

## **Original Research Article**

### **SERUM BILIRUBIN LEVEL IN PATIENTS WITH COPD DURING ACUTE EXACERBATION**

#### **Abstract**

**Aim of the work:** To study the relationship between serum bilirubin level in patients with chronic obstructive pulmonary disease during exacerbation.

**Patients and Methods:** Forty patients (37) males and (3) females patients with

COPD during exacerbation were admitted to chest department, Benha university hospital were included in this study. All patients were submitted to full history taking general and local examination, plain chest x-ray (P.A. and lateral views), Body mass index, Pulmonary function tests (spirometry) before and after bronchodilatation, Electrocardiography, complete blood count, liver function tests, kidney function tests and fasting blood sugar. excluded patients with any disease that may result in elevation of Serum bilirubin like, hepatic diseases, inflammatory bowel diseases, end-stage renal disease, diabetes mellitus, hypertension, ischemic heart, arthritis, cerebral vascular diseases and any systemic infection or inflammation that could be associated with increased bilirubin level. Also patients were excluded if they had tuberculosis, bronchiectasis and malignancy.

**Results:** The level of serum total and indirect bilirubin levels were high in COPD patients with acute exacerbation. Significant negative correlation between serum total and indirect bilirubin with pre- bronchodilator FEV<sub>1</sub>/FVC%, Pre- bronchodilator FEV<sub>1</sub> % and FEF<sub>25-75</sub> %. Non significant negative correlation between serum total bilirubin and smoking index.

**Conclusion:** The bilirubin may be a helpful indicator in COPD exacerbation and the patient may get useful effect with hyper bilirubinemia.

**Key words:** COPD exacerbation, Serum bilirubin, respiratory function tests, smoking index.

## **Introduction**

The prevalence and burden of COPD are projected to increase in coming decade due to combined exposure to COPD risk factors and changing age structure of world's population with more people living longer, and thus reaching the age at which COPD normally developed (1). Bilirubin is metabolite of the haem proteins, mainly hemoglobin. It is excreted into the intestine and bile from the liver. The site of the catabolism of haemoglobin is the reticuloendothelial system (RES) bilirubin is then released into the blood stream where it's bind tightly to albumin and is conjugated to the acid to form bilirubin mono and diglucuronide that are water soluble metabolism or direct bilirubin. Elevation of total serum bilirubin may occur due to excessive hemolysis or destruction of the red blood cells e.g. hemolytic diseases (2). Oxidant/antioxidant imbalance has been implicated in the pathogenesis of chronic obstructive pulmonary disease. Exogenous oxidant are contained in cigarette smoke the 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 mechanism which activate transcription factors leading to up regulation of gene coding for pro-inflammatory and anti inflammatory cytokines and enzyme haem oxygenase and inducible nitric oxide (3). Catalyse the degeneration of haem to bilivirdin which is then reduced to bilirubin producing free ions and carbon monoxide has been suggested to have important antioxidant capacity and significance in protecting lung cells against oxidant exposure. Hemeoxygenase was demonstrated to be induced by variety of injurious stimuli including reactive oxygen species (ROS). Chronic smokers exhibit increased expression of heamoxygenase in their alveolar spaces that have a very important role in the pathogenesis of COPD (4).

## **Aim of the work**

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

### **Patients and Methods**

This study was included 40 patients (37) males and (3) females with acute exacerbation of COPD, were admitted in chest department Benha university hospital between November 2010 and Feb 2012 .All subjects were submitted to full history taking (including smoking history) and clinical examination, body mass index (BMI),radiological examination (plain CXR postero-anterior and lateral views), Electrocardiography, complete blood count, liver function tests including serum total, direct and indirect bilirubin level measurement, kidney function tests , fasting blood sugar, ventilatory function tests (spirometry) before and after bronchodilatation by using Sensor-medics V max series, 2130 spirometer, V6200 Autobox, 6200DL .

#### **Inclusion criteria:**

1-COPD patients were in acute exacerbations.

2-Post-bronchodilator FEV1/FVC < 70% and reversibility is <12% (confirming the diagnosis of COPD).

