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INCREASING SERUM LEVELS OF NEPHRONECTIN BASED ON EXPOSURE DURATION OF SILICA DUST IN MARBLE INDUSTRY WORKERS

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Abstract

Background: *Exposure to silica dust is still an occupational health problem worldwide. Marble industry is one of the industries at risk of causing respiratory disease in its workers. Exposure to silica dust in the airways triggers pulmonary fibrosis via nephronectin (Npnt) as an α8β1 integrin ligand, which is an extracellular matrix protein. This study aims to analyze changes in serum nephronectin (npnt) levels based on duration of exposure to silica dust.*

Methods: *This is cross sectional analytical study. Subjects including marble industry workers. A significant difference test is carried out on 4 groups of subjects (n=50), including marble industry workers with exposure durations of 1-5 years (n=12), 6-10 years (n=14) and >10 years (n=14).), as well as non-marble industry workers (unexposed) as control subjects (n=10). A correlation test is performed to see the relationship between duration of exposure and serum Npnt levels.*

Results: *The median age value in the exposed group is 40.5 (20-67) years. There is a significant (p = 0.012) difference in the median Npnt level of the exposed group {1.699 (0.22-5.27)ng/mL} and the non-exposed group {0.678 (0.21-1.96) ng/mL}. The median value of nephronectin levels in the 10 year exposed group {2.4710 (1.74-5.27) ng/mL} are significantly (p=0.000) different with both the 1-5 year exposed group {0.6960 (0.22-2.27) ng /mL} and compared to the 6-10 year exposed group is also significant (p=0.039) with a median value of {1.0480 (0.27-4.29) ng/mL}.There is a significant (p = 0.000) positive relationship (r = +0.633) between the length of exposure and the level of Npnt.*

Conclusion: *Duration of exposure to silica dust has a significant effect on serum Npnt levels. The longer the marble industry workers are exposed to silica dust, the higher the serum Nephronectin level*

Key words: *nephronectin, silica, marble*

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Introduction

Silica dust exposure is still an occupational health problem worldwide. It was estimated that 2 million people in the United States and 3 million people in Europe were exposed to silica dust in their work environment.[1] In Asia, it was estimated that more than 23 million people in China and 10 million people in India were exposed to silica dust in their work environment. Currently, there is no national data on the prevalence of occupational diseases due to the inhalation of silica dust in Indonesia. Studies conducted in a cement factory showed a radiological suspicion of silicosis of 0.5%. A study conducted at a cement factory in West Java showed that the incidence of silicosis was 2.06% in 1990-2003.[2]

Marble is also a raw material for tiles, tables, and floors. This industry produces fine dust, which is a source of occupational health problems worldwide. Marble industry workers are most at risk of exposure to marble dust which contains calcium carbonate and silica.[3] Continuous exposure to marble dust can reduce lung function and cause various lung diseases such as chronic obstructive pulmonary disease and silicosis.[4] Silicosis is caused by chronic inhalation of large amounts of dust from an environment containing silica particles. Pathological changes in silicosis include the formation of irreversible silicosis nodules and excessive extracellular matrix (ECM) deposition, leading to pulmonary insufficiency. Although the aetiology of silicosis remains unclear, various emerging studies have shown that several specific types of cells and cytokines play an essential role in the process of silicosis.[5]

Nephronectin (Npnt) is an α8β1 integrin ligand which is an extracellular matrix protein. Nephronectin is expressed in various tissues and organs: kidney, lung, choroid plexus, tongue, jawbone, dental epithelium, and facial bone.[6] A study by Lee et al. found that nephronectin (Npnt) levels were elevated in silicosis patients. This result indicates that Npnt plays a role in the initiation and progression of silica-induced pulmonary fibrosis. In addition, decreased lung function (%FEV1) is also associated with high Npnt levels. Lee also found that Npnt was associated with the late phase of pulmonary fibrosis.[7]

Based on the description above, this study aims to analyse changes in nephronectin levels according to the duration of exposure to silica dust in marble industry workers.

Materials and Methods

This is a cross-sectional analytic study with the subjects of marble industry workers in Tulungagung, Indonesia. Samples were obtained through stratified random sampling that met the inclusion and exclusion criteria and obtained 50 subjects divided into four treatment groups. Inclusion criteria included men aged 18-70 years who worked at least one year in the marble industry and signed informed consent. Exclusion criteria were workers with a history of chronic lung disease and workers with malignancy, growth disorders, connective tissue diseases obtained based on interviews and physical examinations.

