The effect of subacute lead exposure on selected blood inflammatory biomarkers and angiogenetic factors

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Abstract: Objectives: The aim of the study was to examine blood levels of selected pro-inflammatory cytokines, C reactive protein (CRP), and selected factors that influence angiogenesis in workers exposed to lead for a short period of time. Methods: The study population consisted of 36 male workers (mean age 41 ± 14 years) exposed to lead for 40 days. Results: The mean blood lead level (BLL) was 10.7 ± 7.67 μg/dl at the beginning of the study, and increased to 49.1 ± 14.1 μg/dl at the end of the study period. The levels of macrophage inflammatory protein 1-α (MIP-1α) were significantly higher after the studied exposure to lead compared to the baseline by 71%. Similarly, the values of CRP increased by 35%. Conversely, the values of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and fibroblast growth factor-basic (FGF-basic) decreased by 14% and 21%, respectively. After the examined period of lead exposure, analysis of correlations showed positive correlations between vascular endothelial growth factor (VEGF) levels and the levels of interleukin 1β (IL-1β) (R = 0.39), interleukin 6 (IL-6) (R = 0.42), and MIP-1α (R = 0.54). Positive correlations were identified between MIP-1α and FGF-basic (R = 0.38), soluble angiopoietin receptor (sTie-2) (R = 0.41), and sVEGFR-1 (R = 0.47). Discussion: Short-term exposure to lead induces the inflammatory response; however, these mechanisms seem to be different from those observed in chronic lead exposure. Subacute exposure to lead may dysregulate angiogenesis via modifications in the levels of angiogenic factors. (J Occup Health 2018; 60: 369-375)

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Introduction

Occupational lead (Pb) exposure occurs during primary and secondary lead smelting, processing and casting of non-ferrous metals, production and recycling of lead-acid batteries, and scraping and sanding lead paint. Over the past several decades, there has been a remarkable reduction in the environmental sources of lead. A downward trend related to the blood lead levels (BLL) of workers occupationally exposed to Pb has been noted in developed countries, such as the U.S. or the U.K. Nonetheless, a large group of workers still remain exposed to Pb. In Poland in 2004-2005, 3297 employees were working in conditions of exposure to Pb at concentrations higher than the maximum allowable concentration (MAC) in the air (0.050 mg/m³). In Poland, BLLs higher than 50 μg/dl cause employees to temporarily leave work until BLL normalizes. Exposure to Pb can be detrimental to the nervous, cardiovascular, skeletal, renal, hematopoietic, and immune systems. Workplace Pb exposure has the ability to cause a pro-oxidant/antioxidant imbalance through the direct generation of reactive oxygen species (ROS). Excessive ROS production has been shown to impact the inflammatory response by modulating intracellular signaling pathways. Several studies have looked for a link between oc-
occupational exposure to lead and the levels of pro-inflammatory biomarkers, such as interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and C reactive protein (CRP)²⁶.

Angiogenesis, the process of new blood vessel formation, is a key component of the pathological processes observed in many disorders, such as cancer, atherosclerosis or cardiovascular disease⁷,8. These disorders are also associated with occupational Pb exposure⁹,10. The impact of Pb on angiogenesis is not completely understood. Several studies suggest a close relationship between ROS and angiogenesis¹¹. Furthermore, in vitro studies indicate the influence of Pb on growth and tube formation by cultured human umbilical vascular endothelial cells (HUVEC)²²,1³. It has been postulated that Pb promotes inflammatory processes via induction of the pro-inflammatory cytokines and modulates angiogenesis in chronically occupational lead exposed workers¹⁶. However, there are no studies on the relationship between other parameters of the immune response and angiogenic factors during short-term lead exposure. To address this issue, the present study was undertaken to examine blood levels of selected pro-inflammatory cytokines, CRP, and selected angiogenic factors in workers exposed to lead for a short period of time.

Material and Methods

Study population

Each study subject provided written consent to participate in the study. Questionnaire data on age, weight, height, Body Mass Index (BMI), work period, and smoking habits were obtained. The BLL served as a biomarker of lead exposure.

The study population consisted of 36 male workers (mean age 41 ± 14 years) exposed to lead for 40 days. Examined subjects were employed in the lead-zinc manufacturing to perform periodic maintenance of blast furnaces and production lines. Of the participants, 18 workers were occupationally exposed to lead for the first time (BLL 4.16 ± 1.62 μg/dl), while the other 18 workers had a history of occupational exposure to lead (BLL 16.95 ± 5.32 μg/dl).

