How to Cite:
Sunita, S., choudhary, R., Jalil, E., & Rao, M. K. (2022). Diagnosis and management of the metabolic syndrome with pulmonary and liver diseases. *International Journal of Health Sciences*, *6*(S1), 6043–6053. https://doi.org/10.53730/ijhs.v6nS1.6294

Diagnosis and management of the metabolic syndrome with pulmonary and liver diseases

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***Abstract*---**Introduction: The metabolic syndrome is a condition characterized by a cluster of alterations including glucose intolerance/ insulin resistance, abdominal obesity, atherogenic dyslipidemia (low concentrations of high-density lipoprotein-cholesterol and high concentrations of triglycerides), elevated blood pressure, a proinflammatory and a prothrombotic state. It increases morbidity and mortality, especially due to cardiovascular disease. Material and Method: This study has been performed in 90 consecutive patients referred to our metabolic outpatient clinic for suspected metabolic disorders. This study conducted among patients attending at Tertiary care teaching hospital over a period of 1 year. Patients underwent a complete clinico-pathology and biochemical work-up, including a liver ultrasonographic scanning (US), as part of the routine clinical examination. MetS was defined by a combination of abdominal obesity, impaired fasting glucose, atherogenic dyslipidemia, and elevated blood pressure. Results: A total of 90 participants (53 males) were included in the study. The characteristics of the eligible subjects stratified by gender and the presence of metabolic syndrome. The BMI, SBP, DBP, waist circumference was statically significant between male and female (all of the parameters, $p<0.05$). Fasting Blood glucose, Total Cholesterol, Serum triglycerides, CRP, serum uric acid,

and serum total bilirubin statically significant between male and female (all of the parameters, $p<0.05$). Pulmonary function tests, such as FEV1, FEV1 % predicted, FVC, FVC1 % predicted and FEV1/FVC ratio were statically significant among male and female. Conclusion: A link between metabolic syndrome (MetS) and lung diseases has been observed. This syndrome has been identified as an independent risk factor for worsening respiratory symptoms, greater lung function impairment, pulmonary hypertension, and asthma.

***Keywords*---**Metabolic Syndrome, Forced Expiratory Volume, Forced Vital Capacity.

Introduction

The metabolic syndrome is a condition characterized by a cluster of alterations including glucose intolerance/ insulin resistance, abdominal obesity, atherogenic dyslipidemia (low concentrations of high-density lipoprotein-cholesterol and high concentrations of triglycerides), elevated blood pressure, a proinflammatory and a prothrombotic state. It increases morbidity and mortality, especially due to cardiovascular disease. [1]

This relationship between MetS and lung function impairment and asthma risk appears to be robust, as several other studies have yielded similar results. However, the extent to which MetS confounds or modifies the asthma-obesity association remains controversial. [2] In contrast, obesity predicted asthma incidence in women after adjustment for MetS. Given these results, it would be interesting to determine the asthma incidence risk for non-obese women diagnosed with MetS. [3] MetS has also been evaluated as a risk factor for other chronic lung diseases, such as COPD and restrictive lung disease. MetS, and DM, and affirmed that MetS may increase the risk of a COPD exacerbation with associated hyperglycemia, hypertriglyceridemia, and C-reactive protein (CRP) elevation. Hyperglycemia may also be associated with worse outcomes after an exacerbation. [4]

Evidence linking MetS and lung impairment or lung disease, including asthma and COPD, continues to grow, and several mechanisms have been proposed to explain why these associations exist. These include the complex effects of insulin and insulin receptors on the lung and the airways, whose interplay begins early in life given their role for normal lung development. [5] In addition, the effect of insulin on airway smooth muscle (ASM) receptors continues as a highly active area of study. MetS was associated with a greater decline in FEV_1/FVC among subjects with asthma vs those without asthma. Even in healthy subjects without diagnosed DM, abnormalities in glucose metabolism can be associated with lung function decrements. [6]

