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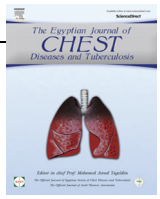

Prevalence of concealed and overt chronic renal failure in patients with COPD

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KEYWORDS

COPD;
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Abstract *Aim:* To assess the prevalence of chronic renal failure (concealed and overt) in patients with COPD.

Patients and methods: This study was conducted on 150 patients who were classified into three groups: Group I: 67 patients with COPD, Group II: 33 COPD patients with co morbidities (diabetes mellitus, hypertension and or ischemic heart disease). Group III: (control group): 50 patients with other diseases such as diabetes mellitus, ischemic heart disease and or hypertension. All patients were subjected to: (1) Full history taking. (2) Complete clinical examination. (3) Anthropometric measurements (weight, height and body mass index). (4) Arterial oxygen saturation. (5) Radiological examination (Plain chest X-ray posterior–anterior view and Pelvi-abdominal ultrasound). (6) ECG and Echocardiography. (7) Spirometry. (8) Laboratory investigations (complete blood picture, erythrocyte sedimentation rate, Liver function tests, serum creatinine, blood urea and uric acid and GFR, total cholesterol, sodium, potassium and chloride concentration).

Results: In group I, there were 8 patients who had CRF (11.94%), 5 patients had overt CRF (7.46%) and 3 patients had concealed CRF (4.48%). In group II, there were 11 patients with CRF (33.33%), 6 patients had overt CRF (18.18%) and 5 patients had concealed CRF (15.15%). In group III, there were 9 patients having CRF (18%), 6 patients had overt CRF (12%) and 3patients had concealed CRF (6%). In COPD (group I and II) the overall prevalence of CRF was 19%.

Conclusion: CRF either concealed or overt may be associated with COPD patients and should be screened, not only by serum creatinine level but also by the estimated GFR to recognize the cases of concealed CRF who have low GFR despite normal serum creatinine level.

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Introduction

COPD is associated with several comorbidities. But it is unknown to which extent it is associated with chronic renal failure [1]. Coronary artery disease, which is highly prevalent in patients with COPD, is associated with vascular kidney disease [2]. Furthermore, both nicotine and selected heavy metals, which are components of smoke, are risk factors for kidney disease. Thus, COPD is expected to be significantly associated with chronic renal failure [3]. Chronic renal failure rises in prevalence with age, and is frequently associated with chronic diseases, such as congestive heart failure and diabetes mellitus. When chronic renal failure presents as comorbidity, it carries negative prognostic implication and impacts the therapeutic strategy [4]. In elderly patients, who are the majority of those suffering from chronic disabling conditions, chronic renal failure is often associated with normal serum creatinine concentration, a condition known as unrecognized or concealed chronic renal failure [5]. In fact, a variable, yet consistent, proportion of patients with COPD have a reduced muscular mass and thus, serum creatinine might be falsely low as the result of decreased creatine release [6]

Aim of the work

The aim of this work was to assess the prevalence of concealed and overt chronic renal failure in patients with COPD.

Subjects and methods

This case control cross sectional study was conducted on 150 patients who were attendant in Benha University Hospitals chest and internal medicine outpatient clinics during the period from October 2013 to April 2015. They were classified into three groups: Group I: 67 patients with COPD. Group II: 33 COPD patients with co morbidities such as diabetes mellitus, hypertension and or ischemic heart disease. All COPD patients were diagnosed according to criteria of GOLD [7]. Group III: (control group): 50 patients with other chronic diseases as diabetes mellitus, ischemic heart disease and or hypertension, all of them were lifelong nonsmokers; they had no symptoms or signs suggestive of any chest diseases.

Exclusion criteria: Patients with diagnosis of cancer, regardless of disease activity, abnormal chest radiography other than that of COPD, Known immune deficiency state as aplastic anemia, leukemia and multiple myeloma, use of drugs which may affect serum creatinine levels or renal function test as ACEI, cyclosporine and chemotherapy drugs (cisplatin, carboplatin, methotrexate and mitomycin), patients with acute or chronic renal failure and on dialysis.

All patients were subjected to the following: (1) Full history taking including history of smoking (2) Complete clinical examination with special attention to manifestations of hyperinflation in the COPD group (increase the antero-posterior diameter, use of accessory muscles of respiration and distant heart sounds). (3) Anthropometric measurements (weight (kg), Height (m), BMI = Wt (kg\Ht (m^2) (4) Arterial oxygen saturation. (5) Radiological examination (Plain chest X-ray posterior-anterior view and Pelvi-abdominal ultrasound). (6) ECG and Echocardiography. (7) Spirometry: by using an automated flow-sensing spirometer (spirolab III Ver 4.3 SN 311860 (Italy)) all COPD patients included in the study performed prebronchodilator and postbronchodilator spirometry according to American Thoracic Society (ATS) criteria [8]. Separate measurements were made before and at least 15 min after two puffs of Salbutamol (200 mg) administered with a metered dose inhaler. Irreversible airway obstruction was defined as a postbronchodilator FEV1/FVC < 0.7 and postbronchodilator change in $FEV_1 < 12\%$ and FEV1 was used to further stage the disease: mild (GOLD stage I, FEV_1 predicted $\geqslant 80\%$), moderate (GOLD stage II, $50\% \leqslant FEV_1$ predicted $< 80\%$), severe (GOLD stage III, $30\% \leqslant FEV_1$ predicted $< 50\%$) and very severe (GOLD stage IV, FEV_1 predicted $< 30\%$ or $30\% \leqslant FEV_1$ predicted $< 50\%$ in the presence of corpulmonale or respiratory failure) [7]. (8) Laboratory investigations: Blood samples were taken for the following investigations:-Complete blood picture -Erythrocyte sedimentation rate (ESR). -Liver function tests: SGPT, SGOT, serum total protein and albumin concentrations. -Kidney function tests: serum creatinine, blood urea -Total cholesterol. -Sodium, potassium and chloride concentration.