The experimental set-up was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (No. KNW/0022/KB1/108/14).

Laboratory procedures

Blood samples were collected from a peripheral vein using tubes (Vacuette; Greiner-Bio, Frickenhausen, Germany) coated with K-EDTA to obtain whole blood, or plain tubes to obtain serum. Serum was collected using centrifugation (3,000 rpm for 10 min at 4°C), aliquoted, and stored at −80°C until analysis. Assessments of BLL were performed using graphite furnace atomic absorption spectrometry in an ICE 3400 system.

Serum CRP concentration was determined using the photometric-turbidimetric test for the quantitative determination of human CRP in serum and plasma (Human Gesellschaft für Biochemica und Diagnostica mbH, Germany). For this method, the linearity is kept up to 25 mg/dl and the lower detection limit is 0.1 mg/dl. No prozone phenomenon was observed up to 40 mg/dl.

Serum levels of interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and macrophage inflammatory protein 1-α (MIP-1α) were evaluated using a Bio-Plex 200 System (Bio-Rad, Hercules, CA). Levels of angiogenic factors such as soluble angiopoietin receptor (sTIE-2), vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), and fibroblast growth factor-basic (FGF-basic) were detected in serum using a Bio-Plex 200 System (Bio-Rad Laboratories Inc., Berkeley, California, USA) according to the manufacturer’s instructions. The results were expressed as pg/ml.

Statistical analysis

All statistical analyses were performed using the Statistica 9.1 PL software program (StatSoft Polska, Warsaw, Poland). Data are reported as mean ± SD or as median and IQR. Shapiro-Wilk’s test was used to verify normality, and Levene’s test was used to verify homogeneity of variances. Statistical comparisons were made using a t-test, a t-test with separate variance estimates, or the Mann-Whitney U-test. Dependent variables were analyzed using the matched-pairs tests: Student’s t-test and Wilcoxon’s test. The Spearman non-parametric correlation was calculated. A p-value < 0.05 was considered statistically significant.

Results

The epidemiologic data are presented in Table 1 and 2. CRP levels and concentrations of lead in the blood are presented in Table 3. The mean BLL was 10.7 ± 7.67 μg/dl at the beginning of the study, and increased to 49.1 ± 14.1 μg/dl by the end of the study period. At the same time, the levels of CRP increased by 35% (Table 3).

The levels of MIP-1α were significantly higher after Pb exposure (71% higher than baseline), while the levels of IL-1β, IL-6 and TNF-α did not change. Simultaneously, the values of sVEGFR-1 and FGF-basic decreased by 14% and 21%, respectively. Levels of other angiogenic factors (sTie-2 and VEGF) did not change due to Pb exposure (Table 4).

Significant differences between the subgroup of workers exposed to lead before the study and those without such exposure are presented in Table 5. There were no significant differences between the subgroups of younger and older workers, smokers and non-smokers, and work-
ers with higher and lower BMIs (data not shown).

At baseline, there were no correlations between the levels of pro-inflammatory cytokines and angiogenic factors (data not shown). After the examined period of Pb exposure, analysis of correlations showed positive correlations between VEGF level and the levels of IL-1β (R = 0.39), IL-6 (R = 0.42), and MIP-1α (R = 0.54). Positive correlations between MIP-1α and FGF-basic (R = 0.38), sTie-2 (R = 0.41), and sVEGFR-1 (R = 0.47) were also shown (Table 6).

The analysis of correlations did not show any correlations between the BLL and the levels of pro-inflammatory cytokines and angiogenic factors (data not shown).

**Discussion**

Epidemiologic and experimental studies have demonstrated that exposure to lead increases the risk of hypertension\(^{15}\), and other research has provided a strong evidence that Pb exposure is a risk factor for ischemic heart disease and the occurrence of functional disturbances within the heart and blood vessels\(^{16}\). Among the explanations for these disorders is the impact of lead on the inflammatory response and angiogenesis\(^{6}\).

