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Low-Level Exposure to Lead as a Cardiovascular Risk Factor

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1. Introduction

Cardiovascular diseases are the main cause of death in many developed and developing countries around the world. Cardiovascular end points (myocardial infarction, stroke or sudden death) are strictly connected with prevalence of classic cardiovascular risk factors, such as smoking, sedimentary lifestyle, obesity, atherosclerotic lipid pattern and arterial hypertension. Also, many 'new' factors have been identified, e.g. hyperhomocysteinemia, increased fraction of small, dense LDL or lipoprotein (a), increased C-reactive protein, increased apo-B/apo-A ratio or some enzymes' increased activities (Skoczynska, 2006). However, traditional risk factors alone (nonmodifiable and modifiable alike) do not fully explain high incidence and mortality from these diseases. The effectiveness of different strategies concentrating on reducing known risk factors does not translate to a satisfactory reduction of incidence and mortality from myocardial infarction or stroke. It is essential to introduce strategies concerning 'new' risk-factors, as well as to identify those that remain unknown.

Heavy metals, such as lead, cadmium and mercury, are the most abundant xenobiotics in human environment. These metals are present in the air, house dust, soil, water, consumer products and some herbal remedies. Main toxicological problems result from these metals' accumulation in soil, water, plants and animals, which is responsible for human exposure to toxic metals many years after the cessation of the emission. The intrauterine exposure, which is especially dangerous, as metals pass the placental barrier (Bellinger et al., 1987), as well as lead exposure in early childhood (Roy et al., 2009), affects strongly immature tissues, mainly the central nervous system. Lead exposure during pregnancy has a clear impact on mental and behavioral development (Hu et al., 2006; Nie et al., 2011). It has been documented that there is no safe lead blood level and that its toxic action is present at levels much lower than previously suspected. Another problem is the existence of combined exposure to heavy metals, toxic and essential alike, in human natural environment. The disturbance in the homeostasis of trace metals (zinc, copper, calcium, iron, selenium) affects lead toxicity in the cardiovascular system (Faure et al., 1991; Kuliczkowski et al., 2004; Skoczynska et al., 1994).

Although the knowledge on low lead exposure effects on the heart and blood vessels is incomplete, it seems justified to put forward a thesis that environmental exposure to lead is a

risk factor for developing a cardiovascular event. In case of this thesis' positive verification, conducted studies, aside from contributing new facts to the knowledge on lead toxicity, may become a set-point for solving practical issues, i.e. means for identification and reduction of lead exposure sources, diagnosis and monitoring of lead toxicity, prophylaxis and treatment of individuals with an increased body lead burden. This would allow to achieve long-term social benefits, such as a decrease in incidence and mortality from cardiovascular diseases.

2. The global decrease in exposure to lead

Together with industrialization and motorization, the world lead production had been rising till 1980s, when it reached over 3.8 million tons per year (Kelly & Matos, 2005). However, since the 1990s, in general, the exposure to lead around the world has declined. It has been caused by the elimination of leaded petrol, the decrease in sales of lead containing water pipes and canned foods, and the recall from production of lead containing paints.

In 1991, US Centers for Disease Control and Prevention (CDC) adopted the blood lead level of 10 μg/dL as a threshold for lead toxicity. In 1995, the same value was assumed by the World Health Organization. The United States National Health and Nutrition Examination Surveys (NHANES) have documented a dramatic decline in blood lead concentrations in US adults and children (Muntner et al., 2005). A decline in blood lead level has been found also in Australia (Rossi, 2008).

Despite legislative changes, in some developing countries the exposure to lead persists on an unchanged level. Only in 2000, in about 100 countries there was an exposure to leaded petrol. Lead is also used in the production of paints that are employed in maritime industry or to paint external building parts (Tong et al., 2000). In industrialized Asian, South and Latin American regions, also lead mining, smelting, battery factories, cottage industries, crystal glass foundries and glazed ceramics manufacturing are important antropogenic lead sources. In the nineties, in some industrial areas of China, the proportion of children with blood lead level exceeding 10 μg/dL reached 99% but in non-industrial regions was about 50% (Shen et al. 1996). Among children older than 18 months, living in the area of Mexico City, 44% had blood lead level higher than 10 μg/dL (Romieu et al., 1995). Similarly, in populations of children living in industrial regions of India, these proportions were disturbingly high and ranged from 40% to 62% (Conference on Lead Poisoning, Bangalore, 1999).

Still, the worst situation concerns Africa and is caused by lack of legislative regulations, low number of epidemiologic studies and little toxicological information (Mathee et al., 2006).

In many developed European countries, i.e. Belgium, Germany, Sweden and the United Kingdom, there was a decline in blood lead level between 1978 and 1988 (Tong et al., 2000). The research project entitled Public Health Impact of long-term, low-level Mixed Element exposure (PHIME) in a susceptible population revealed that the European population has been subjected to a dramatically lower exposure to lead since the abolition of lead from petrol. In spite of this fact, at PHIME Seminar 'Effects of exposure to metals; no margin of safety in Europe' at the European Environment Agency on 10th of February 2011, it was emphasized that 'lead pollution sources must continually be hunted down and stopped'. This recommendation is based on the observation that the level of exposure to lead

associated with a reduced IQ in children seems to be much lower than previously known (Report of PHIME, 2011).

The exposure to lead in populations of Central-Eastern European countries is still dangerously high (Bogunia et al., 2007; Pawlas et al., 2008; Trzcinka-Ochocka et al., 2005). It is a consequence of political and economical neglect in the last decades. One of the main problems is lack of information on the factual level of environmental lead exposure.

3. The dependence of circulatory system changes on body lead burden

Lead does not fulfill any physiological function in the body and can be toxic even at a small blood concentration. At present, it is well documented that some neurological and cardiovascular effects of lead emerge at a blood lead level lower than adopted as a threshold, i.e. below 10 μg/dL. It has been estimated that blood lead level in a natural, non-contaminated environment amounts to 0.016 μg/dL, i.e. about 600 times lower than the standard adopted for children by the CDC (Flegal & Smith, 1992). In the 1980s-90s, it was shown that lead-induced hypertension develops as a result of the environmental exposure associated with the blood lead concentration of 10-40 μg/dL (Cheng et al., 2001; Harlan et al., 1985; Pirkle et al., 1985). Simultaneously, lead-induced changes in blood pressure were not large. Results of 31 meta-analyses showed only a slight increase in blood pressure at a doubled blood lead level; on average 1 mmHg for systolic and 0.6 mmHg for diastolic pressure (Nawrot & Staessen, 2002).

