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Sex impact in Oxidative Stress in Sera of Patients with Chronic obstructive pulmonary disease (COPD)

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ABSTRACT: The present study is designed to Study the effect of sex on the levels of Malondialdehyde (MDA), Ceruloplasmin (Cp), Vitamin (D3) ,Ferritin and High Sensitivity C Reactive Protein (CRP) in patients with Chronic obstructive pulmonary disease (COPD) and healthy individuals.

Subjects: Serum MDA, Cp ,D3, Ferritinand CRPwere measured in (80COPDand 80supposed healthy subjects) sex (40 Male , 40 Female).

Results: The study resulted in a significant increase in MDA, CP, Ferritin, and h-CRP levels in females with COPD compared to healthy females($P \leq 0.05$), and a significant decrease (vitamin D3) levels in the same group($P \leq 0.05$). Significant increase in MDA, CP, Ferritin, and h-CRP levels($P \leq 0.05$) in males with COPD compared to healthy controls, and decreased vitamin D3 levels in the same group.Significant increase in (MDA) and (CP) levels($P \leq 0.05$) in infected females compared to males in the group with COPD. Significant increase in Ferritin , h-CRP levels ($P \leq 0.05$) in males with COPD compared with females with COPD. While there is no difference between males and females with COPD in terms of Vit D3 levels.

Conclusion: There was effect of sex on the studied parameters .Also, there are effects of the disease state on the studied variables.

Keywords: Chronic obstructive pulmonary disease, Malondialdehyde , Ceruloplasmin , Vitamin D3 , Ferritin and High Sensitivity C Reactive Protein .

INTRODUCTION:

The term chronic bronchitis began to be used in the year 1808. [1]While it is believed that the term chronic obstructive pulmonary disease was first used in 1965.[2] It was previously known by a number of different names including: chronic obstructive pulmonary disease, chronic airflow obstruction, chronic lack of airflow, chronic non-specific pulmonary disease, and diffuse obstructive pulmonary syndrome. to describe a lung that did not Officially, the terms "chronic

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bronchitis" and "emphysema" were defined in 1959 at a seminar hosted by Novartis, and in 1962 during a meeting of the Diagnostic Criteria Committee of the American Thoracic Society.[2] In 1814 Charles Badham used the term "catarrh" to describe coughing and excess mucus in chronic bronchitis. René Lennac, the physician who invented the stethoscope, used the term "emphysema" in his book A Treatise on Chest Diseases and Direct Auscultation (1837)collapse when the chest was opened during an autopsy.

He indicated that she did not collapse as usual because it was full of air and the bronchi were filled with mucus. In 1842, John Hutchinson invented the spirometer, which made it possible to measure the vital capacity of the lungs. However, this meter can only measure the volume of air, not its flow, In 1947Tiffinho and Binelli described principles for measuring airflow.[2] Long-term respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) are common, with reported worldwide prevalence rates of almost 5% for both. COPD is associated with high morbidity and high rates of hospital admissions, and is the third leading non-communicable disease cause of death worldwide.

While asthma and COPD are controllable with pharmacological and non-pharmacological treatment strategies, they are not curable.[3] Chronic bronchitis was defined as cough and sputum production occurring on most days of the month for at least 3 mo a year during the 2 yr prior to the study. Fixed airway obstruction was defined as a FEV1 less than 80% predict.[4] In the coming decades, chronic obstructive pulmonary disease (COPD) is expected to occur with increasing frequency, resulting in enormous healthcare expenditures and high mortality. Thus, COPD presents a challenge for clinicians and is a leading public health problem worldwide . However, COPD is almost invariably associated with other chronic conditions and is thus an important component of the epidemy of multimorbidity (due to ageing, smoking, indoor and outdoor pollution, alcohol, inactivity and other risk factors) that affects elderly patients .[5]

Design of study: This study conducted at AL-Hussein Educational Hospital in Al-MuthannaIraq in Biochemistry Laboratory at the period between 1/11/2020 to 1/4/2021.The study included (160) subjects, control (80) and patients (80).The study has been conducted on a total number of supposedly healthy individuals and patients :-

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COPDgroup :80 patients with Systolic COPD [40 males and 40 females] .

control group : control group, consists of 80 supposed healthy subjects [40 males and 40 females] with no history of systematic illness .

Blood Collection :

samples were collected about (10mL) of blood samples of COPD patients and controls were taken and allowed to clot at room temperature in empty disposable tubes centrifuge to separate it in the centrifuge at 3000 rotor per minute (rpm)for 10min,the serum samples were separated and stored at (-20ºC) for later measurement of biochemical parameters, unless used immediately.

