Original Article

New insights into pneumoconiosis: The role of serum angiotensin-converting enzyme in inorganic dust exposure

Bilge Akgündüz[1], Levent Özdemir[2], Anıl Uçan[3]

ORCID:
Bilge Akgündüz: 0000-0002-9398-5173
Levent Özdemir: 0000-0002-3478-5454
Anıl Uçan: 0000-0001-8771-6121

Abstract:

BACKGROUND AND AIM: This study aimed to investigate the relationship between inorganic dust exposure and serum angiotensin-converting enzyme (ACE) levels.

METHODS: This cross-sectional study included 176 patients who applied to the outpatient clinic of occupational diseases. Serum ACE levels were compared between groups with and without inorganic dust exposure. Additionally, patients diagnosed with pneumoconiosis were analyzed in relation to serum ACE levels, pulmonary function test findings, work sector, task, occupation, duration of exposure, pneumoconiosis radiological classification, smoking habits, and obstructive airway disease.

RESULTS: A total of 137 cases (77.8%) had inorganic dust exposure. The mean serum ACE levels was higher in individuals with inorganic dust exposure than in those without exposure (35.65±16.40 U/L vs. 30.85±15.8 U/L, respectively), but the difference was not statistically significant (p=0.105). A negative correlation was observed between serum ACE levels and the forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio in the inorganic dust exposure group (p=0.009). Among individuals exposed to inorganic dust, 82 (59.9%) worked in the ceramic industry. Pneumoconiosis was diagnosed in 61 cases. Patients with pneumoconiosis had higher serum ACE levels compared to those without inorganic dust exposure, with a statistically significant difference (p=0.043).

CONCLUSIONS: Individuals exposed to dust in occupational settings exhibit elevated serum ACE levels.

Keywords:

Angiotensin converting enzyme, dust exposure, pneumoconiosis

*[1]Department of Occupational Diseases, Eskişehir City Hospital, Eskişehir, Türkiye,
[2]Department of Chest Diseases, University of Health Sciences, Samsun Training and Research Hospital, Samsun, Türkiye,
[3]Department of Internal Medicine, Eskişehir City Hospital, Eskişehir, Türkiye*

Address for correspondence:
Dr. Levent Özdemir, Department of Chest Diseases, University of Health Sciences, Samsun Training and Research Hospital, Samsun, Türkiye.
E-mail:
eydu2408@gmail.com

Introduction

The most well-known disease associated with inorganic fibrogenic dust exposure is pneumoconiosis. Alveolar macrophages play an important role in the pathophysiology of pneumoconiosis due to occupational dust exposure, par-

ticularly silica exposure. The phagocytosis of dust particles by alveolar macrophages triggers alveolitis, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1, and arachidonic acid metabolites.[1,2] Studies have demonstrated that insulin-like growth factor-1 and transforming growth factor-beta, secreted by macrophages, initiate the fibrosis process through cell proliferation and fibroblast activation. This inflammatory and fibrotic process is closely linked to the pathogenesis of pneumoconiosis.[2,3] Angiotensin-converting enzyme (ACE), which is secreted by the pulmonary capillary endothelium, reflects alveolar macrophage activity.[4] However, the relationship between ACE levels and inorganic dust exposure, as well as pneumoconiosis caused by such exposures, is unclear.

ACE converts angiotensin I in the renin-angiotensin system into the potent vasopressor angiotensin II and also activates bradykinin, a product of the kallikrein-kinin enzyme system.[4,5] ACE is primarily found on the luminal surface of vascular endothelial cells. In silicosis and other forms of dust-associated lung fibrosis, both endothelial cells and macrophages are considered source of increased serum ACE levels.[6] The serum activity of ACE in pulmonary diseases is of particular interest due to its secretion from the extensive capillary endothelium of the lungs. There is an increase in secretion in granulomatous lung diseases, which can be particularly useful in the diagnosis of sarcoidosis and in monitoring the response to treatment.[7] Studies have shown a relationship between alveolar macrophage activity and serum ACE levels, with ACE activity increasing fivefold in alveolar macrophages in sarcoidosis.[8]