Also other studies performed in the 1980s-90s showed a toxic action of lead at a relatively low exposure, i.e. corresponding to the blood lead concentration of less than 25 μg/dL (Tong et al., 1998). In 2006, in *Circulation*, Menke et al. published data from NHANES analysis showing the association between blood lead level and mortality from both myocardial infarction and stroke. This association was significant at the lead level lower than 10 μg/dL (Menke et al., 2006).

The dependence of changes in the circulatory system on blood lead level is not clear. On the basis of literature, it seems likely that there is an inverse relationship, i.e. a lower exposure is associated with greater cardiovascular changes, similarly to the case of neurotoxic effects of lead in children (Lanphear et al., 2005).

In population studies of people exposed to lead, lead is determined in blood, urine and bone. The most frequently measured indicator of exposure is the blood concentration. Due to a relatively short half-life of lead in the blood (approximately 30 days), this biomarker does not reflect the body lead burden but rather a recent exposure to external or intrinsic sources (e.g. lead released into the blood from storage sites, in conditions such as acidosis, fever or infection). Therefore, a more reliable indicator of quantities of lead accumulated in the body is the bone concentration. Lead is measured in the skeletal system (in the tibia or in the patella) using the method of K-shell x-ray fluorescence (KXRF) (Arora et al., 2009).

The positive correlation between blood lead level and arterial pressure has been well documented. However, lead concentration in the patella better correlates with the occurrence of coronary heart disease than arterial hypertension. Also, it has been suggested that blood lead level is a better predictor of cardiovascular diseases in young people, and lead concentration in the skeleton in elderly (Weisskopf et al., 2009).

4. The lead effect on the cardiovascular system

4.1 Lead and arterial blood pressure

On the basis of numerous population studies in different settings, including prospective studies, it has been well documented that lead induces arterial hypertension. The majority of cross-sectional and prospective studies showed a significant association between blood lead level and systolic or diastolic blood pressure (Apostoli et al., 1992; Ding et al., 1998; Hu et al., 1996; Malvezzi et al., 2001; Micciolo et al., 1994; Schwartz, 1991; Takebayashi et al., 2011; Tsao et al., 2000; Weiss et al., 1988). These associations have been found in populations with different geographic, ethnic, and socioeconomic backgrounds (Martin et al., 2006). A positive correlation was also established between umbilical blood lead level and the occurence of arterial hypertension in pregnancy (Rabinowitz et al., 1987). The development of hypertension in workers chronically exposed to high lead levels has been interpreted as a consequence of lead-induced nephropathy (Agency for Toxic Substances and Disease Registry, 1999; U.S. Environmental Protection Agency, 2006). However, in workers occupationally exposed to lower than nephrotoxic lead levels, low blood lead concentration was found as a predictor of an increased systolic blood pressure (Sirivarasai et al., 2004; Telisman et al., 2001). Similarly, prospective studies showed a correlation between lead bone concentration and systolic blood pressure (Cheng et al. 2001; Glenn et al., 2003).

The impact of confounding factors on the relationship between body lead burden and arterial blood pressure can be reduced in experimental studies. Results of many studies performed on numerous experimental models, on various experimental animals (rats, rabbits, calf), have confirmed the hypertensive effect of small doses of lead and explained various mechanisms of this action. These mechanisms result from lead action on the central and peripheral nervous system (Hoffer et al., 1987; Nehru & Sidhu 2001; Silbergeld 1992; Reckziegel et al., 2011), the vessel wall (Ding et al., 1998; Dursun et al., 2005), the renin-angiotensin system (Rodriguez-Iturbe et al., 2005; Sharifi et al., 2004), the kallikrein system (Carmignani et al., 1999), metabolic processes (Skoczynska et al., 1993; Skoczynska et al., 2004), the generation of free radicals (Stohs & Bagchi 1995; Vaziri et al. 2001; Vaziri & Sica 2004), and intracellular signalling pathways (Carmignani et al., 2000), leading to an increase in the vascular tone, and the peripheral vascular resistance (Fig. 1).

It has been concluded that the evidence is sufficient to infer a causal relationship between lead exposure and arterial hypertension (Brown et al., 2011; Navas-Acien et al., 2007; Weisskopf et al., 2009). However, the most important mechanisms explaining the hypertensive effect of chronic low exposure to environmental lead still need an explanation. Hypertension induced by high doses of lead can be partially explained by the nephrotoxic action of this metal (Batuman, 1993; Navas-Acien et al., 2009). It is possible that also in low-lead exposed individuals an impaired renal function is responsible for a persistent increase in blood pressure, as an inverse association between the glomerular filtration rate and blood lead has been observed in people with blood lead levels as low as 10 μg/dL (Fadrowski et al., 2010), or even 5 μg/dL (Ekong et al., 2006). One of the problems to examine in the future is the exploration of dose – response relationship and the determination of the latency period for lead – induced hypertension.

