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## Serum copper and zinc level as biomarker for dust exposed lung diseases among coal miners

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### Abstract

To elucidate the effect of dust exposure, smoking and alcoholic habit on the serum Copper and Zinc activity as prognosis tool for dust linked lung diseases among coal workers. In the present study, serum Copper and Zinc activity have been examined and correlated with PFT among coal mine workers to determine the extent of lung fibrosis. A cross-sectional study was conducted on two statistically similar groups consisting of 54 dust exposed miners and 50 unexposed control. PFT values using spirometry and serum Cu and Zn level by AAS were determined for all the test subjects. Serum Cu and Zn level increases significantly with duration of dust exposure among miners whereas their PFT values suggest deterioration in lung. Smokers had significantly higher levels of serum Cu ( $87.38 \pm 6.31 \mu\text{g}/\text{dl}$ ) and Zinc ( $80.07 \pm 5.59 \mu\text{g}/\text{dl}$ ) as compared to non-smokers having values  $81.50 \pm 5.01 \mu\text{g}/\text{dl}$  and  $78.62 \pm 3.11 \mu\text{g}/\text{dl}$  respectively. Alcoholic habit further deteriorates the PFT values and increases serum Cu and Zn values. The study reveals that serum Cu and Zn concentrations were found to be at significantly higher levels in exposed workers which increases further with smoking and drinking habits. PFT investigations on these subjects suggest that serum Cu and Zn very well correlates with PFT and is a more sensitive indicator for health status of miner's lung than PFT. This suggests strong possibility of serum Cu and Zn as biomarker for dust linked lung diseases like silicosis.

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## Introduction

Inhalation of crystalline silica for prolonged periods can lead to silicosis, an inflammatory disorder (Castranova and Vallyathan, 2000; Fubini and Hubbard, 2003). Silicosis, coal pneumoconiosis and asbestosis are some of the significant occupational lung diseases which are present even today despite the fact that they are preventable with improvement in hygiene and control of airborne dust in the working environment. Silica dust is released during operations in which rocks, sand, concrete and some ores are crushed or broken. Work in mines, quarries, foundries, construction sites, manufacturing of glass, ceramics and abrasive powders, and masonry workshops are particularly risky.

Chronic obstructive pulmonary disease (COPD) is caused by exposure to respirable crystalline silica and the presence of both obstructive and restrictive lung diseases are significant predictor of early death (Mannino *et al.*, 2003). These diseases culminate into Silicosis and Coal Workers Pneumonociosis (CWP) which develop progressively (progresses even when exposure stops) and irreversibly over decades and currently there is no known cure (Pelclová *et al.*, 2007). Genotoxic and fibrogenic effects of silica and its potential to produce oxidative stress can lead to the development of lung cancer (Tsuda *et al.*, 2002). Extremely high exposures are associated with much shorter latency and more rapid disease progression. The diagnosis of silicosis is mainly based on clinical examination of the subjects including measurement of pulmonary function specially lung volumes and grading of profusion according to the ILO (International Labour Organization) classification of Pneumoconiosis. Although lung function is severely impaired in patients with advanced disease, airway obstruction is common even in silica-exposed workers with no radiological abnormalities (Hnizdo and Vallyathan, 2003; Humerfelt *et al.*, 1998).

Prevention is considered as best remedial step for these diseases having no effective treatment. Early

Diagnosis of these diseases with the help of biomarkers facilitates timely preventive steps ensuring a prolonged healthy life of the affected person. While a number of biomarkers have shown some promising results, none of them so far have been validated fully for clinical use (Gulumian *et al.*, 2006). In addition to reporting new cases, it provides an opportunity for occupational health doctors or hygienists to periodically analyze health records from all workers in an industry or plant and assess the efficacy of prevention activities. One such possible biomarker could be serum Cu levels because literature suggest fibrogenic property in Cu (Kolev and Burkova 1982; Wang *et al.*, 1998). As the primary pathologic changes in silicosis include fibrosis and the proliferation of collagen tissue in the lungs there could be possible association with raised levels of serum Cu. Though the mechanism of increase in serum Cu is still not understood, it has been suggested that an increase in ceruloplasmin levels in silicotics, which contains eight Cu atoms may be responsible for such an increase (Ren and Jiang, 1993). Moreover, other studies have also reported elevated levels of serum Cu in silicotics (Niculescu *et al.*, 1981; Tiwari *et al.*, 2004).