9- The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study Group equation:

$$170 \times [\text{serum creatinine}]^{-0.999} \times [\text{age}]^{-0.176} \times [\text{blood urea}]^{-0.170} \times [\text{serum albumin}]^{0.318} \times (0.762 \text{ for women}) \times (1.180 \text{ for African-American subjects}).$$ [9]

Patients were categorized according to their renal function as having normal renal function (GFR $\geqslant 60$ mL/min/1.73 m^2), concealed CRF (normal serum creatinine and GFR < 60 mL/min/1.73 m^2), or overt CRF (increased serum creatinine and GFR < 60 mL/min/1.73 m^2). The cutoff used for serum creatinine was 1.26 mg/dL in men and 1.04 mg/dL in women [9].

Statistical analysis

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 16 to obtain: (1) Descriptive statistics were calculated for the data in the form of:- Mean and standard deviation for quantitative data, Frequency and distribution for qualitative data. (2) Analytical statistics: In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:- Student's *t*-test and Mann–Whitney test:- Used to compare mean of two groups of quantitative data of parametric and non-parametric respectively. Inter-group comparison of categorical data was performed by using chi square test (X2-value) and fisher exact test (FET). Degree of significance: p value < 0.05 was considered statistically significant (S), p value > 0.05 was considered statistically insignificant, p value < 0.01 was considered highly significant (HS) in all analyses.

Results: (Tables 1–8)

Distribution of the studied groups was shown in Table 1.

Group I included 67 patients, 53males (79.1%) and 14 females (20.9%), group II included 33 patients, 22 males

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Table 1 Distribution of the studied groups.

Group	Associated disease					
	None	DM	HTN	IHD	Combined	Total
Group I (COPD only)	67 (100%)	0 (0.0%)	0 (.0%)	0 (0.0%)	0 (0.0%)	67 (100%)
Group II (COPD with comorbidities)	0 (0.0%)	21 (63.64%)	5 (15.15%)	0 (0.0%)	7 (21.21%)	33 (100%)
Group III (control)	0 (0.0%)	8 (16%)	0 (0.0%)	4 (8%)	38 (76%)	50 (100%)
Total	67 (44.67%)	29 (19.33%)	5 (3.33%)	4 (2.67%)	45 (30%)	150 (100%)

Table 2 Comparison between the studied groups regarding the demographic data.

Variable	Group I	Group II	Group III	*T* test		
				P1	P2	P3
Sex						
Male	53 (79.1%)	22 (66.7%)	36 (72.0%)	0.177	0.0373	0.604
Female	14 (20.9%)	11 (33.3%)	14 (28.0%)			
Age (years)						
Mean ± SD	56.13 ± 9.77	54.85 ± 10.49	58.92 ± 8.47	0.547	0.109	0.055
(Range)	(44–68)	(44–62)	(45–67)			
BMI						
Mean ± SD	22.19 ± 2.81	22.61 ± 3.45	22.43 ± 4.11	0.52	0.711	0.837
(Range)	(17.75–33.33)	(17.8–34.0)	(16.0–38.0)			
Duration of disease(years)						
Mean ± SD	9.1 ± 6.77	15.48 ± 9.91	–	0.001	–	–
(Range)	(2–30)	(2–40)				
Smoking index						
Mean ± SD	505.97 ± 166.97	591.56 ± 222.64	–	0.039	0.001	0.001
(Range)	(150–1000)	(200–1000)				

P1 between group I and group II, P2 between group I and group III, P3 between group II and group III.

(66.7%) and 11 females (33.3%), group III included 50 patients, 36 males (72%) and 14 females (28%) (Table 2). In group I the age ranged from 44 to 68 years with a mean age of 56.13 ± 9.77, in group II it ranged from 44 to 62 years with a mean age of 54.85 ± 10.49, in group III it ranged from 45 to 67 years with a mean age of 58.92 ± 8.47 (Table 2). Regarding the laboratory data, there was a statistically significant difference between group I and II regarding Sao2 as it was lower in group II (94.52 ± 1.72) compared to group I (95.69 ± 2.0 and group III (95.48 ± 0.95) (Table 3).

Regarding hemoglobin concentration, there was a high statistically significant difference between group I and III and between group II and III as it was lower in group III (Table 3). There was a statistically significant difference between group II and III as regards serum urea level as it was higher in group II (Table 3).

