The Long-term Consequences of Exposure to Lead

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ABSTRACT: More than 90% of body lead is stored in bone. The technique of K-X-Ray fluorescence developed in the 1990s has enabled the quantitative measurement of decades of cumulative lead in bone, whereas blood lead levels reflect only recent exposure to lead. Bone lead is mobilized into the blood like bone calcium, as in osteoporosis, and exposes the patient to increased lead load. Many studies have assessed the toxic effect of chronic exposure from childhood to old age in present or former workers in industrial lead, as well as in non-occupational citizens in whom social and environmental circumstances might have induced higher exposure levels. This review points to the effects of elevated levels of bone lead and the associated cognitive decline among the elderly, with lead toxicity being one of the possible causes of degenerative dementia. There is evidence of an association between increased bone lead levels and renal disease, degenerative diseases like cataract, and suggestive but not causal association with blood pressure and hypertension. Community surveys show increased mortality associated with exposure to lead. Removal of sources of lead exposure, for example the use of non-leaded petrol, has reduced lead levels in the population, and there are currently strong recommendations to further lower the present allowed blood lead level to minimize chronic cumulative lead toxicity.

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The effect of chronic lead exposure in elderly persons has not attracted as much attention as the subject of lead toxicity in children, nor has the danger of prolonged low level lead exposure been sufficiently appreciated as a hazard in the elderly population. This paper reviews some of the findings from new technologies that throw light on the consequences of non-occupational and occupational chronic exposure to lead, and their part as possible risk factors for degenerative diseases in old age. Lead exposure exists in two forms:

- *Inorganic lead,* which readily oxidizes, and can be absorbed:
  - through the respiratory tract as lead dust and inhalation from lead-containing objects such as paints and lead pipes
  - through the gastrointestinal tract from contaminated water and foods influenced by lead contents in the soil, particularly as industrial waste
  - from processes such as glazing or manufacture of lead accumulators
  - as a product of lead-containing petrol

- *Organic lead*, such as tetra-ethyl lead, is a central nervous system toxin that is absorbed through the skin and into the brain; toxicity may occur through handling objects treated with organic lead.

LEAD POISONING

Symptoms of acute poisoning include abdominal colic, vomiting, encephalopathy with confusion, and peripheral neuropathies, such as wrist drop, arthralgias, myalgia and muscle weakness. Chronic exposure over months or years adversely affects calcium-dependent enzyme systems, ATP-ases and mitochondrial oxidative phosphorylation and cell growth; interferes with heme synthesis, membrane integrity and steroid metabolism; and causes motor axon degeneration and demyelination. Anemia develops with basophil stippling of red cells and "lead line" in the gums. There is reduced sperm count, developing renal failure, and chronic encephalopathy. Delayed motor and sensory nerve conduction is reflected in prolonged latencies of central and peripheral evoked potentials in lead workers with high blood lead levels, and significant loss of hearing has been reported. Increased body lead leads to reduction of urinary urate excretion and is associated with clinical gout.

SOURCES OF LEAD EXPOSURE

Sources of lead exposure and toxicity today include old piping, and working in certain occupations such as printing, plumbing, the demolition of old houses, and the use of lead-contaminated vessels in the production of olive oil, wine and flour. Another contemporary issue, relevant to the army, is the increase in lead dust that occurs during daily firearm training in an indoor range; it was shown that blood lead levels doubled within the 6 week course [1].

However, there has been a significant decrease in lead exposure in the general community with the introduction in the 1970s of unleaded petrol for motor vehicles. In the United States the mean blood lead levels declined from

15.8 to 2.8 μg/dl between 1976 and 1991 [2]. Similar results were reported from the U.S. National Health and Nutrition Examination Surveys between 1976 and 1991 – from 85% to 5.5% in children, with lead levels > 10 μg/dl in non-Hispanic white children and from 97% to 2.6% in Afro-American children aged 1–5 years [3]. The importance of this finding is twofold – children are more sensitive to the toxicity of lead even at low blood concentrations, and the reduction of blood levels is probably reflected subsequently in a smaller bone storage burden.