Biomarkers may represent signals in the intervening steps between exposure and resultant disease (Pandey and Agarwal, 2012). Different epidemiological studies have individually shown the correlation of serum Cu and Zn levels with different pathologies which have been related to several types of cancer (Jia, 1991; Ma and Jiang, 1993; Malvy *et al.*, 1993; Yoshida *et al.*, 1993; Yücel *et al.*, 1994). Bai *et al.* (1993) indicated that Cu plays a very important part in the progress of lung fibrosis, and zinc (Zn) takes part in the synthesis of collagen in the progression of lung fibrosis. Koniski *et al.* (1985) indicated that fibrosis was promoted by Cu and depressed by Zn. Although serum levels of trace elements in silicotic patients have already been investigated in few studies, the relative importance of Cu and Zn in the progression of silicosis has rarely been documented. The main objective of this study was to investigate serum copper and Zinc levels in

workers exposed to dust containing free crystalline silicon dioxide.

### Materials and methodology

This study was conducted between May 2014 to January 2015, at the Respiratory protection Laboratory of CSIR-Central Institute of Mining and Fuel Research, Dhanbad, India and Tata Iron and Steel Company Limited (TISCO) Jamadoba hospital. This study elucidate the effect of duration of exposure to dust containing silica, smoking and drinking habit on pulmonary function status and serum Cu and Zn activity among dust exposed workers in coal mines of TISCO located in Jharia Coalfields of India. There are about 5000 workers in TISCO (including 3000 miners working underground) who visit to the TISCO Jamadoba hospitals for their routine health checkup. Institutional Ethics committee of CSIR-Central Institute of Mining & Fuel Research, Dhanbad, reviewed and accorded its ethical clearance for the study.

#### Sample selection

Study samples (n=104) were taken randomly from among the employees working in TISCO visiting to the TATA Jamadoba hospital for routine health checkup. The sample consist of both mine workers (n=54) and non-mining workers (n=50). Mine workers were randomly selected from among the 800 underground mine workers visited to the hospital for their health checkup during study period.

They are involved in various types of dust generating mining operations and are therefore exposed to respirable air borne dust on almost regular basis. Non-mine workers are those involved in offices, hospital and general type work in the TISCO and have no direct exposure to dust generating operations. Non-mine worker were taken in the study as a control group. Pulmonary function test (PFT), Serum copper and zinc were examined in 54 workers exposed to airborne respirable dust containing silica and 50 as unexposed control group. General characteristics of study subjects are shown in Table 1.

#### PFT analysis

The pulmonary functions of all the study subjects were measured in TISCO Jamadoba hospital under the supervision of occupational health specialist doctor at the hospital, using spirometer (model: Spirovit SP-10, make: Schiller AG, Switzerland) which was calibrated regularly.

The doctor also facilitated our approach to study subjects. A brief physical and general examination of subjects including anthropometric parameter (height & weight) and demographic parameters (name, age, sex, occupation & smoking habits) was carried out and fed to software of the spirometer. Pulmonary function tests (PFT) were conducted on all the subjects as per prescribed methodology for the equipment. During the test, the subjects were adequately encouraged to perform their optimum level and also a nose clip was applied during the entire maneuver. Tests were repeated three times and the best results were considered for analysis. The parameters measured by the apparatus were forced vital capacity (FVC), forced Expiratory Volume in 1<sup>st</sup>second (FEV<sub>1</sub>), Forced Expiratory Flow and Peak Expiratory Flow (PEFR) with graphic curves.

#### Analysis by AAS

Fasting blood was obtained from controls and exposed group. The serum Cu and Zn levels were determined by means of Atomic absorption spectrophotometer (AAS-Thermo Scientific), CSIR – CIMFR, Dhanbad. Before AAS analysis, the serum samples were diluted 10 times with de-ionized water. Every sample was analyzed in triplicate and the average value was adopted.