Comparing CRP level in the three groups, it was higher in group II than group I and the difference was statistically significant ($p < 0.05$). CRP was also very high in group I and II compared to group III (15.55 ± 4.22, 17.45 ± 5.07, 4.94 ± 3.61 respectively) and the difference was statistically highly significant ($p < 0.001$) (Table 3). There was a statistically significant difference between group I and II as regards GFR as it was lower in group II ($p < 0.05$) (Table 3). Regarding the pulmonary function, there is no statistically significant difference between group I and II as regards pulmonary function parameters (Table 4). Regarding COPD severity most of cases had severe disease (56.71% in group I and 54.54% in group II) (Table 5). The overall prevalence of CRF was 18.7% (28/150). In COPD (group I and II), it was 19% (19/100), while in the control group (group III), it was 18% (9/50) (Table 6). In group I: 8 patients had CRF (11.94%), 5 patients of them had overt CRF (7.46%) and 3 patients had concealed CRF (4.48%). In group II: 11 patients had CRF (33.33%), 6patients of them had overt CRF (18.18%) and 5patients had concealed CRF (15.15). In group III: 9 patients had CRF (18%), 6 patients had overt CRF (12%) and 3patients had concealed CRF (6%) (Table 7).

There was a statistically significant difference between cases with and without renal failure regarding hemoglobin concentrations it was lower in cases with renal failure (Table 8). There was also a statistically significant difference between cases with and without renal failure regarding Sao2 as it was lower in cases with renal failure; there were also an increase in age, urea, total cholesterol and potassium in cases with renal failure (Table 8).

There was a statistically significant increase in the incidence of renal failure in cases with severe and very severe COPD than cases with moderate severity; there was also significant increase in smoking index in cases with renal failure (Table 8).

Discussion

Chronic renal failure (CRF) rises in prevalence with age and is frequently associated with chronic diseases such as congestive heart failure and diabetes mellitus. When present as co mor-

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Table 3 Comparison between the studied groups regarding the laboratory data.

Variable	Group I	Group II	Group III	*T* test		
				P1	P2	P3
Hb concentration(gm/dl)						
Mean ± SD	12.64 ± 1.31	12.83 ± 1.25	11.1 ± 1.24	0.50	0.001	0.001
(Range)	10–15.1	11–15.1	9–14			
SAo2						
Mean ± SD	95.69 ± 2.0	94.52 ± 1.72	95.48 ± 0.95	0.005	0.501	0.001
(Range)	(90–98)	(92–98)	(94–97)			
ESR(mm/h)						
Mean ± SD	35.15 ± 30.29	44.55 ± 29.85	34.88 ± 21.73	0.146	0.957	0.092
(Range)	(5–155)	(5–130)	(5–125)			
Total protein(gm/dl)						
Mean ± SD	7.07 ± 0.27	6.97 ± 0.37	7.04 ± 0.26	0.134	0.596	0.298
(Range)	(6.7–8)	(6–8)	(6.5–8)			
S. albumin(gm/dl)						
Mean ± SD	3.46 ± 0.47	3.58 ± 0.42	3.60 ± 0.54	0.195	0.14	0.906
(Range)	(2.3–5.0)	(2.7–4.5)	(2.8–5.0)			
Creatinine(mg/dl)						
Mean ± SD	1.11 ± 0.36	1.24 ± 0.40	1.11 ± 0.41	0.112	0.96	0.177
(Range)	(0.6–2.6)	(0.6–2.2)	(0.6–2.4)			
Urea(mg/dl)						
Mean ± SD	43.57 ± 30.35	52.3 ± 31.79	40.48 ± 20.89	0.186	0.538	0.044
(Range)	(15–199)	(20–167)	(20–100)			
Total cholesterol(mg/dl)						
Mean ± SD	129.9 ± 17.91	149.94 ± 28.16	124.8 ± 14.74	0.001	0.104	0.001
(Range)	(90–188)	(111–230)	(100–190)			
CRP(mg/L)						
Mean ± SD	15.55 ± 4.22	17.45 ± 5.07	4.94 ± 3.61	0.05	0.001	0.001
(Range)	(5–32)	(12–30)	(1–18)			
Sodium(mEq/L)						
Mean ± SD	137.24 ± 5.43	138.46 ± 6.77	135.46 ± 3.93	0.335	0.051	0.012
(Range)	(121–148)	(126–160)	(124–149)			
Potassium(mEq/L)						
Mean ± SD	4.03 ± 0.71	4.31 ± 0.58	4.1 ± 0.59	0.05	0.563	0.112
(Range)	(3.0–5.5)	(3.1–5.6)	(3.0–5.0)			
Chloride(mEq/L)						
Mean ± SD	99.36 ± 2.61	99.55 ± 2.2	99.78 ± 2.87	0.724	0.409	0.691
(Range)	(94–105)	(95–103)	(95–105)			
GFR						
Mean ± SD	88.64 ± 24.98	76.48 ± 27.77	84.85 ± 25.87	0.03	0.426	0.165
(Range)	(25.8–130.8)	(32.7–130.8)	(30.5–129)			

P1 between group I and group II, P2 between group I and group III, P3 between group II and group III.