Crystalline silica, silicate, and metal dusts are types of inorganic dust that contribute to the development of pneumoconiosis, particularly silicosis.[9] Several inflammatory cytokines are secreted due to macrophage activation and lymphocyte proliferation following the inhalation of silica crystals.[9,10] Acute high-dose exposure may lead to pulmonary alveolar proteinosis, while subacute and chronic exposure can cause granulomatous inflammation and pulmonary fibrosis, potentially progressing to progressive massive fibrosis (PMF).[11] Recent studies have highlighted the association between silica exposure and granulomatous inflammation, noting its similarities to sarcoidosis and even cases of sarcoidosis caused by silica exposure.[12,13] Nordman et al.[14] reported that serum ACE levels varied among lumberjacks and workers

exposed to silica, with higher levels observed in patients with silicosis as well as individuals exposed to silica who had not yet developed the disease. Additionally, the same study found a positive correlation between pneumoconiosis classification and ACE levels.

The relationship between serum ACE levels and dust exposure is unclear in individuals exposed to silica and other inorganic dust. During our literature review, most studies focused on the relationship between ACE levels and inorganic dust exposure, particularly in silica exposure-related silicosis. However, the industrial use of silicon oxide has expanded significantly. Silicon oxide is a crucial component in silica, silicate, and mixed dusts found in industries such as glass manufacturing, brick production, marble processing, foundries, and the metal industry. This study aims to investigate whether there is a relationship between inorganic dust exposure and various factors, including the duration of exposure, type of occupation, presence and classification of pneumoconiosis, smoking status, obstructive airway disease, and serum ACE levels.

Materials and Methods

Study design

This research was designed as a cross-sectional study. The target population consisted of 1,070 patients who applied to the outpatient clinic of Occupational Diseases at Eskişehir City Hospital between January 2021 and April 2022. Serum ACE levels were measured in 243 patients. Patients with incomplete occupational history records and those taking ACE inhibitor medications were excluded from the study. Additionally, individuals who had been exposed to both inorganic and organic dust during their working life were excluded. Due to the low number of female participants (n=6), female cases were also excluded, resulting in a study population of 176 male participants. Among them, 137 had a history of working in sectors with inorganic dust exposure [Fig. 1], while 39 had no history of inorganic dust exposure during their working life.

Measurement of serum ACE levels: Serum ACE levels were measured using the enzyme-linked immunosorbent assay (ELISA) method (Quantikine, R&D Systems, Minneapolis, MN, USA, U/L). In a study by Nordman et al.,[14] the mean ACE levels in the silica-exposed group was reported as 46.6±12.1 U/L. Based on this, the cut-off
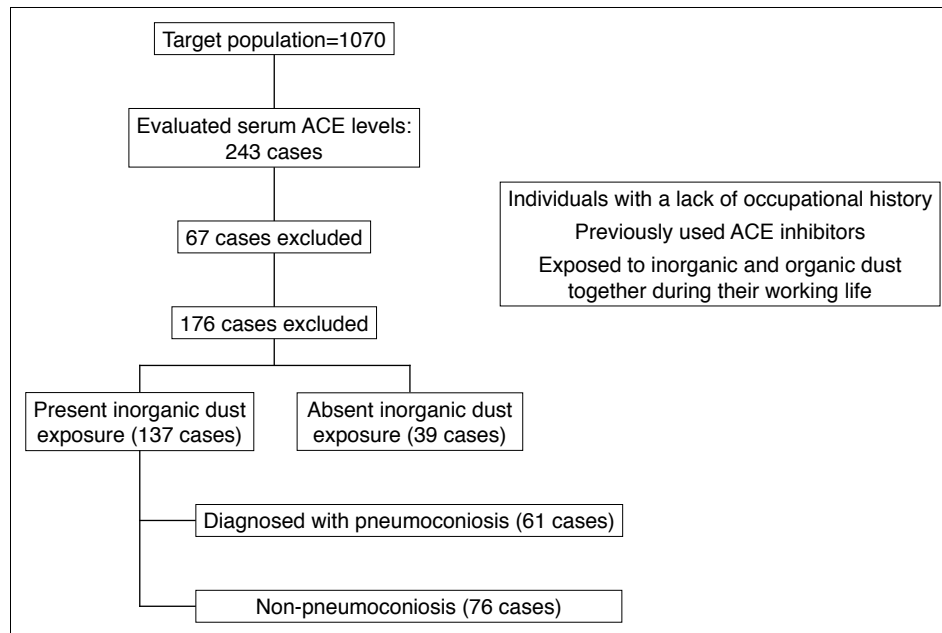
Figure 1: Diagram of the study population
ACE: Angiotensin-converting enzyme

