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The effects of occupational lead exposure on selected inflammatory biomarkers

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In exposure to toxic metals such as lead, determining lead and cytokine levels (IL-6, IL-10, and TNF-α) is essential for early detection of diseases. The aim of this study was to develop an model for early detection of inflammation and onset of atherosclerosis in the absence of clinical findings in young workers, which could help physicians take timely an action and start treatment. This study included 49 metal workers exposed to lead occupationally and 50 unexposed administrative workers (controls) who underwent immunological analysis for cytokines (IL-6, IL-10, and TNF-α) and atherosclerosis markers (h-FABP and VCAM-1), toxicological analysis for lead, and routine biochemical analysis (ALT, AST, creatinine) at the Ankara Occupational and Environmental Diseases Hospital in 2017. Lead levels correlated with IL-6, IL-10, and TNF-α (r=0.469, r=0.521 and r=0.279, respectively, p<0.01) but did not significantly affect h-FABP and VCAM-1 levels.

KEY WORDS: atherosclerosis; cytokines; h-FABP; IL-6; IL-10; TNF-α; VCAM-1

Occupational and environmental exposure to metals and metalloids can cause many pathological conditions, including immunotoxicity. Research has shown that the most important mechanism underlying diseases associated with lead exposure is inflammation (1–3). Inflammation also plays a major role in the development of atherosclerosis (4, 5). It acts at all stages, including fatty streak, plaque formation, and plaque disruption (6). Since the 1970s, atherosclerosis has been considered as an immunoinflammatory disease, in whose development cytokines play a key role (7). Cytokines are small proteins primarily involved in cellular signalling pathways and intracellular inflammatory and immune responses (8). Several mechanisms have been proposed to explain how lead may cause or aggravate atherosclerosis: by inhibiting endothelial physiological functions, by impairing angiogenesis, by inactivating nitric oxide, and by increasing inflammation through cytokines (9, 10).

Lead exposure has always been an actual topic, environmentally and occupationally. Numerous scientific studies have shown the link between lead exposure and cardiovascular abnormalities such as coronary artery disease, atherosclerosis, stroke, peripheral arterial disease, and arterial hypertension (11–14). Many have also established that lead exposure is closely related to inflammation (2, 15, 16) and that it increases pro-inflammatory cytokine production, including tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10) (17, 18).

To improve atherosclerosis risk prediction, recent investigations have focused on the simultaneous use of multiple biomarkers. Besides cytokines, some other biomarkers could help to establish the adverse effects of occupational exposure to lead. In this study we evaluated the potential of the vascular cell-adhesion molecule-1 (VCAM-1) and the heart-type fatty acid binding protein (h-FABP) as predictive markers of lead-related atherosclerosis. VCAM-1 is an immunoglobulin-like adhesion molecule that promotes monocyte adhesion and accumulation on the vessel wall (19) and is critical to the development of atherosclerotic lesions in animal models (20). Fatty acid binding proteins (FABPs) play a key role in the transportation of fatty acids and lipophilic molecules through the cell membrane. As an intra-cardiac protein, h-FABP has been shown to activate inflammation, besides indicating myocardial injury (21). There are several studies that link this protein to chronic clinical conditions, including atherosclerosis (22, 23).

In our study, we aimed to determine the IL-6, IL-10, TNF-α, h-FABP, and VCAM-1 levels in lead-exposed workers to find their association with blood lead levels and standard haematological and biochemical markers commonly used to establish adverse effects of occupational lead exposure that point to increased risk of inflammation and atherosclerosis.

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PARTICIPANTS AND METHODS

Study population and blood sampling

The study included 49 metal recycling workers exposed to lead through their occupation and 50 unexposed administrative workers, who served as control. The inclusion criteria for the exposed group were high blood lead levels (BLL>10 µg/dL) (24) and active job in melting for more than six months. Persons with acute infections, chronic lung disease, diabetes mellitus, diagnosed coronary vascular disease, hypertension, rheumatic diseases, or cancer were excluded from the study.

Both groups were examined and their blood tested at the Ankara Occupational and Environmental Diseases Hospital in 2017. Blood samples (one per participant, totalling 99) were taken for immunological, toxicological, and standard haematological/biochemical analysis at the end of the work shift of the last day of work week following the American Conference of Governmental Industrial Hygienists (ACGIH) industrial toxicological standards (25). All procedures followed the 1964 Helsinki Declaration and its later amendments. All participants gave their informed consent to participate. The study protocol was approved by the Clinical Research Ethics Committee of the Yozgat Bozok University Faculty of Medicine (approval no. 12.10.2016/70).

