Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Chronic Obstructive Pulmonary Disease and Metabolic Syndrome: A Maltese Study on Biomarkers and Clinical Implications

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Purpose: Chronic Obstructive Pulmonary Disease (COPD) and Metabolic Syndrome (MetS) are both characterized by inflammation and appear to be linked. The study aims to characterize COPD in Maltese individuals with diabetes and MetS for the first time. The research project also aims to identify biomarkers that are significantly associated with COPD endpoints in the study population having both COPD and MetS.

Patients and Methods: The study was carried out at Mater Dei Hospital, which is Malta's main general hospital and is government managed. Research subjects were recruited from the Diabetes Clinic. A respiratory questionnaire was administered, followed by the Six-Minute Walk Test (6MWT), Fractional Exhaled Nitric Oxide (FeNO) testing, spirometry and phlebotomy. The American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) criteria were used to diagnose MetS. A post-bronchodilator FEV_1/FVC ratio of less than 0.7 was necessary to diagnose COPD, as recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

Results: The study group consisted of 24 subjects diagnosed with both MetS and COPD. The group showed heterogenous results with a mean St George's Respiratory Questionnaire for COPD total score of 41.7, mean distance on 6MWT of 359m, mean FeNO of 12.2ppb, and mean Forced Expiratory Volume in 1 second of 64.6%. While 62.5% had a modified Medical Research Council score of ≥2, 95.8% had a COPD Assessment Test score of ≥10. One-fourth of the group were at risk for clinical depression, and 20.8% showed severe fatigue. Blood lymphocyte count, ferritin, triglycerides and glucose were significantly associated with multiple respiratory parameters in diabetic MetS subjects with COPD.

Conclusion: The local diabetic MetS study population with COPD is heterogenous, with high levels of depression and fatigue. The emergence of biomarkers in this population has clinical and therapeutic implications.

Keywords: biomarkers, depression, fatigue

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive, debilitating respiratory disease with a global prevalence of around 7.6%.[1] COPD is the third leading cause of mortality in the world, and the only major cause of mortality that is on the increase.[1]

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study was a 3-year observational controlled multi-centre study developed by academic researchers and GlaxoSmithKline®.[2] The ECLIPSE study aimed to define clinically relevant COPD subtypes and to identify parameters, novel biomarkers and genetic factors that may correlate with subtype and disease progression. The investigators recruited COPD patients aged 40–75 years, having a Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage of II–IV. There were two control groups – smokers without

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COPD, and non-smokers. Subjects were investigated at baseline, 3 months and 6 months, followed by 6-monthly reviews of health outcomes, body impedance and oxygen saturation, as well as lung function testing and 6-minute walking distance (6MWD), thoracic computed tomography and biomarker quantification in serum, sputum, urine and exhaled breath condensate.[2] The ECLIPSE study has identified several biomarkers that may have a role in clinical trials aimed at validating future COPD therapies.

COPD is a multi-system disorder, which includes several extra-pulmonary manifestations, including metabolic syndrome (MetS).[3] The prevalence of MetS ranges from 25% to 60% among COPD patients.[4] The aetiological factors that connect the two diseases are poorly understood; these include systemic inflammation and adipose tissue inflammation, as well as an inactive lifestyle, hypogonadism and the sequelae of steroid use.[4] The development of MetS in COPD has been shown to increase COPD progression through oxidative stress, which activates systemic inflammation.[5] In fact, the presence of MetS in COPD is associated with lower quality of life, increased COPD exacerbations and higher all-cause mortality.[6,7] Both MetS and COPD increase cardiovascular morbidity and mortality risk since both diseases involve low-grade inflammation, which is a key component of atherosclerosis.[8]

A thorough literature review on the prevalence of COPD within the MetS population revealed only one study[9] from Bari, Italy, in 2017, whereby authors aimed to study risk factors, clinical and metabolic characteristics among individuals with MetS, COPD or both. A COPD prevalence of 22% was noted among MetS patients, whereas a MetS prevalence of 62% was observed for COPD patients.

Central obesity is the most important cause of airflow obstruction in MetS, through multiple effects on lung function, including abnormal ventilation/perfusion ratio, reduced chest wall and lung compliance, increased work of breathing, decreased ventilatory muscle strength, as well as small airway disease and expiratory flow obstruction.[4,10]

The actual prevalence of MetS in Malta has never been documented, despite a high prevalence of the individual components. Obesity is one of the most challenging public health issues in Malta with 25% of the adult population defined as obese. This ranks Malta as having the highest rate of obesity in Europe.[11] The International Diabetes Federation (2013) records a diabetes prevalence of 10.1% among the population in Malta aged 20–79, placing Malta in the first quartile within the European region.[12] The European Health Examination Survey (EHES) from 2010 showed a prevalence of 23.5% of stage 1 hypertension in Malta, with a further 8.5% having stage 2 hypertension.[13] The EHES also revealed that hypercholesterolaemia is common in Malta, with approximately 42% having a high Low-Density Lipoprotein (LDL) level.[13] To date, suitable information on COPD prevalence in Malta is lacking.[14]

Since there is little research on both COPD and MetS in Malta, this study aims to characterize COPD in Maltese individuals with diabetes and MetS for the first time. While biomarkers of COPD have been studied internationally, less is known about the population having both COPD and MetS. Therefore, the research project aims to identify biomarkers in the study population having both COPD and MetS. The authors hypothesize that certain biochemical characteristics of individuals with COPD and MetS are significantly associated with COPD clinical end-points – these biochemical characteristics would emerge as biomarkers.