Metabolic syndrome (MetS) patients with chronic liver disease are at risk of a higher rate of diagnosis of MetS or diabetes mellitus. [7] Recent studies have shown that MetS might have additional associations with liver disease. Liver cancer is the most severe liver disease. Although MetS is known to promote liver

cancer, there is little evidence of whether MetS is associated with cirrhosis, liver failure, liver fibrosis, and death from liver causes. Several studies have described the relationship between MetS and diabetes and liver cancer, but few have investigated the liver-related events. [8]

In summary, abundant epidemiological and clinical evidence exists to support the important link between MetS and pulmonary and lung function impairment, but the exact nature of this relationship remains unknown, and therefore we deserve further investigation.

Material and Methods

This study has been performed in 90 consecutive patients referred to our metabolic outpatient clinic for suspected metabolic disorders. This study conducted among patients attending at Tertiary care teaching hospital over a period of 1 year. Patients underwent a complete clinico- pathology and biochemical work-up, including a liver ultrasonographic scanning (US), as part of the routine clinical examination. After approval from Institutional Ethics Committee for Research at this centre work was initiated.

Inclusion criteria

Either gender above the age of 18 years who fulfilled criteria for Metabolic Syndrome to evaluate pulmonary function test (Spirometry) abnormalities and Liver disease.

Exclusion criteria

The subjects who reported a clinical history on cardiovascular disease (myocardial infarct, angina pectoris) and pulmonary disease (asthma, chronic obstructive pulmonary disease) or cancer, were excluded based on their survey answers. Those with no pulmonary function test results or body measurements (waist circumference, height) were also excluded.

Definition of metabolic syndrome

MetS was defined by a combination of abdominal obesity, impaired fasting glucose, atherogenic dyslipidemia, and elevated blood pressure. Revised NCEP ATP III criteria require at least three of the following components: (1) abdominal obesity (waist circumference [WC] ≥90 cm for men, or ≥85 cm for women); (2) triglycerides ≥150 mg/dL, and/or drug treatment for elevated triglycerides; (3) high-density lipoprotein (HDL)-cholesterol <40 mg/dL for men, or <50 mg/dL for women; (4) systolic blood pressure (BP) ≥130/85 mmHg or antihypertensive medication treatment, and/or a history of hypertension; and (5) FPG ≥100 mg/dL, and/or treatment with medications for T2D.

Measurement of covariates

Height, weight, WC, and BP was measured during regular medical check-ups in accordance of the heath checkups implementation standard. Brachial BP was

measured after 5 minutes of rest in a sitting position. The BP measurement was repeated if the first measurement exceeded 120/80 mm Hg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Serum samples for measuring FPG, total cholesterol (TC), HDL-cholesterol, and triglyceride levels were obtained after overnight fasting before each examination. Detailed histories of smoking status, alcohol consumption, physical activity, and past medical history were obtained using a self-administered questionnaire. Based on smoking status, subjects were classified into non-smokers, ex-smokers, or current smokers. Individuals who consumed ≥30 g of alcohol per day were defined as heavy alcohol drinkers. Physical activity was categorized by the frequency of ≥20 minutes of strenuous exercise. Hospitals conducting health examinations were certified by the NHIS and regularly monitored for quality control.

Pulmonary function test

Spirometry is the most frequently used measure of lung function and is a measure of volume against time. Spirometry and the calculation of FEV1/FVC allows the identification of obstructive or restrictive ventilatory defects. A FEV1/FVC < 70 % where FEV1 is reduced more than FVC signifies an obstructive defect.

