Original Article

Surfactant Protein D Levels in Cement Workers

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Abstract

Background: Pneumoconiosis occurs almost all over the world. Pneumoconiosis is a threat to cement workers. Serological abnormalities are observed in pneumoconiosis. Surfactant protein D (SP-D) levels were increased in workers exposed to silica. SP-D may be useful as a biomarker for the early diagnosis of pneumoconiosis but it has not been studied in Indonesia.

Methods: This cross-sectional study was conducted with consecutive sampling technique. The number of subjects was 61 people, consisting of 44 workers exposed to cement and 17 controls from September 2017 to March 2018. Serum level of SP-D was measured using ELISA method. Cement exposed workers were workers in the production area and workers in quarry areas.

Results: All of the study subjects were male (100%) with mean age of 42.5 years old. The youngest and oldest subjects were 21 and 55 years old, respectively. Majority of the subjects was in the normal weight group (47.7%). Based on smoking history, there were 26 subjects (59.1%) had never smoked, 12 subjects (27.3%) as smokers, and 6 subjects (13.6%) as former smokers. Duration of exposure <10 years was found in 9 subjects (20.5%) while exposure ≥10 years was observed in 35 subjects (79.5%). Good category of using self-respiratory safety instrument was observed in 5 subjects (11.4%), moderate category in 36 subjects (81.8%) and poor category in 3 subjects (6.8%). Mean serum SP-D levels in the exposed group was 111.027 ng/ml and in control group was 67.648 ng/ml. Serum SP-D levels were significantly higher in the exposed group than control group (*P*=0.014).

Conclusion: Serum SP-D levels was statistically higher in the exposed group than in control group.

Keywords: biomarker, cement worker, serum SP-D levels

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INTRODUCTION

The cement industry in Indonesia displays encouraging developments with increasing production output. This development will certainly be beneficial from an economic point of view, but the negative effects arose from these industrial developments will also have an impact on health.[1] The cement industry causes air pollution both inside and outside the work environment which has an influence on the respiratory system. Work environment factors are defined as potential sources of hazard that may occur in the work environment due to a work process.[2]

Air quality conditions in the work environment can play a role in occupational health. Several studies in cement factories that measured dust exposure, including a study in Tanzania, pointed out high levels of dust exposure in several work areas.[2] Study in Indonesia on 2006 obtained the highest dust levels in mining areas (20.23 mg/m^3), packing (18.47mg/m^3), and limestone crusher (14.98 mg/m^3). The results of this study indicated that there were several working areas in the cement factory with dust levels which did not meet the standard limit compared to the threshold value issued by the Minister of Manpower.[3]

Pneumoconiosis is an occupational lung disease caused by deposition of dust in the lungs and the reaction of lung tissue due to dust exposure.[4] Pneumoconiosis occurs almost all over the world and is a problem that threatens the workers. Data on the prevalence of pneumoconiosis, including silicosis, vary from country to country in the world. The Pathology Automation System (PATHAUT) database, a record of data from pathologists in South Africa, reported autopsy results on the deaths of mining workers with occupational lung disease. In 2014 there were 206 cases of silicosis (19.3% of all autopsy cases).[5] Data from World Health Organization (WHO)

in 2002 reported that 1.288.000 cases of pneumoconiosis occur every year.[6]

In Indonesia, various studies on the effect of dust on workers' health have been carried out, but national data on the prevalence of pneumoconiosis in Indonesia are currently not available. Reports of the effects of cement dust vary. Research on residents living near cement factories by Setiawan and Musawaris mentioned a significantly higher prevalence of impaired lung function and chronic bronchitis in exposed areas than in unexposed areas.[7,8]

Fordiastiko in 2001 revealed that about 9.4% of the chest x-rays (CXR) of cement workers were suspected of having pneumoconiosis with also pulmonary function abnormalities in the form of restriction (7.3%) and obstruction (19.4%).[9] Wihastuti did not find pneumoconiosis in their study.[10] Yunus et al. in 2007 obtained radiological suspicion of pneumoconiosis in 0.5% of cement factory workers.[11]

Efforts to look for the possibility of finding silicosis earlier have begun to be developed. Several serological abnormalities can be found in patients with silicosis, but none can diagnose this disease, and tests performed to detect abnormalities are not routinely carried out.[12] Study by Wang et al. in 2007 found that serum level of Clara cell protein (CC16) was decreased in workers exposed to silica, while the serum level of surfactant protein D (SP-D) was increased. Serum CC16 and SP-D levels could be used as biomarkers for the early diagnosis of silicosis.[13] Study on differences in serum surfactant levels of workers exposed to industrial dust and those who are not exposed is still not widely known even in Indonesia; therefore, this study was proposed and aimed to determine the difference in serum SP-D levels of cement factory workers and the normal population.