value in our study was set at 45 U/L. The primary objective of this study was to evaluate ACE as a biomarker; therefore, other acute-phase reactants were not assessed.

Ethical approval for this study was received from Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Approval Number: 34, Date: 26.07.2022; ID: 2022-188-34; E-25403353-050.99-364098).

The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

Detailed medical and exposure histories, physical examination findings, laboratory results, spirometric measurements, and radiological findings of all patients with dust exposure who applied to the Occupational Diseases Clinic were recorded in the Case Follow-up Form. A comprehensive occupational history was documented, including the sectors in which patients worked, specific tasks performed, occupations held, workplace and environmental exposures (both at work and outside of work), duration of exposure, and working hours per day and per week. Demographic characteristics, laboratory findings, pulmonary function tests results, and radiological findings of patients with and without inorganic dust exposure were obtained from the hospital's electronic database and the Case Follow-up Form. The International Labour Organi-

zation (ILO) pneumoconiosis radiological classification was conducted for patients with inorganic dust exposure, including assessments of pneumoconiosis classification, profusion, and categorization. Patients diagnosed with pneumoconiosis (Category 1 and above) were reported to the Social Security Institution following the decision of the Eskisehir City Hospital Health Committee.

Exclusion criteria
Individuals were excluded from the study if they met any of the following criteria:

- Lack of a documented occupational history,
- Prior use of ACE inhibitors,
- Exposure to both inorganic and organic dust during their working life.

Pneumoconiosis classification and category
The identification of small and large opacities was performed according to the ILO pneumoconiosis assessment category. The profusion was determined by comparison with standard radiographs and classified into one of four categories: 0, 1, 2, or 3.[15] In this study, large opacities were categorized as Category 4.

Statistical analysis
Statistical analyses were performed using Statistical Package for the Social Sciences for Windows, version

Table 1: Baseline demographics of the study population

	Total (n=176)		Individuals with inorganic dust exposure (n=137)		Individuals without inorganic dust exposure (n=39)		p
	n	%	n	%	n	%	
Age (years)	44.73±9.2		44.81±7.8		44.46±13.1		0.897
History of COVID-19	32	18.2	22	16	10	25.6	–
History of pneumonia	10	5.7	3	2.1	7	17.9	–
History of tuberculosis	1	6.3	0	0	1	2.6	–
Industry							
Ceramic			82	59.9	–	–	–
Glass			22	16.1	–	–	–
Marble			11	8.0	–	–	–
Foundry and metal			22	16.1	–	–	–
Duration of exposure (years)	20.15±7.6		20.83±7.6		17.52±7.4		0.026
Pulmonary function test*							
FVC*	92.47±13.7		92.14±13.5		93.73±14.5		0.086
FEV$_1$/FVC*	79.23±9.9		79.89±9.9		76.81±9.6		0.104
Obstruction*	34	20.6	25	15.2	9	5.5	0.037

*: Pulmonary function tests were available for 164 cases. There was a homogeneous distribution in terms of age, exposure duration, forced vital capacity (FVC), and forced expiratory volume in one second/forced vital capacity (FEV$_1$/FVC) ratio between groups with and without inorganic dust exposure. The t-test was applied for comparisons of these parameters. FVC: Forced vital capacity, FEV$_1$: Forced expiratory volume in one second