Liver histology

Liver biopsies were formalin-fixed, paraffin-embedded, and examined for study using hematoxylin-eosin staining. Pathologists independently diagnosed the biopsy specimens blindly, without knowing the patients' clinical data. Any difference in observations was rectified by consensus. The Kleiner score includes three semi-quantitative parameters, which are added to obtain a score of 0-8 points: steatosis according to the hepatocytes percentage with lipid droplets (grade 0: <5%, 1: 5–33%, 2: 33–66%, and 3: >66%), lobular inflammation measured in foci per field (grade 0: none, 1: <2, 2: 2-4, 3: >4), hepatocytes ballooning (grade 0: none, 1: few cells, 2: many cells). Liver fibrosis was also assessed (grade 1: perisinusoidal or periportal, 1A: mild perisinusoidal fibrosis in zone 3, 1B: moderate perisinusoidal fibrosis in zone 3, 1C: only portal/periportal fibrosis, 2: perisinusoidal fibrosis in zone 3, with portal/periportal fibrosis, 3: fibrosis bridges).

Statistical Analysis

Statistical analysis was performed by using the SPSS statistical software version 25.0 for Windows. Data are expressed as the mean ± SD for continuous variables. Student's *t* tests for unpaired data were used for the comparison of mean values.

Result

A total of 90 participants among them 53 were males and 37 were female included in the study. The age BMI and waist circumference was statically significant between male and female (all of the parameters, $p<0.05$).

Table 1
Characteristics of participants between male and female subjects

Variables	Male (n = 53) Mean±SD	Female (n = 37) Mean±SD	P-value
Age (years)	48.43 ±4.64	39.54 ±4.63	<0.05
BMI (kg/m^2)	34.54 ±5.24	29.54 ±4.74	<0.05
Waist circumference (cm)	109.54 ±11.65	89.43 ±8.36	<0.05

SD, standard deviation; BMI, body mass index

Table 2
Blood pressure of participants between male and female subjects

Blood pressure	Male Mean±SD	Female Mean±SD	P-value
SBP (mmHg)	141.65 ±13.75	136.63 ±13.75	<0.05
DBP (mmHg)	93.43 ±9.64	86.54 ±8.74	<0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure.

The SBP and DBP was statically significant between male and female (all of the parameters, $p<0.05$).

Table 3
Biochemical of participants between male and female subjects

Biochemical Parameters	Male Mean±SD	Female Mean±SD	P-value
Fasting Blood Glucose (mg/dL)	106.63 ±10.54	101.4 ± 8.6	<0.05
Total Cholesterol (mg/dL)	201.3 ± 19.3	189.43 ±18.53	<0.05
Serum Triglycerides (mg/dL)	183.43 ±17.54	172.43 ±16.54	<0.05
HDL-C (mg/dL)	47.43 ±5.43	42.65 ±5.76	<0.05
C-reactive protein (mg/dL)	0.41 ±0.02	0.38 ±0.09	<0.05
Serum uric acid (mg/dL)	5.25 ±0.83	4.65 ±0.74	<0.05
Serum total bilirubin (mg/dL)	0.74 ±0.09	0.45 ±0.10	<0.05

HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

In table 3, Fasting Blood glucose, Total Cholesterol, Serum triglycerides, CRP, serum uric acid, and serum total bilirubin statically significant between male and female (all of the parameters, $p<0.05$).

Table 4
Pulmonary Function test of participants between male and female subjects

PFT	Male Mean±SD	Female Mean±SD	P-value
FEV1 (L)	2.32±0.54	2.13 ±0.46	<0.05
FEV1 % predicted	4.03±0.54	3.46 ±0.65	<0.05
FVC (L)	2.25±0.26	2.14 ±0.26	<0.05
FVC % predicted	5.74±0.46	4.77 ±0.64	<0.05
FEV1/FVC	81.63±8.64	87.43 ±8.64	<0.05

FEV1, forced expiratory volume in 1; FVC, forced vital capacity.
In table 3, pulmonary function tests, such as FEV1, FEV1 % predicted, FVC, FVC1 % predicted and FEV1/FVC ratio were statically significant among male and female.