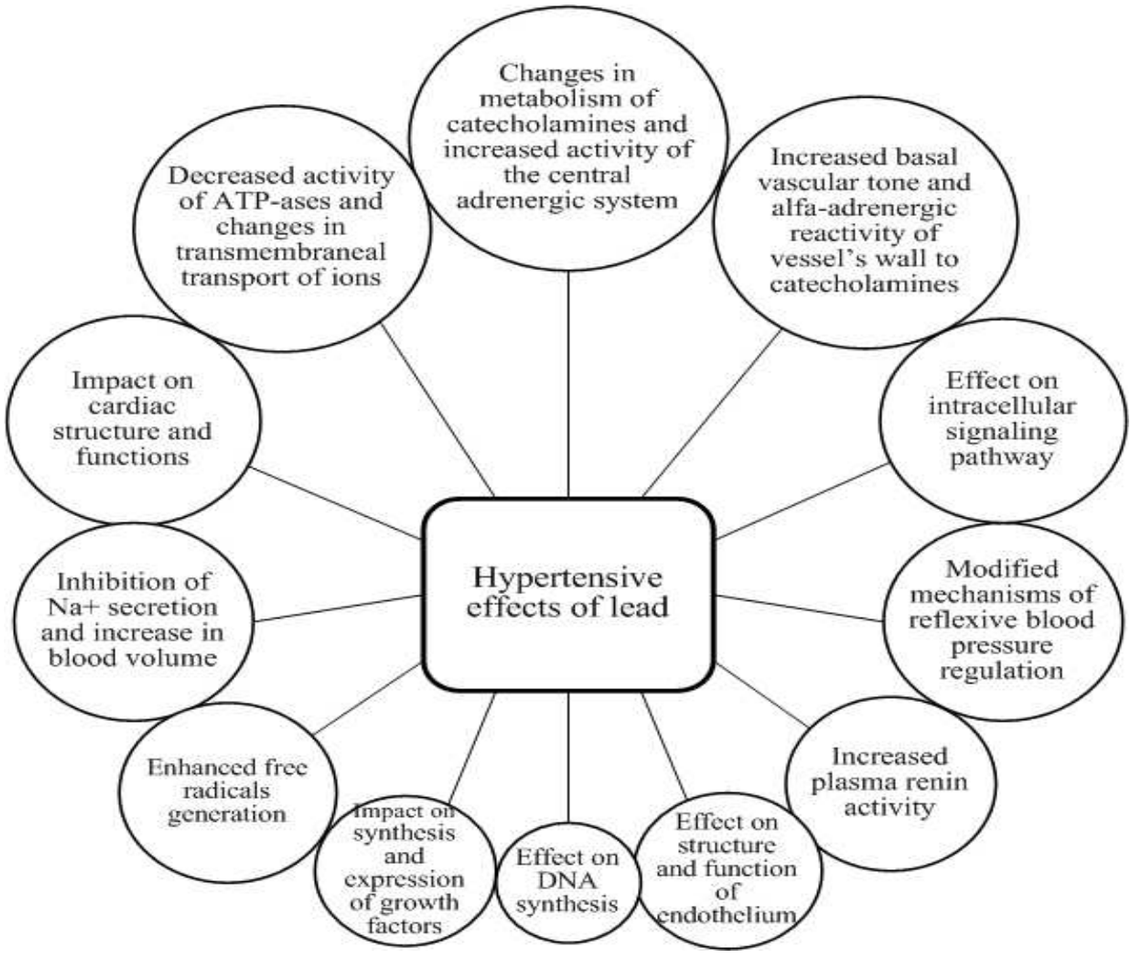


Fig. 1. Cardiovascular mechanisms of the hypertensive effect of low doses of lead (Skoczynska, 2006)

4.2 Lead and atherosclerosis

Aside from arterial hypertension, small amounts of lead cause also metabolic, functional and structural changes in the vessel wall. Some of these changes can accelerate the process of atherosclerosis. In the 1980s, in animal models, low-lead doses induced atherosclerosis was obtained (Revis et al., 1980,1981). Long-term lead exposure, measured by body lead store, was identified as a potential risk of intracranial carotid atherosclerosis in human (Lee et al., 2009). Some of the documented pro-atherosclerotic changes include: changes in lipid metabolism (Gatagonova, 1994; Kasperczyk et al., 2005a), endothelial dysfunctions (Ding et al., 1998; Vaziri et al., 2001), disturbances in essential metals' homeostasis (De Castro et al., 2010; Othman and Missiry, 1998; Wang et al., 2011), as well as an increase in free radicals' generation (Stohs and Bagchi 1995; Vaziri et al. 2001), a procoagulant state (Fujiwara et al., 2000; Kaji et al., 1991) and an inflammatory response (Heo et al., 1998) (Fig. 2).

In our previous studies performed on experimental animals exposed to small doses of lead, we have shown that an increased vessel wall reactivity to the catecholamines vasoconstricting action (Skoczynska et al., 1986; Skoczynska et al., 1987; Skoczynska et al.,

2001), an impaired vasodilatatory effect of acetylcholine (Skoczynska et al., 2005) and changes in vasoactive mediators blood levels (Skoczynska et al., 2003) are preceded by atherogenic dyslipidemia (Skoczynska et al., 1993), an increased lipid peroxidation, especially in the brain (Skoczynska et al.,1994), changes in the renin-angiotensin system (Wrobel & Skoczynska, 2002), and copper and zinc homeostasis (Skoczynska et al., 1994). In copper foundry workers exposed to lead, we have observed changes in vasoactive mediators blood levels (Skoczynska et al., 2002), hypertriglyceridemia (Skoczynska et al., 2007), an increased serum lipid peroxidation (Turczyn et al., 2010) and changes in copper and zinc homeostasis (Skoczynska et al., 2001).