METHODS

This was a cross-sectional study. The sampling consecutive of study subjects was conducted at PT. Semen Tonasa Pangkep, South Sulawesi from September 2017 to March 2018. Study subjects were cement workers of PT. Semen Tonasa who worked in the raw material and production areas. Inclusion criteria for study case were those who worked in the raw material and production work areas, have worked for at least 5 years, male, were willing to participate in the study and signed a letter of consent, were willing to have their blood samples taken and followed the research procedures.

Inclusion criteria for control subjects were not working as cement workers, not living in the surrounding area near the factory, willing to participate in the study and signed the consent letter, willing to have their blood samples taken and followed the research procedures. Exclusion criteria were having a history of pulmonary TB, bronchiectasis, pneumonia, asthma, COPD, lung tumors, and corticosteroid treatment.

RESULTS

The number of subjects in this study was 94 subjects. There were 2 study subjects who were dropped out, 21 study subjects excluded due to incomplete CXR data (20 subjects) and a suspicion of pulmonary TB on CXR (1 subject).

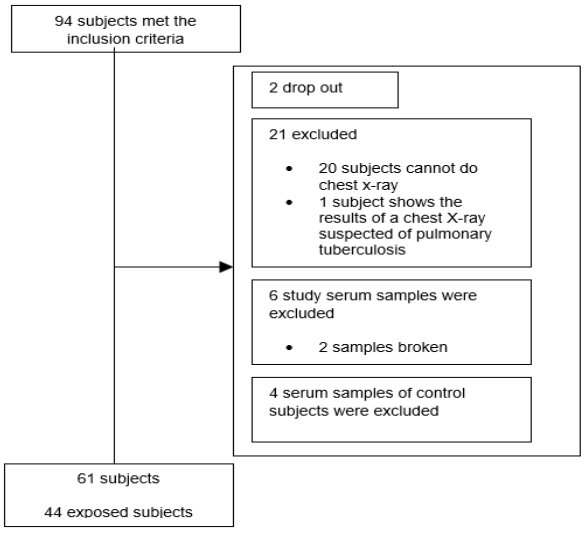

Figure 1. Subject flow that meets the research criteria

About 6 samples of study subjects were excluded because damaged samples (2 samples) and damaged labels (4 samples). There were 4 excluded samples of control subjects due to damaged labels. The total study subjects who met the

criteria were 44 people, while the control subjects were 17 people, as seen in the following (Figure 1).