Table 5
Liver histology according to the presence of metabolic syndrome cases (%)

Liver histology	Male (n = 53) Mean±SD	Female (n = 37) Mean±SD
Fibrosis		
Absent	26 (49.0)	16 (43.2)
Perisinusoidal/pericellular	14 (26.4)	11 (29.7)
Periportal	7 (13.2)	7 (18.9)
Bridging	6 (11.3)	3 (8.1)
Necro-inflammation		
Mild	19 (35.8)	11 (29.7)
Moderate	31 (58.4)	21 (56.7)
Severe	3 (5.6)	5 (13.5)
Fatty infiltration		
Mild	29 (54.7)	23 (62.1)
Moderate	21 (39.6)	12 (32.4)
Severe	3 (5.6)	2 (5.4)

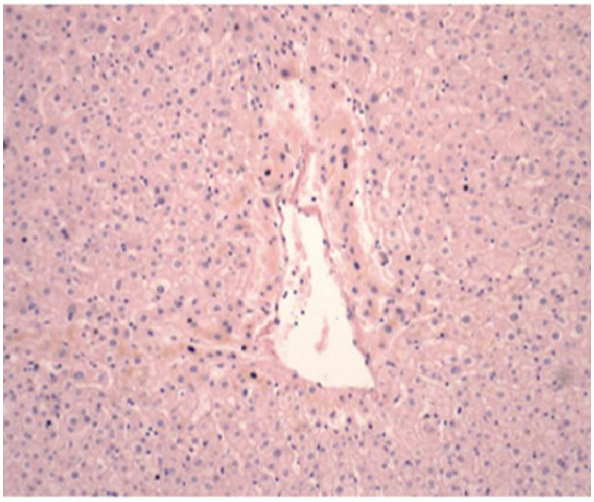

Figure 1: Liver without steatosis

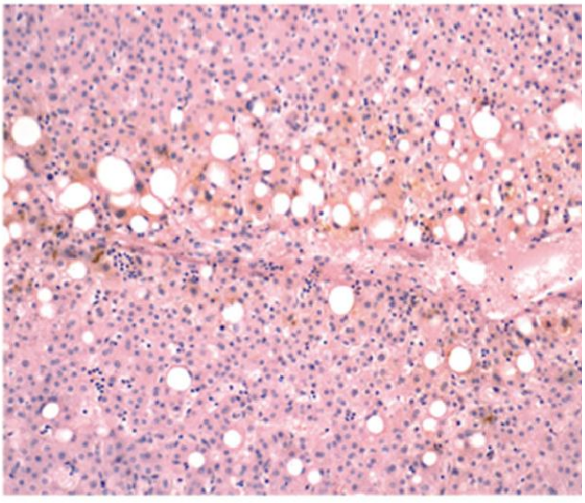

Figure 2: Liver with severe Metabolic associated fatty liver disease

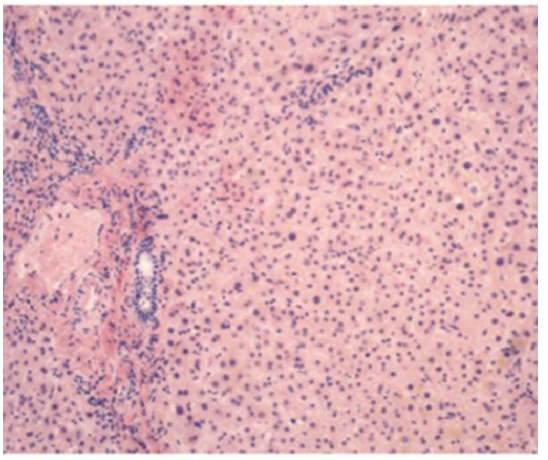

Figure 3: Liver with fibrosis

Management of the Metabolic Syndrome

The primary goal of clinical management in individuals with the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. Even in people with the metabolic syndrome, first-line therapy is directed toward the major risk factors: LDL-C above goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. *First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy.* In addition, metformin, thiazolidinediones, and acarbose will lower risk for type 2 diabetes mellitus in people with IFG or IGT.