#### **Exclusion criteria:**

1- Any disease that may result in elevation of Serum bilirubin .

- Cardiovascular co- morbidities like hypertension, ischemic heart diseases and cerebro-vascular 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 presentation and analysis of the present study was conducted, using the mean, standard deviation, analysis of variance [ANOVA] test and chi-square test by SPSSV(5).

### Results

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

| Item                              | Result                                                 |
|-----------------------------------|--------------------------------------------------------|
| Number                            | 40 patients                                            |
| Age/year                          | mean $\pm$ SD : 54.04 $\pm$ 9.59<br>range (R) :41 – 79 |
| Sex                               | Male :37<br>Female:3                                   |
| BMI ( Kg/m <sup>2</sup> )         | mean $\pm$ SD : 27.67 $\pm$ 6.48<br>R:19.57 - 45.27    |
| Smoking index (cigarette / year ) | mean $\pm$ SD : 481.4 $\pm$ 311.3<br>R:140-1500        |
| Total bilirubin ( mg/dl )         | mean $\pm$ SD : 1.32 $\pm$ 0.73<br>R:0.76-1.98         |
| Direct bilirubin (mg/dl)          | mean $\pm$ SD : 0.37 $\pm$ 0.22<br>R: 0.1-0.95         |
| Indirect bilirubin ( mg/dl)       | mean $\pm$ SD : 0.69 $\pm$ 0.26<br>R: 0.18-1.4         |

The demographic data of the studied patients included, the number of the patients was 40 (37 male and 3 female), the mean BMI was 27.67 $\pm$ 6.48 Kg/m<sup>2</sup>, the mean smoking index 481.4  $\pm$  311.3, the mean total bilirubin 1.32 $\pm$ 0. 73 mg/dl, the mean direct bilirubin 0.37 $\pm$ 0.22 mg/dl and the mean indirect bilirubin 0.69 $\pm$ 0.26 mg/dl. These results revealed higher level of total and indirect bilirubin in COPD patient with acute exacerbation.

(2): Correlation between pre- bronchodilator FEV<sub>1</sub>/FVC % and serum total bilirubin.

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

Significant negative correlation between serum total bilirubin with pre- bronchodilator FEV<sub>1</sub>/FVC% ,in which serum total bilirubin increased with decrease of pre- bronchodilator FEV<sub>1</sub>/FVC% .

Table (3): Correlation between Pre- bronchodilator FEV<sub>1</sub>/FVC % and indirect bilirubin.

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

Significant negative correlation between serum indirect bilirubin with pre- bronchodilator FEV<sub>1</sub>/FVC% ,in which serum indirect bilirubin increased with decrease of pre- bronchodilator FEV<sub>1</sub>/FVC% .

Table (4): Correlation between pre-bronchodilator FEV<sub>1</sub> (% pred.) with serum total bilirubin.

|                                 | R      | P- value |
|---------------------------------|--------|----------|
| Pre- FEV <sub>1</sub> (% pred.) | - 0.78 | < 0.001  |

Significant negative correlation between serum total bilirubin with pre-bronchodilator FEV<sub>1</sub> (% pred.) ,in which serum total bilirubin increased with decrease of pre-bronchodilator FEV<sub>1</sub> (% pred.) .

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

|                        | R      | P- value |
|------------------------|--------|----------|
| Pre-FEV <sub>1</sub> % | - 0.55 | < 0.001  |

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

Table (6): Correlation between FEF<sub>25-75</sub>% predicted with serum total bilirubin.

|                        | R      | P- value |
|------------------------|--------|----------|
| FEF <sub>25-75</sub> % | - 0.34 | < 0.001  |

Significant negative correlation between serum total bilirubin with FEF<sub>25-75</sub>% predicted in which serum total bilirubin increased with decrease of FEF<sub>25-75</sub> %.

Table (7): Correlation between FEF<sub>25-75</sub> % predicted with serum indirect bilirubin.

|                        | R      | P- value |
|------------------------|--------|----------|
| FEF <sub>25-75</sub> % | - 0.17 | < 0.05   |

Significant negative correlation between serum indirect bilirubin with FEF<sub>25-75</sub>% predicted in which serum indirect bilirubin increased with decrease of FEF<sub>25-75</sub> %.