Table 1. Subjects characteristics

Variable	Exposed (n=44) n (%)	Control (n=17) n (%)	Total (n=61) n (%)
Gender			
Male	44 (100)	17 (100)	61 (100)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Age			
<40 years	11 (25)	15 (88.2)	26 (42.6)
≥40 years	33 (75)	2 (11.8)	17 (57.37)
Education			
Low	5 (11.4)	0 (0.0)	5 (8.2)
Moderate	29 (65.9)	0 (0.0)	29 (47.5)
High	10 (22.7)	17 (100)	27 (44.3)
BMI			
Less	1 (2.3)	0 (0.0)	1 (1.63)
Normal	21 (47.7)	9 (52.9)	30 (49.2)
Overweight	14 (31.8)	3 (17.6)	17 (27.9)
Obesity	8 (18.2)	5 (29.4)	13 (21.3)
Smoking History			
Non-smokers	26 (59.1)	17 (100)	43 (70.5)
Ex-smokers	6 (13.6).	0 (0.0)	6 (9.8)
Smokers	12 (27.3)	0 (0.0)	12 (19.7)
IB			
Mild	10 (22.7)	0 (0.0)	10 (16.4)
Moderate	8 (18.2)	0 (0.0)	8 (13.1)
Heavy	0 (0.0)	0 (0.0)	0 (0.0)
PPE			
Good	5 (11.4)	0 (0.0)	5 (8.1)
Moderate	36 (81.8)	0 (0.0)	36 (59)
Bad	3 (6.8)	0 (0.0)	3 (5)
Length of Work			
<10 years	9 (20.5)	0 (0.0)	9 (14.7)
≥10 years	35 (79.5)	0 (0.0)	35 (57.37)
Respiratory Complaints			
Existed	2 (4.5)	0 (0.0)	2 (3.27)
None	42 (95.5)	0 (0.0)	42 (68.8)
Working Areas			
Cement Packer	6 (13.6)	0 (0.0)	6 (14.8)
Kiln	4 (9.1)	0 (0.0)	4 (6.6)
Crusher	10 (22.7)	0 (0.0)	10 (16.4)
Finish mill	6 (13.6)	0 (0.0)	6 (9.8)
Quarry	5 (11.4)	0 (0.0)	5 (8.1)
Raw mill	2 (4.5)	0 (0.0)	2 (3.27)
Silica crusher	6 (13.6)	0 (0.0)	6 (9.8)
Others	5 (11.4)	0 (0.0)	5 (8.2)

All subjects were male (100%). The mean age of the study subjects was 42.5 years, with the youngest subject being 21 years old and the oldest being 55 years old. Subjects in the age group <40 years were 11 subjects (25%), while in the age group >40 years were 33 subjects (75%). Most of the subjects were at moderate education (65.9%), followed by high education level in 10 subjects (22.7%) and low education level in 5 subjects (11.4%).

In general, almost all study subjects had no respiratory complaints (95.5%). In this study, the study subjects worked in 8 areas, namely the cement packing area for as many as 6 subjects (13.6%), the kiln area (an installation that produces cement which has areas such as calcination area, transition area, combustion area and cooling area) for as many as 4 subjects (9.1%), the crusher area for as many as 10 subjects (22.7%), the finishing mill area for as many as 6 subjects (13.6%), the quarry area for 5 subjects (11.4%), the raw mill area for 2 subjects (4.5%), the silica crusher area for 6 subjects (13.6%), and other areas for 5 subjects (11.4%). Table 1 shows the characteristics of the subjects in this study.

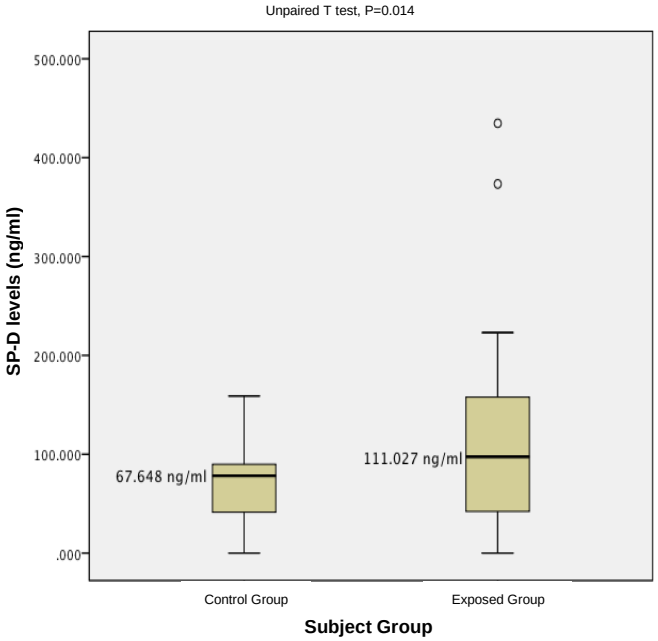

Figure 2. Box plot graph of SP-D levels in the exposed and control groups

In this study, the mean SP-D levels in the exposed group and in the control group were 111.027 ng/ml and 67.648 ng/ml, respectively. Figure 2 is a box plot graph which describes the levels of SP-D in the exposed group and the control group. The difference in SP-D levels between the exposed group and control group was statistically significant with *P*=0.014, as observed in Table 2.

