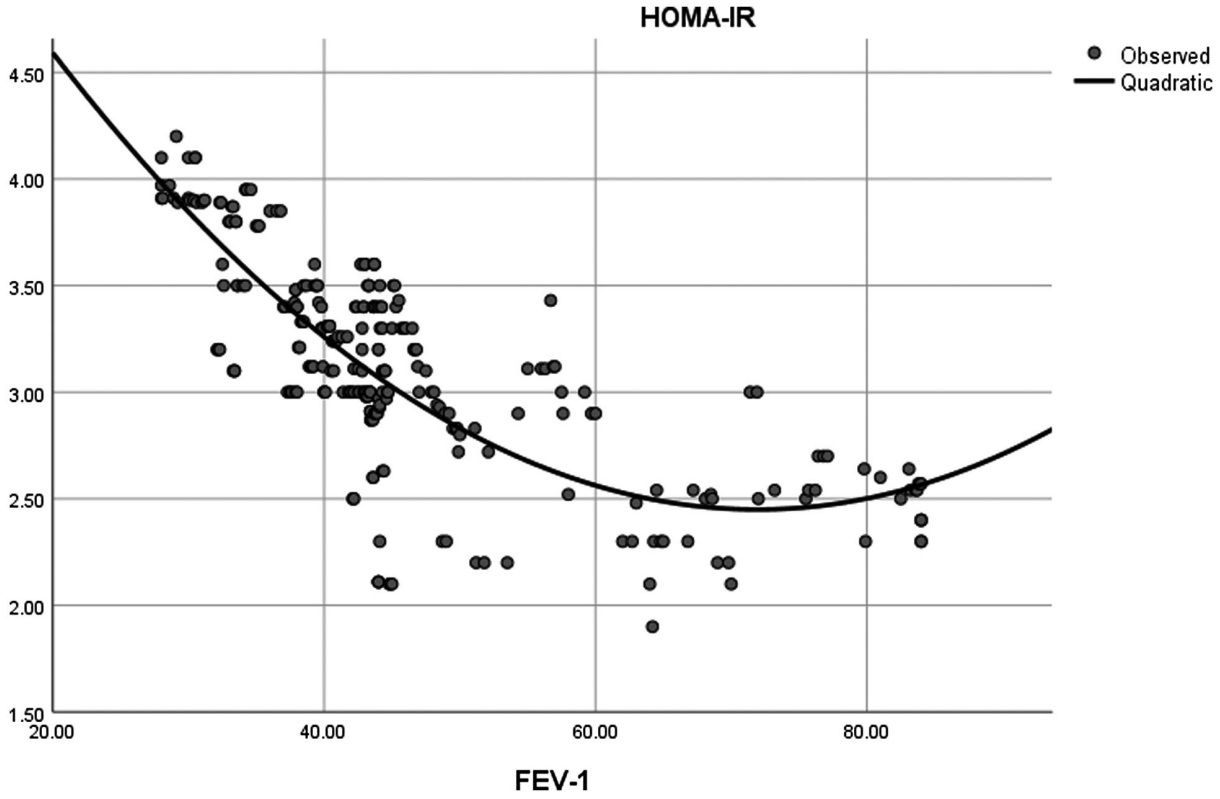

FIGURE 2 Scatter plot of HOMA-IR with FEV_1 with polynomial regression line

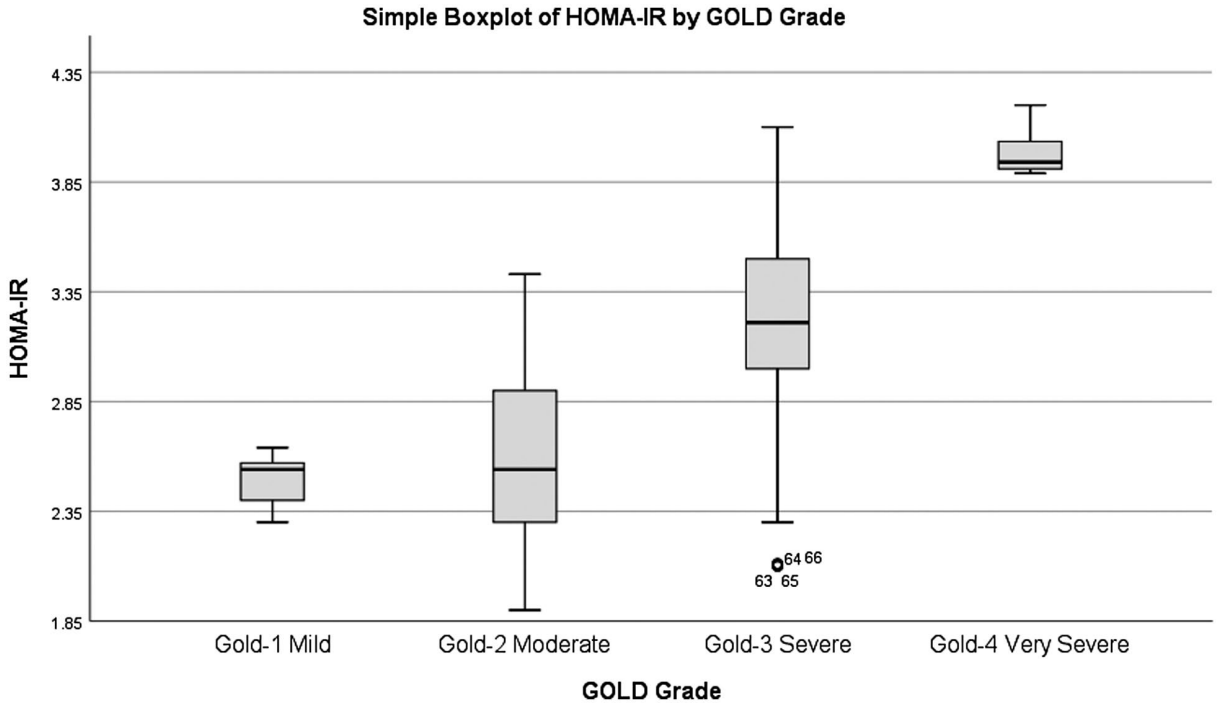

FIGURE 3 Box Plot of HOMA-IR with GOLD Grade

been demonstrated that IR in non-hypoxemic patients with COPD was related to systemic inflammation. This relationship may indicate a contributory factor in the excess risk of cardiovascular disease and type II diabetes in COPD.[31]

In our study we also documented a positive correlation of HOMA-IR with BMI in COPD patients. Thus, patients who are obese are more at risk for having IR. IR is known to be associated with MetS and with presence of IR in COPD

TABLE 3 Cross-tabulation of HOMI-IR groups with BMI groups

			BMI Groups				
			Underweight	**Normal**	**Overweight**	**Obese**	**Total**
HOMA-IR Groups	IR Present	Count	10	75	77	16	178
		%	17.9%	60.5%	100.0%	100.0%	65.2%
	IR Absent	Count	46	49	0	0	95
		%	82.1%	39.5%	0.0%	0.0%	34.8%
Total		Count	56	124	77	16	273
		%	100.0%	100.0%	100.0%	100.0%	100.0%

patients, they are also at risk of developing MetS. This effect has been reported by Piozzolla G et al and have shown significant presence of MetS at 62% in COPD patients.[15] COPD may be considered as a risk factor for new onset (T2DM) because of multiple complex patho-physiological mechanisms namely oxidative stress, inflammation, insulin resistance, weight gain, and changes in the metabolism of adipokines. Insulin resistance (IR) is the decreased tissue response to normal levels of circulating insulin and is associated with an increased risk for cardiovascular disease and metabolic dysfunction. IR has been associated with increased cytokines, including interleukin-6 and tumor necrosis factor alpha soluble receptor, both of which are elevated in patients with COPD.[32] COPD and IR together makeup a downward spiral, meaning COPD worsens the condition of IR which afterwards could lead to worsening of COPD.