Collection of biological samples and laboratory analysis

Biomarkers were analysed in the sera separated from blood samples by centrifugation at 1500 rpm for 10 min and then transferred to 2 mL Eppendorf tubes and frozen to -20 °C. Frozen samples were transferred to the Occupational and Environmental Toxicology Laboratory of the Yozgat Bozok University Science and Technology Application and Research Center (BILTEM) using a cold chain system and stored at -20 °C until analysis.

For IL-6, IL-10, TNF-α, h-FABP, and VCAM-1 analyses we used the respective ELISA kits: KAP1261, KAP1321, KAP1751 (DIAsource ImmunoAssays SA, Louvain-la-Neuve, Belgium), DZE201121214, and DZE201120204 (Shanghai Sunred Biological Technology Co., Shanghai, China) and prepared the samples following manufacturer's instructions for each kit. The samples were then placed on microplates and fed to a CLARIOstar ELISA plate reader (BMG LABTECH, Ortenberg, Germany). The wavelength was set at 450 nm. Five-point calibration curves were used for all biomarker measurements. The r^2 values of the calibration curves were 0.9994, 0.9994, 0.9992, 0.9995, and 0.9997, respectively. For verification we used standards that come with the kits. Linear regression was implemented to obtain all biomarker results.

For lead analysis we took 1 mL of the whole blood sample, placed in a Teflon tube, added 5 mL of suprapure-grade 65 % nitric acid (HNO_3, Merck, Darmstadt, Germany) and 5 mL of ultrapure water (Millipore Direct-Q3, Merck), and digested in a Milestone Start D microwave digestion system (Sorisole, Italy). The digested samples were then transferred to 50 mL polypropylene tubes, added deionised to obtain the total volume of 20 mL, and stored at +4 °C until analysis (26). Lead levels were determined with inductively coupled plasma mass spectrometry (ICP-MS; iCAP Qc model, Thermo Scientific, Waltham, MA, USA). The method was validated with the certified reference material (CRM-Seronorm™ Trace Elements Whole Blood L-2, Billingstad, Norway) and the r^2 value of the calibration curve was 0.9998.

Statistical analysis

For statistical analysis we used the Statistical Package for Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was used to determine differences in the main parameters between the control and exposed group (Table 1). The Pearson test was used to determine 2-tailed correlations between cytokine levels and toxicological-biochemical variables in both groups. Regression analysis was used to understand which of the independent variables correlated with lead levels as the dependent variable. The levels of statistical significance were set at $p < 0.05$ and $p < 0.01$.

RESULTS

Table 1 shows the differences in the main parameters between the groups. The two groups significantly differed in WBC, AST, Pb, IL-6, IL-10, and TNF-α levels but not in h-FABP and VCAM-1 cytokine levels. The exposed workers also had shorter working experience than control, most likely because of health problems at an early age.

The Pearson correlation (Table 2) showed high positive correlations between Pb levels and the IL-6, IL-10, and TNF-α cytokine levels (r=0.469, r=0.521, and r=0.279, respectively, $p < 0.01$). Pb also positively correlated with WBC levels (r=0.252, $p < 0.01$) and negatively with HGB levels (r=-0.200, $p < 0.05$). Creatinine negatively correlated with IL-10 and TNF-a (r=-0.208 and r=-0.246, respectively, $p < 0.01$), and AST negatively correlated with IL-10 (r=-0.020, $p < 0.05$).

Regression analysis (Table 3) did not establish any significant effects of Pb on VCAM-1 or h-FABP levels, but did find a significant correlation between Pb and the cytokines. It accounted for the 7.8 % change in TNF-α levels, the 27.2 % change in the IL-10 levels, and the 22.0 % change in the IL-6 levels ($p < 0.05$).

