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Serum Bilirubin Levels in Patients with COPD during Acute Exacerbation

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Authors' contributions

This work was carried out in collaboration between all authors. Author AAO designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors RMEB and AAESM managed the analyses of the study. Author MAAH managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The Aim of the Work: To study the relationship between levels of serum bilirubin in patients with chronic obstructive pulmonary disease (COPD) during an exacerbation.

Patients and Methods: One hundred fifty (150) patients, including 117 males and 33 females, participated in the study. All patients had been diagnosed with COPD and were experiencing exacerbation; they were admitted to the chest medicine department at Benha University Hospital in Egypt. A full medical history was taken from all patients, and all were given both general and local examinations. The hospital took standard chest x-rays, both posteroanterior (PA) and lateral views. Body mass index (BMI), pulmonary function tests (spirometry) before and after bronchodilation, electrocardiography, a complete blood count, liver function tests, kidney function tests, and fasting blood sugar were also completed. The study excluded patients with any disease that might elevate serum bilirubin, such as hepatic diseases, inflammatory bowel diseases, end-stage renal disease,

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diabetes mellitus, hypertension, ischemic heart disease, arthritis, cerebral vascular diseases, and any systemic infection or inflammation that could be associated with an increase in the bilirubin level. Also, patients were excluded if they had tuberculosis, bronchiectasis, malignancy, or connective tissue disorders.

Results: The levels of serum total and indirect bilirubin were high in COPD patients with acute exacerbation. Significant negative correlation was observed between serum total and indirect bilirubin levels with the following: the pre-bronchodilator ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC); the pre-bronchodilator FEV₁ %, and the forced expiratory flow 25–75 % (FEF_{25–75} %). Non-significant negative correlation was observed between serum total bilirubin levels and the smoking index.

Conclusion: A patient's bilirubin level may be a helpful indicator of COPD exacerbation, and a COPD patient may receive a beneficial effect from some levels of hyperbilirubinemia.

Keywords: COPD exacerbation; serum bilirubin; ventilatory function tests; smoking index.

1. INTRODUCTION

The prevalence and burden of COPD are projected to increase in the coming decade due to the combination of exposure to COPD risk factors and the changing age structure of the world's population. More people are living longer and are reaching the age at which COPD normally develops [1]. Bilirubin is a metabolite of the heme proteins, mainly hemoglobin. It is excreted into the small intestine in bile from the liver. The site of the catabolism of hemoglobin is the reticuloendothelial system (RES). Bilirubin is then released into the blood stream, where it binds tightly to albumin and is conjugated with glucuronic acid to form bilirubin mono- and diglucuronide, which are water-soluble metabolisms of direct bilirubin. Elevation of total serum bilirubin may occur due to excessive hemolysis or destruction of the red blood cells, as occurring in hemolytic diseases [2]. Oxidant/antioxidant imbalance has been implicated in the pathogenesis of chronic obstructive pulmonary disease. Exogenous oxidants contained in cigarette smoke form a major risk factor for COPD and are produced by the inflammatory cells that characterize the pathology of COPD. Oxidative stress induces a cascade of signaling mechanisms that activate transcription factors leading up to regulation of gene coding for pro-inflammatory and anti-inflammatory cytokines, enzyme heme oxygenase, and inducible nitric oxide [3]. It has been suggested that catalyzing the degeneration of heme to biliverdin (which is then reduced to bilirubin-producing free ions and carbon monoxide) would have an important antioxidant capacity and significance in protecting lung cells against oxidant exposure. Heme oxygenase was demonstrated to be induced by a variety of injurious stimuli, including reactive oxygen

species (ROS). Chronic smokers exhibit increased expression of heme oxygenase in their alveolar spaces, which has a very important role in the pathogenesis of COPD [4].

1.1 Aim of the Work

To study the relationship between serum bilirubin levels and chronic obstructive pulmonary disease patients during an exacerbation.

2. PATIENTS AND METHODS

This study included 150 patients, with 117 males and 33 females with acute exacerbation of COPD. The patients were admitted to the chest medicine department at Benha University Hospital between November 2010 and February 2013. A full medical history was taken for all patients, including a smoking history. Each patient was given a clinical examination. The hospital computed body mass index (BMI) for each patient; performed a radiological examination with standard chest x-rays of both posteroanterior and lateral views; administered electrocardiography; took a complete blood count; conducted liver function tests, including serum total, direct, and indirect bilirubin level measurements; and completed kidney function tests, fasting blood sugar, ventilatory function tests (spirometry) before and after bronchodilation using the Sensor Medics Vmax series, 2130 spirometer, V6200 Autobox, 6200DL.