22.0 (SPSS Inc., Chicago, IL, USA). Frequencies and percentages were calculated for categorical variables, while numerical variables were reported as mean, median, and standard deviation. The normality of the variables was tested using the Shapiro-Wilk test. For normally distributed numerical variables, the t-test was applied when comparing two groups, while the analysis of variance (ANOVA) test was used for comparisons involving more than two groups. Tamhene's T2 test was applied as a post hoc comparison test. The Mann-Whitney U test was used for numerical variables that did not follow a normal distribution. Categorical variables were analyzed using the chi-square test, and the Pearson correlation test was used for correlation analysis. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the 176 male patients included in the study was 44.73±0.69 years. The majority of the participants were current smokers (n=109, 61.9%), while 25 individuals (14.2%) had never smoked. Among the 151 (85.8%) smokers, the mean smoking duration was 17.6±10.1 packsyears. There was no statistically significant difference between serum ACE levels and smoking status (non-smokers: 31.6±16.3; current smokers: 35.1±14.8, and former smokers: 36.8±19.6; p=0.540). A total of 32 cases (18.2%) had

a prior history of Coronavirus Disease 2019 (COVID-19). Inorganic dust exposure was detected in 137 cases (77.8%), and 61 cases were diagnosed with pneumoconiosis. The mean forced vital capacity (FVC) was 4.19±0.06 mL (92.47±1.07%), the mean forced expiratory volume in one second (FEV$_1$) was 3.29±0.06 mL (89.69±1.24%), and the FEV$_1$/FVC ratio was 79.23±0.77%. The demographic characteristics of the cases are provided in Table 1 and 2.

The distribution of participants across industries with inorganic dust exposure was as follows: 82 (59.9%) worked in the ceramic sector, 22 (16.1%) in the glass sector, 11 (8.0%) in the marble sector, and 22 (16.1%) in the metal and foundry sectors. The mean serum ACE levels for all cases was 34.59±16.3 U/L. A total of 48 cases (27.3%) had serum ACE levels of 45 U/L or higher.

The mean serum ACE levels in individuals with inorganic dust exposure was higher than in those without exposure (35.65±16.40 U/L vs. 30.85±15.8 U/L, respectively); however, the difference was not statistically significant (p=0.105). Among the 61 patients with both inorganic dust exposure and pneumoconiosis, the mean serum ACE levels was 38.55±19.02 U/L. Although there was no statistically significant difference in serum ACE levels between individuals with and without pneumoconiosis among those exposed to inorganic dust, serum ACE levels were higher in patients with pneumoconiosis

Table 2: Baseline demographics of the study population

Variable	Group	n	Median	Q1-Q3	Z	U	p
Smoking (pack-years)	Exposed to inorganic dust	137	15.0	7.25–25.0	-1.685	2199.50	0.092
	Not exposed to inorganic dust	39	13.0	0.0–23.0			
Serum ACE level (IU/L)	Exposed to inorganic dust	137	33.0	23.0–47.0	-1.930	2130.00	0.054
	Not exposed to inorganic dust	39	28.0	21.0–38.0			
FEV_1 (%)	Exposed to inorganic dust	130	93.0	81.75–101.0	-1.045	1952.50	0.296
	Not exposed to inorganic dust	34	87.5	74.5–103.25			