DISCUSSION

With this study we aimed to develop a model for the early detection of inflammation and onset of atherosclerosis

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Table 1 Differences in parameters between control and exposed groups

Parameter	Groups						Significance	
	Control			Exposed			Mann-Whitney U test	p
	Mean	Median	Range	Mean	Median	Range		
Age (years)	42.00	40.00	33.5–51.25	32.57	31.00	28.00–37.00	523.50	**<0.001**
BMI (kg/m²)	27.67	27.13	25.69–29.02	26.65	26.82	25.51–27.73	1054.50	0.233
Work duration (years)	13.74	8.00	5.75–24.00	3.29	2.00	1.00–2.00	326.50	**<0.001**
WBC	7.28	7.02	6.01–8.44	8.12	7.70	7.10–9.43	921.50	**0.034**
HGB (g/dL)	15.47	15.40	14.90–16.42	14.91	15.30	14.55–15.85	976.00	0.081
HCT (%)	45.87	45.75	43.55–48.25	45.04	45.00	43.35–47.15	1094.50	0.361
PLT (10³/μL)	233.46	238.00	209–267	235.98	229.00	186.00–282.00	1224.00	0.994
ALT (U/L)	26.68	22.00	17–28	24.06	19.00	14.00–33.00	1106.00	0.404
AST (U/L)	21.60	20.00	17–25	19.14	19.00	15.00–22.00	963.00	**0.046**
Creatinine (μmol/L)	0.83	0.82	0.77–0.90	0.81	0.80	0.75–0.90	1057.00	0.235
Pb (μg/dL)	2.73	1.55	1–3.02	21.44	19.30	16.10–26.95	0.000	**<0.001**
VCAM-1 (ng/mL)	8.55	7.58	4.59–11.14	8.17	7.66	4.80–9.28	1204.00	0.883
h-FABP (ng/mL)	2.52	1.82	1.53–3.01	2.60	1.81	1.61–3.26	1191.00	0.812
TNF-α (pg/mL)	3.70	4.43	1.97–4.94	4.76	4.65	4.13–5.23	871.50	**0.013**
IL-10 (pg/mL)	33.23	36.54	27.77–39.58	43.69	41.92	39.27–45.97	452.00	**<0.001**
IL-6 (pg/mL)	24.38	20.49	16.42–27.73	49.34	49.00	34.70–59.08	348.00	**<0.001**

Significant differences are in boldface (p<0.05 or p<0.001)
Abbreviations: BMI – body mass index; WBC – white blood cells; HGB – haemoglobin; HCT – haematocrit; PLT – platelets; ALT – alanine aminotransferase; AST – aspartate aminotransferase; VCAM-1 – vascular cell-adhesion molecule-1; h-FABP – heart-type fatty acid-binding protein; TNF-α – tumour necrosis factor alpha; IL-10 – interleukin 10; IL-6 – interleukin 6

in young workers exposed to lead in the absence of clinical signs and symptoms. Occupational lead exposure significantly reflected on the increased levels of pro-inflammatory cytokines IL-6, IL-10, and TNF-α but did not significantly affect h-FABP and VCAM. A study with similar age groups reported BLLs of 9.70±4.20 μg/dL in pottery workers and 21.70±8.80 μg/dL in foundry workers (27). Both groups of exposed workers had significantly higher plasma IL-10 and TNF-α, but not IFN-γ, IL-2, IL-4, and IL-6. In contrast, another study (2) reported lower TNF-α levels in lead-exposed battery plant workers than controls, but not significantly (p>0.05). An environmental study (28) that determined the effects of lead on human semen reported higher IL-7, IL-10, IL-12, and TNF-α levels in a group highly exposed to lead, while the levels of IL-1β, IL-2, IL-4, IL-6, IL-8, and IFN-γ did not change significantly.

The strong correlations between BLLs and the levels of IL-6, IL-10, and TNF-α in our study evidence the inflammatory effect of lead, which may lead to the onset of atherosclerosis, even though clinical signs and symptoms may be absent in young people at the early stage. Our group was probably too young to show a correlation between lead exposure and h-FABP and VCAM-1. h-FABP is a novel biomarker for acute myocardial injury and infarct (29, 30) and a predictor of short-term mortality (31). In atherosclerosis

and inflammation studies about VCAM, there are conflicting reports about its predictive potential for early atherosclerosis. An old study (32) on human coronary arteries from explanted hearts showed no correlation between VCAM-1 and underlying inflammatory cells. Other studies (33–36) have shown that VCAM is a sensitive biomarker for the acute coronary syndrome, but the absence of significant correlations with the cytokines and BLL in our study suggest that it cannot be used as a predictor of atherosclerosis associated with occupational exposure to lead.

One limitation of our study was that we did not analyse serum nitric oxide levels or other oxidative stress parameters mediating lead toxicity. Knowing these parameters could have helped us to better understand the cytotoxic effects of lead and better interpret the observed inflammation and atherosclerosis marker findings. Hopefully one of our future studies will address this issue.

