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Is Serum Cholesterol A Risk Factor For Ischemic Heart Disease In Patients With Chronic Obstructive Pulmonary Disease?

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Abstract
Background*: Frequent coexistence of Chronic Obstructive Pulmonary Disease (COPD) and Ischemic Heart Disease (IHD) is often speculated to be related to lipid abnormalities. However studies reveal contradicting results, thus raising serious doubts about higher prevalence of dyslipidemia as reason for this coexistence. The objectives of this study were to examine the characteristics of lipid metabolism in COPD and to evaluate causal association between dyslipidemia and IHD among COPD subjects.*
Methods*: This was a retrospective analysis of data from 98 COPD subjects randomly selected from the hospital medical records database. All eligible subjects were males with current or past history of smoking, with no evidence of active infections, chronic inflammatory disease or malignancy. None had history of statin intake prior to index measurement of lipid profile. Data extracted were analyzed using SPSS 19 version. A recently published data from reference population were used for comparison.*
Results*: Most prevalent comorbidities were systemic hypertension (SHT), IHD and diabetes mellitus (DM). Prevalence of IHD was significantly higher than the reference population. Prevalence of hypertriglyceridemia was significantly lower in COPD subjects who also had low mean total cholesterol level than the reference population. On logistic regression analysis, elderly age and low HDL cholesterol predicted coexistence of IHD among COPD subjects independent of DM, SHT and duration of COPD. Other lipid parameters were not associated with increased prevalence of IHD among the study subjects.*
Conclusion*: This study has highlighted that atherogenic pattern of lipid profile among COPD subjects was comparable with that of reference population. Increased risk of IHD among COPD patients appears to be related to factors other than quantitative aspects of lipid metabolism (dyslipidemia) which warrants investigations.*
Keywords: *Chronic obstructive pulmonary disease, Ischemic heart disease, dyslipidemia.*

I. Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by chronic airway inflammation in response to noxious stimuli resulting in airflow obstruction that is not fully reversible (1). World health organization predicts that by 2020, COPD will become third leading cause of death (currently fourth) and fifth leading cause of disability (currently twelfth) worldwide (2, 3). COPD has many extra-pulmonary manifestations of which ischemic heart disease (IHD) coexist frequently with COPD determining its morbidity and mortality rates. Large population based studies have also shown that COPD patients are two or three times more at risk for cardiovascular mortality which accounts for about 50% of the total number of deaths (4, 5, 6). The pathogenetic mechanism of this coexistence, though is unclear, is frequently speculated to be related to lipid metabolism in COPD patients. A deranged lipid profile is expected in COPD, for various reasons like smoking, age factor, steroid intake etc. However several studies have raised serious doubts about whether dyslipidemic state is characteristic for COPD and whether it can explain the increased risk of ischemic heart disease in these patients. This study is intended to clear these doubts with specific focus on quantitative lipid profile of COPD patients and its association with prevalence of ischemic heart disease in this subset of general population. COPD and IHD being two of top five major killer diseases, the rationale behind this study is to identify pathogenetic mechanisms linking these diseases that might open up therapeutic potential to contain the mortality and morbidity in above settings.

II. Materials And Methods

It was a retrospective analysis of data from 98 consecutive COPD subjects visiting a tertiary care chest clinic, aged 40 years and above, whose index measurement of lipid profile was documented prior to any history of statins / steroids intake. The eligible subjects registered during a period from January 2014 to December 2014, were recruited by random sampling method, whose files were then used for data extraction. All recruited subjects were free from active infections and did not have other chronic inflammatory diseases during the index

measurement of lipid profile. Those who were surviving a malignancy and those who had history suggestive of asthma were excluded from the study. Subjects with history of intake of statins prior to the index lipid measurement were also excluded. After obtaining approval from the institutional ethics committee, the data were extracted from medical records of the study subjects and compared with the recently published data from the reference population (7).Those variables with more than 25% missing data were excluded from the analysis and no attempt was made to impute for these missing data.