#### Statistical analysis

The results obtained are reported as mean  $\pm$  standard deviation (SD). To find the influence of year of exposure and other parameters on Serum Cu and Zinc concentration, the student t test was used. All statistical analyses were performed using SPSS software windows (Version 16.0) and a significance criterion of probability value of  $p < 0.05$  was used.

**Results**

Study was conducted for 104 participants in which 50 were controls subject with no direct exposure of dust and 54 subjects were coal mine workers in Jharia coalfields, India. A majority of the workers were drillers, belt operator, mining Sirdar and LHD operator; these operations are responsible for significant airborne respirable dust generation in

mines. Their mean age was 41.28±6.75 for control and 41.5± 4.81 years for ARD exposed group. The physical parameters of the study groups are described in Table 1. Student’s t-tests were conducted in both the study groups and P values were assessed to ascertain the similarity of the study groups using null hypothesis.

Table 1. General characteristics of control and airborne silica exposed group.

	Control	ARD exposed Workers	P Value
Number of subject	50	54	-
Age (Years)*	41.28±6.75	41.5± 4.81	0.42
Weight Kg*	64.4±12.30	64.20±8.98	0.46
Height (cm)*	165.66± 7.76	164.75±7.53	0.27
Smoker	20	10	-
Non-Smoker	30	30	-
Alcohol Consumption	None	9	-
Alcoholic& Smoker	None	5	-

Values are presented in geometric means; p values were assessed by the Student’s t-test.

\*Significant at p < 0.05.

The study results for Lung Function Test (PFT) obtained from spirometry tests and serum Copper & Zinc level obtained from AAS analysis for both control and ARD exposed group are presented in Table 2. The results for all the three parameters are presented as

mean ± standard deviation (SD) for the respective study groups. Study results of the two groups were statistically compared using student’s t-test and determination of p value considering the significance level at < 0.05.

**Table 2.** Comparison of PFT, Serum Cu and Serum Zn level among control and Airborne silica exposed group. Values are presented in geometric means; significant at p < 0.05.

Parameters	Control	ARD exposed Workers	P Value
Subjects in study group	50	54	-
PFT value %	78.67±6.81	64.16±9.52	<0.00001
Serum Cu (µg/dl)	79.67±5.20	89.29±7.91	<0.00001
Serum Zn (µg/dl)	76.90±3.34	83.97±6.83	<0.00001

Study results were classified to show the effect of duration of dust exposure on health status. Accordingly, the PFT values, Serum Cu and Serum Zn values for control group (having no exposure), low exposure (<15 years of exposure) and high exposure (≥ 15 years of exposure) are summarized in Table 3. This study group consists of subjects (in both control and exposed groups) having no smoking and alcoholic habits.

The results were further classified to assess the impact of smoking and alcoholic habits on the health. Accordingly, study group for the exposed subject consisted of 3 sub groups viz., (a) non-smoker and non-alcoholic, (b) only smoker or only alcoholic, (c) both smoker as well as alcoholic. Since there was no alcoholic the control subjects, the study groups among the control were smoker and non-smoker only. These results are presented in Table 4, 5 and 6.

**Table 3.** Variation of Serum Copper and Zinc level in workers (without smoking and alcoholic habit) with duration of exposure.

Parameter	No Exposure Control (n=30)	Low Exposed Group (n=16)	P value	Low Exposed Group (n=16)	High Exposed Group (n = 14)	P value
Serum Cu (µg/dl)	78.45±5.04	83.92±6.32	0.001*	83.92±6.32	90.30 ± 6.49	0.005*
Serum Zn (µg/dl)	76.13±3.32	80.09 ± 4.56	0.0007*	80.09 ± 4.56	84.38± 6.64	0.02*
FEV <sub>1</sub> /FVC %	78.90±7.62	73.69±5.62	0.01*	73.69±5.62	66.68±6.05	0.001*

Values are presented in geometric means; p values were assessed by the Student’s t-test.

n – numbers of Subjects; \* significant at p < 0.05.

**Discussion**

An important cause of pneumoconiosis in India is inhalation of coal dust (Naidoo *et al.*, 2004). Exposure to respirable coal dust changes the lung volumes and capacities which we can easily determine through the

Spirometry. This may cause obstructive, restrictive, or mixed ventilatory defects. FEV<sub>1</sub> is an ideal screening tool because it detects ventilatory defects reflecting obstructive patterns.