Historically, lead poisoning was probably common among the upper classes of Roman society. The deaths of some emperors and high officials have been attributed to the addition of lead solutions to drinking fluids, particularly wine and port, and probably also to leaded water pipes [4]. Evidence of gout has been found in skeletal remains of Romans at Cirencester, England, and an eyewitness account was given by one Musonius (ca. 20–90 AD) of "[many] persons troubled with gout, dropsies and colics and the like…who live upon prepared dainties." It is likely that the 'pandemic' of gout reflected high blood uric acid levels resulting from the excessive exposure to lead [4].

In the 19th century, lead poisoning from the extensive use of lead in many industrial processes in Britain was a significant occupational hazard. However, even recently there have been outbreaks of raised blood lead or toxicity. In 2003 higher levels of lead were detected in the U.S. population, especially in children, in certain districts of Washington DC. The cause was eventually attributed to the change of disinfectant in the public water supply from chlorine to chloramine. The consequent rise of blood lead levels in the population that used this water supply was imputed to the leaching of lead from the interior of the pipes due to the change induced by chloramine in the reduction-oxidation equilibrium at their surface. The addition of orthophosphate reduced the lead in the water [5]. Another recent epidemic of lead poisoning occurred in Israel in the 1980s, when in just a few months multiple cases of lead poisoning were diagnosed in Arabs from a specific area in Samaria. These cases, including a girl suffering from polyneuritis and her mother from confusion, were admitted to Jerusalem hospitals. The public health investigation eventually traced the cause to lead contamination in the domestic processing of flour in a particular group of Arab villages [6,7].

METABOLISM AND MEASUREMENT

In the body 95–99% of ingested lead is sequestered in erythrocytes and dispersed through soft tissues and bone and is also found in hair and nails. The metabolism of lead that is stored in bone parallels that of calcium, and the resorption of calcium in osteoporosis is accompanied by passage of lead from bone into blood. In the blood its half-life is up to 30 days and it is excreted in the urine; its storage in bone can remain for more than 20 years.

The body content of lead can be detected by measuring blood levels, which reflect exposure in the month previous to testing; and bone levels by means of K-X-Ray fluorescence, a technique that was developed in the last 20 years and that measures lead content in the cortex of the tibia and the patellar trabecula [8,9] and reflects storage of lead over long periods. This measurement is particularly relevant to the elderly in whom elevated bone lead concentrations may represent chronic toxicity. Elevation of blood levels may occur through mobilization of lead from the bone due to acidosis or hypocalcemia or in hyperthyroidism. In post-menopausal women who did not take estrogen replacement therapy the estrogen deficiency-induced osteoporosis was associated with elevated blood lead levels resulting from increased release into the blood of stored lead in bone [10].

Children absorb 40% of a dose of lead compared to 10% in adults, and retain 30% of lead absorbed compared to 1% in adults. Blood levels of 10 μg/dl or more in children are considered toxic, but even lower levels may impair development and cognitive function. Toxicity from increased blood lead concentration in infancy occurs following high lead exposure in the mother during pregnancy

The technique of K-X-Ray enables quantitative estimates over many decades of lead storage in bone, whereas blood levels assess exposure to lead within the previous month

[6,11,12]. The excess absorption of lead in children may result in increased storage levels in bone during adulthood, and therefore environmental protection from exposure to lead is particularly important during childhood. In the elderly, elevated blood levels of lead indicate recent environmental exposure, e.g., from house demolition and work with lead pipes, from the production of wine or olives in domestic lead-containing vessels, or accidental contamination from toxic waste in rivers. However, findings in elderly people in the community showed only a weak correlation between blood levels of lead with those of bone, and the significance of testing was that "blood lead is the best available estimate of recent dose, while tibia lead is an estimate of lifetime retained cumulative dose" [13], as for example in elderly retired workers from plants manufacturing batteries [14].

Before the present decade of the 21st century blood levels of lead below 10 μg/dl were accepted as safe, although in children levels above 10 μg/dl were associated with toxicity. In adults, threshold safety levels were reduced in 1971 to 40 μg/dl, to 30 μg/dl in 1975, and to 25 μg/dl in 1985. Later surveys showed that toxic manifestations may occur even below these blood levels. Since blood concentrations reflect

mainly recent exposure, measurements of bone lead levels in the tibia or patella express the actual long-term exposure more accurately. The twin measurements in adults and the elderly of blood and bone lead in the past few years have revealed important associations of lead toxicity with certain degenerative diseases in adulthood, and subclinical oxidative chronic lead toxicity has been suggested as possibly responsible for some of the diseases and degenerative phenomena in old age [15].