Knowledge of the characteristics and biomarkers of this population would help the clinician better understand how to assess the MetS patient with COPD, particularly with regard to symptoms, exacerbations, respiratory parameters and biochemical characteristics. In addition, there may be implications for treatment with the aim of reducing morbidity and mortality in COPD and MetS.

Material and Methods

Participant Recruitment

The study complies with the Declaration of Helsinki and was approved by the Research Ethics Committee of the Faculty of Medicine and Surgery at the University of Malta (Reference Number FRECMDS_1819_125). Participants were recruited from the Diabetes Clinic at Mater Dei Hospital, which is Malta's main general hospital. The convenience sampling method was used. Research subjects with Type 2 Diabetes Mellitus (DM) and aged between 40 and 75 years were given an information sheet by an independent healthcare worker. Those who were willing to participate were asked to sign a consent form by the investigator. Both the information sheet and consent form were available in Maltese and in English.

Participants were briefly interviewed at the Diabetes Clinic to check for any exclusion criteria. These exclusion criteria were similar to those of the ECLIPSE study,[2] and included:

- a history of respiratory disease other than COPD (such as asthma, bronchiectasis, interstitial lung disease)
- a history of diabetic or pre-diabetic conditions other than type 2 DM (such as type 1 DM, impaired glucose tolerance, impaired fasting glucose, gestational DM)
- a history of malignancy in the past 5 years
- a history of other inflammatory disorders (such as rheumatoid arthritis and inflammatory bowel disease)
- a history of infection or respiratory exacerbation or use of systemic steroids in the past 4 weeks
- the inability to give consent.

Type 2 diabetic subjects aged 40–75 years having no exclusion criteria were asked to attend Mater Dei Hospital on a separate occasion for further data collection. Participant recruitment and data collection occurred between March 2021 and December 2022.

Data Collection Session

The data collection session was carried out at the Outpatients Department of Mater Dei Hospital. The session consisted of an interview followed by measurement of various clinical parameters and finally phlebotomy. Participants were asked to fast for eight hours prior to their session and to wear comfortable clothing and shoes.

Participant demographics were recorded, and each subject was given a two-digit code for anonymisation purposes. The interview started off with a drug history, followed by a smoking history. Respiratory symptoms were recorded through the St George's Respiratory Questionnaire for COPD patients (SGRQ-C), COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) scores, while the CES-D (Centre for Epidemiological Studies – Depression) scale was utilized to evaluate depressive symptoms, and the FACIT (Functional Assessment of Chronic Illness Therapy). Fatigue scale was utilized to study fatigue, as in the ECLIPSE study.[2] Any respiratory exacerbations (in or outside of hospital) were recorded.

Waist circumference was measured at the uppermost part of the iliac crests after a normal expiration as suggested by the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) criteria[15] to diagnose metabolic syndrome. Blood pressure (BP) measurement was carried out with a manual sphygmomanometer. Height and weight were measured using a stadiometer; thereafter, Body Mass Index (BMI) was calculated in kg/m^2. The six-minute walk test (6MWT) was then performed in order to obtain the six-minute walking distance (6MWD). Fractional exhaled Nitric Oxide (FeNO) was measured, and this was followed by Spirometry. The BODE index was calculated from BMI, spirometry, mMRC scale and 6MWD.

Biochemical Testing

A venous blood sample was then taken and sent to the Pathology Department at Mater Dei Hospital for complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), renal profile, procalcitonin, ferritin, fibrinogen, vitamin D, liver function tests, lipid profile, glycosylated haemoglobin (HbA1c), fasting blood glucose, N-terminal pro brain natriuretic peptide (NT-proBNP) and creatine kinase (CK). The correct order of draw of blood tubes was used, in line with the Clinical and Laboratory Standards Institute recommendations.[16]

Presence of Metabolic Syndrome

The AHA and NHLBI criteria were used to diagnose Metabolic Syndrome.[15] These necessitate at least 3 of these criteria in order to diagnose MetS:

- Waist circumference of at least 102 cm in men or 89 cm in women, measured at the top of the iliac crest at the end of a normal expiration.
- Triglyceride level of at least 1.70 mmol per L, or receiving pharmacologic therapy for elevated triglyceride levels.

- HDL cholesterol level of less than 1.05 mmol per L in men or less than 1.30 mmol per L in women, or receiving pharmacologic therapy for reduced HDL cholesterol levels.
- Systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg, or receiving pharmacologic therapy for hypertension.
- Fasting glucose level of at least 5.6 mmol per L, or receiving pharmacologic therapy for elevated fasting glucose levels.

All patients were diabetic patients and therefore fulfilled the last criterion. The presence of two other criteria therefore was necessary to diagnose the metabolic syndrome. As recommended by AHA and NHLBI, patients receiving an anti-hypertensive agent automatically fulfilled the blood pressure criterion, patients receiving fibrate therapy automatically fulfilled the triglyceride criterion, and patients receiving statin therapy automatically fulfilled the HDL cholesterol criterion.

Presence of Chronic Obstructive Pulmonary Disease

A post-bronchodilator FEV_1/FVC ratio (Forced Expiratory Volume in 1 second over Forced Vital Capacity ratio) of less than 0.7 was necessary to diagnose Chronic Obstructive Pulmonary Disease, as recommended by GOLD guidelines.[17] GOLD group was calculated from mMRC scale and number of exacerbations. Subjects with a smoking history who had a post-bronchodilator FEV_1/FVC ratio of 0.7 or more were deemed not to fulfil the criterion for COPD.