Table (8): Correlation between serum bilirubin and smoking index .

|               | R     | P- value |
|---------------|-------|----------|
| Smoking index | - 2.1 | > 0.05   |

Non significant negative correlation between serum total bilirubin and smoking index

### Discussion

The current study was done to assess the relationship between serum bilirubin level in patients with chronic obstructive pulmonary disease during exacerbation, the demographic data of the studied patients included, the number of the patients was 40 (37 male and 3 female), the mean BMI was  $27.67 \pm 6.48$  Kg/m<sup>2</sup>, the mean smoking index was  $481.4 \pm 311.3$  cigarette / year, the mean total bilirubin was  $1.32 \pm 0.73$  mg/dl, the mean direct bilirubin was  $0.37 \pm 0.22$  mg/dl and the mean indirect bilirubin was  $0.69 \pm 0.26$  mg/dl. These results revealed higher level of total and indirect bilirubin in COPD patient with acute exacerbation. This result in agreement with cohort study among 504206 adult from the UK primary care research database (the health improvement network with serum bilirubin level recorded with no evidence of hepatopillay or heamolytic diseases they recorded that, relatively higher levels of bilirubin were associated with a lower risk of respiratory disease including COPD and lung cancer. (2).The present study revealed significant negative correlation between serum total and indirect bilirubin with pre- bronchodilator FEV<sub>1</sub>/FVC% , Pre-bronchodilator FEV<sub>1</sub> % and FEF<sub>25-75</sub> %. These results mean serum total and indirect bilirubin increased with decrease of FEV<sub>1</sub>/FVC% , Pre- bronchodilator FEV<sub>1</sub> % and FEF<sub>25-75</sub> % during COPD exacerbation. These results in agreement with Jama etal. 2011. They concluded that, beneficial effects of elevated serum bilirubin-within the range- have been observed on respiratory health. Higher bilirubin concentrations were associated with lower incidence of lung cancer, chronic obstructive lung disease and lung cancer mortality, as well as height-standardized lung function previous population-based studies. These results suggest that bilirubin might have protective effects in tissues exposed to the outer environment, such as the lungs, possibly by counteracting subclinical inflammation(6). A cohort study done by Ivan et al. 2013 concluded that ,elevated serum bilirubin was associated with improvement of FEV<sub>1</sub>/FVC and FEF<sub>25-75</sub> in general

population this study was done over Swiss general populations(number = 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 (8, 9). 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, as bilirubin penetrates cell walls at physiological pH values (10). Besides scavenging oxidants, bilirubin inhibits membrane-bound nicotinamide adenine dinucleotide phosphate-oxidase, one of the major intracellular sources of reactive oxygen species (11). Furthermore, bilirubin infusions have been shown to down-regulate inflammation in murine lung injury models (12). 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 lipids also, Animal studies have revealed that bilirubin has a greater affinity in preventing oxidation of lipids than proteins, (13) and inhibition of bilirubin synthesis results in significant increases in lipid peroxidation products(14) Within human lungs, lipid peroxidation causes damage to multiple cell membrane components and impairs cell structure and permeability(15) Patients with COPD have higher levels of lipid peroxidation products in sputum, (16) and 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 (17). COPD is also associated with oxidative stress despite smoking cessation, (18) 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 was adjusted for smoking status(18).

The study revealed, non significant negative correlation between serum total bilirubin and 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 (6). This finding can be explained by, Bilirubin in human plasma appears to be depleted on exposure to reactive oxidative species such as those found in cigarette smoke, which could explain these findings (6) Thus, passive smoking or cigarette type (e.g. 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 (19).

### **Conclusion and recommendations**

This study support the hypothesis that bilirubin has a protective effect on COPD disease, possibly through its anti-oxidant actions. Bilirubin may prove useful as an easily accessible and readily available **blood-based** COPD biomarker. Further researches are needed to investigate the causal association between bilirubin level and COPD patients outcomes **for the better understanding of the mechanisms leading** to the potential use of targeted clinical treatment that mildly suppressing some enzymatic activity and increase bilirubin level.

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