■ LEAD, GOUT AND RENAL DISEASE

Lead, like other metals (mercury, cadmium, arsenic), has toxic effects on renal tubular function causing uric acid retention, and toxic levels above 80 µg/dl are associated with deteriorated renal function. Mitochondrial dysfunction and cell degeneration are induced by accumulation of lead in the proximal convoluted tubule, and ischemic changes and glomerular fibrosis occur with cortical atrophy and focal areas of scarring.

The mobilization of lead with Ca Na2EDTA in symptomless hypertensive patients with renal failure resulted in an increase in blood lead that induced hypertension and renal failure [16]. More recent research showed that in residents living near an iron foundry or near where there had recently been zinc-processing works, blood lead levels exceeded the World Health Organization recommendation of 20 µg/dl and were 29% higher in men who reported exposure to metals in their workplace. In a random population sample of 965 men and 1016 women, age range 20–88 years, there was an inverse correlation between lead levels and creatinine clearance, even after stratification for age. A tenfold increase in blood lead was associated with a 10 ml decrease in creatinine clearance per minute after adjustment for age, high body mass index, diuretic treatment and influence of blood pressure (odds ratio 3.76, 95% confidence interval 1.37–10.4, $P = 0.01$) [17]. The authors speculated that renal dysfunction had not caused the lead retention, because observations on hypertensive patients with creatinine clearances ranging from 29 to 90 ml/minute showed no differences in blood lead levels, and in patients with a variety of causes for renal failure the blood lead levels were similar. However, in diabetics an increase in tibia lead levels was associated with a 17-fold serum creatinine increase compared to non-diabetics [18].

In the Veteran Affairs Normative Aging Study with follow-up beginning in 1960, a correlation was sought between blood and bone lead levels, uric acid levels and the incidence of gout in 777 subjects [19]. In 34% the serum uric acid was above 7.0 mg/dl, and 6.7% of the subjects met the criteria for gout. The blood lead level was 5.9 µg/dl (within a normal range) in contrast to the high patellar trabecular level of 30 (µg/dl), which was found to also predict serum uric acid levels. A saturated model with all the covariates showed a positive association between bone lead and uric acid ($P = 0.027$) [19]. In another study [20], gout in 27 of 111 healthy subjects was strongly correlated with increased lead burden compared with 84 without gout, and the lower urate clearance in the gouty subjects increased after chelation. Thus, high exposure to lead, recently or from chronic accumulation, impairs renal function, and the association with increased uric acid may also predispose to gout.

■ LEAD AND HYPERTENSION

A 3 year case-control follow-up of 1171 subjects in the Veteran Affairs Normative Aging Study revealed that whereas blood and bone levels in the group as a whole were low or hardly different from the general population, those with high blood pressure did have higher blood and bone levels than non-hypertensives (odds ratio 1.5), suggesting that long-term accumulation of lead may be a risk factor for developing hypertension [21]. In occupational lead exposure there was an association between raised levels of blood and tibia lead and increases in blood pressure. Moreover, in genotypic variations in the vitamin D receptor in lead-exposed populations the BB allele raised the incidence of hypertension through an effect on lead absorption from the gastrointestinal tract in contrast to those with vitamin D receptor bb allele. Since there were no differences in bone or blood levels, it was suggested that the bb allele genotype modifies the propensity to lead toxicity [22,23].

In a cross-sectional analysis in the Baltimore Longitudinal Memory community study (2001–2002) of a random selection of 964 subjects aged 50–70, at the first visit there was a strong association between blood lead and small increases in systolic and diastolic blood pressure but there was no association between blood lead levels and hypertension. Tibia lead, however, was a significant predictor of hypertension (odds ratio 1.24 associated with increase of tibia lead from 11.9 to 24.8 µg/g), especially in the Afro-American ethnic population, but the odds ratio was reduced to 1.17 when the ethnic and socioeconomic status was included. The authors concluded that recent lead exposure has an acute effect on blood pressure, and cumulative dose indicated by tibia lead is a risk factor for hypertension [24]. An association of blood lead levels and baseline blood pressure was reported in a 4 year follow-up study (1997–2001) of Korean lead workers, average age 41, with 8.5 years of exposure. For an annual rise of 10 µg/dl in blood lead levels there was a yearly increase in systolic blood pressure of 0.9 mmHg, suggesting an acute as well as a cumulative effect of lead on blood pressure [25].