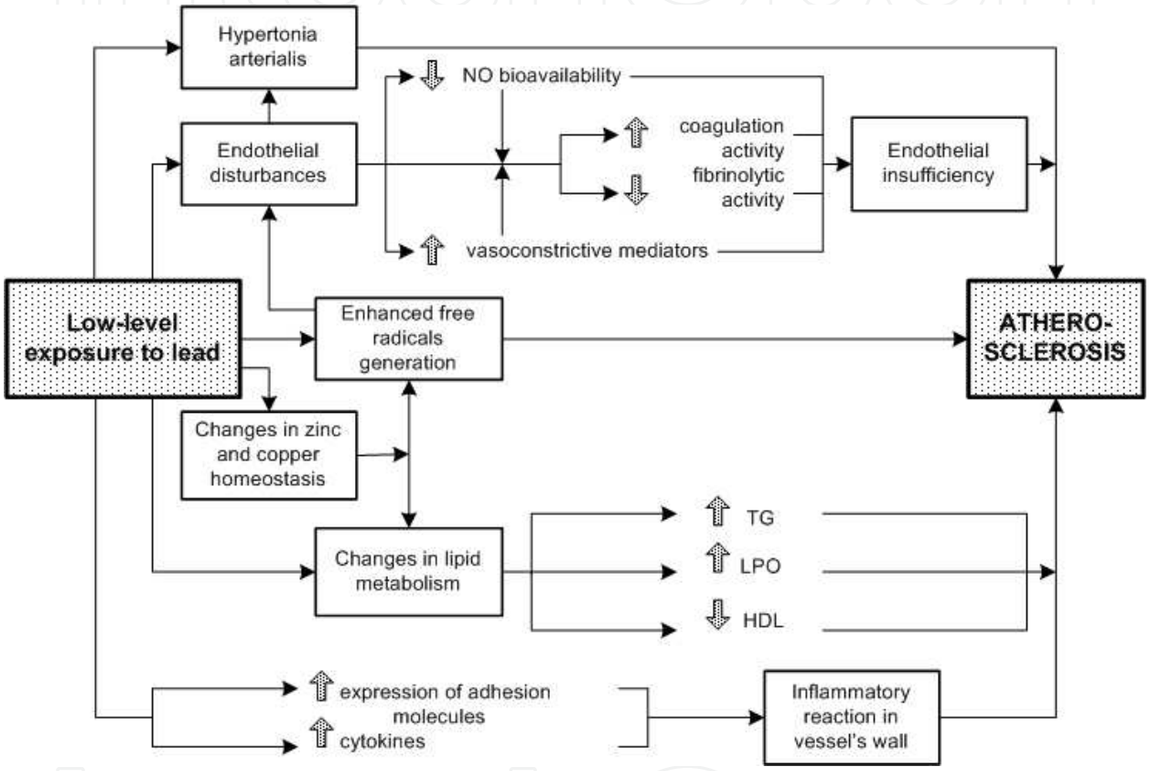


Fig. 2. Possible mechanisms of the pro-atherosclerotic action of lead (Skoczynska, 2006)

4.3 Lead and intermediate or immediate cardiovascular end points

Lead-induced changes in the circulatory system affect the occurrence of cardiovascular end points in lead exposed populations. Intermediate indicators of these events are functional and structural changes in the heart, such as changes in the left ventricular mass, heart rate, heart rate variability or electrocardiographic abnormalities. The 24-hour electrocardiographic evaluation performed in our centre in groups of men occupationally exposed to lead (copper foundry workers) showed that various heart rhythm disorders were more frequent as compared to the controls. A more frequent incidence of tachycardia (Gajek et al., 2004; Poręba et al., 2010a), a decreased heart rate variability (Poręba et al., 2011), and abnormal parameters of heart rate turbulence (Poręba et al., 2010a) were observed. In another group of men with arterial hypertension, occupationally exposed to lead, the study has demonstrated a significantly more frequent manifestation of left ventricular diastolic dysfunction and an

increase in local arterial stiffness (Poręba et al., 2010b). However, lead exposed workers without hypertension also had an impaired diastolic function, compared with nonexposed controls (Beck & Steinmetz-Beck, 2005). In our earlier study, it was estimated that a ten-year risk of fatal cardiovascular disease (SCORE) in crystal glassworks' employees exposed to lead was higher in comparison to other workers (Doroszko et al., 2008). Also lipid disturbances were associated with the occupational exposure to lead (Skoczynska et al., 2007). All these changes were related to a relatively high blood lead level (above 40 μg/dL). Our newest experimental studies, using nuclear magnetic resonance, seem to confirm an increased incidence of left ventricular diastolic dysfunction in rats poisoned with small doses of lead (data in press).

In other studies, steel workers (Kasperczyk et al.,2005b) or battery workers (Tepper et al., 2001) exposed to lead displayed a higher left ventricular mass and/or a lower ejection fraction, compared to administrative workers from the same factories. On the other hand, in other studies, the interventricular septum and the left ventricular wall thickness determined in refinery workers with high blood lead level were similar to those determined in workers with lower blood lead concentration. Simultaneously, the decrease of diastolic cardiac function was more significant in the lead poisoned group (Zou et al., 1995). It may be concluded that results of studies performed on populations occupationally exposed to lead are inconsistent and the data on how lead affects the heart is insufficient. It remains unknown, for example, if lead, regardless of its hypertensive effect, leads to left ventricular diastolic dysfunction or changes heart rate variability.

There is no conclusion regarding the exact nature of lead influence on ECG. Since the 1970s, it has been known that lead increases heart sensitivity to noradrenaline arrhythmogenic action and causes bradycardia. Lead negative chronotropic action was associated with the blocking of heart beta adrenoreceptors activity (Bertel et al., 1978; Tsao et al. 2000). In various electrocardiographic studies, a significantly higher prevalence of heart ventricles repolarization disorders and heart rhythm disturbances was observed in groups of workers exposed to lead, in comparison to controls (Gatagonova 1995; Sroczynski et al., 1990). Among 775 men who participated in the Normative Aging Study, bone lead levels were found to be positively associated with heart rate, corrected QT and QRS intervals, especially in younger men. Additionally, a risk of intraventricular or atrioventricular block increased in men with elevated bone lead levels, whereas blood lead level was not associated with any of the electrocardiographic disturbances (Cheng et al., 1998; Eum et al., 2011). Authors of these studies suggest that the cumulative exposure to low lead levels causes electrocardiographic conduction disturbances. These disorders may be associated with the occurrence of different variants of genes involved in iron metabolism, such as hemochromatosis or heme oxygenase-1 genes. Park et al. found evidence that these genes' variants increase the impact of low-level lead exposure on the prolonged QT interval (Park et al., 2009). However, intermediate cardiovascular outcome varied across studies, and findings were incoherent.

Similarly, results of epidemiologic studies on the association between environmental low-lead exposure and immediate cardiovascular disease end points (coronary heart disease, stroke and cardiovascular disease other than arterial hypertension) are inconsistent. One of the first studies that analyzed a correlation between blood lead level and the incidence of coronary heart disease or stroke was The British Regional Heart Study. In this study, 7371

men aged 40 to 59 from 24 British towns were followed-up for 6 years. After allowing confounding effects of cigarette smoking and a town of residence, there was no evidence that blood lead level is a risk factor for major ischemic heart disease or stroke (Pocock et al., 1988). Also the study performed among 1052 inhabitants of Copenhagen County, who had the mean blood lead concentration of about 7 μg/dL in women and 18 μg/dL in men, and were observed for over 14 years, demonstrated a significant ($p<0.03$) risk for total mortality associated with blood lead but the risk for fatal and nonfatal cardiovascular disease or coronary complications was not significant (Møller & Kristensen, 1992).