Serum angiotensin-converting enzyme (ACE) levels, forced expiratory volume in one second (FEV_1, %), and smoking (pack-years) were not distributed homogeneously between groups with and without inorganic dust exposure. Therefore, the Mann-Whitney test, a nonparametric test, was used for comparisons. Z: Test statistics, U: Test statistics, FEV_1: Forced expiratory volume in one second
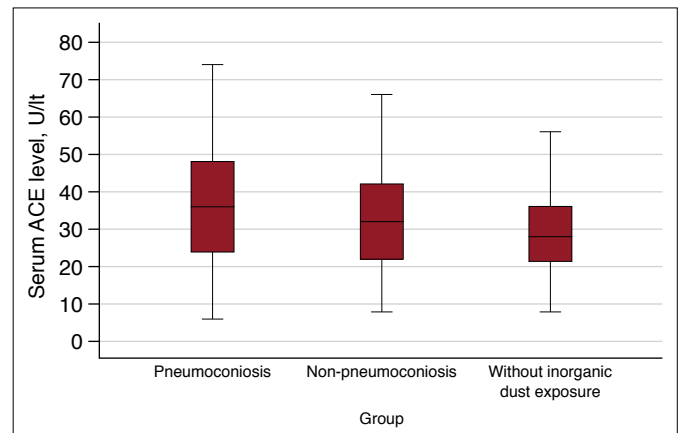
Table 3: Comparison of serum angiotensin-converting enzyme (ACE) levels between pneumoconiosis and non-pneumoconiosis cases by occupation in the inorganic dust exposure group

	Pneumoconiosis (n=61)		Non-pneumoconiosis (n=76)		p
	n	Serum ACE	n	Serum ACE	
Ceramic	41	38.68±20.1	41	32.22±14.1	0.086
Glass	10	38.77±19.8	12	37.5±13.7	0.995
Marble	1	18.00	10	34.4±10.2	0.162
Foundry and metal	9	38.66±13.9	13	33.07±13.8	0.454

compared to those without inorganic dust exposure, and there was a statistical difference (p=0.043) [Fig. 2].

Among the cases exposed to inorganic dust, 61 (34.7%) were diagnosed with pneumoconiosis. No significant difference was found in ACE levels between individuals with pneumoconiosis and those with inorganic dust exposure without pneumoconiosis when analyzed based on occupation, working hours, cigarette pack-years, and pulmonary function test results (Table 3).

In the ILO pneumoconiosis chest radiography reading, the predominant opacity in 41 cases (67.2%) was a nodular density increase in the "p" dimension. In 15 (24.6%) cases, the predominant opacity was nodular density in the "q" dimension. In two cases, the dominant opacity was in the "r" and "s" dimensions. Among the cases diagnosed with pneumoconiosis, 22 (36.1%) had a profusion of 1/1, making it the most common category, followed by 2/3 profusion in seven cases (11.5%). A profusion of 0/1 was observed in four cases (6.6%). PMF lesions with large opacities were present in seven cases (11.5%). The predominant opacity was less than 1.5 mm in 43 patients with pneumoconiosis, while it was ≥1.5 mm in 18 patients. Although serum ACE levels were higher in patients with predominant opacities of ≥1.5 mm, the difference was not statistically significant [Fig. 3]. Cases with category 2 pneumoconiosis had higher serum ACE levels, with a statistically significant difference

Figure 2: Comparison of serum angiotensin-converting enzyme (ACE) levels in pneumoconiosis, non-pneumoconiosis, and individuals without dust exposure

observed between category 2 and both category 1 and category 3 groups (Table 4) [Fig. 4].

A negative correlation was observed between serum ACE levels and the FEV_1/FVC ratio in individuals with inorganic dust exposure (p=0.009). Serum ACE levels did not correlate significantly with age, smoking duration, exposure time, FEV_1, or FVC levels in terms of inorganic dust exposure or the presence of pneumoconiosis. While serum ACE levels were higher in cases with pneumoconiosis and obstruction, no statistically significant difference was observed in serum ACE levels between those with and without obstruction.
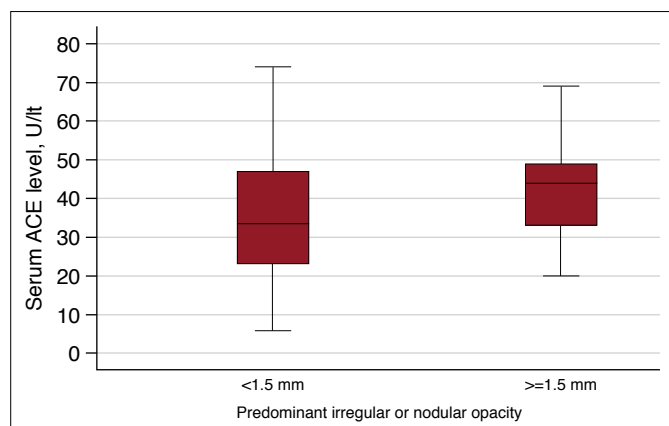
Figure 3: Comparison of serum angiotensin-converting enzyme (ACE) levels based on opacity dimensions