> High bone (tibia) levels of lead in the elderly may be released into the blood – e.g., along with calcium resorption of senile osteoporosis – and cause toxicity

Although a meta-analysis of 23 studies in 1995 showed that a twofold increase in blood lead was associated with a rise in SBP of 1 mmHg and in DBP of 0.6 mmHg, the authors doubted if there was a causal relationship between blood lead and hypertension [26]. In a prospective study from the same group no consistent relationship was noted between changes over 5.2 years in blood pressure and blood levels of lead in 728 persons aged 20–82. The explanation for these negative findings could be underestimation of the association due to errors in measurements of BP or lead in blood or bone, or that blood lead levels reflect recent exposure to lead, whereas in other studies bone lead levels were more consistent predictors of hypertension [24,27].

Racial differences in the U.S. were demonstrated in the positive relation between blood pressure and blood lead in Afro-American men and women, but not in white men and women, in a sample of 14,953 participants aged over 18 in a National and Health Nutrition Examination Survey [28]. Many of the studies point out that a low socioeconomic level may be associated with more environmental dangers from lead exposure in childhood and insufficient preventive care in adults, and stress that public health measures should aim to decrease environmental exposure to lead at all ages.

> **Present-day blood levels of lead within the "normal" range may be associated with lead toxicity and possibly contribute to the pathogenesis of degenerative brain diseases in old age, necessitating the further decrease of lead levels beginning in childhood**

In summary, recent studies in the aging population have demonstrated associations between bone lead and hypertension, particularly subject to the findings of higher tibia lead levels in relation to ethnicity and low socioeconomic background [24]. A modest link between blood lead and small increases in blood pressure suggests that lead may well be implicated in the genesis of hypertension in the population overall [27].

■ LEAD AND CARDIOVASCULAR DISEASE

The influence of lead on the vascular system was shown by the genesis of ischemic heart disease in a 10 year follow-up study of a cohort of 837 community dwellers. Higher levels of bone lead and blood lead were found among those who showed new signs of ischemic heart disease during this period [29]. The evidence from database searches for an association between blood lead levels and ischemic heart disease was suggestive but not sufficiently robust because of the small number of subjects and the relative lack of consistency of the results, but some cases of myocardial infarction and stroke were associated with blood lead levels of even less than 5 μg/dl [27].

SBP = systolic blood pressure
DBP = diastolic blood pressure

High blood lead levels were associated with a heavier burden of peripheral arterial disease from the one-time blood lead level due to current exposure, or to mobilization of stores from bone [30]. Tibia lead levels above the median were positively associated with increased pulse pressure, suggesting that chronic lead accumulation may contribute to the stiffness of aging arterial walls. In all these studies great care was exercised to exclude confounders – medical, physiological and socioeconomic factors that could also influence these associations.

■ BLOOD AND BONE LEAD LEVELS AND COGNITIVE FUNCTION IN THE ELDERLY

Exposure to vapors or chemically treated metals such as mercury, manganese and lead has deleterious effects on brain function, ranging from disturbed cognitive function to frank encephalopathy and degenerative parkinsonism. Brain damage is common from high exposure, especially to lipophilic organic tetra-ethyl lead, ranging from peripheral neuritis to acute confusion and dementia [6,7]. Recent studies have shown cognitive disturbances following long-term exposure that was demonstrated in the measurements of bone lead concentrations.