Inclusion Criteria

1. COPD patients in acute exacerbations
2. Post-bronchodilator FEV₁/FVC < 70% and reversibility < 12% (confirming the diagnosis of COPD)

Exclusion Criteria

1. Patients were excluded if they had any disease that might result in the elevation of serum bilirubin.
 - Cardiovascular comorbidities like hypertension, ischemic heart diseases, and cerebrovascular diseases
 - Hemolytic disorders
 - Diabetes mellitus
 - Inflammatory bowel diseases
 - Arthritis
 - Hepatic cirrhosis
 - End-stage renal disease
 - Any systemic infection or inflammation that could be associated with increased bilirubin level
2. Patients were also excluded if they had tuberculosis, bronchiectasis, malignancy, or connective tissue disorders.

Statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM) and SAS, version 9.2 (SAS Institute, Inc.).

3. RESULTS

The demographic data of the studied patients: the number of patients was 150 (117 male and 33 female); the mean age (in years) was 49.12 ± 10.17 ; the mean BMI was 27.67 ± 6.48 Kg/m²; the mean smoking index was 481.4 ± 311.3 ; the mean total bilirubin level was 1.32 ± 0.73 mg/dl; the mean direct bilirubin level was 0.37 ± 0.22 mg/dl; and the mean indirect bilirubin level was 0.69 ± 0.26 mg/dl. These results revealed a higher level of total and indirect bilirubin in COPD patients with acute exacerbation.

4. DISCUSSION

The current study was done to assess a possible relationship between serum bilirubin levels in patients with chronic obstructive pulmonary disease (COPD) during exacerbation. The demographic data of the studied patients included the following: the number of patients was 150 (117 male and 33 female); the mean BMI was 27.67 ± 6.48 Kg/m²; the mean smoking index was 481.4 ± 311.3 cigarettes/year; the mean total bilirubin level was 1.32 ± 0.73 mg/dl; the mean direct bilirubin level was 0.37 ± 0.22 mg/dl; and the mean indirect bilirubin level was 0.69 ± 0.26 mg/dl. These results revealed higher levels of total and indirect bilirubin in COPD

patients with acute exacerbation. This result is in alignment with a cohort study among 504,206 adults from the UK primary care research database. In the health improvement network, with serum bilirubin levels recorded with no evidence of hepatobiliary or hemolytic diseases, relatively higher levels of bilirubin were associated with a lower risk of respiratory diseases, including COPD and lung cancer. [2] The present study revealed a significant negative correlation between serum total and indirect bilirubin levels with pre-bronchodilator FEV₁/FVC %, pre-bronchodilator FEV₁ % and FEF₂₅₋₇₅ %. These results mean serum total and indirect bilirubin increased with the decrease of FEV₁/FVC %, Pre-bronchodilator FEV₁ % and FEF₂₅₋₇₅ % during COPD exacerbation. These results are in agreement with Jama et al., 2011. The Jama study concluded that beneficial effects of elevated serum bilirubin—within a specified range—have been observed on respiratory health. Higher bilirubin concentrations were associated with a lower incidence of lung cancer, chronic obstructive lung disease, and lung cancer mortality, as well as height-standardized lung function in previous population-based studies. These results suggest that bilirubin might have protective effects in tissues exposed to the external environment, such as the lungs, possibly by counteracting subclinical inflammation [5]. A cohort study done by Ivan et al., 2013 [6], concluded that elevated serum bilirubin was associated with improvement of FEV₁/FVC and FEF₂₅₋₇₅ in the general population (this study was done with a Swiss general population numbering 4195). The significant associations with FEF₂₅₋₇₅ % and FEV₁/FVC might point to an inverse relationship with small airway obstruction. Due to their large surface area, small airways are an important compartment of chronic respiratory disease development [7,8]. We can currently only speculate about the mechanisms by which serum bilirubin might influence lung function. Intracellular mechanisms may be more important in the lung than the known effects in serum and blood vessels, because bilirubin penetrates cell walls at physiological pH values [9]. Besides scavenging oxidants, bilirubin inhibits membrane-bound nicotinamide adenine dinucleotide phosphate-oxidase, one of the major intracellular sources of reactive oxygen species [10]. Furthermore, bilirubin infusions have been shown to down-regulate inflammation in murine lung injury models [11]. Oxidative stress in COPD is generated by both endogenously-produced oxidants and exogenous sources such as

cigarette smoke. Oxidants induce damage to proteins, DNA, and lipid. Animal studies have revealed that bilirubin has a greater affinity for preventing oxidation of lipids than proteins [12], and inhibition of bilirubin synthesis results in significant increases in lipid peroxidation products [13]. Within human lungs, lipid peroxidation causes damage to multiple cell membrane components and impairs cell structure and permeability [14]. Patients with COPD have higher levels of lipid peroxidation products in sputum [15], and the serum levels of these products are higher in patients with severe airflow limitation, compared with those with moderate limitation. Thus, bilirubin may protect the COPD lung by inhibiting lipid peroxidation [16]. COPD is also associated with oxidative stress despite smoking cessation [17], and this persistent inflammation may overwhelm the capacity of biliverdin reductase to recycle oxidized bilirubin, resulting in lower serum bilirubin in those with higher levels of oxidative stress—regardless of smoking status. Smoking has also been associated with lower serum bilirubin and may further deplete bilirubin, resulting in borderline significance when this relationship is adjusted for smoking status [17].