bidity, CRF carries negative prognostic implications and impacts the therapeutic strategy [10]. It is unknown to which extent COPD is associated with CRF and the relationship between renal failure and COPD is largely undescribed. A proportion of patients with COPD have a reduced muscular mass, and thus, serum creatinine might be falsely low as the result of decreased creatine release [11]. In the present study, there was no statistically significant difference between the 3 studied groups regarding BMI (Table 2). This result wasn't in accordance with Elmahallawy and Qora, who studied the prevalence of CRF in COPD patients, their study included 300 COPD patients and 300 controls with other diseases, in their study BMI was significantly increased in the control than in COPD group [12], as weight loss can be frequently found in COPD patients and is considered to be part of the commonly prevalent non pulmonary sequel of the disease [13]. The difference in results between the present and the former study can be explained by the different distribution of the control groups. Regarding duration of disease, there was a statistically significant difference between group I and II as it was longer in group II. This result was in accordance with Elsawy, who studied the prevalence of chronic renal failure in COPD patients; her study measured the GFR for 527 subjects (327 COPD patients and 200 diabetic patients) using the Modification of

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Table 4 Comparison between group I and II regarding pulmonary functions.

Pulmonary functions	Group I	Group II	St *t* test	*p* value
FEV1% (mean ± SD) Range	36.07 ± 7.47 (18–51)	37.27 ± 7.8 (17–55)	0.743	0.459
FEV1/FVC% (mean ± SD) Range	63.87 ± 6.27 (44–60)	63.15 ± 11.27 (45–65)	0.407	0.685
Post bronchodilator FEV1 change%(mean ± SD) Range	3.73 ± 2.95 0–11%	3.82 ± 3.15 0–9%	0.135	0.893

Table 5 Comparison between group I and II regarding COPD severity.

Degree of severity	Group I	Group II	FET	*p* value
Moderate	11 (16.41)%	9 (27.8)%	1.39	0.514
Severe	3 8 (56.71)%	18 (54.54)%		
Very severe	18 (26.9)%	6 (18.2)%		

Table 6 Distribution of the studied groups regarding the presence of renal failure.

RF	Group		
	Group I and II	Group III	Total
Present	19 (19%)	9 (18%)	28 (18.7%)
Absent	81 (81%)	41 (82%)	22 (81.3%)
Total	100 (100%)	50 (100%)	150 (100%)

Diet in Renal Diseases (MDRD) study group equation; in her study, disease duration was significantly increased in COPD with either HTN or DM than those with COPD only (*p* 0.000) [14]. As regards smoking index, there was a statistically significant difference between group I and II as it was higher in group II and between group I and III as it was higher in group I and between group II and III as it was higher in group II, this result was also in agreement with Elsawy as smoking index was significantly increased in COPD with either HTN or DM than those with COPD only (*p* 0.000) [14]. This may explain the relation between smoking and other co morbidities such as hypertension, DM and coronary heart diseases as follows: (1) The immediate noxious effects of smoking are related to sympathetic nervous overactivity which increases myocardial O_2 consumption through a rise in blood pressure, heart rate and myocardial contractility [15]. (2) The incidence of hypertension is increased among those who smoke 15 or more cigarettes per day [16]. (3) Several studies in Korea have reported that smoking was associated with an increased risk for the development of DM [17]. In addition, smoking causes increase insulin resistance [18]. (4) Smoking is a well-known risk factor for coronary heart diseases [19]. It is caused probably by vascular disability via its pathological changes such as arteriosclerosis through the mechanisms of inflammation and endothelial dysfunction [20]. In the present study, there was a statistically significant difference between group II and III as regards serum urea level as it was higher in group II. This result was also in agreement with Elsawy, in her study blood urea in group II (COPD with comorbidities) was 42.56 ± 26.71 while in group I (COPD alone) it was 36.48 ± 12.64 [14]. This may be attributed to associated diseases such as DM as plasma urea concentration increases in diabetic patients [21]. Regarding serum cholesterol, it was higher in group II than group I and group III and the difference was statistically highly significant ($p < 0.001$). This increase in serum cholesterol in group II (COPD with comorbidities) may be due to other associated diseases such as hypertension and DM in which there is increase in total cholesterol. It was explained by the following: (1) The epidemiological investigations have found that hypertensive patients frequently have a concomitant increase in serum cholesterol level [22]. Moreover, there is evidence that cholesterol induces endothelial dysfunction in experimental and clinical studies by reducing the bioavailability of endothelium-derived nitric oxide [23]. (2) Smokers have higher fasting triglycerides and lower high density lipoprotein and high proportion of low density lipoprotein particles [24]. (3) According to the American Diabetes Association, people with DM have higher rates of cholesterol abnormalities than the rest of population and this contributes to the higher rates of heart diseases in people with DM [25]. Comparing CRP level in the three groups, it was higher in group II than group I

Table 7 Comparison between the studied groups regarding the presence of renal failure (overt and concealed).

Group	Renal failure				
	Overt	Concealed	Total	FET	*p* value
Group I	5 (7.46%)	3 (4.48%)	8 (11.94%)	0.43	0.892
Group II	6 (18.18%)	5 (15.15%)	11 (33.33%)		
Group III	6 (12%)	3 (6%)	9 (18%)		
Total	17 (60.71%)	11 (39.29%)	28 (100%)		

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Table 8 Comparison between COPD patients with and without renal failure regarding (age, Hb concentration, Sao2, total cholesterol, urea, potassium, sodium, GFR, duration of disease, smoking index, BMI, CRP and severity of the disease).