Data analysis was performed using SPSS version 19 (IBM corporation) in two stages. First stage involved comparison of our data with the published data from reference population. The second stage was subgroup comparison of data between COPD subjects with and without IHD. The data were examined initially for normality of distribution and homogeneity of variance. The comparison of quantitative variables between the groups was carried out by using student's t test. Categorical variables were compared by using Chi Square test and odds ratio was evaluated. A p value of < 0.05 will be considered significant. Logistic regression analysis was employed using clinical and biochemical covariates to derive association between lipid parameters and ischemic heart disease in subjects with COPD and the odds ratio was expressed with 95% confidence interval.

III. Results

In all, data from 98 COPD subjects revealed a mean age of 67.86 + 8.48 years with a mean BMI of 23.77 + 5.18 kgs/m2. Sociodemographic characteristics are summarized in table 1. All were males of whom majority were current smokers (68.3%) and lived in urban areas (80.6%). Almost half of the study population had coexisting ischemic heart disease (49%) and other prevalent comorbidities were diabetes mellitus (48%) and systemic hypertension (51%)(Figure 1). Atherogenic pattern of lipid parameters were defined as per National Cholesterol Education Program (NCEP) guidelines 2001 (8). Prevalence of hypercholesterolemia, high LDL cholesterol, low HDL cholesterol and hypertriglyceridemia among the COPD subjects and the reference population are compared in table 2. COPD subjects had lesser prevalence of hypertriglyceridemia than the reference population. Prevalence of other dyslipidemic patterns among the study subjects was similar to the reference population. Mean total cholesterol value was significantly lower among COPD subjects than the reference population and other lipid parameters were not different between the groups (Table 3). On subgroup analysis of study population using logistic regression analysis, ischemic heart disease among COPD subjects was predicted by elderly age (Odds ratio 1.095; 95% CI 1.035 – 1.160; P = 0.003) and low HDL cholesterol (Odds ratio 5.614; 95% CI 2.013 – 15.65; P = 0.001) independent of cofounders like diabetes mellitus, systemic hypertension and duration of COPD.

IV. Figures And Tables

Table 1: Sociodemographic characteristics of the study population.

Sociodemographic and disease characteristics		N = 98
Age (in Years)		67.86 ± 8.48
Male Gender		96 (100%)
BMI (Kg / m2)		23.77 ± 5.18
Dwelling	Urban	79 (80.6%)
Rural		19 (19.4%)
Smoking status	Current	67 (68.3%)
Former		31 (31.6%)
Alcohol intake	Never	50 (51%)
Current intake		29 (29.5%)
Former		19 (19.3%)

Table 2: Comparison of prevalence of atherogenic lipid profile between COPD subjects and the reference population.

Atherogenic lipid profile	Prevalence in study population (%)N=98	Prevalence in reference population (%)N=657
Total cholesterol ≥ 200 mgs / dL	12 (12.2%)	120 (18.3%)^{NS}
LDL Cholesterol ≥ 130 mgs / dL	13 (13.3%)	103 (15.8%)^{NS}
HDL cholesterol ≤ 40 mgs / dL	64 (65.3%)	452 (68.9%)^{NS}
Triglycerides ≥ 150 mgs /dL	16 (16.3%)	201(30.6%)*

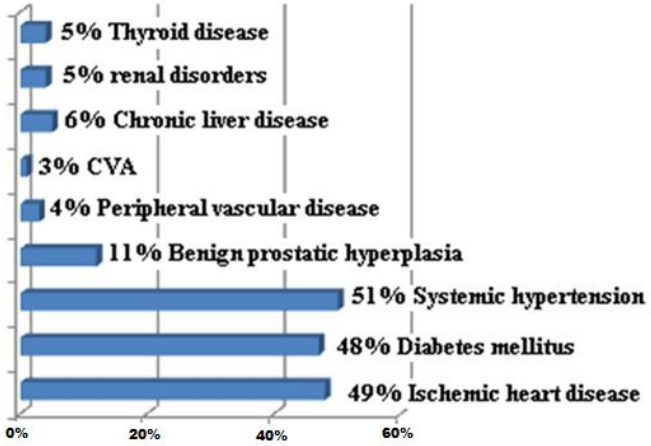
* $P < 0.01$; NS = not significant;

Table 3: Comparison of lipid profile of COPD subjects and the reference population.