On the contrary, studies published during 2002-2006 showed an increased cardiovascular mortality in the general population environmentally exposed to lead among individuals with blood lead levels from 20 μg/dL to 5 μg/dL.

The Second National Health and Nutrition Examination Survey (NHANES II), a national cross-sectional survey of the general US population conducted from 1976 to 1980, showed that individuals with blood lead levels of 20 to 29 μg/dL between 1976 and 1980 (15% of the US population at the time) experienced significantly increased all-cause, circulatory, and cardiovascular mortality from 1976 through 1992. After including the role of potential confounders, individuals with baseline blood lead levels of 20 to 29 μg/dL had a 46% increase in all-cause mortality (rate ratio (RR), 1.46; 95% confidence interval (CI), 1.14-1.86) and a 39% increase in circulatory mortality (RR, 1.39; 95% CI, 1.01-1.91), when compared to those with blood lead levels of less than 10 μg/dL (<0.5 μmol/L). All-cause mortality for those with blood lead levels of 10 to 19 μg/dL (0.5-0.9 μmol/L) was intermediately increased and statistically insignificant (Lustberg & Silbergeld, 2002).

The association between blood lead levels and increased all-cause and cardiovascular mortality was observed also at blood lead levels substantially lower than 20 μg/dL. In the Third National Health and Nutrition Examination Survey, which from 1988 to 1994 recruited 13,946 adult participants who were followed-up for up to 12 years for all-cause and cause-specific mortality, the geometric mean blood lead level in study participants was 2.58 μg/dL. After the multivariate adjustment, hazard ratios (95% CI) of participants in the highest tertile of blood lead (≥ 3.62 μg/dL) and those in the lowest tertile (< 1.94 μg/dL) were 1.25 (1.04 to 1.51; P(trend) across tertiles = 0.002) for all-cause mortality and 1.55 (1.08 to 2.24; P(trend) across tertiles = 0.003) for cardiovascular mortality. Blood lead level was significantly related to both myocardial infarction and stroke mortality, and the association was evident at levels ≥ 2 μg/dL) (Menke et al., 2006).

The second study based on the Third NHANES US community concerned 9,757 participants ≥ 40 years old put in three categories, depending on blood lead level: <5 μg/dL (the reference category), 5 to <10 and ≥10 μg/dL. The relative risk of mortality from all causes was 1.24 (95% confidence interval (CI), 1.05-1.48) for those with blood levels of 5 to <10 μg/dL and 1.59 (95% CI, 1.28-1.98) for those with blood levels ≥ 10 μg/dL (p for trend < 0.001) (Schober et al., 2006). To conclude, both studies based on the Third NHANES have documented an association between blood lead below 10 μg/dL and mortality among U.S. adults.

Also occupational exposure seems to be associated with an increased risk of cardiovascular diseases. In 1963, Dingwall-Fordyce and Lane published results of an analysis of the causes of death among workers who had been exposed to lead. There were 425 pensioners, 184 of

whom had died; additionally, 153 deaths occurred among an unknown number of employees who had not yet reached the retirement age. This analysis provided evidence that heavy exposure to lead was associated with an increased incidence of deaths from cerebrovascular catastrophes (Dingwall-Fordyce & Lane, 1963). The study of 1261 typesetters exposed to low lead doses, started in 1961 and followed until the end of 1984, confirmed the increased cerebral mortality in workers subjected to prolonged exposure. The all-cause standardized mortality ratio was 0.74, the cardiac mortality ratio was 0.63, whereas the ratio for cerebrovascular disease was 1.35 (at the edge of statistical significance). For printers employed for 30 years or more, the cardiovascular mortality ratio was 1.68 (95% CI: 1.18-2.31; p = 0.002) (Michaels et al., 1991). In turn, in the prospective study described by Robinson in 1974, over 20 years (1947-67) the risk of mortality in a group of 592 tetraethyl lead workers and in a group of 660 non-exposed workers was similar. No difference between the two groups in either total mortality or mortality from specific diseases was found (Robinson, 1974). Other retrospective observation which covered 4.556 workers occupationally exposed to lead, diagnosed during 1970-1992, revealed increased total mortality (670 deaths; SMR = 108; 95% CI: 100-116) in comparison to the general population. However, the risk of cardiovascular mortality was significantly increased only in the subcohort with high exposure (153 deaths; SMR = 129; 95% CI: 109-151) (Wilczynska et al., 1998).

In analyses of results obtained from 13,043 South Korean lead workers with mean geometrical blood lead level of 6.01 μg/dL, the impact fractions for cardiac disease among lead workers would be estimated as about 5-13 times higher than those of the general population. Manufacture of accumulators, manufacture of other electronic valves, tubes, and components, and manufacture of accessories for motor vehicles were identified as a relatively important industry. Other industrial processes of relative importance included battery assembly, acid treatment and other soldering (Kim et al., 2008). Also in population of 420 male bus drivers in Thailand, with blood lead level ranging from 2.5 to 16.2 μg/dL (the mean of 6.3 ± 2.2 μg/dL), using the second derivative finger photoplethysmogram (SDPTG) as a marker of the cardiovascular risk, and allowing age, body mass index and lifestyle factors, a significant correlation between blood lead and SDPTG-AI was found (Kaewboonchoo et al., 2010).