The collected data were characteristics and clinical history of patients using patient data research forms, respiratory signs and symptoms using CXR (chest x-ray) photos as the tools for evidence, and serum Npnt levels using 3 ml of the subject's blood specimen. The measurement of serum Nephronectin levels used ELISA device (Cat. No. E5745Hu).

A significant difference test was conducted for serum Npnt levels in 4 groups of subjects, namely marble industry workers with consecutive exposures of 1-5 years (12 subjects), 6-10 years (14 subjects), >10 years (14 subjects), and healthy subjects who were not marble industry workers (unexposed) as control subject (10 subjects). Analysis of the difference test using one-way ANOVA if the data was normal, followed by post-hoc analysis with Bonferroni. If the normality of the data was not fulfilled, a non-parametric test with the Kruskal-

Wallis test is carried out, and it is significant if $p \leq 0.05$.

A correlation test of serum Npnt levels was also conducted in 4 groups of subjects using linear regression analysis. If the normality of the data was not fulfilled, a non-parametric test with an ordinal regression test was carried out, the magnitude of the correlation was expressed by r (-1 to +1).

Results

The mean age of the subjects was 40.08 ± 10.99 years. Based on the length of exposure, the shortest exposure time was one year, and the longest was 39 years. Most workers had an exposure duration of 6-10 (35%) and exposure duration of more than ten years (35%). Most of the workers (55%) were smokers with a mild Brinkman Index. Most subjects used masks, but it was not according to standards (45%). In this case, the use of masks that meet the standards is surgical masks covered with cloth masks. According to the subject's CXR, 90% of the subjects had a normal X-Ray, and 10% with an abnormal X-Ray. The abnormal chest x-ray was in the form of chronic bronchitis in 5% of the subjects, 2.5% of the hilar thickening, and 2.5 % of subjects with minimal pleural effusion. Patient characteristics are described in Table 1.

There was a significant ($p = 0.012$) increase in Npnt levels in marble industry workers compared to non-marble industry workers (control subjects). The mean value of Npnt levels of marble industry workers (1.7517 ± 1.20218 ng/mL) was significantly higher than the Npnt levels of control subjects who were not marble industry workers (0.8014 ± 0.61660 ng/mL). The mean serum Npnt levels are described in Figure 1.

There was a significant result from the comparison of the mean Npnt level between the ten years exposed group and 1-5 years exposed group ($p<0.00$) and 6-10 years exposed group ($p=0.039$). This result indicates that the mean Npnt level of the >10 years exposed group was significantly different ($p=0.00$) from the other three groups, including the unexposed group.

However, there was no significant result for the comparison of the mean Npnt level between 1-5 years exposed group and 6-10 years exposed group ($p=0.08$), 1-5 years exposed group and control group ($p=0.922$), and 6-10 years exposed group and control group ($p=0.089$).

In conclusion, the results were shown to be significant only at >10 years of exposure compared to other groups. Nephronectin levels in the exposed groups and control group and the results of comparison test are described in Table 2 and Table 3.

Table 1. Characteristics of Subjects (n=40)

Characteristics	N	(%)	Median (min-max)
Age (years)			40,5 (20 - 67)
Working duration (years)			
• 1-5 years	12	30	
• 6-10 years	14	35	
• >10 years	14	35	
Cumulative duration of exposure (hours-years)			
Smoking			
• Smokers	22	55	
• Ex-smokers	5	12,5	
• Non-smokers	13	32,5	
Brinkmann Index (n=22)			
• Mild (0-199)	2\0	90,9	
• Moderate (200-599)	2	9,09	
• Severe (> 600)	0	0	
Use of Personal Protective Equipment (PPE)			
• Never use any masks	8	12.5	
• Sometimes use non-standard masks	17	42,5	
• Always use non-standard masks	18	45	
• Sometimes use standard masks			
• Always use standard mask			
Clinical Symptoms of Respiratory Disorders			
• No symptoms	40	100	
• no symptoms for more than 2 weeks	0	0	
Chest X-ray			
• Normal lung	36	90	
• Pathologic lung	4	10	