Recently, there has been increasing interest in the relationship between IR, increase in BMI, obesity, and COPD. It has been suggested that decrease in oxidative capacity and systemic hypoxia may play a role in the pathogenesis of COPD in obese patients. In our study there was no significant difference in the BMI and FEV_1 values among gender. Our study demonstrated significantly high prevalence of IR in non-hypoxemic COPD patients and its strong correlation with BMI and FEV_1. Our results were similar to study done by Bolton CE et al in which fasting plasma glucose, insulin, and inflammatory mediators were measured in 56 COPD patients and 29 healthy subjects. The results of their study reported that there were greater insulin resistance in non-hypoxemic patients with COPD as compared with healthy subjects. Additionally their study also demonstrated increase in the levels of circulating inflammatory mediators specifically interleukin-6 and tumor necrosis factor α soluble receptor.[31] A number of studies have demonstrated that increasing BMI and obesity is more prevalent in patients of COPD as compared to the general population.[33,34] Obesity in turn results in expiratory airflow limitation and worsening dyspnea due to its extrapulmonary restrictive component, which results in functional decline. Vaz D et al. in their study reported that insulin resistance in patients of COPD was associated with greater severity of airway obstruction and lower FEV_1 as compared to patients without IR.[35] This was similar to our study which demonstrated negative correlation of HOMA-IR with lung function.

IR has known associations with diabetes mellitus (DM), metabolic syndrome (MetS), and obesity,[11,36] and some new associations are reported recently including mental health and COPD.[10,15] MetS is one of the comorbidities complicating the clinical course of COPD and functional decline in the patients of COPD. An association between MetS and COPD has been observed in several studies. The overall prevalence of MetS is reported to be 21%–50% in patients of COPD.[30,37] Therefore, coordinated management of diverse aspects of COPD is needed to improve the quality of life and morbidity in these patients. Our study limitations were that we did

TABLE 4 Pearson's correlation between BMI, FEV-1, FVC & FVC

		BMI	**FEV-1**	**FVC**	**HOMA-IR**
BMI	Pearson correlation	1	−0.893**	−0.830**	0.780**
	Sig. (two-tailed)		0.000	0.000	0.000
FEV-1	Pearson correlation	−0.893**	1	0.954**	−0.707**
	Sig. (two-tailed)	0.000		0.000	0.000
FVC	Pearson correlation	−0.830**	0.954**	1	−0.731**
	Sig. (two-tailed)	0.000	0.000		0.000
HOMA-IR	Pearson correlation	0.780**	−0.707**	−0.731**	1
	Sig. (two-tailed)	0.000	0.000	0.000	

**Correlation is significant at the 0.01 level (two-tailed).

not checked for inflammatory markers and for MetS in our patients.

5 | CONCLUSIONS

Our study indicates strong associations insulin resistance, BMI, and FEV_1. Causalities in these relationships are yet to be determined, although on balance it is more likely that low lung function leads to insulin resistance, but mechanisms are not yet identified.

6 | AUTHORSHIP CONTRIBTIONS

F.F. Zuberi is the guarantor and takes responsibility for the integrity of the content of the article, study processes, and data and is corresponding author. N. Bader, T. Rasheed, and B.F. Zuberi were involved in study implementation, data analysis, and interpretation. F.F. Zuberi and B.F. Zuberi were involved in study design, data interpretation, and critical review of the manuscript. All authors take responsibility for the integrity of the data analysis and approve the final version of the manuscript.

ETHICS

Ethical approval was taken from IRB of Dow University of Health Sciences, Karachi, Pakistan.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available as its supplementary material.

ORCID

Faisal Faiyaz Zuberi https://orcid.org/0000-0001-9067-0021
Bader Faiyaz Zuberi https://orcid.org/0000-0001-7695-3922