**Table 4.** Correlation between Serum Cu & Zn level (µg/dl) in Control and ARD exposed group.

Parameters	Control Serum Cu (µg/dl) (n)	Exposed Serum Cu (µg/dl) (n)	P values	Control Serum Zn (µg/dl) (n)	Exposed Serum Zn (µg/dl) (n)	P values
Non-Smoker and non-alcoholic	78.45±5.04 (30)	86.90±7.07 (30)	<0.00001*	76.13±3.32 (30)	82.09±5.94 (30)	<0.00001*
Only Smokers	81.50±5.01 (20)	87.38±6.31 (10)	0.004*	78.06±3.11 (20)	80.07±5.59 (10)	0.106**
Normal PFT	80.56±5.52 (10)	93.13±7.65 (10)	0.0002*	76.93±2.61(10)	83.21±9.98(10)	0.03*

Values are presented in geometric means; p values were assessed by the Student’s t-test.

n – numbers of Subjects; \* significant at p < 0.05; \*\* not significant p > 0.05.

The present study was designed to quantify resulting abnormalities in lung function in workers exposed to coal dust particles as compared to their un-exposed control. For the study, 54 coal mine workers engaged in various mining activities having significant airborne respirable dust generation potential were taken. Control consisted of 50 subjects having no direct exposure to ARD. Both the study groups have statistically similar physical parameters of height, weight and age as evidenced by student’s t-test with significance level p<0.05 in Table 1.

The present study demonstrates that prolonged exposure to coal dust markedly decreased the pulmonary function FEV<sub>1</sub>/FVC (%) relative to their controls group (Table 2).

The results is more visible and conclusive on the comparing the FEV<sub>1</sub>/FVC (%) values of unexposed control, low exposed (<15 years of exposure) group

and high exposed group (≥ 15 years of exposure) which shows increasing deterioration of lung function tests (Table 3). Results of Table 2 and Table 3 further reveal strong correlation of serum Cu and serum Zn values of a subject with their PFT values. Table 2 demonstrates statistically significant (p<0.05) increase of serum Cu and Zn level in exposed subject as compared to their control whereas Table 3 suggest increasing trend of serum Cu and Zn level in unexposed control, low exposed (<15 years of exposure) group and high exposed group (≥ 15 years of exposure). A box plot of PFT (FEV<sub>1</sub>/FVC), serum Cu and serum Zn among no exposure control, low exposure (< 15 years) and high exposure group (≥15 years) presented in Figure 1 clearly demonstrates the decrease of PFT value and increase of serum Cu and serum Zn value with year of exposure.

Results contained in Table 6 explains the effect of smoking and alcoholic habits on PFT values as well as

serum Cu and Zn level among control and exposed subject. The PFT values for non-smoker & non-alcoholic, only smoker or only alcoholic, alcoholic smoker among exposed group have 70.42±6.74, 58.40±4.94, 48.45±1.11 respectively which shows a deteriorating trend in lung from exposed subjects without smoking and alcoholic habit, any one of two

habits and both the habits. Similarly, an increasing serum Cu values 86.90±7.07, 90.70±7.93, 98.23±5.64 and serum Zn values 82.09±5.94, 84.81±7.10, 92.01±5.06 have been observed in exposed subjects without smoking and alcoholic habit, any one of two habits and both the habits (Table 5).

**Table 5.** Correlation between Serum Cu & Zn level (µg/dl) in ARD exposed workers with different habit.

Parameters	Exposed Non Smoker & non Alcoholic (n =30)	Exposed smokers or alcoholic (n=19)	P values	Exposed smokers or alcoholic (n=19)	Exposed smokers Alcoholic & Smoker (n=5)	P values
FEV <sub>1</sub> /FVC %	70.42±6.74	58.40±4.94*	<0.00001*	58.40±4.94*	48.45±1.11	0.0001*
Serum Cu (µg/dl)	86.90±7.07	90.70±7.93	0.04*	90.70±7.93	98.23±5.64	0.03*
Serum Zn (µg/dl)	82.09±5.94	84.81±7.10	0.07**	84.81±7.10	92.01±5.06	0.02*

Values are presented in geometric means; p values were assessed by the Student's t-test.

n – numbers of Subjects; \*significant at p < 0.05; \*\* not significant p > 0.05.