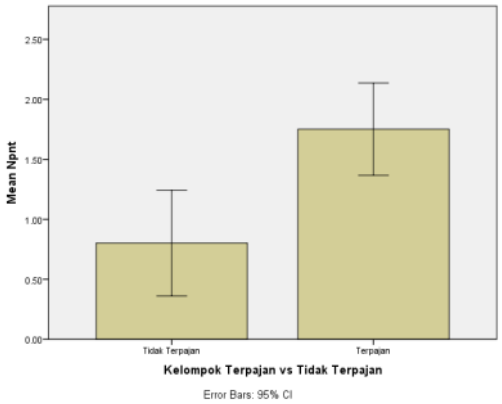

Figure 1. Comparison of the Mean Value of Serum Nephronectin Levels between the Exposed Group and the Unexposed Group

Table 2. Nephronectin levels in the exposed groups and the control group

Exposure	N	Median (Min-Max)
Unexposed	10	0,6780 (0,21 - 1,96) ng/mL
Exposure 1-5 years	12	0.6960 (0.22 - 2.27) ng/mL
Exposure 6-10 years	14	1.0480 (0.27 - 4.29) ng/mL
Exposure > 10 years	14	2.4710 (1.74 - 5.27) ng/mL

Table 3. Comparison of Nephronectin Level's Median between Four Exposure Groups

Comparison of Npnt levels		p
Control	Exposed 1-5 year	0.922
Control	Exposed 6-10 year	0.089
Control	Exposed ≥ 10 year	0.000*)
Exposed 1-5 year	Exposed 6-10 year	0.080
Exposed 1-5 year	Exposed ≥ 10 year	0.000*)
Exposed 6-10 year	Exposed ≥ 10 year	0.039*)

*) P- Value < 0.05 are significant

Relationship between duration of exposure and Npnt levels. There was a very close relationship (p=0.000) between duration of exposure and cumulative duration of exposure with Npnt levels. Therefore, the duration of exposure and the cumulative duration of exposure to silica dust significantly affect Npnt levels in marble industry workers. This study also showed that the duration of exposure and the cumulative duration of exposure was directly proportional to the Npnt levels (positive correlation value +0.633 for the duration of exposure and +0.633 for the cumulative duration of exposure).

Accordingly, the longer a worker is exposed to silica dust, the higher the Npnt serum level of the worker. On the other hand, the shorter a worker is exposed to silica dust, the lower the serum Npnt level. The duration of exposure and the cumulative duration of exposure is depicted in Figure 2 and Figure 3.

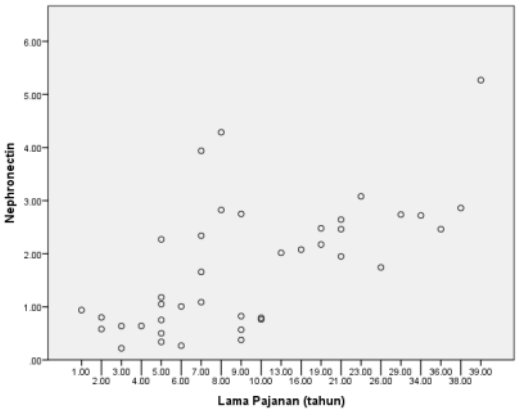

Figure 2. *Scatter Plot* of Exposure to Nephronectin Levels

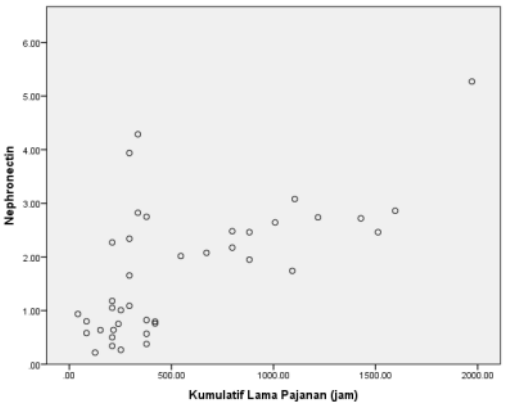

Figure 3. *Scatter Plot* of Cumulative Length of Exposure to Nephronectin Level

To remove the potential bias within this study, we analyse 3 confounding variables of age, smoking behaviour, the use of Personal Protective Equipment (PPE), and duration of exposure as independent variable. The result showed that all combined four variables significantly (p=0.000) affected Nephronectin

levels in marble industry workers. The duration of exposure and smoking behaviour significantly (p=0.000 and p = 0.048 with R = 0.470) affected Npnt levels in marble industry workers, where the duration of exposure had a stronger effect than smoking behaviour.