Statistics

Statistical Package for the Social Sciences (SPSS®) Version 29.0.0.0 was utilized for data analysis. In order to check for correlations between the clinical parameters and the biochemical characteristics, the Pearson Correlation Test or the Spearman Correlation Test was used. The normality of the clinical parameter (dependent variable) was first checked using the Shapiro–Wilk test. If the clinical parameter showed a normal distribution (Shapiro–Wilk p-value more than 0.05), then the Pearson Correlation Test was used to correlate the clinical parameter with the blood parameters. If the clinical parameter showed a distribution which was not normal (Shapiro–Wilk p-value less than 0.05), then the Spearman Correlation Test was used to correlate the clinical parameter with the blood parameters. Those blood parameters which, on the basis of the Pearson Correlation Test or the Spearman Correlation Test, showed a p-value of less than 0.05, were deemed to have a significant relationship with the clinical parameter.

Strengths of the Study

This study is the first research project to date on the characteristics of COPD in MetS in Malta. There is also a paucity of international data on this population, and therefore this study is of worldwide interest.

The data collection protocol consists of multiple extensively studied tools, resulting in a robust assessment of each subject. The strict inclusion and exclusion criteria add to the reliability of the study.

Limitations of the Study

One limitation is related to the AHA and NHLBI definition of MetS. The investigator noted that all participants with type 2 diabetes mellitus were found to fulfil the criteria for metabolic syndrome; there were no subjects with DM but not MetS. This is because according to the AHA and NHLBI criteria used to diagnose MetS, patients receiving an anti-hypertensive agent automatically fulfilled the blood pressure criterion, patients receiving fibrate therapy automatically fulfilled the triglyceride criterion, and patients receiving statin therapy automatically fulfilled the HDL cholesterol criterion. Type 2 DM patients are often prescribed a statin irrespective of cholesterol level and may be prescribed Angiotensin Converting Enzyme Inhibitor (ACEI) therapy for proteinuria irrespective of blood pressure; hence, they fulfil three criteria necessary for a diagnosis of MetS even though their HDL cholesterol level and blood pressure may be normal.

A second limitation is related to the GOLD spirometric criterion for COPD. GOLD necessitates a post-bronchodilator FEV_1/FVC ratio of less than 0.7 to diagnose COPD.[17] In the context of obesity, which is a major component of the

metabolic syndrome, the FVC may be lowered, raising the FEV_1/FVC ratio.[18] Therefore, patients who potentially may have been classified as COPD may not fulfil the criterion for COPD simply because they are obese.

A further limitation is the sample population size. This was small due to the strict exclusion criteria. Furthermore, the coronavirus disease 19 (COVID-19) pandemic resulted in difficulties with participant recruitment for the study; eligible participants may not have been willing to attend for the data collection session for fear of contracting the COVID-19 virus whilst at hospital. The small sample population size may limit statistical power. In addition, the convenience sampling method may introduce an element of selection bias. The participants were not followed up to assess for progression; this constitutes another limitation.

The results may be confounded by a number of factors such as age, gender, smoking status, and the use of medication. These confounding factors are a source of potential bias.

Results

Phenotyping of COPD in Metabolic Syndrome

Twenty-four subjects were found to have COPD and MetS. This included 14 males (58.3%) and 10 females (41.7%). The mean age was 67, and the median was 68. About 54.2% (n = 13) were current smokers while 45.8% (n = 11) were ex-smokers.

Table 1 shows the descriptive statistics for SGRQ-C Total Score in the study group, along with the three components of the SGRQ-C. From a maximum of 100 (indicating worst health), the mean SGRQ-C Total Score was 41.7 ± 3.8 (standard error, SE), with a range of 60.5. Of the three components, the Activity Score showed the largest mean value (67.7 ± 4.8 SE from a maximum of 100), followed by the Symptoms Score (53.9 ± 4.0 SE from a maximum of 100). The Impacts Score had the lowest mean, at 21.8 ± 4.0 SE (from a maximum of 100). All three component scores showed a wide range in values.

Table 2 shows the descriptive statistics for mMRC scale and for CAT. The mMRC score ranged from 1 to 4; no subjects had a mMRC of 0. The mean mMRC scale was 2.4 ± 0.3 SE. Of note, 62.5% (n = 15) of subjects had a mMRC score of ≥2 – these are considered as high symptom subjects. From a maximum of 40 (indicating worst health), the mean CAT score was 19.8 ± 1.4 SE. The range for CAT score was 28. Of note, 95.8% (n = 23) of subjects had a CAT score of ≥10.

Table 3 shows the descriptive statistics for CES-D and for FACIT Fatigue scale. The mean CES-D score was 9.2 ± 2.4 SE, from a maximum of 60, with higher scores indicating worse health. The range was 37, and 25.0% (n = 6) of subjects had a CES-D score of ≥16, conferring a risk for clinical depression. From a maximum of 52, the mean FACIT Fatigue score was 40 ± 2.5 SE, with raised scores denoting less fatigue. The range was 41, and 20.8% (n = 5) of subjects had a FACIT Fatigue score of <30, indicating severe fatigue.