Lipid profile in Serum	Study population (Mean ± SD)N=98	Reference population (Mean ± SD)N=657
Total cholesterol (mgs / dL)	157.7 ± 40.09	167 ± 41*
LDL Cholesterol (mgs / dL)	94.4 ± 37.20	100 ± 32^{NS}
HDL cholesterol (mgs / dL)	37.88 ± 12.8	40 ± 11^{NS}
Triglycerides (mgs /dL)	109.6 ± 70.3	116 ± 58^{NS}

* $P < 0.05$; NS = not significant;

Figure 1: Comorbid conditions among COPD subjects.



V. Discussion

In this study we found that ischemic heart disease was one of the most prevalent comorbidities among COPD subjects which was significantly higher than that observed in the general population. Contrary to the speculations we also found that lipid profile of COPD subjects were almost similar to that of the reference population. The most common dyslipidemic parameter among COPD subjects was low HDL cholesterol which was not different from the reference population. Surprisingly, prevalence of hypertriglyceridemia was lesser and the mean serum total cholesterol level was lower than the reference population. Within the study population, only low HDL cholesterol strongly predicted the occurrence of IHD among COPD subjects whereas other lipid parameters had no predictive role. Elderly age showed a modest association with coexistence of COPD and IHD. Important confounders like diabetes mellitus, systemic hypertension and duration of COPD did not influence the above mentioned association.

Several studies have raised serious doubts about whether dyslipidemic state is characteristic for COPD and whether it can explain the increased risk of ischemic heart disease in these patients. We found only two studies that identified proatherogenic lipid profile in patients with COPD (9, 10). However, a significant number of studies indicate that COPD patients have a varying pattern of lipid profile which cannot be classically described as "proatherogenic". Basili S et al found that total cholesterol, triglycerides, LDL and HDL cholesterol were not different between COPD and control subjects (11). One Indian study by Nillawar et al showed that there was no difference in any of the lipid parameters between COPD subjects and age matched control subjects (12). A similar pattern of lipid profile was noted by Mills NL et al who also found increased arterial stiffness, a marker of atherosclerosis, among their COPD subjects than controls (13). Some studies have even reported a lipid profile in COPD patients that is expected to protective against atherosclerotic damage of vasculatures (14, 15). Reed RM et al (14) studied retrospectively, 126 patients with advanced stages of COPD awaiting lung transplantation and found that COPD subjects had lower mean LDL cholesterol and higher mean HDL cholesterol compared with reference population without COPD. Around 60% of these subjects were found to have angiography proven coronary artery disease which the authors concluded to be unrelated to HDL cholesterol level.

Our data as also other studies cited above conclude that quantitative abnormalities of lipids (Dyslipidemia) alone cannot explain the higher prevalence of IHD among COPD patients and that there could be other unknown mechanisms for frequent coexistence of COPD and IHD which need to be explored. Recent evidence from other disease models indicates dysfunctional HDL cholesterol as possible link between these two major killer diseases (16,17).

Most of the studies cited above, except Reed et al., compared their data with a smaller sized control group to derive conclusions. Our study had an edge over these studies by using published data from a reference population which represented same sociocultural background as that of the study population. This reference data with sufficient sample size gave enough power to our conclusions derived from a relatively smaller study sample which otherwise formed a major limitation in our study.

VI. Conclusion

In the context of frequent coexistence of COPD and IHD, we conclude that COPD subjects have lipid profile which is quantitatively indifferent from the general population. Only low HDL cholesterol independently and strongly predicted occurrence of ischemic heart disease among COPD subjects whereas other lipid parameters were not associated with the coexistence of these two diseases. Increased risk of ischemic heart

disease among COPD patients appears to be related to factors other than quantitative aspects of lipid metabolism (dyslipidemia) which warrants investigations. We recommend epidemiological studies involving COPD population to further substantiate the relationship between lipid metabolism and occurrence of IHD among COPD patients. We also recommend studies to explore mechanistic links between these two major killer diseases paving way for drug targets which could revolutionize the existing management strategies.

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