REFERENCES

1. Vestbo J, Hurd S, Agustí A, Jones P, Vogelmeier C, Anzueto A. Gold executive summary. *Am J Respir Crit Care Med*. 2013;347(10).
2. Ukena C, Mahfoud F, Kindermann M, et al. The cardiopulmonary continuum systemic inflammation as 'Common Soil'of heart and lung disease. *Int J Cardiol*. 2010;145(2):172-176.
3. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in copd. *Chest*. 2005;128(4):2640-2646. https://doi.org/10.1378/chest.128.4.2640
4. Khan GM, Zuberi FF, Bizat-uz-Zahra S, Ghafoor L. Frequency of blood eosinophilia in newly diagnosed chronic obstructive pulmonary disease patients. *Pak J Med Sci*. 2020;36(4):750-754. https://doi.org/10.12669/pjms.36.4.1624
5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442.
6. Gupta SS, Gothi D, Narula G, Sircar J. Correlation of BMI and oxygen saturation in stable copd in Northern India. *Lung India*. 2014;31(1):29-34. https://doi.org/10.4103/0970-2113.125891
7. Zhou Y, Wang D, Liu S, et al. The association between BMI and Copd: the results of two population-based studies in Guangzhou, China. *COPD*. 2013;10(5):567-572. https://doi.org/10.3109/15412555.2013.781579
8. Hellgren MI, Daka B, Jansson PA, Lindblad U, Larsson CA. Insulin resistance predicts early cardiovascular morbidity in men without diabetes mellitus, with effect modification by physical activity. *Eur J Prev Cardiol*. 2015;22(7):940-949. https://doi.org/10.1177/2047487314537917
9. Fragoso A, Mendes F, Silva AP, Neves PL. Insulin resistance as a predictor of cardiovascular morbidity and end-stage renal disease. *J Diabetes Complications*. 2015;29(8):1098-1104. https://doi.org/10.1016/j.jdiacomp.2015.05.010
10. Scott EM, Carpenter JS, Iorfino F, et al. What is the prevalence, and what are the clinical correlates, of insulin resistance in young people presenting for mental health care? a cross-sectional study. *BMJ Open*. 2019;9(5):e025674. https://doi.org/10.1136/bmjopen-2018-025674
11. Jiang B, Chen Y, Zhou K, et al. Comparison of abdominal obesity and fatty liver and their association with insulin resistance and metabolic syndrome in chinese adults. *Obesity (Silver Spring)*. 2019;27(5):707-715. https://doi.org/10.1002/oby.22432
12. Dahan MH, Reaven G. Relationship among obesity, insulin resistance, and hyperinsulinemia in the polycystic ovary syndrome. *Endocrine*. 2019;64(3):685-689. https://doi.org/10.1007/s12020-019-01899-9
13. Chan SMH, Selemidis S, Bozinovski S, Vlahos R. Pathobiological Mechanisms underlying metabolic syndrome (Mets) in chronic obstructive pulmonary disease (Copd): clinical significance and therapeutic strategies. *Pharmacol Ther*. 2019;198:160-188. https://doi.org/10.1016/j.pharmthera.2019.02.013.
14. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365(9468):1415-1428. https://doi.org/10.1016/S0140-6736(05)66378-7
15. Piazzolla G, Castrovilli A, Liotino V, et al. Metabolic syndrome and chronic obstructive pulmonary disease (Copd): the interplay among smoking, insulin resistance and vitamin D. *PLoS One*. 2017;12(10):e0186708. https://doi.org/10.1371/journal.pone.0186708
16. Breyer M-K, Spruit MA, Hanson CK, et al. Prevalence of metabolic syndrome in Copd patients and its consequences. *PLoS One*. 2014;9(6):e98013. https://doi.org/10.1371/journal.pone.0098013
17. Díez-Manglano J, Barquero-Romero J, Almagro P, et al. Copd patients with and without metabolic syndrome: clinical and functional differences. *Intern Emerg Med*. 2014;9(4):419-425. https://doi.org/10.1007/s11739-013-0945-7
18. Esteghamati A, Ashraf H, Khalilzadeh O, et al. Optimal Cut-Off of homeostasis model assessment of insulin resistance (Homa-Ir) for the diagnosis of metabolic syndrome: third national surveillance of risk factors of non-communicable diseases