4.4 Lead and peripheral artery disease

There have been no prospective studies on the association of blood lead with peripheral arterial disease (PAD). However, the relative risk for PAD, comparing blood lead levels ≥ 2.47 μg/dL versus < 1.03 μg/dL, in a cross-sectional analysis of NHANES 1999–2002, was 1.92. Data was obtained from 1999 to 2000, from 2125 participants who were ≥ 40 years of age. Peripheral arterial disease was defined as a condition with an ankle brachial index lower than 0.9 in at least one leg (Muntner et al., 2005). After adjustment for demographic and cardiovascular risk factors, the odds ratios of peripheral arterial disease, comparing the second, third and fourth quartile of blood lead level with the lowest quartile, were 1.63, 1.92 and 2.88, respectively. It was concluded that blood lead (as well as cadmium) is associated with an increased prevalence of peripheral arterial disease in the general U.S. population (Navas-Acien et al., 2004). Simultaneously, lead levels in urine (contrary to cadmium) were not associated with PAD at the levels found in this population (Navas-Acien et al., 2005). In turn, the observed association of homocysteine level and PAD can be completely explained by confounding due to smoking, increased blood lead and cadmium levels and impaired

renal function (Guallar et al., 2006). The disturbances in homocysteine metabolism (Poręba et al., 2005) and the negative linear correlation between blood lead levels and the ankle-brachial index (Doroszko et al., 2008) were found also in workers occupationally exposed to lead; however, the latter relationship was discovered only in a subgroup of workers with a normal lipid pattern. Results obtained by Schafer et al. showed that hyperhomocysteinemia could be a mechanism that underlies lead effects on the cardiovascular and central nervous systems, possibly offering new targets for prevention of long-term consequences of lead exposure (Schafer et al., 2005).

In 2009, Weisskopf et al. published results of the analysis of all observational studies from database searches and citations regarding lead, intermediate and immediate cardiovascular end points. Studies in general populations have identified a positive association between lead exposure and coronary heart disease, cardiac mortality, cerebral mortality and peripheral arterial disease. Estimates of the relative risk of cardiovascular mortality in workers exposed to lead varied widely across occupational studies; with positive, inverse or null correlations. The positive association between lead levels and cardiovascular mortality occurred in workers with the heaviest exposure. Authors concluded that the evidence is suggestive but not sufficient to infer a causal relationship of lead exposure and clinical cardiovascular outcomes. There is also a suggestive but insufficient evidence to infer a causal relationship of lead exposure and heart rate variability (Weisskopf et al., 2009).

5. Genetic polymorphisms and lead toxicity

Human sensitivity to toxic effect of heavy metals differs depending on age, sex, general health status, quantitative and qualitative alimental deficiency, diet, smoking, lifestyle, place of inhabitancy and socioeconomical status, hygienic habituation, total occupational and environmental exposure to xenobiotics. Some of the critical effects of lead result from lead interference with enzymatic processes responsible for the synthesis of heme. These include the inhibition of delta-aminolevulinic acid dehydratase (ALAD), changes in the concentration of delta-aminolevulinic acid in urine (ALA-U), blood (ALA-B) or plasma (ALA-P), changes in the concentration of coproporhyrin in urine and zinc protoporphyrin (ZP) in blood. As a result of exposure to lead, there is a decrease in activity of blood pyrimidine nucleotidase (P5'N) and nicotinamide adenine dinucleotide synthetase (NADS), as well as changes in nucleotides' blood content. All these effects have been used as biomarkers of lead toxicity (Skoczynska, 2006). Genetic polymorphisms that affect lead toxicokinetics and toxicodynamics may be important factors modifying the risk of harmful effects of lead in vulnerable populations.

Differences in lead effect on the heme synthesis pathway, observed between different representatives of the same population exposed to lead, may be determined by different types of the ALAD gene. In turn, the differences between heme precursors levels in different ALAD genotypes can be related to a varied lead affinity to different ALAD isozymes. Thus, ALAD1 homozygotes (a genotype more frequent than ALAD 1-2) might be more susceptible to disturbances in heme metabolism caused by lead exposure than ALAD2 carriers (Sakai et al., 2000; Suzen et al., 2003). ALAD 1-1 subjects might be also more susceptible to the cytogenetic effect of lead than ALAD 1-2 subjects (Alexander et al., 1998; Dyudu & Suzen 2003). ALAD polymorphisms may be also involved in the emergence of lead-induced arterial hypertension. In terms of exposure to large doses of lead, ALAD polymorphisms are

associated with lead-induced renal hyperfiltration (Weaver et al., 2003). It has been shown, that ALAD 1-2 variants affect the presence of the association between renal function and bone (the tibia or the patella) lead level. Similarly, variant B of the vitamin D receptor gene modifies renal sufficency, although only in young population exposed to high doses of lead (Weaver et al., 2006). Also the impact of endothelial nitric oxide synthase (eNOS) gene polymorphisms on kidney function has been demonstrated in employees exposed chronically to lead: the presence of the Asp allele was associated with higher serum creatinine than the genotype Glu/Glu (Weaver et al., 2003). Lead and selected genes, i.e. vitamin D receptor (VDR) and ALAD genes, may influence blood pressure and risk of hypertension. In a group of workers, 798 exposed to lead and 135 non-exposed, VDR genotypes (BB and Bb vs. Bb), lead concentration in the blood and in the tibia, and the amount of lead bound by dimercapto-succinic acid were all positive predictors of systolic blood pressure. Lead exposed individuals with the VDR B allele, mainly heterozygotes, had systolic blood pressures that were 2.7-3.7 mm Hg higher than in workers with the bb genotype. VDR genotype was also associated with diastolic blood pressure; lead workers with the VDR B allele had diastolic blood pressures that were 1.9-2.5 mm Hg higher than in lead workers with the VDR bb genotype ($p = 0.04$). In addition, compared to lead workers with the VDR bb genotype, workers with the VDR B allele had a higher prevalence of hypertension (adjusted odds ratio (95% confidence interval) = 2.1 (1.0, 4.4), $p = 0.05$) and a larger increase in blood pressure with age (Lee et al., 2001).

In the analysis described by Scinicariello et al., on the basis of data obtained from adults who participated in the Third NHANES, whose DNA was available (n=6,016), multivariable logistic and linear regressions stratified by race/ethnicity were used to examine whether blood pressure was associated with the ALAD gene and blood lead levels. Blood lead level was associated with systolic pressure in non-Hispanic whites and with hypertension, systolic and diastolic pressures in non-Hispanic blacks, but not in Mexican Americans. Non-Hispanic white ALAD2 carriers of the highest blood lead level quartile had a significantly higher adjusted prevalence odds ratio for hypertension compared with ALAD1 homozygous individuals. In addition, a significant interaction between lead concentration and the ALAD2 allele, in relation to systolic blood pressure, was shown in non-Hispanic whites and non-Hispanic blacks (Scinicariello et al., 2010).