Figure 4: Comparison of serum angiotensin-converting enzyme (ACE) levels across pneumoconiosis categories

Discussion

The association between serum ACE levels and sarcoidosis is well established.[7] Several studies have also reported elevated ACE activity in silicosis.;[6,16] however, only a few studies have specifically examined silica exposure. Workers exposed to inorganic dust in various occupations that contribute to the development of pneumoconiosis may have altered ACE levels, but this association is unclear. In this study, we compared the fibrogenic effects among 137 workers from the marble, ceramic, glass, metal, and foundry industries, all of whom were exposed to inorganic dust, with those employed in dust-free environments. Our findings indicate that inorganic dust exposure alone did not impact ACE levels, whereas patients diagnosed with pneumoconiosis had considerably higher ACE levels than individuals without inorganic dust exposure.

Previous studies have found that workers exposed to crystalline silica and those diagnosed with silicosis exhibit higher serum ACE levels.[17,18] In a study of stone workers, exposure to silica without silicosis resulted in serum ACE levels that were 1.05 times higher than those observed in workers exposed to wood dust.[16] Similarly, in our study, exposure to inorganic dust increased ACE levels by 1.16 times. For the first time, we compared ACE levels across different occupational categories. Serum ACE levels were similar across workers in the ceramics, marble, glass, metal, and foundry industries, as well as in those working in non-inorganic dust environments.

Similar to crystalline silica, silicates, metal dust, and mixed dust have been shown to damage lung tissue and induce fibrosis.[19,20] While some studies have linked met-
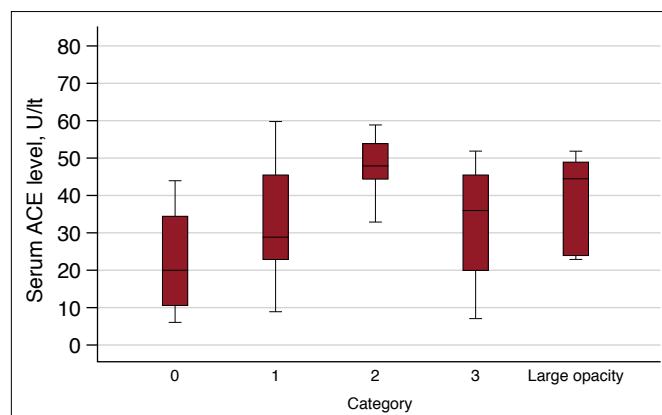
al dust and silica exposure to sarcoid-like granulomatous inflammation, the resulting lung parenchymal damage was similar across exposure types.[12,21] Our investigation demonstrated that dust type did not impact serum ACE levels, suggesting a comparable mechanism for lung inflammation. Pneumoconiosis cases in the ceramic, glass, and metal foundry sectors exhibited similar ACE levels, except for those in the marble industry.

This study examines serum ACE levels in relation to pneumoconiosis, distinguishing it from previous research. The significantly lower ACE levels in individuals unexposed to inorganic dust may suggest that all pneumoconiosis-causing inorganic dusts damage lung parenchyma and promote fibrosis through a similar mechanism.