in Iran (Surfncd-2007). *Nutr Metab (Lond)*. 2010;7:26. https://doi.org/10.1186/1743-7075-7-26.
19. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: gold executive summary. *Eur Respir J*. 2017;49(3). https://doi.org/10.1183/13993003.00214-2017
20. Qu HQ, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB. The definition of insulin resistance using Homa-Ir for Americans of Mexican descent using machine learning. *PLoS One*. 2011;6(6):e21041. https://doi.org/10.1371/journal.pone.0021041
21. Lee YB, Kim YS, Lee D-H, et al. Association between Homa-Ir and lung function in korean young adults based on the Korea national health and nutrition examination survey. *Sci Rep*. 2017;7(1):11726. https://doi.org/10.1038/s41598-017-11337-3
22. Kiran Z, Majeed N, Zuberi BF. Comparison of frequency of insulin resistance in patients with chronic obstructive pulmonary disease with normal controls. *Pak J Med Sci*. 2015;31(6):1506-1510. https://doi.org/10.12669/pjms.316.7983
23. Dennis RJ, Maldonado D, Rojas MX, et al. Inadequate glucose control in type 2 diabetes is associated with impaired lung function and systemic inflammation: a cross-sectional study. *BMC Pulm Med*. 2010;10:38. https://doi.org/10.1186/1471-2466-10-38.
24. Kalhan R, Tran BT, Colangelo LA, et al. Systemic inflammation in young adults is associated with abnormal lung function in middle age. *PLoS One*. 2010;5(7):e11431. https://doi.org/10.1371/journal.pone.0011431
25. Sunyer J, Pistelli R, Plana E, et al. Systemic inflammation, genetic susceptibility and lung function. *Eur Respir J*. 2008;32(1):92-97. https://doi.org/10.1183/09031936.00052507
26. Jia Q, Morgan-Bathke ME, Jensen MD. Adipose tissue macrophage burden, systemic inflammation, and insulin resistance. *Am J Physiol Endocrinol Metab*. 2020;319(2):E254-E264. https://doi.org/10.1152/ajpendo.00109.2020
27. Mansyur MA, Bakri S, Patellongi IJ, Rahman IA. The association between metabolic syndrome components, low-grade systemic inflammation and insulin resistance in non-diabetic indonesian adolescent male. *Clin Nutr ESPEN*. 2020;35:69-74. https://doi.org/10.1016/j.clnesp.2019.12.001.
28. Patel AR, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med*. 2011;5(5):647-662. https://doi.org/10.1586/ers.11.62
29. Wells CE, Polkey MI, Baker EH. Insulin resistance is associated with skeletal muscle weakness in Copd. *Respirology*. 2016;21(4):689-696. https://doi.org/10.1111/resp.12716
30. Minas M, Kostikas K, Papaioannou AI, et al. The association of metabolic syndrome with adipose tissue hormones and insulin resistance in patients with copd without co-morbidities. *COPD*. 2011;8(6):414-420. https://doi.org/10.3109/15412555.2011.619600
31. Bolton CE, Evans M, Ionescu AA, et al. Insulin resistance and inflammation - a further systemic complication of Copd. *COPD*. 2007;4(2):121-126. https://doi.org/10.1080/15412550701341053
32. Baba S, Takashima T, Hirota M, Kawashima M, Horikawa E. Relationship between pulmonary function and elevated glycated hemoglobin levels in health checkups: a cross-sectional observational study in Japanese participants. *J Epidemiol*. 2017;27(11):511-515. https://doi.org/10.1016/j.je.2016.10.008
33. Franssen FM, O'Donnell DE, Goossens GH, Blaak EE, Schols AM. Obesity and the lung: 5. Obesity and Copd. *Thorax*. 2008;63(12):1110-1117. https://doi.org/10.1136/thx.2007.086827
34. Katz P, Iribarren C, Sanchez G, Blanc PD. Obesity and functioning among individuals with chronic obstructive pulmonary disease (Copd). *COPD*. 2016;13(3):352-359. https://doi.org/10.3109/15412555.2015.1087991
35. Vaz DVM, Shiang T. Insulin resistance, lung function and exacerbation rate in chronic obstructive lung disease. *Eur Respir J*. 2015;46(59). https://doi.org/10.1183/13993003
36. Fatima F, Ahsan N, Nasim A, Alam F. Association of fetuin-a with dyslipidemia and insulin resistance in type-ii diabetics of Pakistani population. *Pak J Med Sci*. 2020;36(2):64-68. https://doi.org/10.12669/pjms.36.2.1106
37. Watz H, Waschki B, Kirsten A, et al. The metabolic syndrome in patients with chronic bronchitis and copd: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest*. 2009;136(4):1039-1046. https://doi.org/10.1378/chest.09-0393

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Zuberi FF, Bader N, Rasheed T, Zuberi BF. Association between insulin resistance and BMI with FEV_1 in non-hypoxemic COPD out-patients. *Clin Respir J*. 2021;00:1–9. https://doi.org/10.1111/crj.13336