AN EARLY INDICATOR FOR PULMONARY FIBROSIS IN ASBESTOS EXPOSURE: THE SERUM LEVEL OF TYPE III PROCOLLAGEN PEPTIDE

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SUMMARY

Serum type III procollagen peptide (PIIIP) levels were measured in 29 asbestos-exposed workers and in 29 healthy controls. Mean serum PIIIP level was 16.9 ± 2.9 (SD) ng/ml in exposed workers and 11.6 ± 2.9 (SD) ng/ml in the referent group, the difference being highly significant. Mean serum PIIIP level in moderately exposed subjects (<0.1–0.2 fibres/ml) was significantly higher than in controls; PIIIP values in workers exposed to a higher air fibre concentration (0.2–3.8 fibres/ml) proved significantly elevated in comparison to controls and moderately exposed subjects, thus suggesting a dose-effect relationship. In 12 workers personal monitoring of exposure showed a clear correlation (r=0.69) between estimated asbestos dose (fibres/ml x years of exposure) and serum PIIIP levels. Moreover levels of PIIIP in the serum were found to be on average significantly higher in workers with reduced forced vital capacity. Serum PIIIP level seems to be a promising index for monitoring early asbestos-induced pulmonary fibrotic effects.

INTRODUCTION

The diagnosis of asbestos related non-malignant lung disease is based upon clinical signs, impairment of lung function tests and radiographic findings.

Radiological and clinical evidence has been reported to be less sensitive to the presence of asbestosis and other interstitial fibrosis than histopathological examination.[4,6] On the other hand, only very early detection of the pulmonary fibrogenic response may prevent progression to severer stages of asbestosis.

Recent studies suggest that the pathogenesis of pulmonary fibrosis might be related to changes in the structure and function of pulmonary collagen rather than to an increase of its absolute amount.[6] An increase of type III collagen has been observed in bioptic lung samples taken from patients in early stages of cryptogenic pulmonary fibrosis[6] and from subjects with active fibrotic disease.[2] However, type III collagen was reduced in post-mortem lung samples taken from patients who had died from pulmonary fibrosis[7] and from patients with a longer duration of the disease.[6]

These findings suggest the hypothesis of an increased synthesis of type III collagen during the early stages of the disease followed by a decrease later.

Type III collagen is synthetized within the collagen producing cells in a precursor form as procollagen with specific N-terminal and C-terminal extension peptides at the ends of the molecule. These peptides are cleaved in stoichiometric amounts by specific peptidases during secretion of the newly formed collagen from the cell.[3]

N-terminal peptide can be measured in serum and its level shows a positive correlation to the type III/type I collagen ratio measured biochemically in lung tissues.[6]

Our study aimed to measure PIIIP serum levels in subjects exposed to asbestos in order to investigate the usefulness of the test in the biological monitoring of asbestos exposure.

MATERIALS AND METHODS

29 male workers occupationally exposed to asbestos fibres and employed in two factories producing cement-asbestos products were examined. All the subjects, whose mean age was 36 years, were currently exposed at the moment of the study and their mean exposure time was 7.9 years (range 1–25 years).

Airborne asbestos fibre exposure was evaluated by stationary and/or personal sampling according to the AIA 1979 reference method.[1] The workers were mainly exposed to chrysotile, but in one factory crocidolite was also present (up to 30% of the total airborne asbestos).

According to the air sampling data the subjects were divided into two groups: group 1 comprising 17 workers exposed to low concentrations (up to 0.2 fibres/ml) and group 2 including workers also exposed to crocidolite and to a higher concentration of total asbestos fibres (range 0.2–3.8 fibres/ml). 2 workers were considered exposed but not assigned to either group since air determinations for their specific job were lacking.

Cases were compared to a reference group of 29 healthy male subjects matched for age, tobacco and alcohol consumption.

A standardized questionnaire was used and appropriate biochemical indices performed on cases and controls to rule out liver and/or collagen diseases, which could influence the results of the test.