Conflicts of interest

None to declare.

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Table 2 Pearson's correlation coefficients for all parameters

N=99	Age (year)	BMI	WBC	HGB (g/dL)	HCT (%)	PLT (10³/μL)	ALT (U/L)	AST (U/L)	Creatinine (μmol/L)	Pb (μg/dL)	IL-6 (pg/mL)	IL-10 (pg/mL)	TNF-a (pg/mL)	h-FABP (ng/mL)	VCAM-1 (ng/mL)
Age (year)	1	-0.07	-0.05	0.02	-0.037	0.052	-0.11	-0.083	-0.022	-0.425	-0.284	-0.386	-0.272	0.039	-0.13
WBC			1	0.11	0.106	0.271**	0.034	0.005	-0.212*	0.252**	0.054	0.232*	0.189	0.177	-0.15
HGB (g/dL)				1	0.896**	-0.019	0.230*	0.154	-0.041	-0.200*	-0.161	0.045	0.043	0.073	-0.01
HCT (%)					1	-0.176	0.249*	0.138	-0.067	-0.132	-0.074	0.076	0.114	0.036	-0.01
PLT (10³/μL)						1	0.161	0.133	-0.048	-0.014	0.127	-0.118	-0.085	0.229*	0.011
ALT (U/L)							1	0.707**	0.113	-0.164	-0.048	-0.115	-0.005	0.036	0.072
AST (U/L)								1	-0.087	-0.246*	-0.144	-.0201*	-0.019	-0.14	0.03
Creatinine (μmol/L)									1	-0.116	-0.007	-0.208*	-0.246	0.024	0.083
Pb (μg/dL)										1	0.469**	0.521**	0.279**	-0.07	-0.01
IL-6 (pg/mL)											1	0.350**	0.174	0.013	0.082
IL-10 (pg/mL)												1	0.606**	0.102	0.108
TNF-a (pg/mL)													1	0.182	0.028
h-FABP (ng/mL)														1	0.135
VCAM-1 (ng/mL)															1

Correlation is significant at *p<0.05; **p<0.01
Abbreviations: WBC – white blood cells; HGB – haemoglobin; HCT – haematocrit; PLT - platelets; ALT – alanine aminotransferase; AST – aspartate aminotransferase; VCAM-1 – vascular cell-adhesion molecule-1; h-FABP – heart-type fatty acid binding protein; TNF-α – tumour necrosis factor alpha; IL-10 – interleukin 10; IL-6 – interleukin 6

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Table 3 Regression analysis for Pb and independent variable

Dependent variable	F	Beta	t	R²
IL-6	28.720*	0.469	5.359*	0.220
IL-10	38.042*	0.521	6.168*	0.272
TNF-a	8.594*	0.279	2.932*	0.078

Abbreviations: TNF-α – tumour necrosis factor alpha; IL-10 – interleukin 10; IL-6 – interleukin 6

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Učinci profesionalne izloženosti olovu na izabrane upalne biomarkere

Pri izloženosti toksičnim metalima poput olova, utvrđivanje razina olova i upalnih citokina (IL-6, IL-10 i TNF-α) ključno je za rano otkrivanje bolesti. Cilj je ovoga ispitivanja bio osmisliti model za rano otkrivanje upala i ateroskleroze u mladih radnika profesionalno izloženih olovu dok se još nisu pojavili klinički znakovi i simptomi. Zahvaljujući tomu, liječnici bi mogli pravovremeno započeti liječenje. Ispitivanje je obuhvatilo 49 metalskih radnika izloženih olovu i 50 neizloženih administrativnih radnika (kontrolna skupina) koji su bili podvrgnuti imunološkim testovima na citokine (IL-6, IL-10 i TNF-α) i na markere ateroskleroze (h-FABP i VCAM-1), toksikološkomu testu na olovo te rutinskim biokemijskim testovima (ALT, AST, kreatinin) u Bolnici za profesionalne i okolišne bolesti u Ankari 2017. Razine olova u krvi korelirale su s razinama IL-6, IL-10 odnosno TNF-α (r=0,469, r=0,521, odnosno r=0,279, p<0,01), ali nisu značajno utjecale na razine h-FABP odnosno VCAM-1.

KLJUČNE RIJEČI: ateroskleroza; citokini; h-FABP; IL-6; IL-10; TNF-α; VCAM-1