**In vitro** studies have demonstrated dose-dependent immunomodulatory effects of Pb\(^{17,18}\), and human studies have found that occupational lead exposure is associated with altered levels of certain pro-inflammatory cytokines, although the majority of studies focus only on chronic lead exposure. Valentino et al.\(^{5}\) reported higher plasma TNF-α in workers chronically exposed to Pb (BLL = 9.1-46.0 μg/dl) compared to non-exposed workers. However, the level of IL-6 did not change in this study. Similar results were obtained in lead recycling plant workers (BLL = 30.7 μg/dl), who exhibited significantly higher TNF-α than controls\(^{20}\). Our previous study on chronically Pb exposed workers (BLL = 37.0 μg/dl) demonstrated not only higher levels of TNF-α, but also higher levels of IL-6 and IL-1β\(^{19}\).

In this study, BLL increased significantly from 7 μg/dl to 49.1 μg/dl over 40 days. However, this remarkable increase was not associated with any significant alterations in IL-1β, IL-6, or TNF-α levels. However, at the same time we found a significant increase of the serum CRP level (35%). These results indicate that the CRP elevation observed during short-term lead exposure is likely caused by mechanisms associated with other pro-inflammatory factors. The results of the National Health and Nutrition Examination Survey (NHANES), based on a population of more than 9000 people environmentally exposed to Pb, demonstrated that the odds of having elevated CRP levels was 77% greater in a group with BLLs ≥ 30.9 (μg/l) than in a group with BLLs < 11.6 (μg/l)\(^{14}\). Similarly, it has been shown that the mean values of CRP were significantly higher in workers with occupational lead exposure compared to control subjects\(^{20,21}\).

Elevated levels of CRP in lead exposed populations may have many clinical implications. CRP is a pro-inflammatory factor which powerfully predicts future cardiovascular disorders\(^{22}\). Previous in vitro studies have detected the effects of CRP on chemokine and adhesion molecule levels. Montecucco et al.\(^{23}\) demonstrated a CRP-induced increase in the concentration of MIP-1α in human adherent monocytes. In addition, an in vitro investigation on human peripheral blood mononuclear cells (PBMC) showed that lead exposure results in a dose-dependent increase of MIP-1α production by PBMCs\(^{24}\). MIP-1α is a small protein belonging to the C-C subfamily of chemokines, inducible proteins that exhibit a variety of pro-inflammatory activities. MIP-1α has been proposed to induce production of IL-1β, IL-6 and TNF-α; however, this effect was not observed in this study. Our data suggest a possible early effect of lead on pro-inflammatory markers, which may be related to the ability of MIP-1α to recruit pro-inflammatory cells, especially lymphocytes and monocytes\(^{25}\).

Similar to the pro- and anti-inflammatory balance, the angiogenic balance plays an important role in various

| Table 1. Epidemiologic data for study subjects |
|---------------------------------------------|
| **Mean** | **SD** |
| Lead exposure duration (days) | 40 | 3 |
| Work period (years) | 15 | 12 |
| Age (years) | 41 | 14 |
| Height (cm) | 176 | 6.7 |
| Weight (kg) | 79.7 | 12.6 |
| BMI (kg/m²) | 25.9 | 3.7 |
| Smokers (%) | 69.4 | - |

| Table 2. Epidemiologic data for the subgroups of workers with and without a history of occupational lead exposure. |
|---------------------------------------------------------------|
| **N-HOE** | **HOE** |
| **Mean** | **SD** | **Mean** | **SD** |
| Work period (years) | 13.3 | 12.9 | 17.6 | 11.6 |
| Age (years) | 37.7 | 14.2 | 44.6 | 12.4 |
| Height (cm) | 174.2 | 6.1 | 176.5 | 7 |
| Weight (kg) | 77 | 12.9 | 81.4 | 12.2 |
| BMI (kg/m²) | 25.3 | 3.8 | 26.1 | 3.7 |

N-HOE: no history of lead exposure, HOE: workers with a history of lead exposure
pathological and physiological processes\(^{30}\). It has been shown that inorganic elements may influence the regulation of angiogenesis and vascular function\(^{30}\). Thus, it is essential to establish the possible ability of lead to maintain or alter angiogenesis. There are only a few in vitro studies showing changes in angiogenetic factors due to the toxic action of lead. In cultured vascular smooth-muscle cells, lead had a stimulatory effect on angiogenesis\(^{30}\). Another study demonstrated that lead inhibits tube formation by cultured human vascular endothelial cells in a dose- and time-dependent manner\(^{30}\). These discrepancies appear to be a result of different study protocols.