Methods:

Lipid peroxidation Marker (Serum MDA): MDA concentrations were calculated, using the molar extinction coefficient of MDA (ε_{MDA})equal to 1.56 x105 mol^{-1}. cm^{-1}[6].

Serum Cp:
concentration was measured by the method of [7] which using the extinction coefficient of Cp (ε Cp) equal (0.68) to calculate it concentration

Serum VIt D3

All reagents and specimens must be allowed to come to room temperature before use. All reagents must be GENTLY mixed without foaming. Once the procedure has started, all steps should be completed without interruption [8]

Serum Ferritin

The e411 assay uses two monoclonal mouse antibodies to form the sandwich complex in the assay. Total duration of assay: 18 minutes as [9]

Serum High Sensitivity C Reactive Protein

Prior to assay, allow reagents to stand at room temperature (18-25°C).

Gently mix all reagents before use[10].

Statistical Analysis: Used in statistical analysis was done using Microsoft Excel 2010,the results were expressed as mean ± standard deviations (mean ± SD). Tow way ANOVA-test was used to

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compare parameters in different studied groups. P-values ($P \leq 0.05$) were considered statistically significant.

RESULTS:

The study resulted in a significant increase in MDA, CP, Ferritin, and h-CRP levels in females with COPD compared to healthy females($P \leq 0.05$), and a significant decrease (vitamin D3) levels in the same group($P \leq 0.05$). Significant increase in MDA, CP, Ferritin, and h-CRP levels($P \leq 0.05$) in males with COPD compared to healthy controls, and decreased vitamin D3 levels in the same group.Significant increase in (MDA) and (CP) levels($P \leq 0.05$) in infected females compared to males in the group with COPD. Significant increase in Ferritin , h-CRP levels ($P \leq 0.05$) in males with COPD compared with females with COPD. While there is no difference between males and females with COPD in terms of Vit D3 levels. .

Table1 :- Serum MDA ,Cp,VitD3,Ferritin and CRP concentrations of all sex groups

Parameters / Groups	MDA	Cp	Vit.D3	Ferritin	hs-CRP
F-CON	2.57 ± 0.44^{c}	4.84 ± 0.84^{b}	69.34 ± 11.74^{a}	61.17 ± 4.66^{c}	3.20 ± 0.89^{c}
F-COPD	4.04 ± 0.93^{a}	5.68 ± 1.32^{a}	15.75 ± 1.48^{b}	192.26 ± 55.33^{b}	7.53 ± 1.94^{b}
M-CON	2.52 ± 0.58^{c}	3.36 ± 1.04^{c}	71.87 ± 12.33^{a}	73.76 ± 13.79^{c}	3.67 ± 0.78^{c}
M-COPD	3.15 ± 0.95^{b}	5.22 ± 1.49^{ab}	18.37 ± 4.11^{b}	220.40 ± 53.09^{a}	8.44 ± 1.65^{a}
L.S.D	0.39	0.44	3.23	14.36	0.51

Each value represents mean ± SD values with non-identical superscript
(a , b or c … etc.) were considered significantly differences ($p \leq 0.05$).
HF: Patients with Heart Failure group.
LSD : Low significantly differences .

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Chart:- Serum MDA ,Cp and CRP concentrations of all sex groups