Table 4 shows the descriptive statistics for COPD exacerbations and hospitalisations. The mean number of exacerbations over the past year was 0.6 ± 0.2 SE, with half of them resulting in hospitalisation (0.3 ± 0.1 SE). The mean number of exacerbations ever was 1.7 ± 0.3 SE, with more than half resulting in hospitalisation (1.0 ± 0.3 SE). The ranges for exacerbations ever and for hospitalisations ever were both 6.

Table 1 Descriptive Statistics for SGRQ-C

	SGRQ-C Total Score	SGRQ-C Symptoms Score	SGRQ-C Activity Score	SGRQ-C Impacts Score
Mean	41.7	53.9	67.7	21.8
Standard Error of Mean	3.8	4.0	4.8	4.0
Median	33.6	53.8	64.1	14.7
Mode	19.1	65.2	100.0	4.6
Standard Deviation	18.4	19.6	23.5	19.6
Range	60.5	74.2	77.5	62.1

Table 2 Descriptive Statistics for mMRC and CAT

	mMRC	CAT
Mean	2.4	19.8
Standard Error of Mean	0.3	1.4
Median	2.0	19.5
Mode	1.0	16.0
Standard Deviation	1.3	6.7
Range	3.0	28.0

Table 3 Descriptive Statistics for CES-D and FACIT Fatigue Scale

	CES-D	FACIT Fatigue
Mean	9.2	40.0
Standard Error of Mean	2.4	2.5
Median	3.5	46.5
Mode	0	49.0
Standard Deviation	11.9	12.1
Range	37.0	41.0

Table 4 Descriptive Statistics for COPD Exacerbations and Hospitalisations

	COPD Exacerbations Over Past Year	COPD Hospitalisations Over Past Year	COPD Exacerbations Ever	COPD Hospitalisations Ever
Mean	0.6	0.3	1.7	1.0
Standard Error of Mean	0.2	0.1	0.3	0.3
Median	0	0	2.0	1.0
Mode	0	0	0	0
Standard Deviation	0.8	0.6	1.6	1.4
Range	3.0	2.0	6.0	6.0

Table 5 shows the descriptive statistics for the metabolic parameters. The mean waist circumference was 118 cm ± 3.0 SE, with a range of 59 cm. Mean systolic BP (124.6 mmHg ± 3.4) and mean diastolic blood pressure (69.6 mmHg ± 2.0) were within normal limits, though the range was wide for both. Mean BMI was 32.0 kg/m^2 ± 1.3 SE, and therefore in the obese range. Range for BMI was 26 kg/m^2.

Table 6 shows the descriptive statistics for the respiratory tests carried out. While the mean 6MWD was 359 m ± 23.4 SE, the range was 376 m. Of note, one-third of subjects had a 6MWD of less than 350 m – this is associated with increased mortality in COPD. The mean FeNO result was 12.2 ppb ± 2.6 SE, which was well within the normal range (<25 ppb). Two subjects had an intermediate result (25–50 ppb), and one subject had a high result (>50 ppb). The mean FEV_1 was 64.6% ± 3.5 SE, with a range of 54. When divided according to FEV_1, 58.3% of the sample population were GOLD stage 2 subjects, 29.2% were classified as GOLD stage 1, and 12.5% were classified as GOLD stage 3. There were no GOLD stage 4 subjects. From a maximum of 10 points, the mean BODE index was 2.75 ± 0.4 SE, with a range of 6.

Table 5 Descriptive Statistics for Metabolic Parameters

	Waist Circumference (cm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	BMI (kg/m^2)
Mean	118.0	124.6	69.6	32.0
Standard Error of Mean	3.0	3.4	2.0	1.3
Median	113.5	120.0	70.0	31.2
Mode	105.0	120.0	70.0	21.2
Standard Deviation	14.6	16.6	9.7	6.5
Range	59.0	60.0	40.0	26.0

Table 6 Descriptive Statistics for Respiratory Tests

	6MWD (m)	FeNO (ppb)	FEV_1 (%)	BODE
Mean	359.0	12.2	64.6	2.8
Standard Error of Mean	23.4	2.6	3.5	0.4
Median	403.8	9.5	65.5	2.5
Mode	120.0	0.0	83.0	2.0
Standard Deviation	114.4	12.5	17.0	1.8
Range	375.6	53.0	54.0	6.0

Figure 1 shows the distribution according to GOLD group. One-third of patients were classified as Group A, and another third as Group B. Only 8.3% were classified as Group C, while 25% were classified as Group D.

Table 7 shows the descriptive statistics for all blood parameters of subjects with COPD and MetS. This includes blood white cell count (WCC), neutrophil count (Neut), lymphocyte count (Lymph), eosinophil count (Eos), haemoglobin level (Hgb), red cell distribution width (RCDW), platelet count (Plts), mean platelet volume (MPV), creatinine (Cr), erythrocyte