Variable		RF			
		Present (19)	Absent (81)	St *t* test	*p* value
Age(years)					
Mean ± SD		71.26 ± 7.59	57.91 ± 8.37	6.36	0.001
Hb concentration(gm/dl)					
Mean ± SD		11.7 ± 61.1	12.1 ± 7.3	$X^2 = 4.24$	0.04
Sao2					
Mean ± SD		94.21 ± 2.2	95.56 ± 1.8	2.75	0.007
Urea(mg/dl)					
Mean ± SD		88.58 ± 45.02	36.57 ± 14.44	8.76	0.001
Total cholesterol(mg/dl)					
Mean ± SD		156.05 ± 32.8	131.93 ± 18.37	4.35	0.001
Potassium(mEq/L)					
Mean ± SD		4.59 ± 0.68	4.01 ± 0.63	3.54	0.001
GFR					
Mean ± SD		44.41 ± 8.5	94.06 ± 19.33	10.92	0.001
severity	Moderate	1 (5.3%)	1 (1.2%)	FET = 8.75	0.011
	Severe	9 (47.4%)	65 (80.2%)		
	Very severe	9 (47.4%)	15 (18.5%)		
Duration of disease(years)					
Mean ± SD		15.06 ± 10.93	10.57 ± 8.05	1.83	0.072
Smoking index					
Mean ± SD		605.88 ± 235.77	480.43 ± 164.82	2.38	0.021
BMI					
Mean ± SD		22.2 ± 4.03	21.95 ± 2.65	0.295	0.769
CRP(mg/L)					
Mean ± SD		16.22 ± 3.52	17.2 ± 5.16	0.745	0.459
Sodium(mEq/L)					
Mean ± SD		138.4 ± 8.81	138.25 ± 5.05	0.085	0.933

and the difference was statistically significant ($p < 0.05$). CRP was also very high in group I and II compared to group III and the difference was statistically highly significant ($p < 0.001$). Chronic inflammation in COPD is orchestrated by multiple inflammatory cells and mediators in the airways and the lung tissues induced by inhalation of noxious gases and particular matter, this persistent inflammatory response in the lungs is also associated with a significant systemic inflammatory response yielding adverse clinical outcomes, so called systemic effects of COPD [26]. It is clearly established that some inflammatory markers rise in systemic circulation [27], of the blood-based biomarkers, CRP has shown the greatest promise [28]. Smoking, as well as COPD itself, the most commonly encountered risk factor for the disease is also responsible for rise in serum CRP levels [29]. In the current study, there was a statistically significant difference between group I and II as regards GFR as it was lower in group II ($p < 0.05$). This is in agreement with Elsawy, who reported that the mean ± SD of calculated GFR by MDRD in COPD was 82.63 ± 23.30 ml/min/1.73 m^2, while in COPD with either HTN or DM was 80.99 ± 26.64 ml/min/1.73 m^2 [14].These results may be due to associated diseases as several lines of evidence have shown that smoking increases the risk and progression of diabetic nephropathy [30]. Analysis of a number of risk factors showed a 1.6-fold increases risk of nephropathy among smokers [31]. DM is the most common cause of renal failure, accounting for nearly 44% of new cases. The cause of diabetic nephropathy is not well understood, but it is thought that increased blood sugar, advanced glycation end product formation and cytokines may be involved in the development of diabetic nephropathy. DM causes changes in the body metabolism and blood circulation, which likely combine to produce excess reactive O_2 species. These changes damage the glomeruli of the kidneys which lead to albuminuria [32]. The prevalence of reduced GFR is also high in older hypertensive patients [33]. Elmahallawy and Qora reported that the mean estimated GFR in their COPD group was 75.20 ± 35.78 ml/min/1.73 m^2,while for the control group it was 92.04 ± 25.54 ml/min/1.73 m^2 with highly significant decrease in GFR in COPD group ($p < 0.01$) [12]. The lower GFR in COPD group in their study may be attributed to that their patient were older with more severe airflow limitation and 68% of them had chronic respiratory failure.

In our study, the overall prevalence of CRF was 18.7% (28/150). In COPD (group I and II), it was 19% (19/100), while in the control group (group III), it was 18% (9/50). In group I, 8 patients had CRF (11.94%), 5 patients of them had overt CRF (7.46%) and 3 patients had concealed CRF (4.48%). In