This trend is clearly visible in Figure 2. This demonstrates the deteriorating effect of smoking and alcoholic habits on human health which plays a negative catalytic effect among in subjects exposed to air borne respirable dust. Increase in serum Cu and

Serum Zn has also been observed in exposed smoker (Cu: 87.38±6.31, Zn: 80.07±5.59 as compared to controlled smoker (Cu: 81.50±5.01, Zn: 78.06±3.11) corroborating the deteriorating effect of smoking on health.

**Table 6.** Study results for PFT, serum Copper and serum Zinc in subjects with alcoholic and smoking habits as compared to non-smoker and non-alcoholic for control and exposed study groups.

Parameter	Control			Airborne silica Exposed group		
	Non-Smoker and non-alcoholic (n= 30)	non- Only Smoker (n =20)	Non-Smoker and non-alcoholic(n = 30)	Only Smoker or Alcoholic (n =19)	Alcoholic & Smoker (n = 5)	
Age	39.73± 7.24	43.6 ± 5.30	39.56± 5.44	44.26± 2.35	42.6±1.34	
FEV <sub>1</sub> /FVC %	78.90±7.62	78.33± 5.55	70.42±6.74	58.40±4.94	48.45±1.11	
Serum Cu (µg/dl)	78.45±5.04	81.50±5.01	86.90±7.07	90.70±7.93	98.23±5.64	
Serum Zn (µg/dl)	76.13±3.32	78.06±3.11	82.09±5.94	84.81±7.10	92.01±5.06	

Pulmonary parameters of the predicted values shows more significantly decline (p value <0.0001) in ARD exposed smoker or alcoholic as compared in control smokers Table 6. The difference was found to be statistically significant (P<0.05). According to Townsend *et al.* (2011) "FEV<sub>1</sub>/FVC is the first measurement to be evaluated to distinguish obstructive from non-obstructive patterns. When the FEV<sub>1</sub>/FVC and FEV<sub>1</sub> are both less than the lower limit of normal (LLN), airways obstruction is present" (Townsend *et al.*, 2011). It is evident from Table 6 the concentration of serum Cu and Zn for non-smoker

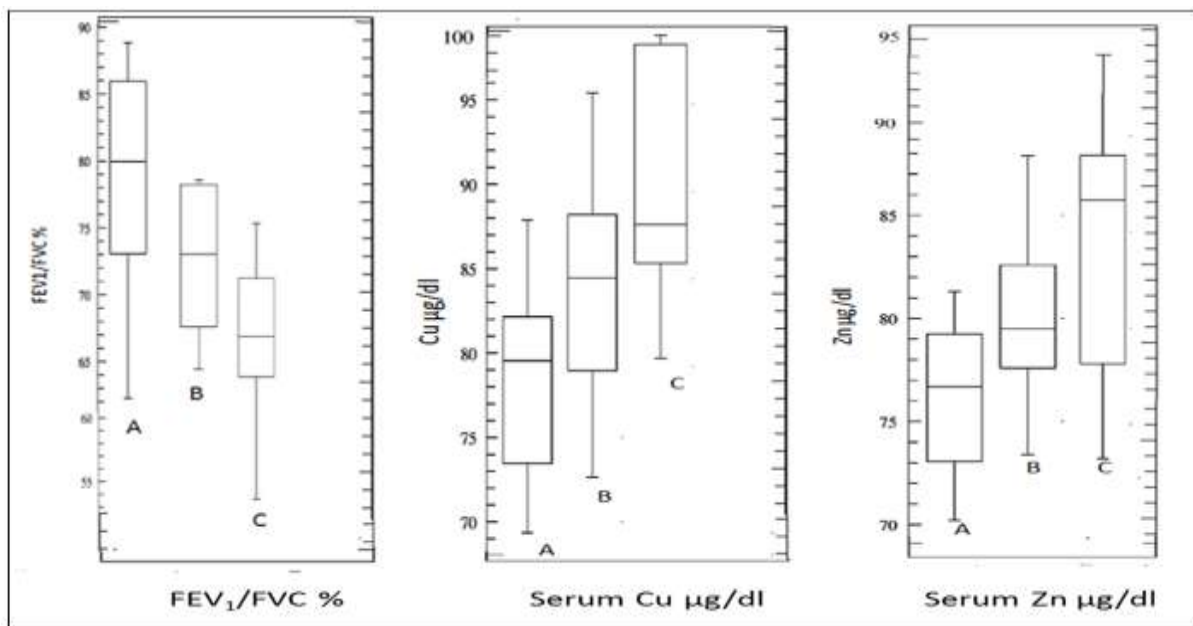
and non-alcoholic workers in exposed were 86.90±7.07 µg/dl and 82.09±5.94µg/dl respectively whereas these values for controls were 78.45±5.04 µg/dl and 76.13±3.32 µg/dl respectively which shows statistically significant increase (p<0.05) in similar group after exposure. The means serum Copper levels in control smoker and exposed smoker were 81.50±5.01 µg/dl and 87.38±6.31 µg/dl showing statistically significant increase (p<0.05), however the corresponding difference in Zn levels (78.62±3.11 µg/dl and 80.07±5.59 µg/dl) are statistically non-significant (p>0.05). Although the study suggests