Also a mutation of the hemochromatosis gene (HFE H63D) has been associated with changes in blood pressure, examined as the pulse pressure (the difference between systolic and diastolic blood pressure) within the Normative Aging Study between 1991-2001. Baseline bone lead levels, markers of the cumulative lead exposure, are associated with steeper increases in pulse pressure in men with at least one H63D allele (p-interaction = 0.03 for tibia and 0.02 for patella), compared with men with only wild types or C282Y variant (Zhang et al., 2010). HFE variants are associated also with increased blood lead levels in young children (Hopkins et al., 2008).

Lead induces arterial hypertension in the consequence of low exposure, which may be not manifested by a toxic effect on the marrow, kidneys or other organs. The existence of lead hypertensive effect, in the range of blood concentration lower than 40 μg/dL, has been supported by numerous experimental and population studies. However, the presence of a significant correlation between blood lead level and systolic and/or diastolic blood pressure has not been confirmed by all of performed epidemiologic tests. These discrepancies can be

explained by the fact that lead-induced hypertension results rather from the past than from the current exposure, and hence arterial pressure values should be rather related to bone than to blood lead level. The occurrence of polymorphisms of genes involved in lead toxic effect may stand for another explanation. Interactions between lead toxicity and ALAD or HFE genes polymorphisms were observed in occupational and epidemiologic studies. These polymorphisms, occurring singularly or in an association with other polymorphisms (e.g. the vitamin D receptor gene), seem to be involved in lead-induced hypertension. Results of experimental studies indicate that the correlation between lead exposure, arterial blood pressure and the presence of polymorphisms of angiotensin converting enzyme and beta(2)adrenergic receptor genes should be analyzed in the general population. It is likely that studies of these polymorphisms, gene-to-gene interactions and interactions between genes and environmental factors may provide the identification of causes of so called spontaneous hypertension (Skoczynska, 2008).

6. Problems related to lead toxicity

It has been established that low level exposure to lead induces arterial hypertension. However, the data of many studies is suggestive but insufficient to infer that low level exposure to lead increases the occurrence of cardiovascular end points. The causal interference between lead exposure and immediate as well as some of intermediate end points needs a further explanation. The dose-effect relationship in the cardiovascular action of lead also remains unclear. It is possible that only low and recent exposure to lead is associated with arterial hypertension. Perhaps, there is an inverse relationship between blood lead levels and blood pressure values, similarly as in neurotoxic effects of lead in young organisms. It is also possible that cardiac end points are associated with long-term exposure to lead, which would be implied by the existent relationship between the patella lead and the occurrence of coronary heart disease.

Subsequently, blood lead level, most often determined spectrophotometrically, is variable and depends not only on external but also internal exposure. Factors such as fever, alcohol and acidosis cause a mobilization of lead from organs and from the skeleton. A single measurement of blood lead should be therefore verified, which is frequently practiced in occupationally exposed but would be difficult to apply to the general population. In turn, bone (the tibia or the patella) lead concentration, an established marker of accumulated lead, is determined using the method of K-shell x-ray fluorescence. This marker is more stable in comparison to blood lead but more difficult and expensive to measure.

In the population analysis of data on lead cardiovascular effects, it is indispensable to determine the role of confounding factors. The presence of a greater number of these factors cause incoherence in studies' results. Factors such as race, education, income, urban versus rural location and socioeconomic status should be considered. There are especially great difficulties in establishing how hypertension impacts relations between low exposure to lead and other than hypertension lead effects. Hypertension may result from lead action or occur independently but in each case constitutes a factor that confounds relations between lead and e.g. coronary heart disease or stroke. Similarly, disturbances in lipid and homocysteine metabolism or trace metals homeostasis may be simultaneously confounding factors and results of lead action.

7. Chelation treatment for lead poisoning

The chelation treatment has historically been used to reduce body lead burden in patients with severe symptoms of poisoning with lead. Chelating agents are organic compounds capable of linking together metal ions to form complex ring-like structures, which are subsequently excreted with urine. Effectiveness of chelation depends on whether the chelating agent is able to reach the intracellular site where the heavy metal is firmly bound. This intracellular availability is conditioned by many factors, e.g. ionic diameter, intra/extracellular compartmentalization and excretion pathway. Hydrophilic chelators are most effective in metals' excretion with urine, but they weaken complex intracellular metal deposits, whereas lipophilic chelators can redistribute toxic metals to lipid-rich organs, e.g. the brain (Andersen & Aaseth, 2002).

The chelation is usually performed using calcium disodium ethylenediamine tetra acetic acid ($CaNa_2EDTA$) and a preceeded administration of calcium. A contraindication to chelation is hypocalcemia or renal insufficiency. Also D-penicillamine and British anti-lewisite (BAL) have been used as antidotes for acute and chronic poisoning. 2, 3-dimercaprol (BAL) has long been the mainstay of chelation therapy for lead or arsenic poisoning. A thiol chelating agent, meso-2,3,-dimercaptosuccinic acid (DMSA), an analogue of BAL, has been tried successfully in animals as well as in a few cases of human lead and arsenic intoxication. DMSA could be a safe and effective method of treatment, but one of the major disadvantages of chelation with DMSA is its inability to remove lead from the intracellular sites because of its lipophobic nature (Kalia & Flora, 2005).

Even after many years of chelation, an effective treatment of patient poisoned with lead is difficult to obtain. New trends in chelation therapy including combined treatment are promising. This includes the use of structurally different chelators or a combination of an adjuvant and a chelator to provide better clinical and biochemical recovery, in addition to lead mobilization. Kalia et al. compared the therapeutic efficacy of captopril and DMSA, either individually, or in combination, against arsenite induced oxidative stress and metal mobilization in rats. Interestingly, combined administration of captopril and DMSA had a remarkable effect in depleting total arsenic concentration from blood and soft tissues. In addition, captopril administration during chelation treatment had beneficial effects particularly on the protection of inhibited blood ALAD activity (Kalia et al., 2007).