Table 1. Demographic data of studied patients, showing number, age, sex, body mass index, smoking index, and serum bilirubin (total, direct, and indirect)

Item	Result
Number	150 patients
Age/year	mean ±SD: 49.12±10.17 range (R) :38 – 75
Sex	Male :117 Female:33
BMI (Kg/m ²)	mean ±SD : 27.67±6.48 R:19.57 - 45.27
Smoking index (number of cigarettes/day X number of years)	mean ±SD : 481.4±311.3 R:140-1500
Total bilirubin (mg/dl)	mean ±SD : 1.32±0.73 R:0.76-1.98
Direct bilirubin (mg/dl)	mean ±SD : 0.37±0.22 R: 0.1-0.95
Indirect bilirubin (mg/dl)	mean ±SD : 0.69±0.26 R: 0.18-1.4

The study revealed, non-significant negative correlation between serum total bilirubin and the

smoking index (P-value > 0.05). Jama et al., 2011, also identified an inverse association between bilirubin and smoking intensity that was not statistically significant in the European cohort [5]. This finding can possibly be explained by the fact that bilirubin in human plasma appears to be depleted on exposure to reactive oxidative species, such as those found in cigarette smoke [5]. Thus, passive smoking or cigarette type (such as unfiltered) could have slightly confounded the results, but this seems unlikely given that adjusting for smoking intensity and duration had almost no effect on the associations [18].

Table 2. Correlation between pre-bronchodilator FEV₁/FVC % and serum total bilirubin

	R	P- value
Pre-FEV ₁ /FVC %	- 0.39	< 0.001

Significant negative correlation between serum total bilirubin levels with pre-bronchodilator FEV₁/FVC, in which serum total bilirubin increased with the decrease of pre-bronchodilator FEV₁/FVC

Table 3. Correlation between Pre-bronchodilator FEV₁/FVC % and indirect bilirubin

	R	P- value
Pre-FEV ₁ /FVC %	- 0.22	< 0.05

Significant negative correlation between serum indirect bilirubin levels with pre-bronchodilator FEV₁/FVC %, in which serum indirect bilirubin increased with the decrease of pre-bronchodilator FEV₁/FVC %

Table 4. Correlation between pre-bronchodilator FEV₁ (% pred.) with serum total bilirubin

	R	P- value
Pre- FEV ₁ (% pred.)	- 0.78	< 0.001

Significant negative correlation between serum total bilirubin with pre-bronchodilator FEV₁ (% pred.), in which serum total bilirubin increased with the decrease of pre-bronchodilator FEV₁ (% pred.)

Table 5. Correlation between pre-bronchodilator FEV₁ (% pred.) with serum indirect bilirubin

	R	P- value
Pre-FEV ₁ %	- 0.55	< 0.001

Significant negative correlation between serum indirect bilirubin with pre-bronchodilator FEV₁ (% pred.), in which serum indirect bilirubin increased with the decrease of pre-bronchodilator FEV₁ (% pred.)

Table 6. Correlation between FEF25-75 % predicted with serum total bilirubin

	R	P- value
FEF25-75 %	- 0.34	< 0.001

Significant negative correlation between serum total bilirubin with FEF₂₅₋₇₅ % predicted in which serum total bilirubin increased with the decrease of FEF25-75%

Table 7. Correlation between FEF25-75 % predicted with serum indirect bilirubin

	R	P- value
FEF25-75 %	-0. 17	< 0.05

Significant negative correlation between serum indirect bilirubin with FEF₂₅₋₇₅ % predicted in which serum indirect bilirubin increased with the decrease of FEF25-75%

Table 8. Correlation between serum total bilirubin and the smoking index

	R	P- value
Smoking index	- 2.1	> 0.05

Non-significant negative correlation between serum total bilirubin and the smoking index in which serum total bilirubin slightly increased with the decrease of smoking index

5. CONCLUSION AND RECOMMENDATIONS

This study supports the hypothesis that bilirubin has a protective effect on COPD, possibly through its anti-oxidant actions. Bilirubin may prove useful as an easily accessible and readily available blood-based COPD biomarker. Further research studies are needed to investigate the causal association between bilirubin level and COPD patient outcomes, to facilitate a better understanding of the mechanisms that might lead to the use of a targeted clinical COPD treatment that mildly suppresses some enzymatic activity and increases bilirubin level.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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