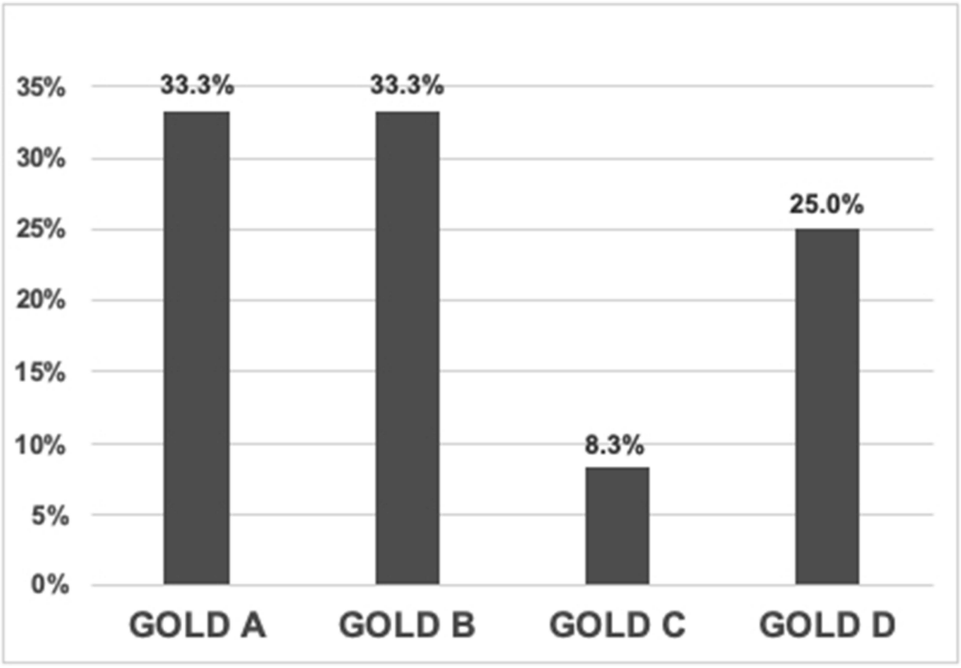

Figure 1 Distribution according to GOLD group.

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Table 7 Descriptive Statistics for Blood Parameters

	WCC	Neut	Lymph	Eos	Hgb	RCDW	Plts	MPV
Mean	9.9	6.1	2.6	0.2	14.0	13.9	282.0	10.9
Standard Error of Mean	0.4	0.4	0.1	0.0	0.4	0.3	12.1	0.3
Median	9.5	6.0	2.6	0.2	14.0	13.7	277.0	10.7
Mode	6.7	5.2	2.1	0.2	13.4	12.1	179.0	9.6
Standard Deviation	2.2	1.8	0.7	0.1	1.7	1.7	59.3	1.2
Range	8.9	7.1	2.7	0.3	6.7	7.2	258.0	5.4
	Cr	**ESR**	**CRP**	**Procal**	**Ferritin**	**Fibrinogen**	**VitD**	**ALP**
Mean	93.0	17.6	8.6	0.1	89.6	3.5	18.1	105.2
Standard Error of Mean	8.2	3.4	3.4	0.0	18.2	0.2	2.2	10.0
Median	83.5	12.5	5.1	0.0	59.9	3.5	18.5	90.0
Mode	75.0	5.0	12.5	0.0	30.0	3.7	0.0	65.0
Standard Deviation	40.0	16.5	16.6	0.0	89.2	0.7	10.7	48.9
Range	184.0	78.0	84.5	0.1	319.0	3.1	44.0	170.0
	Chol	**LDL**	**HDL**	**Triglyc**	**HbA1c**	**Gluc**	**BNP**	**CK**
Mean	4.3	2.1	1.2	2.2	7.9	8.2	565.4	116.7
Standard Error of Mean	0.2	0.2	0.1	0.3	0.2	0.7	352.1	13.5
Median	4.2	2.0	1.2	1.7	7.9	7.4	109.5	103.5
Mode	2.4	2.0	1.2	1.1	9.4	2.7	0	186.0
Standard Deviation	1.0	0.7	0.3	1.4	1.2	3.6	1725.0	66.0
Range	3.4	2.6	1.1	5.8	4.3	14.1	8474.0	258.0

sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (Procal), ferritin, fibrinogen, vitamin D (VitD), alkaline phosphatase (ALP), total cholesterol (Chol), LDL cholesterol (LDL), HDL cholesterol (HDL), triglycerides (Triglyc), haemoglobin A1c (HbA1c), glucose (Gluc), N-terminal pro brain natriuretic peptide (BNP) and creatine kinase (CK).

Biomarkers of COPD in Metabolic Syndrome

The following clinical parameters were found to be normally distributed (Shapiro–Wilk test p-value >0.05): SGRQ-C Symptoms Score, SGRQ-C Activity Score, CAT, FEV_1, BODE index. The Pearson Correlation Test was therefore used to correlate these parameters with the blood parameters.

The following clinical parameters were found to have a distribution that was not normal (Shapiro–Wilk test p-value <0.05): SGRQ-C Total Score, SGRQ-C Impacts Score, mMRC scale, CES-D, FACIT Fatigue Scale, COPD Exacerbations over the past year, COPD Hospitalisations over the past year, COPD Exacerbations ever, COPD Hospitalisations ever, 6MWD, FeNO. The Spearman Correlation Test was therefore used to correlate these parameters with the blood parameters.

Table 8 shows the correlations between biochemical parameters and COPD clinical end-points, which were significant (Pearson or Spearman Correlation Test p-value <0.05). The correlation co-efficient (r) for each significant correlation is included in Table 8. The lymphocyte count was the biochemical parameter, which was associated with most COPD clinical end-points. Specifically, blood lymphocyte count was positively correlated with FACIT Fatigue Scale and 6MWD, and negatively correlated with SGRQ-C Activity Score, COPD Hospitalisations over the past year, COPD Hospitalisations ever, and FeNO. Blood ferritin, triglycerides and glucose were also associated with multiple COPD clinical end-points. Ferritin was negatively correlated with SGRQ-C Symptoms Score, CAT, COPD Hospitalisations ever and BODE index. Triglyceride levels were positively correlated with SGRQ-C Total Score, SGRQ-C Symptoms Score and CAT. Glucose levels were positively correlated with SGRQ-C Total Score, SGRQ-C Activity Score and COPD Hospitalisations ever.