group II, 11 patients had CRF (33.33%), 6patients of them had overt CRF (18.18%) and 5patients had concealed CRF (15.15). In group III, 9 patients had CRF (18%), 6 patients had overt CRF (12%) and 3patients had concealed CRF (6%). In a study by Elsawy, concealed CRF in COPD group was 17.55% (46\262) while 1.52% (4\262) had overt CRF, in COPD with comorbidities, 18.46% (12\65) had concealed CRF while 6.15% (4\65) had overt CRF, and in the control group 10% (20\200) had concealed CRF while 2% (4\200) had overt CRF. The main finding of her study was the high prevalence of chronic renal failure (concealed and overt) among patients with COPD [14]. In Elmahallawy and Qora study, the overall prevalence of CRF was 46% in the study group and 22% in the control group. In their study, in COPD group, concealed CRF was 26% and overt CRF was 20% while in the control group, 10% of patients had concealed CRF and 12% of patients had overt CRF [12], the higher frequency of CRF in this study may be explained by: - First: 68% of their patients had chronic type 2 respiratory failure. Second: 72% of their patients had very severe COPD. Raffaele et al. found that the overall prevalence of CRF was 43.0% in the COPD group and 23.4% in the control group (DM hypoalbuminemia and skeletal muscle diseases) [7]. According to National kidney foundation, [34], if serum creatinine greater than 1.26 mg\dl for men and 1.04 mg\dl for women, it is considered a reliable marker of CRF. The GFR is frequently decreased in patients with COPD despite normal serum creatinine, so in our study (28.6%) of COPD patients have low GFR despite normal serum creatinine (concealed CRF) in comparison to (10.7%) in the control group. In a large multinational survey addressing the impact of COPD in North America and Europe in 2000, done by Rennand et al. (11.3%) of participating COPD patients were found to have CRF [35]. Gestel et al. studied the association between COPD and CKD in 3358 patients who underwent elective vascular surgery between January 1990 and December 2006 in the Netherlands, they found that COPD was associated with a higher risk of prevalent CKD as COPD patients were 2.19 times more likely to have concealed CRF and 1.94 times more likely to have overt CRF than controls [36]. Lower figures were found by Gjerde et al. who studied the prevalence of undiagnosed renal failure in COPD patients in Western Norway, they found that the prevalence of patients having CRF (GFR < 60 ml\min\1.73m2) was 9.6% in female COPD patients and 5.1% in male COPD patients [37]. Chandra et al. also found a significant association between radio graphically measured emphysema in COPD patients and GFR, participants with 10% more emphysema had GFR which was lower by 4, 4 ml\min\1.73m2 ($p = 0.01$) [38]. The association between COPD and CRF may be explained by several factors. First; it was found that arteriolar renal resistance is increased in COPD patients, perhaps because of local adrenergic discharge secondary to hypercapnia, in the initial phase of COPD, renal perfusion is usually normal but as the disease worsens, particularly as CO_2 retention develops, renal blood flow decrease. $PaCO_2$ has been found to correlate inversely with ERPF (effective renal plasma flow) and with the ability to excrete sodium and water. Hypercapnia may cause renal vasoconstriction directly and indirectly by stimulating sympathetic tone as detected by the increase in the circulating levels of norepinephrine [39]. Second; both nicotine and selected heavy metals as lead and cadmium, which are components of smoke, are risk factors for CRF. Nicotine causes nephropathies with an increased incidence of microalbuminurea progressing to proteinuria [40]. Third; COPD is generally recognized as a cause of systemic inflammation. Pro-inflammatory cytokines, especially (TNFα), play an important role in the disease process. In addition to pulmonary inflammation, several other parts of the body are affected resulting in muscle wasting, weight loss, diabetes, osteoporosis, atherosclerosis and renal dysfunction. So, the systemic inflammation seen in patients with COPD might explain the association between COPD and CRF [41]. Fourth, Pulmonary hypertension secondary to COPD, may be associated with the progression of kidney diseases [37]. Fifth, coronary artery disease, which is highly prevalent in COPD patients, is associated with vascular kidney disease [42]. This high prevalence of CRF found in COPD patients might explain the association between COPD and a large number of other comorbidities:- First; renal impairment is expected to be associated with decreased activity of renal α1 –hydroxylase with subsequent lower levels of the mean serum 25-hydroxy vitamin D than those with normal renal function. This may be an important factor underlying the association between COPD and osteoporosis [43]. Second, the prevalence of anemia in COPD patients is thought to be secondary to chronic inflammation and to a lesser extent to iron and folate deficiencies [39]. Third, CRF is associated with increased serum levels of inflammatory biomarkers and pro-thrombotic molecules. Thus, CRF may add to the factors explaining the association between COPD and cardiovascular diseases [44]. Finally, most drugs commonly used in the treatment of COPD exacerbations and comorbidities and as a result, the association between COPD and CRF will make COPD patients at high risk for adverse drug reactions to water soluble drugs so drug prescribing and dosing should be adjusted [45]. In the current study, there was a statistically significant difference between COPD patients with and without renal failure regarding hemoglobin concentrations as it was lower in cases with renal failure and this can be explained as CRF may be an important underlying cause of anemia through impaired production of erythropoietin [46]. In this study, there was a statistically significant difference between COPD patients with and without renal failure regarding Sao2 as it was lower in cases with renal failure. The relation between hypoxia and renal failure may be due to the effect of hypoxia which induces collagen messenger RNA expression and induces tissue inhibitors of metalloproteinases. Hypoxia also promotes the trans-differentiation of proximal tubular cells into myofibroblasts [47]. In our study, there was a statistically significant increase in the incidence of renal failure in COPD patients with severe and very severe COPD than cases with moderate severity. This may be explained by the fact that patients with severe COPD in the stable state may have a reduced or absent renal functional reserve [48]. Raffaele et al. reported that GFR values were not significantly associated with COPD severity, the investigators noted (older age and select co morbidities more than COPD severity-are associated with renal dysfunction in COPD) [3]. Corsonello et al. stated that the correlation between renal function and COPD severity warrants further investigations [45]. In the current study, there was significant increase in smoking index in COPD patients with renal failure as both nicotine and selected heavy metals as lead and cadmium, which are components of smoke, are risk factors for CRF. Nicotine causes nephropathies with an

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increased incidence of microalbuminurea progressing to proteinuria [40]. Lead and cadmium cause nephrotoxicity in the form of tubular proteinuria and glomerular dysfunction evidenced by an increased excretion of high molecular weight proteins and increased levels of creatinine in plasma and giving rise to a glomerular type proteinuria [49].