increase in serum Cu & Zn level in smoker compared to non-smokers, the increase was maximum (Cu:  $98.23 \pm 5.64 \mu\text{g/dl}$  and Zn:  $92.01 \pm 5.06 \mu\text{g/dl}$ ) in exposed subject having both smoking and alcoholic habits (Table 6).

All the aforementioned data analysis and discussion suggest the following:

Long-term occupational exposure to airborne

respirable dust containing free silica is associated with an increased risk for respiratory diseases such as silicosis, tuberculosis, chronic bronchitis, chronic obstructive pulmonary disease and lung cancer. Pulmonary function test (FEV<sub>1</sub>/FVC %) is an established clinical diagnostic tool for health status of the lung. The present study results also support this which shows decreases in PFT values in exposed subjects as compared to non-exposed control.



**Fig. 1.** Box plot of PFT (FEV<sub>1</sub>/FVC), serum Cu and serum Zn among no exposure control, low exposure (< 15 years) and high exposure group (≥15 years). A= No exposed control (n=30), B= Low exposed group (n=16) (< 15 years), C= high exposed group (n=14) (≥15 years). The median (middle quartile) marks the mid-point of the data and is shown by the line that divides the box into two parts. Half the scores are greater than or equal to this value and half are less. Values represented as mean ±SD. The results is statically significant (p<0.05).

The study suggests excellent correlation of PFT values with serum Cu and Zn values. The serum Cu and Zn values increase with decreased in PFT values. The correlation further consolidates when the results are compared in further classified groups viz, (a) no exposure, low exposure (<15 years) and high exposure (>15 years) groups and (b) no habit (non-smoker and non-alcoholic), any one habits (either smoking or alcoholic) and both the habits (smoker and alcoholic) among exposed subjects.

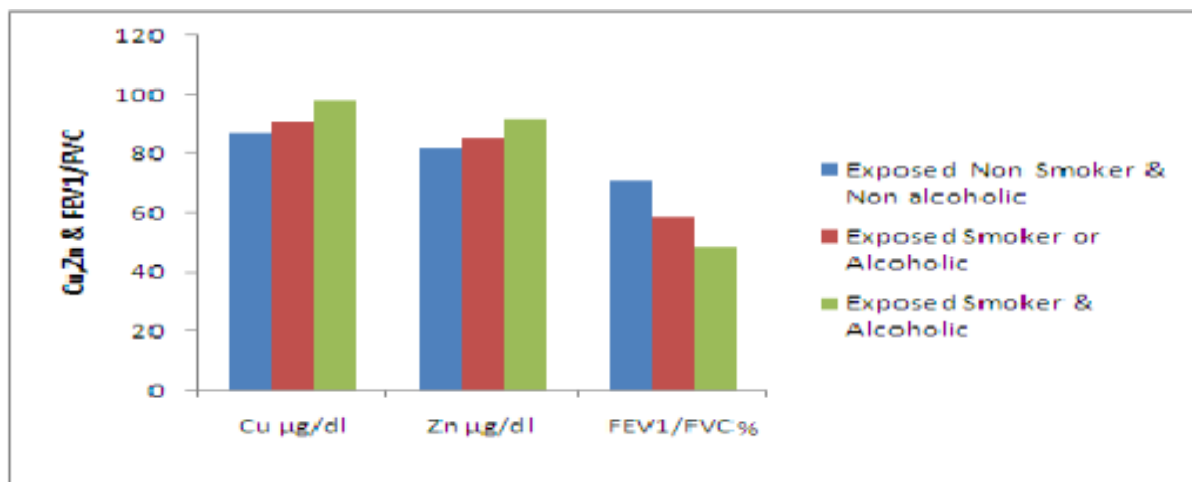
The study results further suggest that Serum Cu and