Thus, 47% of Nephronectin levels data diversity was influenced by the four independent variables using the multiple regression model, while other factors outside the model only influenced 53%. On the other hand, the age of workers and the use of PPE had no significant effect on Npnt levels (p=0.0795 and p=0.582). The resume of significant value of confounding factors are described in Table 4.

Table 4. Resume of significant value of confounding factors

Confounding Factors	Significant Value
Duration of exposure	0.003
Age	0.795
Smoking	0.048
Use of PPE	0.582

In this study, we also want to know whether change of nephronectin level followed by abnormality of CXR of marble industry workers. Based on logistic regression analysis, the significance value of the simultaneous test is 0.481, and the partial test with a significance value of 0.505. Therefore, the levels of Npnt had no significant effect on the CXR of the marble industry workers.

The duration of exposure did not significantly affect the CXR of the marble industry workers in this study. The logistic regression analysis results found that the significance value of the simultaneous and partial test of the variable length of exposure was 0.511 and 0.499. Therefore, can be concluded that duration of exposure had no significant effect on CXR of the marble industry workers.

Discussion

The subjects in this study were men aged 18 to 67 years with an average age of 40.08 ± 10.99 years. In a previous study conducted by Khoiroh, who also used marble workers as subjects, the average age of marble industry workers was around 46-55 years old.[8] However, there's different from study by Imran et al, with the results shows that average age of marble industry workers was 29,92 year ± 6,19 years old.[9] Productive human resources in Indonesia have entered the working age or productive age, namely 15 to 64 years. This data shows that the workers in the marble industry are classified as productive age.

Workers with 1-5 years of exposure to silica dust were 12 subjects (30%), 6-10 years exposure were 14 subject (35%), and >10 years were 14 people (35%). These results are consistent with Khoiroh's research, where most marble industry workers have worked for 13 to 19 years,[8] in El-Gammal *et al.*'s research for 5 to 35 years.[3]

The number of subjects smokers were 22 people (55%). Eryani (2015) showed that several factors affect lung function capacities: age, gender, years of service, length of work, work history, disease history, nutritional status, smoking habits, and exercise habits.[10] This study follows Wijaya's research (2019), where 83.6% of stone processing workers exposed to silica dust had a smoking habit.[2] Research from Fathmaulida (2013) also shows that smoking habits were found in limestone processing workers by consuming 13 cigarettes per day. However, the relationship between smoking and lung disorders in these workers did not show a significant relationship.[11] Several findings have shown that smokers exposed to silica dust are more likely to develop clinical silicosis than non-smokers exposed to the same dose.[12] Thus, education for workers about smoking cessation is important to reduce the adverse effects of silica dust exposure on health.

Most research subjects always used masks but not according to the standard, namely 18 people (45%). This finding is similar to the research conducted by Hutomo in 2016 to see the level of knowledge regarding the use of PPE for furniture industry workers in Jepara, Indonesia. In this study, it was found that

most of the respondents used PPE masks (47.6%), although knowledge about the types of masks was not good (46%).[13]

All subjects did not experience clinical symptoms of respiratory distress. It is different from what Sahrun found (2018) that mining, metal, and ceramic workers who spend ± 8 hours/day, which inhales ± 3500L of air, including dust particles or other contaminants at work, will be exposed to clinical manifestations of lung disease.[14]

There was a significant increase in Npnt levels in marble industry workers compared to control subjects (p= 0.012). These results are consistent with Lee et al.'s study, which showed that there were higher levels of Nephronectin in patients exposed to silica dust than in normal patients (who were not exposed). Nephronectin also plays an essential role in inducing and developing pulmonary fibrosis due to silicosis.[7]

There is a relationship between the differences in serum levels of Nephronectin (Npnt) according to the duration of exposure to silica dust in marble workers. In this study, the results were shown to be significant at >10 years of exposure. The main factors that play a role in the pathogenesis of silicosis are dust particles and the response of the body, especially the respiratory tract, to these dust particles. Chemical composition, physical properties, dose, and duration of exposure determine whether or not silicosis can occur easily. The amount of inhaled crystalline silica depends on the concentration and particle size (<5μm) as well as individual susceptibility.[10] The most common crystalline forms of silica in the workplace include quartz, tridymite, and cristobalite. Quartz contains the highest free silica, so workers exposed to these crystals provide a fast latency period.[15] Workers with high silica exposure categories have a 30 times higher risk of death than workers with low or no exposure to crystalline silica.[16]

These results showed that the duration of exposure and the cumulative duration of exposure to silica dust significantly affected Npnt levels in marble industry workers. This study also showed that the longer a worker is exposed to silica dust, the higher the Npnt serum level of the worker. This follows research from Alonso *et al.* in Spain, which showed that the duration of exposure to silica dust for 15-20 years had a significant effect on the incidence of silicosis.[17] According to procedures, the shorter duration of marble workers in Indonesia can be caused by improper PPE rules. Thus, to have high levels of Npnt as an indicator of silicosis, the exposure time is shorter, starting at the 10th year of exposure compared to the study from Alonso,[17] which began in the 15th year.