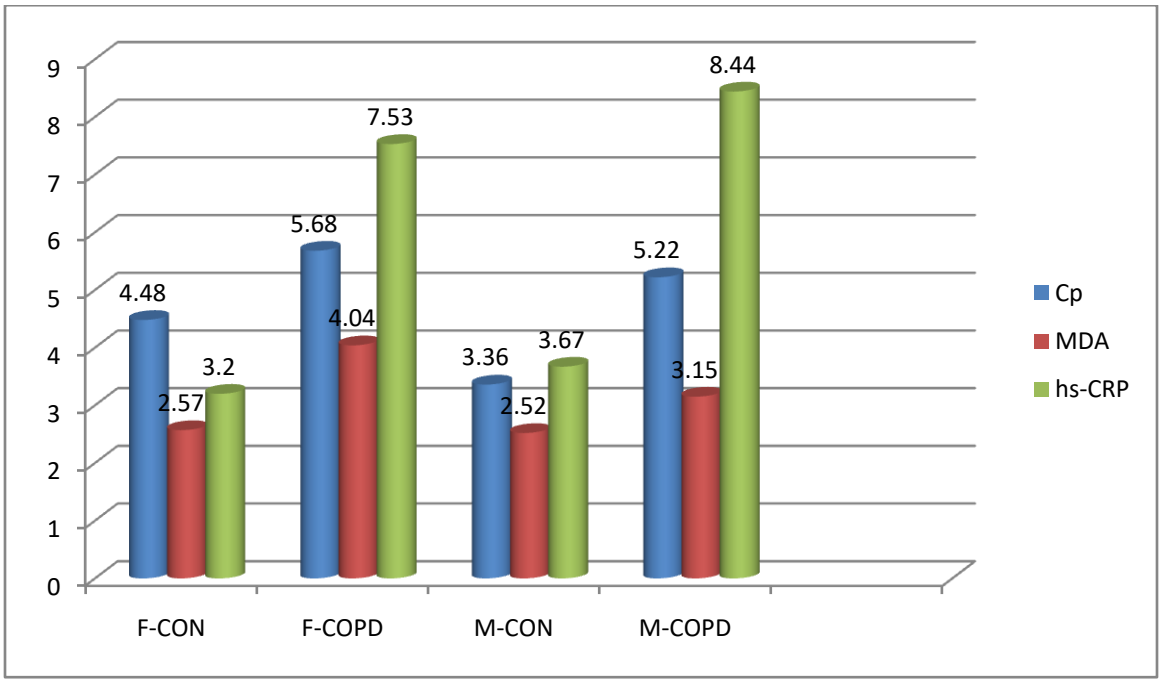
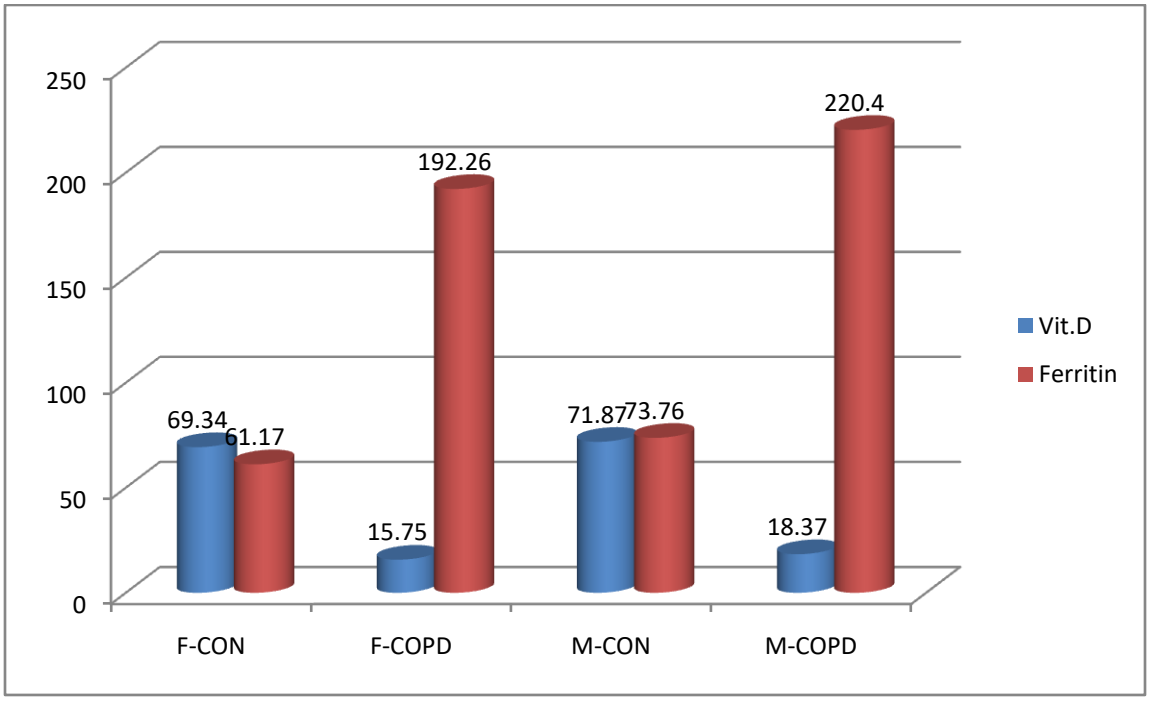


Chart:- SerumVitD3 and Ferritin concentrations of all sex groups



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DISSCUSSION: Oxidative stress is as disorder in equilibrium between (ROS) ,free radicals (FRs) ,and endogenous antioxidant defence mechanisms [11] The oxidative stress caused by the oxidant–antioxidant imbalance leads to inactivation of ant proteinases, inducing airspace epithelial inflammatory injury, increased influx of neutrophils into the lungs, mucus hyper secretion and transcription of prionflammatory factors [12]. For this reason, oxidative stress is believed to play a central role in the pathogenesis of COPD.