Discussion

One of the defining features of MetS is hyperlipidemia, which provides another potential mechanism linking MetS and lung function impairment, due to fatty acid-induced inflammation. Circulating levels of fatty acids are regulated by insulin-stimulated uptake and release of TGs and free fatty acids (FFAs) by adipocytes. [9] However, in MetS, adipose tissue is not able to efficiently regulate fat storage, and excess TGs and FFAs remain in circulation. [10] A lipotoxic state can develop as these FFAs can activate innate immune responses via a plethora of inflammatory mechanisms, such as pattern recognition receptor (PRR) activation, intracellular signaling pathways, and endoplasmic reticulum stress. [11]

Among the MetS components, abdominal obesity has the strongest association with lung function impairment. [12] In adults, chronically elevated insulin levels are associated with reduced lung function in patients with or without a diagnosis of DM. One of the defining features of MetS is hyperlipidemia, which provides another potential mechanism linking MetS and lung function impairment, due to fatty acid-induced inflammation. Circulating levels of fatty acids are regulated by insulin-stimulated uptake and release of TGs and free fatty acids (FFAs) by adipocytes. [13]

However, in MetS, adipose tissue is not able to efficiently regulate fat storage, and excess TGs and FFAs remain in circulation. [14] A lipotoxic state can develop as these FFAs can activate innate immune responses via a plethora of inflammatory mechanisms, such as pattern recognition receptor (PRR) activation, intracellular signaling pathways, and endoplasmic reticulum stress. [15]

Indeed, Liver disease almost doubles the risk of developing metabolic syndrome in the next few years. [16] Liver disease is often combined with metabolic diseases, such as obesity, type 2 diabetes, hyperlipidemia, and hypertension, such comorbidity can lead to a significant increase in the risk of mortality. [17] A key characteristic of Liver disease, highlighting the association of the disease with the metabolic syndrome, is insulin resistance, which may have several mechanisms of development. [18] Insulin resistance not only mediates further impairment of metabolic parameters, but may also increase inflammation in non-alcoholic steatohepatitis (NASH), as evidenced by the frequently more severe histopathological changes in the liver in patients with type 2 diabetes. [19] Histological differences in Liver disease in obese and non-obese patients are minimal and consist of a lower degree of steatosis in people with Liver disease without obesity and a higher degree of fibrosis in Liver disease without obesity. [20]

It has been shown that individuals with Liver disease demonstrate a high risk of coronary atherosclerosis, regardless of the presence or absence of obesity. [21] There is evidence that patients with Liver disease and underweight may have a higher risk of developing diabetes and cardiovascular diseases than overweight people without Liver disease. [22] It is believed that an important place in the pathophysiology of Liver disease is occupied by systemic and hepatic insulin resistance, de novo lipogenesis, disorders in the structure of the intestinal microbiota, local and systemic inflammation, and oxidative stress. [23]

Conclusion

Each MetS component contributes to lung disease. It is unclear whether treating MetS will reduce its effects on the respiratory system. Despite this uncertainty, optimally treating each component of MetS is a sensible way to minimize the risk of respiratory comorbidity. Our findings highlight the FVC and FEV1 are inversely associated with the accumulation of metabolic syndrome components and also independently associated with each component of metabolic syndrome. Therefore, this relationship might receive more attention and even urge action to be taken on metabolic components in the context of poor pulmonary function. The presence of metabolic alterations has a severe and multifaceted impact on the liver, and is responsible for a higher risk of liver-dependent and -independent mortality. Knowledge on the epidemiology, pathophysiology and diagnosis of both Liver diseases and metabolic syndrome and the findings that strongly support the association of non-alcoholic fatty liver disease as a possible component in the cluster of metabolic syndrome.

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