Conclusion

Chronic renal failure may be associated with COPD and should be screened for not only by serum creatinine level but also by the estimated GFR to recognize the cases of concealed CRF who have low GFR despite normal serum creatinine level because its recognition might either directly affect clinical practice or has prognostic implications. The increase in age, urea, total cholesterol, potassium, severity of airway obstruction, smoking index, low Sao2 and low hemoglobin concentration in COPD patients may increase the possibility of this association.

References

[1] L.M. Fabbri, K.F. Rabe, Complex chronic comorbidities of COPD, Eur. Respir. J. 31 (1) (2007) 204–212.
[2] R.A. Preston, M. Epstein, Ischemic renal disease: an emerging cause of chronic renal failure and end stage renal disease, J. Hypertens. 15 (12 Pt 1) (1997) 1365–1377.
[3] A. Raffaele, C. Andrea, P. Claudio, B. Salvatore, P. Giuseppe, Chronic renal failure, a neglected comorbidity of COPD, Chest 137 (4) (2010) 831–837.
[4] F.A. McAlister, J. Ezekowitz, M. Tonelli, P.W. Armstrong, Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study, Circulation 109 (8) (2004) 1004–1009.
[5] R.J. Middleton, R.N. Foley, J. Hegarty, et al, The unrecognized prevalence of chronic kidney disease in diabetes, Nephrol. Dial. Transplant. 21 (1) (2006) 88–92.
[6] E. Ischaki, G. Papaatheodorou, E. Gaki, I. Papa, N. Koulouris, S. Loukides, Body mass and fat-free mass indices in COPD: relation with variables expressing disease severity, Chest 132 (1) (2007) 164–169.
[7] Global initiative for chronic obstructive lung disease (GOLD), Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary (revised 2011). <http://www.goldcopd.com>.
[8] American Thoracic Society, Standardization of spirometry, Am. J. Respir. Crit. Care Med. 152 (3) (1995) 1107–1136.
[9] A.S. Levey, J.P. Bosch, J.B. Lewis, et al, Modification of diet in renal disease study group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation, Ann. Intern. Med. 130 (6) (1999) 461–470.
[10] J. Joseph, M. Koka, W.S. Aronow, Prevalence of moderate and severe renal insufficiency in older persons with hypertension, diabetes mellitus, coronary artery disease, peripheral arterial disease, ischemic stroke or congestive heart failure in an academic nursing home, J. Am. Med. Dir. Assoc. 9 (4) (2008) 257–259.
[11] R.A. Inclazi, A. Corsonello, C. Pedone, S. Battaglia, G. Paglino, V. Bellia, Chronic renal failure: a neglected comorbidity of COPD, Chest 137 (2010) 831–837.
[12] I.A. Elmahallawy, M.A. Qora, Prevalence of chronic renal failure in COPD patients, Egypt. J. Chest Dis. Tuberculosis 62 (2013) 221–227.
[13] P.J. Barnes, S.D. Shapiro, R.A. Pauwels, Chronic obstructive pulmonary disease: molecular and cellular mechanisms, Eur. Respir. J. 22 (2003) 672–688.
[14] S. Elsawy, S. Abu Bakr, S. Oraby, T. Saied, Elkhair O. Abu, Prediction of chronic renal failure in patients with chronic obstructive pulmonary disease, Eur. Respir. J. 44 (2014) P3627. ArticleInfo & Metrics.
[15] B. Najem, A. Houssiere, K.A. Patna, et al, Acute cardiovascular and sympathetic effects of nicotine replacement therapy, Hypertension 47 (2006) 162.
[16] T.S. Bowman, J.M. Gaziano, J.E. Buring, H.D. Sesso, A prospective study of cigarette smoking and risk of incident hypertension in women, JAM Coll. Cardiol. 50 (2007) 2085.
[17] N.H. Cho, J.C. Chan, H.C. Jang, S. Lim, H.L. Kim, S.H. Choi, Cigarette smoking is an independent risk factor for type 2 diabetes. A four year community based prospective study, Clin. Endocrinol. (OXF) 271 (2009) 679–685.
[18] S. Attvall, J. Fowelin, L. Lager, H. Von Schenck, U. Smith, Smoking induces insulin resistance: a potential link with the insulin resistance syndrome, J. Intern. Med. 233 (1993) 327–332.
[19] A.P. Burke, A. Farb, G.T. Malcom, Y.H. Liang, J. Smialek, R. Virmani, Coronary risk factors and plaque morphology in men with coronary disease who died suddenly, N. Engl. J. Med. 336 (18) (1997) 1276–1282.
[20] N.R. Cook, J.A. Cutler, E. Obarzanek, J.E. Buring, K.M. Rexrode, S.K. Kumanyika, L.J. Appel, P.K. Whelton, Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP), BMJ 334 (7599) (2007) 334.
[21] A.I. Adler, R.J. Stevens, S.E. Manley, et al, Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study, Kidney 63 (2003) 225–232.
[22] M. Laurenzi et aland on behalf of the Gubbio Study Group, Multiple risk factors in hypertension: results from the Gubbio Study, J. Hypertens. 8 (Suppl. 1) (1990) S7–S12.
[23] H. Hayakawa, L. Raij, Relationship between hypercholesterolemia, endothelial dysfunction and hypertension, J. Hypertens. 17 (1999) 611–619.
[24] B. Eliasson, S. Attval, M.R. Taskinen, U. Smith, The insulin resistance syndrome, Arterioscler. Thromb. 14 (1994) 1946–1950.
[25] American Diabetes Association, Standards of medical care in diabetes—2016, Diabetes Care 39 (suppl 1) (2016) S1–S106.
[26] A. Agusti, Systemic effects of COPD. What we know and what we don't but should, Proc. Am. Thorac. Soc. 4 (2007) 522–528.
[27] E.F. Wouters, Local and systemic inflammation in COPD, Proc. Am. Thorac. Soc. 2 (2005) 26–33.
[28] D.D. Sin, S.F. Man, Biomarkers in COPD: are we there yet?, Chest 133 (2008) 1296–1298
[29] J. Danesh, J. Muir, Y.K. Wong, et al, Risk factors for coronary heart disease and acute-phase proteins. A population-based study, Eur. J. 20 (1999) 954–959.
[30] E. Ritz, Nephropathy in type 2 diabetes, J. Intern. Med. 245 (1999) 111–126.
[31] P. Mehler, B. Jaffers, S. Biggerstaff, R. Schrier, Smoking as a risk factor for nephropathy in non-insulin dependent diabetics, J. Ger. Intern. Med. 13 (1998) 842–845.
[32] Cao, Pathogenesis of diabetic nephropathy, J. Diabetes Invest. 2 (4) (2011) 243–247.
[33] I. Rahman, Oxidative stress in pathogenesis of chronic obstructive pulmonary disease: cellular and molecular mechanisms, Cell Biochem. Biophys. 43 (1) (2005) 167–188.
[34] National Kidney Foundation, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification, Am. J. Kidney Dis. 39 (2 Suppl. 1) (2002) S1–S266.