Serum PIIIP measurements were performed by the radioimmunoassay method described by Rhode et al.[8] The mean recovery at different PIIIP concentration varied between 89 and 104% and the coefficient of variation within run ranged between 7–15%.

RESULTS

The level of serum PIIIP in the exposed subjects and in the referent group is reported in Table I. The mean value was 11.6 ± 2.9 (SD) ng/ml in controls and 16.9 ± 2.9 (SD) ng/ml in the exposed subjects. The difference between the means is highly significant.

Neither in cases nor in controls was a significant difference in serum PIIIP levels found between smokers and nonsmokers or between alcohol drinkers and non-drinkers. It must be stressed that in both groups alcohol assumption was moderate.

When subjects with low and higher exposure were separately considered again a significant increase of serum PIIIP values was found in comparison to the referent group. The workers exposed to higher levels of airborne asbestos fibres showed the highest values of PIIIP in serum (Table II). From these data it seems possible to infer a dose-effect relationship between the exposure to asbestos fibres and serum PIIIP values.

To verify this hypothesis we compared the serum PIIIP level and the individual "dose" expressed as fibres/ml/years in 12 subjects, monitored repeatedly by personal air samplers and taking into account the years of duration of exposure (Figure 1). A significant regression line was found with a coefficient of correlation of 0.69 ($p < 0.01$). This relationship should be considered valid for short-term exposure periods, since all the 12 subjects studied were exposed for less than 5 years.

To evaluate whether the concentration of PIIIP in serum bears some relationship to possible asbestos related effects, we measured the forced vital capacity (FVC) and the volume expired in the first second (FEV_1) in the exposed subjects. In the workers with a reduced FVC and FEV_1 a significant increase as a mean of the serum PIIIP was evident when compared to the workers showing no impairment of lung function tests (Table III).

Since, according to our results, tobacco and alcohol consumption is not related to serum PIIIP values, and possible age-related effects have also been ruled out by matching criteria, the difference in serum concentration of PIIIP seems to be ascribable only to the exposure to asbestos fibres. The different level of the PIIIP in groups with different exposure intensity suggests a dose-dependent increase as demonstrated further by the clear relationship between the number of fibres/ml/years and the serum levels of PIIIP.

It must also be stressed that a significant increase of PIIIP is already evident at exposure levels of 0.2 fibres/ml or less, a finding which suggests the need to reconsider the threshold for asbestos related pulmonary effects.

Further studies are certainly needed on the biological meaning of serum PIIIP levels, but our results suggest that the test may represent a promising index for early asbestos induced fibrotic effects and should be considered for the biological monitoring of exposed workers.

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Table I
Serum PIIIP Values in Controls and in the Exposed Workers

	number of subjects	serum PIIIP (ng/ml) meon	DS	significance of the difference
CONTROLS	29	11,64	2,92	
				p < 0,0001
EXPOSED WORKERS	29	16,86	2,91	

Table II

Serum PIIIP Values in Controls and in the Exposed Workers

	number of subjects	serum PIIIP (ng/ml) mean	DS	significance of the difference vs controls
CONTROLS	29	11,64	2,92	
EXPOSED WORKERS				
Group 1	17	15,23	2,70	$p < 0,005$
Group 2	9	19,00	4,39	$p < 0,003$

Significance of the difference between group 1 and group 2 : $p < 0,05$

Group 1: low exposure workers (<0,1-0,2 ff/ml)

Group 2: higher exposure workers (0,2 - 3,8 ff/ml)