The therapeutic efficacy of melatonin or N-acetylcysteine (NAC) in reducing lead concentration in blood and other soft tissues was studied individually and in combination with DMSA. Administration of melatonin and NAC individually provided protection to the antioxidant defense, which disturbed by lead may significantly compromise a normal cellular function. Administration of melatonin and NAC (a thiol containing antioxidant) provided an increase in tiobarbituric acid levels, reduced glutathione and oxidized glutathione contents in tissues, which suggests these drugs' ability to act as free radical scavengers and to protect cells against toxic insult. In turn, a combined treatment of DMSA and NAC provided more pronounced efficacy in restoring altered biochemical variables and in reducing body lead burden than monotherapy with DMSA. The results suggest the involvement of ROS in lead toxicity and a pronounced beneficial role of NAC in therapeutic implications of lead poisoning, when co-administered with a thiol chelator (DMSA). They also support the hypothesis that cellular redox status may be significantly reversed by

utilizing a thiol containing an antioxidant compound. Authors concluded that combined therapy with an antioxidant moiety and a thiol-chelating agent may be a better choice for treating plumbism (Flora et al., 2004a).

It has been suggested that a concomitant administration of an antioxidant could play a significant and important role in abating a number of toxic effects of lead, when administered with thiol chelators. Flora et al. also investigated the effect of taurine, an amino acid and a known antioxidant, either alone or in combination with DMSA, in the treatment of subchronic lead intoxication in male rats. DMSA was able to increase the activity of ALAD, while both taurine and DMSA were able to significantly increase GSH level and bring them towards normal. In animals treated with taurine, there has been a reduction of changes of biochemical parameters indicative of oxidative stress, especially in the brain. The data also implied a promising role of taurine during chelation of lead, as a possible potentiator of the depletion of blood, liver and brain lead, compared to DMSA alone (Flora et al., 2004b).

Chelation is a beneficial therapy in case of chronic intoxication with heavy metals. This therapy is of smaller significance in case of acute poisoning, which is a result of a complex clinical situation. Acute metal intoxication usually proceeds with multiorgan distress syndrome, determining contraindications to treatment with chelators. Symptoms of kidney or liver dysfunction limit credibility of indicators monitoring chelator's effectiveness. As a rule, patients need the intensive care and symptomatic treatment. However, the moment chelators are allowed to include, the chelation therapy can determine the prognosis. In workers occupationally exposed to heavy metals, chelation can serve as a prognostic procedure, useful in occupational risk estimation. It also enables to undertake appropriate actions. Temporary or lasting discontinuation of work in exposition to lead, before clinical symptoms appear, results in a significant decrease in the occupational lead poisoning.

However, due to metal accumulation in tissues, chelation is not a fully effective therapy and needs repeated doses of drugs, usually administered through the parenteral way. A combined therapy, an antioxidant plus chelator, does not seem to be the best choice for all of the patients poisoned with metals. This therapy can be beneficial only if an antioxidant is simultaneously a chelator, as it is in case of N-acetylcysteine. Then, the additive impact of both chelators is expected. The effectiveness of the therapy with an antioxidant is significantly dependent on patient's oxidative status at the beginning of the treatment. This effect, due to the antioxidant potential, can be beneficial as well as aggravating. It concerns especially metals which do not undergo Fenton's reaction: cadmium, lead, mercury. Additionally, the use of antioxidants without chelators, i.e. in the prevention of cardiovascular diseases, showed only equivocal benefits resulting from the antioxidant supplementation. Moreover, some of patients showed an increased number of cardiovascular end points and incidence of neoplasms. New long-term chelators, consisting of structurally different components (including N-acetylcysteine), are needed.

To summarize, chelation is a common therapy in case of poisoning with toxic metals but it is only partially satisfactory because of metal accumulation in tissues. A combined therapy with long term, structurally different chelators could become a viable alternative in the future.

In developed countries, workers occupationally exposed to lead at high concentrations (i.e. copper founders) are subjected to biological monitoring. Chelation, which is practised as a part of the monitoring, decreases body burden with toxic metals. In the nearest future, it is essential to began a study on the effect of chelation on arterial blood pressure and cardiovascular end points in workers exposed to lead.

8. Plan for the future

Current investigations, which will continue after previous clinical, epidemiologic and experimental studies, are to explain whether environmental exposure to lead is a risk factor for development of vascular changes in the heart, brain and legs. They are also designed to explain the role of homocysteine and lead-iron interactions in cardiac and vascular effects of lead. The final purpose of project is the assessment of environmental exposure to lead as a lowering average life expectation factor.

Further cross-sectional and prospective studies, combined epidemiological and toxicological, on the presence of the relationship between blood lead concentrations and prevalence of coronary heart disease, stroke and peripheral artery disease are needed. Confounding factors' (male sex, age over 65, smoking, hypertension, diabetes and abnormal lipid pattern) influence on studied relations should be considered. DNA isolation should be conducted in order to determine the frequency of genetic polymorphisms that may influence the presence of a relationship between blood lead levels and ischemic heart disease or stroke. It should also be researched whether polymorphisms of determined genes (e.g. beta receptor and vitamin D receptor genes, or PPAR alpha and lipoprotein lipase genes) affect lead-induced hypertension or lead-induced changes in the lipid pattern. Moreover, the determination of iron and homocysteine role in lead toxic effects is needed.

Obtained results may confirm the thesis that environmental exposure to lead is a risk factor for developing a cardiovascular event. In case of a positive verification, conducted studies may become a set-point for solving practical issues, i.e. providing means of reducing sources of lead exposure and/or lead toxicity (chelators, antioxidants). Probably, current environmental safety standards for blood lead level ought to be lowered. A criterion for elevated lead exposure screening needs to be verified not only in children but also in adults. The risk assessment of lead exposure impact should include lead cardiovascular effects. The risk assessment of cardiovascular end points should include the information on lead exposure.

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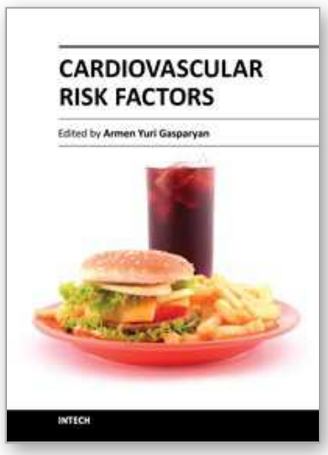
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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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