The four independent variables, namely Duration of Exposure, Age, History of Cigarettes and Use of Personal Protective Equipment (PPE), significantly affected Nephronectin levels in marble industry workers (p = 0.000). The duration of exposure and smoking had a significant effect on the levels of Npnt in marble industry workers, and the duration of exposure had a stronger effect than smoking (p = 0.000 and p = 0.048 with R = 0.470). These results are also supported by research from Lee et al. in Japan, which showed a relationship between Nephronectin levels in subjects exposed to silica dust, but there was no relationship between age and Npnt levels.[7] Wijaya et al found that 83.6% of stone processing workers exposed to silica dust had a smoking habit. However, there were no significant results in the same study between smoking habits and serum TGF-β1 as a biomarker of silica in the blood. This is due to the small proportion of subjects in the study.[2]

In contrast, smoking can cause an increase in serum TGF-β1 levels due to the immunosuppressive effect of TGF-β1 on the immune system. Smokers with 20 cigarettes per day have a higher mean serum TGF-β1 level than non-smokers and smokers with consumption of <20 cigarettes per day. Serum TGF-β1 levels increase with the increase in the number of cigarette consumption.[18]

This study concluded that the levels of Npnt have no significant effect on the CXR of marble industry workers. CXR is one of the essential tools in detecting pneumoconiosis (asbestosis, silicosis, and pneumoconiosis in coal miners). On exposure to silica dust, the development of opacity with a diameter of more than 1 cm will be seen. The standard of the CXR interpretation method has been determined by the International Labour Office (ILO).[19] Even though the standard has been used, there is still variability between readers of the CXR results. Radiographs may also be less sensitive to early-stage changes produced by exposure to dust. For example, it was estimated that about 20% of asbestos-exposed workers with pulmonary fibrosis on pathological examination do not show any abnormal changes detected on radiographs. CXR alone is inadequate to serve as a surveillance tool or to detect occupational lung disease. Bronchitis is difficult to detect on CXR. Emphysema is accurately detected only at an advanced stage.[19]

In a study conducted by Lopes in 2008, there was a more significant difference between specialist doctors who read CXR on the results of small opacity readings. The inter-reader variability is less at significant opacity. However, despite these limitations, CXR is still an efficient tool for follow-up evaluation of workers exposed to silica, as it is an inexpensive procedure and subjects are exposed to only low doses of radiation. This study found that the diagnosis of silicosis using a CT scan is better than CXR for early detection of the early phase of the disease and detection of progressive massive fibrosis.[20]

A study conducted by Austin, 2021 also states that CXR alone is not sufficient to detect occupational lung disease. It is recommended to use CT (Coumputed Tomography) scan to diagnose occupational lung disease because CT scan sensitivity is higher for early detection of disease and has better accuracy for determining disease patterns.[21]

This study proved that the length of exposure does not significantly affect the CXR of marble industry workers. This result was not in line with the study conducted by Mitra in 2015 on stone crushing factory workers in Lakshmi, India, which found that the longer the duration of exposure, the higher the prevalence of CXR with statistically significant positive silicosis ($P < 0.05$).[22]

Conclusions

The duration of silica dust exposure has a significant effect on increasing serum Nephronectin levels. The longer the marble industry workers were exposed to silica dust, the higher the serum Nephronectin level

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Article Error You may need to use an article before this word. Consider using the article **the**.

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P/V You have used the passive voice in this sentence. You may want to revise it using the active voice.

Wrong Article You may have used the wrong article or pronoun. Proofread the sentence to make sure that the article or pronoun agrees with the word it describes.

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Sentence Cap. Review the rules for capitalization.

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Frag. This sentence may be a fragment or may have incorrect punctuation. Proofread the sentence to be sure that it has correct punctuation and that it has an independent clause with a complete subject and predicate.

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Possessive

Hyph. Review the rules for using punctuation marks.

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PAGE 6

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PAGE 7

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PAGE 8