Table 2. Serum SP-D levels based on the exposed group and the control group

	Research Group	n	Mean	SD	*P**
SP-D (ng/ml)	Exposed	44	111.027	91.654	0.014
	Control	17	67.648	41.092	

Note= *Unpaired T-test

This study obtained that the mean serum SP-D level in the <40 years age group was lower (87.624 ng/ml) compared the age 40 years (118.827 ng/ml). The correlation between serum SP-D levels and the age group of the study subjects was not statistically significant (*P*=0.241), which can be seen in Table 3.

From table 3, the serum SP-D levels in low BMI group, normoweight, overweight and obese groups were 434.693 ng/ml, 122.357 ng/ml, 94.183 ng/ml, and 70.300 ng/ml, respectively. The correlation between serum SP-D levels and the BMI group of study subjects was statistically significant (*P*=0.001).

The mean results of serum SP-D levels in the mild IB group and the moderate IB group were 74.947 ng/ml and 106.264 ng/ml. The association between SP-D levels and IB was not statistically significant (*P*=0.324). In this study, the mean serum SP-D levels were 126.368 ng/ml in the non-smoker group, 51.584 ng/ml in the ex-smoker group, and 107.506 ng/ml in the smoker group. The correlation between serum SP-D levels and smoking history was not statistically significant (*P*=0.198).

In this study, the mean SP-D levels among subjects with good PPE use, moderate PPE use and bad PPE use were 66.782 ng/ml, 105.702 ng/ml, and 248.656 ng/ml, respectively. The correlation between SP-D levels and PPE use was statistically significant (*P*=0.016). Based on the post hoc analysis, it was found that the association between good PPE use and moderate PPE use was not significantly different with *P*=1.000, but the association between good PPE use and bad PPE use was significantly different with *P*= 0.016.

Mean SP-D level for subjects with <10 years length of work was 65.425 ng/ml, while those with ≥10 years length of work group was 112.753 ng/ml. The correlation between SP-D levels and the duration of the workgroup was statistically significant with *P*=0.015, and it can be observed in Table 3.

Table 3. Correlation of Serum SP-D Levels with Age, BMI, Smoking History, IB, PPE and Length of Work

Variable	SP-D levels (ng/ml)				
	n	Mean	SD	Post Hoc	*P*
Age					
<40 years	11	87.624	64.904	----	0.241*
≥40 years	33	118.827	98.594	----	
BMI					
Low	1	434.693	----		
Normoweight	21	122.357	83.099	----	0.001**
Overweight	14	94.183	58.176	----	
Obese	8	70.300	88.172	----	
Smoking History					
Non-smoker	26	126.368	108.552	----	
Ex-smoker	6	51.584	61.327	----	0.198**
Smoker	12	107.506	43.021	----	
IB					
Mild	26	126.368	108.552	----	
Moderate	10	74.947	46.018	----	0.324**
Heavy	8	106.264	63.532	----	
PPE					
Good	5	66.782	56.977	Ref***	
Moderate	36	105.702	105.702	1.000***	0.014**
Bad	3	248.656	248.665	0.016***	
Length of Work					
<10 years	9	65.425	44.589	----	0.015*
≥10 years	35	112.753	97.285	----	

Note = *Unpaired T-test; **One-way anova test; ****Post hoc*

Table 4. Description of SP-D Serum Levels by Work Area

Work Area	SP-D levels (ng/ml)					
	N	Mean	Med	SD	Min	Max
Cement packer	6	130.7	129.347	18.077	108.8	158.12
Kiln	6	74.48	80.284	24.791	40.1	97.260
Crusher	12	108.7	127.484	89.05	0.000	223.12
Finishing mill	10	118.5	109.059	63.443	26.4	199.93
Quarry	5	115.1	45.092	180.66	4.10	434.69
Silica crusher	9	128.1	74.695	140.03	6.17	373.41
Raw mill	8	45.7	45.713	2.634	43.85	47.576
Others	7	113.4	111.337	69.192	43.85	210.28

DISCUSSION

This was the first study in Indonesia regarding serum SP-D level as a biomarker of occupational lung disease in cement workers. Previous studies have investigated serum SP-D level as a biomarker for various lung diseases, including ARDS, pulmonary fibrosis, alveolar proteinosis, pulmonary tuberculosis, sarcoidosis, asthma, pneumonia, COPD, bronchiectasis, panbronchiolitis, and silicosis.[14]