The elevated serum ACE levels observed in silicosis remain unexplained. Capillary endothelial cells exhibit

Table 4: Comparison of serum angiotensin-converting enzyme (ACE) levels based on international labour organization (ILO) pneumoconiosis classification

	Serum ACE level	p
Dominant opacity dimension		
<1.5 mm (n=43)	37.62±20.55	0.645
≥1.5 mm (n=18)	40.11±15.08	
Category		
0 (n=4)	22.50±16.29	0.043
1 (n=31)	35.15±21.36	
2 (n=16)	49.50±11.21	
3 (n=4)	32.75±18.90	
4 (n=7)	39.50±12.72	
Large opacity		
A (n=2)	34.50±14.84	
B (n=2)	47.00±2.82	
C (n=3)	39.66±14.97	

increased ACE expression. Inflammatory cells that produce fibrogenic and inflammatory cytokines, along with growth factors, contribute to the development of pneumoconiosis, including silicosis. Fibrosis is hypothesized to be driven by alveolar macrophages.[6] According to Romano et al.,[22] fibrotic involvement may lead to elevated ACE levels in interstitial lung disease. In sarcoidosis, mononuclear phagocytic cells and alveolar macrophages are the primary sources of ACE. The elevated serum ACE levels in pneumoconiosis likely result from dust phagocytosis and alveolar macrophage degranulation.[1,6,23]

Stone and coal miners had higher silica exposure and serum ACE levels than the control group; however, no association was found between serum ACE levels and radiological profusion categories.[14] Yano et al.[24] examined 107 patients with silicosis and identified a correlation between profusion category and serum ACE levels, though no difference was observed between those with and without large opacities. Our study found considerably higher serum ACE levels in patients classified as profusion category 2. However, radiographic opacity size did not correlate with ACE levels. These findings contribute to the ongoing debate regarding the utility of ACE levels in monitoring disease progression and underscore the need for further research to evaluate fibrosis.

A study on stone workers found no correlation between the duration of silica exposure and serum ACE levels.[14] In contrast, Beshir et al.[6] reported that longer exposure durations were associated with increased ACE levels. Pneumoconiosis has a latent period between exposure and disease onset, with cumulative exposure dose playing a critical role in determining disease manifestation and fibrosis development.

Smoking contributes to lung parenchyma, obstructive airway disorders, and respiratory bronchiolitis-associated interstitial lung disease. Tiwari et al.[16] found no difference in serum ACE levels between smokers and non-smokers exposed to silica. However, smokers and patients with silicosis exhibited serum ACE levels that were 2.46 times higher than those of non-smokers. Smoking alters lung parenchyma and airways, leading to increased ACE release from alveolar macrophages. Additionally, smoking may induce ACE release from the endothelium due to vascular endothelial injury; however, this remains hypothetical.

This study had certain limitations. Comparing subjects with and without inorganic dust exposure from different occupational groups presents challenges, but the primary limitation is the lack of comparison between homogeneous groups. The absence of variation in blood ACE levels across different occupations suggests that neither the exposure agent nor a single sector influenced ACE levels. Additionally, the study was constrained by the small number of pneumoconiosis cases with large opacities.

Conclusion

Serum ACE levels in individuals exposed to inorganic dust may serve as an indicator of pneumoconiosis. Smoking damages lung parenchyma, and the combined effects of dust exposure and smoking may synergistically cause fibrosis. In pneumoconiosis, smokers exhibit elevated serum ACE levels.

Dust control is essential for preventing pneumoconiosis, a significant occupational illness. Pneumoconiosis is the most common occupational disease in developing countries. Laboratory tests that detect inflammatory markers at the cellular level before the radiological diagnosis of fibrosis should include serum ACE and other relevant biomarkers.

Ethics Committee Approval
The study was approved by the Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (No: 34, Date: 26/07/2022).

Conflicts of Interest Statement
There are no conflicts of interest.

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Nil.

Use of AI for Writing Assistance
This study did not utilize artificial intelligence (AI)-enabled technologies, including large language models (LLMs), chatbots, or image generators.

Author Contributions
Concept – B.A., L.Ö., A.U.; Design – B.A., L.Ö., A.U.; Supervision – B.A., L.Ö., A.U.; Resource – B.A., L.Ö., A.U.; Materials – B.A., L.Ö., A.U.; Data collection &/or processing – B.A., L.Ö., A.U.; Analysis and/or interpretation – B.A., L.Ö., A.U.; Literature search – B.A., L.Ö., A.U.; Writing – B.A.; Critical review – B.A., L.Ö., A.U.

Peer-review
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