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[35] S. Rennard, M. Decramer, P.M. Calverley, et al, Impact of COPD in North America and Europe in 2000: subjects perspective of confronting COPD, Eur. Respir. J. 20 (4) (2002) 799–805.
[36] M. Van Gestel, S.E..Hoeks. Chonchol, et al, Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients, Nephrol. Dial. Transplant. 2009 (2009) 1–5.
[37] B. Gjerde, P.S. Bakke, T. Ueland, J.A. Hardie, T.M. Eagan, The prevalence of undiagnosed renal failure in a cohort of COPD patients in Western Norway, Respir. Med. 106 (2012) 361–366.
[38] D. Chandra, J.A. Stamm, P.M. Palevsky, et al, The relationship between pulmonary emphysema and kidney function in smokers, Chest 11 (2012) 1456.
[39] P.W. Jones, G. Harding, B. Berry, I. Wiklund, W.H. Chen, Leidy N. Kline, Development and first validation of the COPD Assessment Test, Eur. Respir. J. 34 (2009) 648–654.
[40] H.P. Hansen, K. Rossing, P. Jacobsen, et al, The acute effect of smoking on systemic haemodynamics, kidney and endothelial functions in insulin-dependent diabetic patients with microalbuminuria, Scand. J. Clin. Lab. Invest. 56 (1996) (1996) 393–399.
[41] M.J. Sevenoaks, R.A. Shockley, Chronic obstructive pulmonary disease, inflammation and co-morbidity—a common inflammatory phenotype?, Respir Res. 7 (2006) (2006) 70.
[42] J.B. Soriano, G.T. Visick, H. Muellerova, N. Payvandi, A.L. Hansell, Patterns of comorbidities in newly diagnosed COPD and asthma in primary care, Chest 128 (4) (2005) 2099–2107.
[43] N.R. Jorgensen, P. Schwarz, Osteoporosis in chronic obstructive pulmonary disease patients, Curr. Opin. Pulm. Med. 14 (2) (2008) 122–127.
[44] M.G. Shlipak, L.F. Fried, C. Crump, et al, Elevations of inflammatory and pro-coagulant biomarkers in elderly persons with renal insufficiency, Circulation 107 (1) (2003) 87–92.
[45] A. Corsonello, C. Pedone, F. Corica, et al, Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients, Arch. Intern. Med. 165 (7) (2005) 790–795.
[46] R. Woodman, L. Ferrucci, J. Guralnik, Anemia in older adults, Curr. Opin. Hematol. 12 (2) (2005) 123–128.
[47] J.T. Norman, I.M. Clark, p.l. Garcia, Hypoxia promotes fibrogenesis in human renal fibroblasts, Kidney Int. 58 (2000) 2351–2366.
[48] R.A. Sharkey, E.M. Mulloy, I.A. Kilgallen, S.J. O'Neill, Renal functional reserve in patients with severe chronic obstructive pulmonary disease, Thorax 52 (5) (1997) 411–415.
[49] P. Satarug, Y. Ujjin, Vanavanitkun, et al, Effects of cigarette smoking and exposure to cadmium and lead on phenotypic variability of hepatic CYP2A6 and renal function biomarkers in men, Toxicology 204 (2004), 161–17.

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