Oxidative stress in COPD patients involves the abnormal production of reactive oxygen species and reactive nitrogen species, which directly or indirectly damage several intracellular components, such as nucleic acids, proteins and lipids. In physiological conditions, the phospholipids of cell membranes are hydrolyzed by phospholipase-producing nonesterified arachidonic acid that undergoes peroxidation either through an enzymatic pathway (COXs and lipoxygenases), or through nonenzymatic mechanisms involving reactive oxygen species, reactive nitrogen species, transition metals and other free radicals[13].

The peroxidation of polyunsaturated fatty acids results in their transformation into lipid hydroperoxides, which subsequently interact with enzymatic or nonenzymatic antioxidants or decompose after reacting with metal ions or iron-containing proteins, forming hydrocarbon gases, unsaturated aldehydes (including MDA) and F_2-isoprostanes as by-products[14]. The hydrocarbon ethane, another by-product of these reactions, has been found to be increased in COPD patients, and negatively correlates with pulmonary function, suggesting that lipid peroxidation plays a relevant role in the pathogenesis of COPD [15].

Ceruloplasmin, the major serum inhibitor of lipid peroxidation has been documented as a main extracellular antioxidant in serum and plays a role in preventing lung injury, and an abnormality in its oxidative inhibition could be involved in pathogenesis of COPD. [16] The lung which is continuously exposed to endogenous or exogenous oxidants [17] is protected against oxidative challenge by well-developed antioxidant systems. Increased oxidative stress not only produces direct injurious effects in the lungs, but also activates the molecular mechanisms that initiate lung inflammation [18] and may have a role in many of the processes thought to be involved in the complex pathological events that results in COPD.

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Oxidative stress is one of the major patho-physiologic hallmarks in the development of COPD. Ceruloplasmin, the major serum inhibitor of lipid peroxidation [19] has been documented as a main extracellular antioxidant in serum [20], inhibiting ferrous ion stimulated lipid peroxidation and is known to be involved in the decomposition of lipid peroxides [21]. Ceruloplasmin protects protease inhibitor from oxidative inactivation [22]. It has been reported that ceruloplasmin activity play a role in preventing lung injury and an abnormality of ceruloplasmin oxidative inhibition could be involved in the pathogenesis of COPD [22].

Gc-globulin has two different biological functions in relation to inflammation, both of which could be involved in the development of COPD. First, Gc-globulin has been shown to interact directly with neutrophils to increase their chemotactic rates to the C5a peptide produced during the activation of the complement cascade[23]Second, Gc-globulin is known to undergo conversion to a potent macrophage activating factor (MAF) .

Because current hypotheses suggest that neutrophils and macrophages damage the lung by the release of toxic free radicals and proteases, variability among Gc-globulin isoforms, with respect to these functions, could play a part in determining the degree of damage to the lung parenchyma.[24] VitD deficiency could result in altered host defense of the lung with subsequent growth of an abnormal flora that triggers inflammation.

Acute exacerbations of COPD are an important cause of hospitalization and lead to a faster decline in FEV_1 [25]. Exacerbations are triggered by viruses, bacteria, atypical strains, or a combination of these [26].Tissue Alveolar macrophages are iron- and ferritin-rich in smokers and COPD patients, but both lung epithelial and endothelial cells are also potential sources. As previously mentioned, mainstream cigarette smoke contains little iron[27] We hypothesize that iron accumulates as a biological response to continuous smoke exposure. Specifically, smoke exposure leads to altered responses to hypoxia, higher erythropoietin (EPO) levels[28] This may in turn lead to changes in iron uptake and release in macrophages globally, including in the lung, to increase iron availability for hemoglobin synthesis[29]

High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker that shows an inflammatory reaction and tissue damage, [30].Its production is stimulated by inflammatory cytokines, Interleukin-6 (IL6) and α-Tumor Necrosis Factor. The hs-CRP plays important role in eliciting

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the inflammatory processes [31]C-reactive protein (CRP) is an acute-phase protein synthesised predominantly by the hepatocytes in response to tissue damage or inflammation. It reflects the total systemic burden of inflammation of individuals[32] and has been shown to be increased in COPD in stable condition[33] and during exacerbations[34].

It is also a predictor of hospitalisation and mortality in patients with chronic respiratory failure[35] . CRP is higher in patients with poor forced expiratory volume in one second (FEV1) and in those who smoke [36]. Finally, elevated levels of CRP seem to predict cardiovascular risk in patients with COPD [37] and can decrease with inhaled and systemic corticosteroids [38], oral statin therapy [39] and exercise [40].

Conclusions: There was effect of sex on the studied parameters . There was effect of Pathological case on the studied parameters.

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