All subjects (100%) in this study were male. This was because there were no female workers in the affordable population. In this study, the highest mean serum SP-D level was obtained in subjects working in cement packer area, namely 130.796 ng/ml. The difference in surfactant levels by gender was not fully understood, but the study from Sorensen GL et al. reported that SP-D levels were increased in males.[15]

The mean age of the study subjects was 42.5 years, there were more study subjects in the age group ≥40 years (75%). The mean serum SP-D level was higher in the ≥40 years age group (118.827 ng/ml) than in the <40 years age group. In these two age groups, there were differences in SP-D levels although statistically, it was not significant (*P*=0.241). Study subjects in the age group ≥40 years had longer working hours than those <40 years, this could possibly be the cause of differences in SP-D levels. Sorensen GL et al. mentioned that SP-D levels escalated with increasing age.[15]

Majority of the study subjects had no respiratory complaints (95.5%). Only 2 subjects had respiratory complaints. These subjects obtained SP-D levels of 149.013 ng/ml and 15.696 ng/ml. Both had normal chest X-rays, so they were not excluded from the study. One subject had cough for 2 weeks, while the other had cough for 5 days.

About 26 subjects (59.1%) were non-smokers, followed by 12 active smokers (27.3%) and 6 ex-smokers (13.6%). The highest mean serum SP-D level was observed in the non-smoker group (126.368 ng/ml), while the lowest was in the ex-smoker group (51.584 ng/ml). The relationship between serum SP-D levels and smoking history was not statistically significant (*P*=0.198). The mean level of SP-D in the former smokers was lower than in other groups. This result might be influenced by nutritional status because most former smokers had nutritional status in the obesity category. The SP-D levels among obese subjects were found to be lower than other categories. The results obtained in the smoking and non-smoking groups were also likely to be influenced by nutritional status because most subjects of the smoking and non-smoking groups had good nutrition.

Injury to AT-II epithelial cells will lead hyperpermeability of the epithelial-endothelial barrier, leading to an increase in blood surfactant levels. Cigarette smoke can cause injury to AT-II epithelial cells so that low molecular weight surfactant proteins such as SP-A will escape into the blood vessels before SP-D, which has a larger molecular weight. This result is in line with the study of Kobayashi et al. which showed that it was statistically significant for serum SP-A levels but not significant for SP-D levels.[16]

Among the smokers and ex-smokers, mild IB was found in 10 subjects (22.7%), moderate IB in 8 subjects (18.2%), however, severe IB was not obtained in study subjects (0.00%). The mean level of SP-D in the moderate IB group (106.264 ng/ml)

was higher than in the mild IB (74.947 ng/ml). Nevertheless, the correlation between SP-D levels and IB was not statistically significant (*P*=0.324). This was in line with the study of Zaky et al. Higher mean SP-D level was observed in subjects with moderate IB.[17] Kobayashi explained that surfactant protein levels could predict AT-II cell epithelial cell injury induced by cigarette smoke.[16]

Moderate (fair) category of adherence in PPE use was found most in 36 subjects (81.8%), followed by 5 subjects in the good category (11.4%) and the bad category in 3 subjects (6.8%). The highest mean SP-D level was obtained in bad PPE use (248.656 ng/ml), followed by moderate (105.702 ng/ml) and good PPE use (66.782 ng/ml). The correlation between SP-D levels and PPE use was statistically significant (*P*=0.016), however, the post hoc analysis mentioned that good PPE use and moderate PPE use were not significantly different (*P*=1.000). Nonetheless, good PPE use and bad PPE use were significantly different (*P*=0.016). The use of masks is one of the efforts to prevent occupational diseases in the work environment which protects workers from the hazard of exposure to cement dust. According to PPE use in the form of masks, good adherence showed lower results than poor adherence.[18]