A correlation between scores of the Folstein Mini-Mental Screening test and bone lead, but not blood lead, showed that scores below 24/30, the accepted cutoff point for dementia, were associated with high levels of lead in patellar bone, leading to the conclusion that significant lead stores in trabecular bone amplified the effect of age on deteriorating cognitive scores [15,31]. In further studies of the Veterans Affairs Normative Aging Study similar progressive impairment involving several cognitive domains in relation to bone lead were demonstrated when the mini-mental testing was done on two occasions 3.5 years apart, particularly constructional praxis and reaction time, with an inverse relationship on most of the other cognitive tests, such as WAIS and CERAD verbal fluency [32,31]. Similarly, in the Baltimore cross-sectional study, impaired performance on the Raven matrices was associated with high tibia lead but not blood lead, and there was no modification by inclusion of race/ethnicity. Decline in cognitive function in the domains of verbal memory, visuo-constructive ability and learning was found in lead-manufacturing workers tested 16 years after ceasing this work and was correlated with high tibia levels of lead [33]. It was also suggested in a 15 year longitudinal investigation of former lead workers that the cognitive decline in aging might be caused in part by longstanding neuro-toxicants such as lead. In more extensive population surveys of former

workers in inorganic and organic lead, magnetic resonance imaging showed that increased tibia lead was associated with brain volume decrease and with more white matter lesions. The authors suggested that these findings were equivalent to the cognitive decline in the elderly over a 5 year period [34]. Moreover, from the social data in many of these studies we may conclude that higher occupational and non-occupational exposure among lower socioeconomic groups from childhood could also account for the increased tibia lead and the resulting cognitive impairment in adulthood.

Because excess lead is toxic to mitochondrial function and interferes with calcium homeostasis, damage may involve multiple organs and cellular function. For example, tibia lead was found to be a significant predictor of cataract, even after adjustment for age, smoking and diabetes, and possible associations with Parkinson's disease have been suggested among subjects with higher quartiles of lead exposure.

■ BODY LEAD AND MORTALITY

Studies in the last 20 years have confirmed the lethal effect of lead as a metabolic poison on the general population. In 4292 participants in the cross-sectional Second National Health and Nutrition Examination Survey (NHANES) in 1976-1980 with follow-up until 1992, subjects with blood lead levels of 20–29 μg/dl (15% of the U.S. population at that time) – compared with those whose blood levels were lower than 10 μg/dl – had an increase of 46% all-cause mortality (rate ratio 1.46), 39% cardiovascular mortality (rate ratio 1.39) and 68% cancer mortality (rate ratio 1.68) [35]. In the Third NHANES study during 1988–1994 of 13,496 subjects whose blood lead was < 10 μg/dl, the geometric mean blood lead level was 2.58 μg/dl, and the hazard ratios for all-cause mortality of those with a blood level > 3.62 μg/dl and those with < 1.94 μg/dl was 1.25 and 1.55 for cardiovascular mortality, respectively [36]. A possible mechanism of the increased cardiovascular mortality has been postulated – namely, that renal glomerular and tubular pathology from lead exposure may act as an intermediate mechanism leading to vascular damage [37]. Potential confounders must be considered, such as brain changes due to age, hypertension, cerebrovascular disease, metabolic disorders, race, socioeconomic condition in childhood and later life, physical health of respondents, smoking and alcoholism, ethnicity, and physical environmental conditions [2,38].

CONCLUSIONS

The striking conclusion is the association of increased mortality with levels of blood lead that are considerably lower than the present acceptable cutoff points. It is clear that blood lead levels in adults below the accepted "safe" level of 10 μg/dl cannot exclude the risk of lead toxicity, which might have accumulated from exposure many years previously, as proved

by high trabecular bone levels in older people. Lead-induced brain disorders may mimic or exaggerate degenerative or vascular brain disease symptoms because of occupational or non-occupational exposures to environmental lead [39].

The associations of degenerative brain disease in adults and the elderly complement those in children in whom developmental defects in the first decade of life may occur concomitantly with blood lead levels lower than those dictated by law today, implying that there is no certainty of the threshold level of lead toxicity [40]. Moreover, associations have been shown between the accepted safe levels of blood lead and the finding of degenerative vascular disease, hypertension and renal disease. These associations have been demonstrated up to old age by the more efficacious measurement of lead storage in bone over many decades. Higher occupational and non-occupational exposure among those who had a low socioeconomic level in childhood could also account for the increased tibia lead level and the resulting cognitive impairment in adulthood. The ecological ubiquity of lead points to the public health necessity to achieve blood lead levels lower than 10 μg/dl in children and adults to ensure lower bone concentrations throughout the course of life and thereby guarantee safety from the environmental hazard of even minimal lead exposure.

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