Table 8 Significant Correlations Between Biochemical Parameters and COPD Clinical End-Points

Biochemical Parameter	COPD Clinical End-Point	Correlation	Correlation Co-efficient	Statistical Significance
WCC	SGRQ-C Symptoms Score	Positive	r=0.345	p=0.049
Neut	SGRQ-C Symptoms Score	Positive	r=0.373	p=0.036
Lymph	SGRQ-C Activity Score	Negative	r=–0.438	p=0.016
Lymph	FACIT Fatigue Scale	Positive	r=0.425	p=0.019
Lymph	COPD Hospitalisations over the past year	Negative	r=–0.437	p=0.033
Lymph	COPD Hospitalisations ever	Negative	r=–0.606	p=0.002
Lymph	6MWD	Positive	r=0.424	p=0.039
Lymph	FeNO	Negative	r=–0.448	p=0.028
Eos	CAT	Negative	r=–0.506	p=0.006
Eos	FACIT Fatigue Scale	Positive	r=0.346	p=0.049
RCDW	CAT	Positive	r=0.357	p=0.044
Procal	FeNO	Positive	r=0.411	p=0.046
Ferritin	SGRQ-C Symptoms Score	Negative	r=–0.347	p=0.048
Ferritin	CAT	Negative	r=–0.365	p=0.040
Ferritin	COPD Hospitalisations ever	Negative	r=–0.450	p=0.027
Ferritin	BODE index	Negative	r=–0.418	p=0.042
Fibrinogen	SGRQ-C Symptoms Score	Positive	r=0.457	p=0.012
ALP	6MWD	Negative	r=–0.454	p=0.026
Chol	COPD Exacerbations ever	Negative	r=–0.435	p=0.034
LDL	FACIT Fatigue Scale	Positive	r=0.400	p=0.026
LDL	COPD Exacerbations ever	Negative	r=–0.542	p=0.006
Triglycerides	SGRQ-C Total Score	Positive	r=0.373	p=0.036
Triglycerides	SGRQ-C Symptoms Score	Positive	r=0.372	p=0.037
Triglycerides	CAT	Positive	r=0.396	p=0.028
HbA1c	6MWD	Negative	r=–0.413	p=0.045
Glucose	SGRQ-C Total Score	Positive	r=0.377	p=0.035
Glucose	SGRQ-C Activity Score	Positive	r=0.367	p=0.039
Glucose	COPD Hospitalisations ever	Positive	r=0.636	p=0.001
NT-proBNP	6MWD	Negative	r=–0.578	p=0.003

Discussion

Phenotyping of COPD in Metabolic Syndrome

For the first time, the Maltese diabetic metabolic syndrome population with COPD was studied and a number of characteristics were identified. Most parameters showed a wide range, indicating heterogeneity amongst this group.

While a mean SGRQ-C Total Score of 41.7 resulted from this study, a literature review showed a lack of previous SGRQ-C data in COPD subjects within the MetS population. Whereas the mean Activity Score and the mean Symptoms Score were both relatively high, the Impacts Score was considerably lower. This suggests that although patients were symptomatic and had impairment in activities, they felt that their respiratory condition had a low level of impact on their lives.

The mean mMRC score was 2.4; international data on COPD in MetS are once again lacking. Interestingly, 62.6% were high symptom subjects as suggested by a mMRC score of ≥2. In a recent Indian study which identified MetS in COPD, 89% of COPD + MetS subjects had an mMRC ≥2, however data was collected from COPD patients admitted with an exacerbation and therefore it is likely that they were highly symptomatic.[19]

On the other hand, when using the CAT score, the vast majority of subjects (95.8%) were classified as high symptom subjects (CAT score of ≥10). While GOLD considers CAT ≥10 and mMRC ≥2 to be comparable cut-off scores for high symptom subjects,[17] the percentage of subjects with a CAT ≥10 was much larger than that of subjects having a mMRC ≥2, implying that the two scores may not be equivalent when assessing symptomatology.

One-fourth of subjects were at risk for clinical depression since they had a score of 16 or greater. Data on depression in MetS + COPD is lacking, however both conditions are known to be associated with depression. A systematic review on COPD patients reported a depression prevalence of 30% in COPD.[20] A large Japanese study found a significant association between MetS and antidepressant use, with an adjusted odds ratio of 1.53.[21] The fact that a considerable fraction (25%) of subjects with MetS + COPD are at risk of depression, has multiple implications. Firstly, there is an argument for screening these patients to identify depressive symptoms, and referring for psychiatric treatment – this may lead to an improvement in quality of life. Moreover, the presence of depression in this patient group may lead to increased healthcare burden due to increased medication use, increased outpatient visits, and increased hospitalisations in a mental health institution.

From the study group, 20.8% had a score of less than 30, indicating severe fatigue. Prior prevalence data on fatigue in MetS + COPD is not available. A systematic review of 196 studies showed a fatigue prevalence ranging from 17% to 95% in COPD.[22] The presence of fatigue among subjects with MetS + COPD may lead to time off work and therefore economic consequences for the employer. Fatigue may also reduce household productivity, leading to financial consequences and family conflict.