Inflammation may promote angiogenesis in a number of ways. Many pro-inflammatory cytokines, such as TNF-\(\alpha\), IL-6, and IL-1\(\beta\), may have also angiogenic activity\(^{30}\). Moreover, an in vitro study has shown that MIP-1\(\alpha\) promotes VEGF expression and angiogenesis in human osteosarcoma cells by down-regulating miR-374b expression via JNK, ERK, and p38 signaling pathways\(^{30}\). Our results reveal that MIP-1\(\alpha\) levels positively correlate with the levels of VEGF, FGF-basic, sTie-2, and sVEGFR, while the levels of IL-1\(\beta\) and IL-6 correlated with the level of VEGF. Similar correlations between the levels of pro-inflammatory cytokines and angiogenic factors were not observed prior to lead exposure. These results indicate that short-term lead exposure triggers mechanisms that link angiogenesis and inflammation.

Recent experimental studies suggest that Pb may modulate angiogenesis via induced interleukin 8 (IL-8) gene expression\(^{30}\) through the mitogen activated protein kinase (MAPK) pathway and activator protein 1 (AP-1)\(^{30}\). Furthermore, IL-8 is also one of the pro-inflammatory cytokines\(^{30}\). Dobrakowski et al.\(^{30}\) showed that the level of IL-8 was significantly increased by 34\% compared to baseline after a short-term exposure to lead. This observation also supports the hypothesis that lead exposure may indirectly affect angiogenesis. In the present study, we reported that the serum levels of sVEGFR-1 and FGF-basic were significantly decreased due to short-term lead exposure. The soluble form of VEGFR-1 retains its high-affinity binding to VEGF, and is likely to negatively regulate VEGF availability by sequestering the ligand and by forming inactive heterodimers with membrane-bound VEGF receptors\(^{30}\). In light of this, our results suggest that

### Table 3. Blood lead level (BLL) and C reactive protein level (CRP) before and after subacute exposure to lead.

| Pro-inflammatory cytokines | Before exposure | After exposure | Relative change % | \(p\) |
|----------------------------|-----------------|----------------|-------------------|------|
|                            | Mean SD         | Mean SD        |                   |      |
| BLL (\(\mu\)g/dl)          | 10.7 7.68       | 49.1 14.2      | 359%              | <0.001 |
| CRP (mg/l)                 | 7.17 4.37       | 10.95 5.77     | 34%               | 0.035 |

\(p\)-value: comparison between values obtained before and after exposure to lead using Student’s t-test or Wilcoxon’s test.

### Table 4. The levels of pro-inflammatory cytokines and angiogenic factors before and after subacute exposure to lead.

| Pro-inflammatory cytokines | Before exposure | After exposure | Relative change % | \(p\) |
|----------------------------|-----------------|----------------|-------------------|------|
|                            | Median IQR      | Median IQR     |                   |      |
| IL-1\(\beta\) (pg/ml)      | 0.25 0.13       | 0.25 0.17      | 0%                | 0.632 |
| IL-6 (pg/ml)               | 2.07 3.25       | 2.34 2.74      | 13%               | 0.925 |
| TNF-\(\alpha\) (pg/ml)     | 5.31 6.77       | 4.46 5.96      | -16%              | 0.157 |
| MIP-1\(\alpha\) (pg/ml)    | 1.04 0.84       | 1.77 2.21      | 71%               | 0.013* |

| Angiogenic factors         | Median IQR      | Median IQR     |                   |      |
|----------------------------|-----------------|----------------|                   |      |
| sTIE-2 (pg/ml)             | 18455 8183      | 18326 9491     | -1%               | 0.246 |
| VEGF (pg/ml)               | 72.20 66.40     | 63.53 65.94    | -12%              | 0.850 |
| sVEGFR-1 (pg/ml)           | 6997 3530       | 6015 3995      | -14%              | 0.048* |
| FGF-basic (pg/ml)          | 461 164         | 367 127        | -21%              | 0.017* |

IQR: interquartile range, IL-1\(\beta\): interleukin 1\(\beta\), IL-6: interleukin 6, TNF-\(\alpha\): tumor necrosis factor \(\alpha\), MIP-1\(\alpha\): macrophage inflammatory protein 1-\(\alpha\), sTIE2: soluble angiopoietin receptor, VEGF: vascular endothelial growth factor, sVEGFR-1: soluble vascular endothelial growth factor receptor-1, FGF-basic: fibroblast growth factor-basic

\(p\)-value: comparison between values obtained after and before exposure to lead using the Mann-Whitney U test.