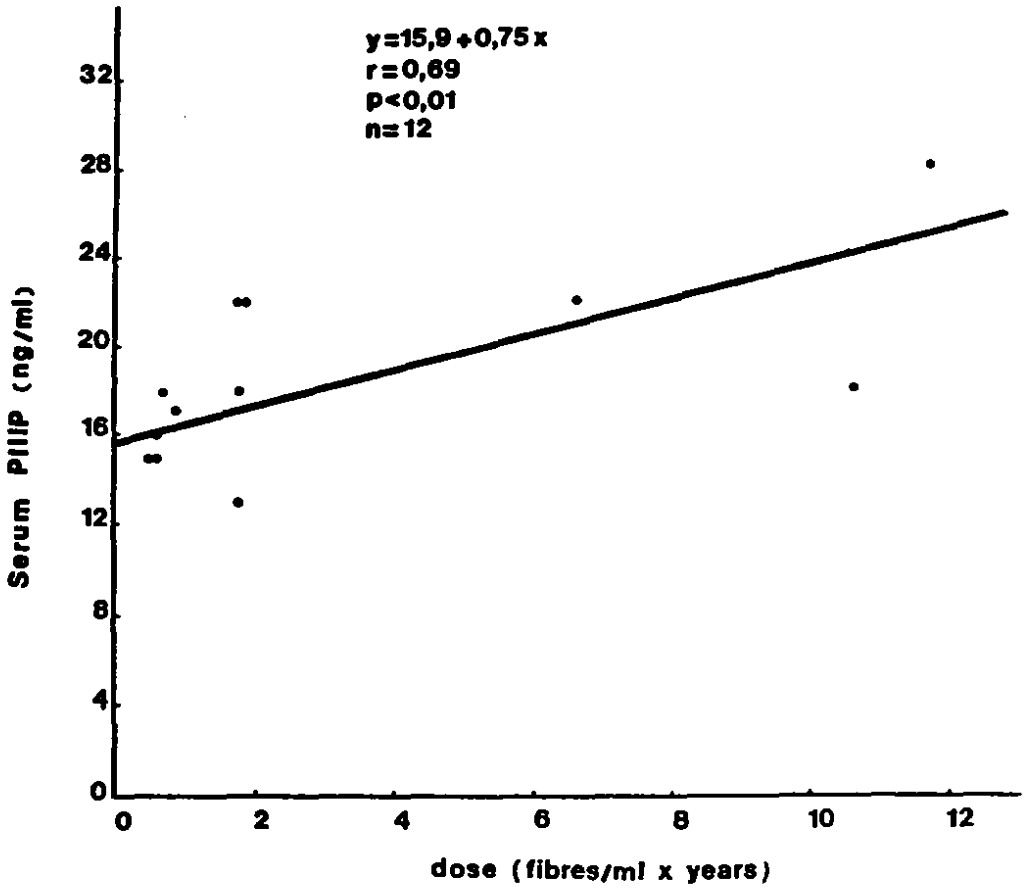

Figure 1. Relationship between asbestos dose (fibres/ml × years of exposition) and serum PIIIP values in the exposed workers.

Table III

Serum PIIIP in Asbestos Exposed Workers Subdivided According to Pulmonary Function Test Results

	Number of subjects	serum PIIIP (ng/ml) mean	DS	significance of the difference
FVC ≥100% ref. value	15	14,93	2,12	p < 0,005
FVC < 100% ref. value	12	19,25	4,14	
FEV1 ≥100% ref. value	12	15,17	2,04	p < 0,03
FEV1 <100% ref. value	15	18,20	4,38	

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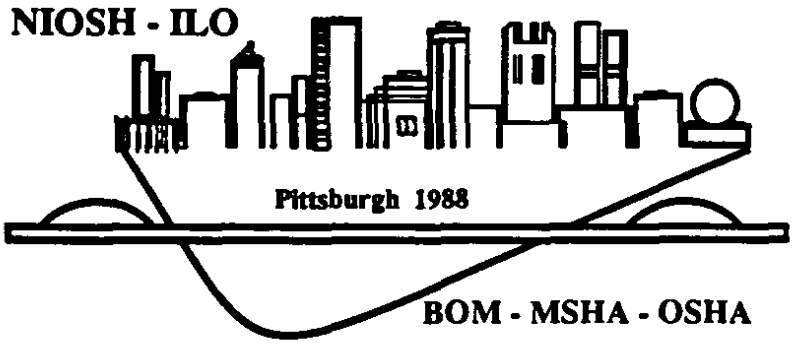

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