The results show that more than half of the COPD exacerbations ever resulted in hospitalisation. COPD hospitalisations are known to result in significant morbidity and mortality, as well as high costs for the local health service.[23] It is therefore essential to recognise MetS + COPD subjects who are at risk of exacerbation and to manage them with the appropriate treatment to prevent the exacerbation.

The wide range in 6MWD indicates heterogeneity in exercise tolerance within the study group, with some subjects having a much higher exercise tolerance than others. One-third had a 6MWD of less than 350m, which is associated with increased mortality in COPD. Recognising subjects with MetS + COPD who are at a higher risk of mortality is important because close follow-up and optimal treatment should be ensured particularly in these cases.

While the mean FeNO was found to be 12.2ppb, three subjects (12.5%) had a FeNO level of ≥25ppb. While no previous studies on FeNO were carried out in MetS + COPD, an American study found a prevalence of elevated FeNO ≥25ppb of 13.0% among COPD patients with no asthma history.[24] FeNO has also been shown to be correlated to the presence of MetS since it reflects inflammatory and oxidative stresses, which are key to the pathogenesis of MetS.[25]

The mean FEV_1 was 64.6%, with most subjects being classified as GOLD stage 1 or 2, and therefore having an FEV_1 of above 50%. Of note, there were no subjects with a FEV_1 value of <30%, and therefore no GOLD stage 4 subjects. A 2014 Spanish study showed that COPD subjects who had MetS had a greater FEV_1 than those who did not have MetS.[26] The finding that obese COPD subjects have better lung function than non-obese COPD subjects has been reproduced in other studies.[26] There are multiple explanations for this interesting finding. Firstly, obese subjects report increased dyspnoea compared to non-obese subjects, prompting them to seek medical help sooner, therefore leading to a diagnosis of COPD at an earlier stage.[27] Moreover, since malnutrition has been associated with emphysema, obesity could act as a protective factor.[28] Finally, obesity is associated with lower levels of tobacco exposure since it is known that ex-smokers gain weight when compared to current smokers.[29]

The study group showed a mean BODE index of 2.75. No previous data on BODE index in MetS + COPD is available. The BODE index is known to predict mortality, as well as predict healthcare resource utilisation in COPD.[30] This highlights the importance of calculating the BODE index in subjects with MetS + COPD in order to identify who is most at-risk and therefore optimize management to reduce mortality and reduce costs for the national health service.

The spread amongst all four GOLD groups (A to D) is to be expected due to the heterogeneity in symptoms and exacerbations. While previous data on MetS + COPD is lacking, a large Greek study on COPD showed a comparable distribution, with 18% in Group A, 60% in Group B, 1% in Group C, and 21% in Group D.[31]

The blood parameter data presented in the Results section provide important information on the biochemical nature of COPD in MetS. A wide variation in most blood parameters can be noted, due to the heterogenous nature of the group. Correlations between these blood parameters and COPD clinical characteristics are described in the next section.

Biomarkers of COPD in Metabolic Syndrome

Blood lymphocyte count, ferritin, triglycerides and glucose were significantly associated with multiple respiratory parameters in diabetic MetS subjects with COPD. These blood parameters therefore emerged as biomarkers of COPD in MetS. The authors acknowledge the small sample size and recommend further larger studies to shed more light on these biomarkers. Confounding factors (such as age, gender, smoking status, and medication use) may have also influenced the results.

Lymphocyte Count

The lymphocyte count was found to be the most robust biomarker of COPD in MetS. This was significantly positively correlated with 6MWD and FACIT Fatigue score, and negatively correlated with SGRQ-C Activity score, COPD Hospitalisations over the past year, COPD Hospitalisations ever and FeNO.

High cortisol levels (for example, due to stress) result in low lymphocyte levels through glucocorticoid stimulation of apoptosis of pre-B-cells as they leave bone marrow tissue.[32] In fact, low lymphocyte levels are an indicator of the stress response, and have previously been linked to poor outcomes in several pathologies such as coronary artery disease and heart failure.[33] There is now emerging evidence of such an association within COPD. A 2020 Korean study on COPD showed that low lymphocyte levels were correlated with a low 6MWD as well as a low quality of life.[34] The local study supports these two findings, and adds additional information: low lymphocyte levels are also associated with increased symptoms on the SGRQ-C Activity score and increased past COPD hospitalisations.

Another new finding that emerges from this local study is the inverse relationship between lymphocyte count and FeNO levels. High FeNO levels are connected to eosinophilic bronchial inflammation and are classically due to asthma;[35] however, a systematic review has shown a mild elevation of FeNO in COPD.[36] The mechanism behind the mildly raised FeNO levels in COPD needs to be explored,[36] and the inverse relationship between lymphocytes and FeNO may be important to the pathogenesis.

Ferritin

Ferritin was found to have a negative correlation with SGRQ-C Symptoms Score, CAT, COPD Hospitalisations ever, and BODE index.

Ferritin has a direct anti-inflammatory effect through the induction of anti-inflammatory cytokines and a resultant decrease in free radical damage.[37] Hypoferritinaemia would therefore lead to increased inflammation levels, which would be reflected in increased symptoms, hospitalisations and COPD severity as assessed by BODE index. This has clinical implications: patients with low ferritin levels are at increased risk of COPD complications.