Zn values are more sensitive parameters for health status of the lung which is demonstrated by the fact that the exposed subjects having normal PFT values shows statistically significant increase in serum Cu (control  $80.56 \pm 5.52 \mu\text{g/dl}$ , exposed  $93.13 \pm 7.65 \mu\text{g/dl}$ ,  $p = 0.0002$ ) and Zn (control  $76.93 \pm 2.61 \mu\text{g/dl}$ , exposed  $83.21 \pm 9.98 \mu\text{g/dl}$ ,  $p = 0.03$ ) as compared to unexposed control (table 4). This suggests the possibility of serum Cu and Zn as biomarkers for dust linked lung diseases.

Finding of the presents study gets strength from the

earlier studies which suggest that Cu has a fibrogenic property (Kolev and Burkova, 1982; Wang *et al.*, 1998). This is explained by increase in ceruloplasmin levels in silicotics which contains eight Cu atoms and may be responsible for such an increase (Ren and

Jiang, 1993). Earlier Study by Baiet *al.*, (1993) also highlight important role of Cu in the progress of lung fibrosis, and participation of Zn in the synthesis of collagen during this process.



**Fig. 2.** Comparison between Serum Copper, Serum Zinc & Pulmonary Function Test among ARD exposed groups Non smokers & non alcoholic (n=30, mean age  $39.56 \pm 5.44$ ), exposed smoker /exposed alcoholic (n=19, mean age  $44.26 \pm 2.35$ ) and exposed smokers & exposed alcoholic (n=5, mean age  $42.6 \pm 1.34$ ).

Since respirable dust exposure-linked lung fibrosis disease is non-curable, their early diagnosis and prognosis using indirect biological parameters called biomarkers provides a better way to deal with the deadly disease. Thus, a Biomarker may enhance the diagnostic accuracy of occupational and environmental illness & ultimately result into prevention of disease. In addition, biomarkers are likely to enhance the understanding of the dose response relationship between exposure to a hazard and an illness. Ultimately, their use may help to evaluate the effectiveness of various control measures.

### Conclusion

Study was conducted for PFT values, serum Cu and serum Zn level among 54 air borne respirable dust exposed coal mine workers and was compared with those of control group of 50 subject having no direct exposure to dust. The control and exposed groups have characteristically similar physical parameters having no significant statistical difference in age weight and height.

PFT value decreases with increase in airborne respirable dust exposure level suggest deteriorating health status of lungs. Decrease in PFT value corresponds to increase in serum Cu and serum Zn level.

This suggests serum Cu and serum Zn level of air borne respirable dust exposed subject as diagnostic tool of health of the lung. Smoking and Alcoholic habits has negative catalytic effect on dust exposed subject leading to faster development of dust linked lung disease. Serum Cu and serum Zn level are more sensitive parameters which are demonstrated by their increased values among dust exposed group despite normal level of PFT values.

Foregoing conclusions suggests strong possibility of serum Cu and Zn levels as biomarkers for dust linked diseases in coal mine worker. Since dust linked lung disease leads to irreversible and incurable coal workers pneumoconiosis (CWP) and Silicosis including lung cancer such Biomarkers may be a very useful prognostic tool for these diseases.



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