* Statistically significant (\(p < 0.05\)).
lead simultaneously dysregulates angiogenesis-triggering pro- and antiangiogenic mechanisms. It is possible that Pb may have impact on sVEGFR-1 transcription via interactions with GATA proteins[36]. These proteins are transcription factors that bind GATA DNA elements through Cys, structural zinc-binding domains, which are the potential targets for lead[37]. The influence of lead on FGF-basic is also documented in the previous studies. Kaji et al.[38] have shown that lead at 0.5 and 5.0 μM concentrations significantly reduced the ability of FGF-basic to stimulate vascular endothelial cells. These changes may be caused by direct lead-induced inhibition of the production and/or the activity of FGF-basic[39]. Furthermore, lead-induced alterations in heparan sulfate proteoglycans at the vascular endothelial cell surface[40] may lead to lower bioavailability of FGF-basic[41].

Earlier studies indicate that the impact of lead on angiogenic factors depends on the duration of exposure rather than BLL. We showed that a subgroup of workers with a history of occupational exposure to lead consistently had increased FGF-basic and VEGF levels compared to baseline, while the opposite results were observed in the subgroup of workers without a history of occupational exposure to lead. This observation suggests that Pb may modulate angiogenic factors levels through different mechanisms, depending on the duration of exposure.

The results of this study should be evaluated in the context of its limitations. The possible confounding role of inorganic elements such as other metal ions was not taken into consideration and is probably the major limitation of this study. Moreover, it is possible that the study was underpowered to detect significant differences in

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### Table 5. The comparison between the subgroups of workers with and without a history of occupational exposure to lead

|          | N-HOE n=18 | HOE n=18 | p  | Relative change % |
|----------|------------|----------|----|--------------------|
|          | Median     | IQR      | Median | IQR    |
| a: BLL (μg/dl) | 3.70       | 2.60     | 17.10 | 9.30   | 0.000 | 362% |
| b: BLL (μg/dl) | 45.52      | 6.20     | 48.60 | 22.00  | 0.438 | 8%  |
| D: BLL (μg/dl) | 39.70      | 6.90     | 30.90 | 26.40  | 0.028 | −22% |
| a: MIP-1α (pg/ml) | 1.08       | 0.70     | 0.90  | 1.20   | 0.825 | −19% |
| b: MIP-1α (pg/ml) | 0.80       | 1.54     | 2.70  | 2.07   | 0.002 | 245% |
| D: MIP-1α (pg/ml) | 0.03       | 1.28     | 1.20  | 2.70   | 0.011 | 4800% |
| a: VEGF (pg/ml) | 67.89      | 60.54    | 75.80 | 74.70  | 0.899 | 12%  |
| b: VEGF (pg/ml) | 50.07      | 39.93    | 82.20 | 70.40  | 0.020 | 64%  |
| D: VEGF (pg/ml) | −15.27     | 67.56    | 14.20 | 58.05  | 0.041 | −193% |

N-HOE: no history of lead exposure. HOE: workers with a history of lead exposure, a: levels at baseline, b: levels at the end of the study period, D: median of differences between the (a) and (b) values. p-value: comparison between N-HOE and HOE subgroups using the Mann-Whitney U test. p-values < 0.05 were considered statistically significant.

### Table 6. Correlations between levels of pro-inflammatory cytokines and angiogenic factors after subacute exposure to lead.

| Angiogenic factors | VEGF | FGF-basic | sTie-2 | sVEGFR-1 |
|-------------------|------|-----------|--------|---------|
| Pro-inflammatory cytokines |      |           |        |         |
| IL-1β             | 0.39 | NS        | NS     | NS      |
| IL-6              | 0.42 | NS        | NS     | NS      |
| TNF-α             | NS   | NS        | NS     | NS      |
| MIP-1α            | 0.54 | 0.38      | 0.41   | 0.47    |

Spearman’s rank correlation was used to test correlations between angiogenic factors (columns) and pro-inflammatory cytokines (rows). R-values are shown for the statistically significant correlations (p < 0.05). NS: not significant.
measured parameters.

Conclusions

Short-term exposure to lead induces inflammatory responses, but the mechanisms seem to be different from those observed in chronic lead exposure. Additionally, subacute exposure to lead may dysregulate angiogenesis via modification of the levels of angiogenic factors.

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Conflicts of interest: None declared.

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