Moreover, since ferritin is a marker of iron stores, the results of the local study signify that iron deficiency is associated with poor respiratory outcomes. Iron deficiency is a frequent finding in COPD, and it may occur in the absence of anaemia.[38] The iron deficiency state in COPD may be due to systemic inflammation[36] as well as nutritional deficiencies.[39] Iron deficiency impacts the production of erythrocytes and respiratory enzymes, and therefore may have important implications in COPD.[39]

The association between iron deficiency and increased morbidity in MetS + COPD has therapeutic implications since iron deficiency can be corrected with iron therapy. Treatment of iron deficiency is of benefit in other chronic pathologies but is poorly studied in COPD.[38,39] A 2020 study has shown that correction of low iron levels in COPD with subcutaneous erythropoiesis stimulating agents and intravenous iron may improve dyspnoea.[40] There may therefore be a role for routine screening and for treatment of iron deficiency in MetS + COPD as an inexpensive yet effective clinical intervention.[41]

Triglycerides

Plasma triglyceride levels were found to be positively correlated with SGRQ-C Total Score, SGRQ-C Symptoms Score, and CAT. Higher symptomatology in the presence of high triglyceride levels has not been previously described in the literature, and it is clinically relevant. A recent meta-analysis revealed that triglyceride levels were raised in COPD when

compared to healthy subjects and advocated the screening of COPD patients for high triglyceride levels in order to reduce cardiovascular complications.[42] In fact, a 2012 study on MetS in COPD showed that from the components of MetS, it is the triglyceride component that is associated with increased mortality in COPD.[43]

Glucose

Plasma glucose levels were positively correlated with SGRQ-C Total Score, SGRQ-C Activity Score and with COPD Hospitalisations ever.

Chronic hyperglycaemia results in the formation of advanced glycation end products (AGEs) which lead to the production of reactive oxygen species, triggering a chronic inflammatory response.[44,45] In fact, AGEs have been implicated in the pathophysiology of COPD.[46] This may explain why high glucose levels were associated with high COPD symptom scores in the local study.

This association has clinical implications, as hyperglycaemia is frequently encountered in clinical practice, and could be reflected in increased COPD symptoms. Moreover, high glucose levels are amenable to treatment, and this raises the question whether improvement in glucose levels results in improvement in COPD symptoms. While the local study emphasizes the importance of regulating glycaemic levels in COPD, more studies are needed to check if correcting high glucose levels results in a decrease in symptomatology.

While the local study showed a positive correlation between plasma glucose levels and COPD hospitalisations ever, a 2022 Iranian study revealed that higher HbA1c levels were linked to increased COPD exacerbations.[47] In fact, a systematic literature review concluded that diabetes may worsen COPD progression due to the consequences of high glucose levels on lung physiology, inflammation and risk of bacterial infection.[48]

Conclusion

The Maltese diabetic MetS population with COPD is heterogenous, showing a wide range in SGRQ-C Total Score, SGRQ-C Symptoms Score, SGRQ-C Activity Score, SGRQ-C Impacts Score, mMRC, CAT, CES-D, FACIT Fatigue, COPD Exacerbations, 6MWD, FEV1, BODE, GOLD Group and in the Blood Parameters. High levels of depression are prevalent in this population, suggesting a role for screening and treating for depression. High levels of fatigue are prevalent in this population, which may have economic consequences.

In the Maltese diabetic population with COPD, the lymphocyte count was the biomarker that was significantly correlated with most COPD clinical characteristics – including 6MWD, FACIT Fatigue, SGRQ-C Activity score, COPD Hospitalisations and FeNO. Hypoferritinaemia is associated with increased morbidity in this population, suggesting a role for screening and treating for iron deficiency. Hypertriglyceridaemia and hyperglycaemia are associated with increased morbidity in this population, highlighting the importance of good lipid and glucose control. These findings may guide future larger-scale longitudinal studies on the field of COPD and MetS.

Abbreviations

6MWD, Six-Minute Walking Distance; 6MWT, Six-Minute Walk Test; ACEI, Angiotensin Converting Enzyme Inhibitor; AGE, Advanced Glycation End product; AHA, American Heart Association;; ALP, Alkaline Phosphatase; BMI, Body Mass Index; BODE, Body mass index, lung Obstruction, Dyspnoea, Exercise capacity; CAT, COPD Assessment Test; CBC, Complete Blood Count; CES-D, Centre for Epidemiological Studies – Depression; Chol, Total Cholesterol; CK, Creatine Kinase; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus Disease 19; Cr, Creatinine; CRP, C-Reactive Protein; DM, Diabetes Mellitus; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; EHES, European Health Examination Survey; Eos, Eosinophil count; ESR, Erythrocyte Sedimentation Rate; FACIT, Functional Assessment of Chronic Illness Therapy; FeNO, Fractional Exhaled Nitric Oxide; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; Gluc, Glucose; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HbA1c, Glycosylated Haemoglobin; HDL, High Density Lipoprotein cholesterol; Hgb, Haemoglobin level; LDL, Low Density Lipoprotein cholesterol; Lymph, Lymphocyte count; MetS, Metabolic Syndrome; mMRC, modified Medical Research Council; MPV, Mean Platelet Volume; Neut, Neutrophil count; NHLBI, National Heart Lung and Blood Institute; NT-proBNP, N-Terminal pro Brain Natriuretic Peptide; PPB, Parts Per Billion;

Plts, Platelets; Procal, Procalcitonin; RCDW, Red Cell Distribution Width; SE, Standard Error; SGRQ-C, St George's Respiratory Questionnaire for COPD patients; SPSS, Statistical Package for the Social Sciences; Triglyc, Triglycerides; VitD, Vitamin D; WCC, White Cell Count.

Disclosure

The authors report no conflicts of interest in this work.

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