Most of the subjects had length of work ≥10 years (79.5%). The correlation between SP-D levels and length of work was not statistically significant, (*P*=0.292). Mean SP-D level in subjects with working duration ≥10 years was higher (112.753 ng/ml) than those <10 years (65.426 ng/ml). Although not statistically significant, the increase in SP-D levels was parallel with the increase in length of work over 10 years. The longer the exposure lasts, the number of particles which settle in the lungs also elevates. Every inhalation of 500 particles per cubic millimeter of air induces the alveoli to receive at least 1% of the particles.[27]

If the concentration reaches 1000 particles per cubic millimeter, 10% of that amount will be deposited in the lungs. Concentrations exceeding 5000 particles per cubic millimeter are often associated with pneumoconiosis. Pneumoconiosis due to dust will occur after the patient has been in contact with dust for a long time.[19] Abnormalities are rare when exposure is still less than 10 years.[20] In this study, all subjects were not proven to have pneumoconiosis because it might be related to the concentration of inhaled dust exposure, and there was still an effect of medium category of mask adherence. Although the study subjects did not have pneumoconiosis, SP-D levels pointed out an increase in the results with the escalating duration of exposure.

The work area was one of the factors which could affect the occurrence of occupational lung disease. Portland cement will not cause silicosis because it does not contain free silica, but the manufacture of cement uses a mixture of silica sand containing free silica with varying levels so that silicosis can occur in workers in the raw material area, cleaners, workers in closed rooms and slag milling.[16,21] Although all subjects did not exhibit silicosis, the SP-D levels in the cement packer, finish mill, silica crusher, crusher areas were quite high compared to subjects in the control group.

The difference in SP-D levels in the exposed and control groups was statistically significant with a *P*-value of 0.014. This could be influenced by adherence to PPE, nutritional status, and the length of work. Studies on differences in SP-D levels in lung disease with control groups have been carried out in various diseases. Study on subjects with fibrotic lung disease obtained a mean SP-D level of 339 ng/ml while the control group had 66 ng/ml.[14]

Subjects with alveolar proteinosis, pulmonary TB, sarcoidosis had mean SP-D levels of 461 ng/ml, 119 ng/ml, and 104 ng/ml, respectively, while it was 66 ng/ml in the control group.[14] A study from Wang et al. of factory workers exposed to silica, factory workers with suspected silicosis, and factory workers diagnosed with silicosis mentioned that the SP-D results were significantly different on the suspected silicosis group and the silicosis group compared to controls.[13]

The difference of SP-D levels in the control group and the group exposed to cement dust that was not diagnosed with pneumoconiosis were found to be statistically significant. The mechanism by which SP-D is present in serum is stated by several hypotheses,

namely: elevated apoprotein concentration gradient between the alveoli and the circulation, increased pulmonary capillary permeability, destruction of the barrier between the alveolar epithelium and the endothelium epithelium, i.e injury to the basement membrane and escalated clearance of surfactant from the circulation. The detectable level of SP-D in serum can be used as a non-invasive diagnostic tool in several lung diseases.[21]

The highest dust content was observed in the cement packer area of 31.45 mg/m^3, followed by the crusher area of 9.78 mg/m^3, the finishing mill area of 4.41 mg/m^3, and the raw mill area of 0.52 mg/m^3. Previous study in Indonesia revelaed that the dust content in cement packer area was 18.47 mg/m^3, in mining area was 20.23 mg/m^3, and in crusher area was 14.98 mg/m^3, while the raw mill and finishing mill areas were both <10 mg/m^3.

In cement packer area, there was an increase in dust content. Elevated levels of dust which exceed the NAV can be a risk factor for pneumoconiosis in cement workers. Tungu mentioned that with a decrease in total dust content, there was also an increase in lung function among cement workers.[22]

LIMITATION

This study employed limited population for control subjects even though it was in accordance with the operational definition. All research subjects were listed as workers working in the production and raw material areas, but there were still cement workers who were not registered as employees of PT Tonasa in the work area, so that researchers could not enroll them as study samples. Researchers could not select the location of work areas to evaluate the dust content.

CONCLUSION

Most subjects aged ≥40 years with good nutritional status, were non-smokers, had medium category of PPE use and mostly had length of work ≥10 years. The difference of SP-D levels in the exposed group compared to the control group was statistically significant. The correlations of serum SP-D levels to age, smoking history, IB, length of work were not statistically significant among the study subjects.

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CONFLICT OF INTEREST

None.

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