Association between Acute Lead Exposure in Indoor Firing Ranges and Iron Metabolism

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Abstract

Background: Iron deficiency and lead poisoning are common and are often associated. This association has been suggested previously, mainly by retrospective cross-sectional studies.

Objective: To assess the impact of short-term lead exposure at indoor firing ranges, and its relationship to iron, ferritin, lead, zinc protoporphyrin, and hemoglobin concentrations in young adults.

Methods: We conducted a clinical study in 30 young healthy soldiers serving in the Israel Defense Forces. Blood samples were drawn for lead, zinc protoporphyrin, iron, hemoglobin and ferritin prior to and after a 6 week period of intensive target practice in indoor firing ranges.

Results: After a 6 week period of exposure to lead dust, a mean blood lead level increase ($P < 0.0001$) and a mean iron ($P < 0.0005$) and mean ferritin ($P < 0.0625$) decrease occurred simultaneously. We found a trend for inverse correlation between pre-exposure low ferritin levels and post-exposure high blood lead levels.

Conclusions: The decrease in iron and ferritin levels after short-term lead exposure can be attributed to competition between iron and lead absorption via divalent metal transport-1, suggesting that lead poisoning can cause iron depletion and that iron depletion can aggravate lead poisoning. This synergistic effect should come readily to every physician's mind when treating patients with a potential risk for each problem separately.

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Lead has been used in industry and in households for centuries. Populations are exposed to lead chiefly via paints, cans, plumbing, fixtures and leaded gasoline. Since the 1970s significant exposure at firing ranges has also been recognized as a potential source of lead exposure [1]. Lead-containing dust is produced by the combustion of lead-containing primers, the friction of bullets against the gun barrel, and fragmentation as bullets strike the backstop [1]. The inorganic lead dust inhaled into the lungs is highly bioavailable, with an absorption rate close to 100%. Absorption also takes place throughout the gastrointestinal tract by active transporters [2]. Once absorbed, lead accumulates in three components: blood, soft tissue, and bone. Lead has an estimated half-life of 35 days in blood, 40 days in soft tissue, and 20–30 years in bone [3]. Lead is a poison that affects virtually every system in the body. The most deleterious effects of lead are on erythropoiesis, kidney function, and the central nervous system.

The threshold of lead poisoning in adults has gradually decreased in recent decades. Prior to 1970, blood lead levels > 60 µg/dl defined significant lead poisoning. In 1971 the threshold for blood lead levels was reduced to 40 µg/dl. This was subsequently reduced to 30 µg/dl in 1975 and 25 µg/dl in 1985, and to ≥ 10 µg/dl in young children [4]

Iron deficiency and lead poisoning are common and are often associated. Both conditions are known to cause microcytic anemia and appear to produce a more severe form of anemia when in combination [5]. It has been shown that lead workers have significantly low hemoglobin and iron levels [6]. Moreover, iron deficiency was found to be associated with subsequent lead poisoning due to increased gastrointestinal lead absorption [7].

Military shooting instructors are defined as "lead workers" who are obligated to undergo occupational medical follow-up. We found that one of our military unit's shooting instructors had a lead level of 48 µg/dl, raising the possibility of potential lead poisoning in a group of soldiers following an intensive period of indoor firing. Moreover, these soldiers are routinely being assessed for iron depletion during their intense training period as they are at risk for "sports anemia" [8]; and since there is a known influence of lead poisoning on iron metabolism, these two clinically important blood tests were joined.

The objective of this observational study was to determine the impact of short-term occupational lead exposure and its correlation to iron metabolism and hemoglobin status.

Patients and Methods

The study involved the use of data from a group of 30 young and healthy soldiers (age range 19–21 years) serving in the Israel Defense Forces. Blood samples were drawn for lead, zinc protoporphyrin, iron, hemoglobin and ferritin after the soldiers were defined as a risk group.

The soldiers were about to start a 6 week period of daily target practice in indoor firing ranges. They all lived and trained together for a year before and throughout the 6 weeks shooting period. Exclusion criteria for this report were: a) soldiers who were found to be iron depleted (ferritin < 20 µg/L) and were treated with iron supplements 6 months or less prior to the study period; and b) soldiers who had donated blood within 6 months prior to the study. Throughout this period they underwent a physician's assessment and had no clinical complaints or symptoms attributed either to lead poisoning or to iron-deficient anemia.

Since this report is part of data collected in routine follow-up of this army unit, ethical approval was not necessary.

Laboratory methods

Biochemical and hematological analysis of blood were performed on fresh samples obtained on the first and last day of the 6 week period. The blood was sent within 2 hours to the same laboratory. Lead and zinc protoporphyrin were measured in a whole-blood sample using the furnace atomic absorption method (Perkin Elmer, Analyser 800, USA) and hematofuorimeter method (Helena Laboratories, Proto Fluor-Z, USA) respectively. Hemoglobin was measured using absorption spectrophotometry (Cell-Dyn® 4000, Abbott Diagnostics, USA). Iron was measured using a commercial immunoturbidimetric assay (Tina-quant® with Roche/Hitacchi 917 analyzer, Roche Diagnostics GmbH, Germany). Serum ferritin was measured using a commercial electrochemilu-minescence immunoassay (Roche Elecsys® 2010).

Statistical analysis

The Statistical Analysis System (SAS Institute Inc, Cary, NC, Vs 9) was used to analyze the data. Data were analyzed for normality. Paired *t*-test analysis was used to compare blood serum levels before and after the shooting exercise. Correlation analysis was used to study the relationship between pre-exposure ferritin levels and post-exposure lead levels. A *P* value of < 0.05 was considered significant.

Results

Pre- and post-exposure differences were statistically significant for mean lead level increase (*P* = 0.0001) and mean iron decrease (*P* = 0.0005), with marginal significance for mean serum ferritin decrease (*P* = 0.0625). Hemoglobin, mean corpuscular volume and zinc protoporphyrin levels were stable with no statistically significant difference before and after the exposure. Results are presented in Table 1.

Lead levels rose by 100% in the soldiers, while iron and ferritin decreased by 72.4% and 68.7% respectively. The results are shown in Figure 1. There was a trend of correlation between pre-exposure ferritin and post-exposure lead (Pearson correlation coefficient = -0.28) [Figure 2].

Table 1. Lead, zinc protoporphryn, hemoglobin, iron and ferritin in soldiers before and after lead exposure in the indoor firing range

|	N	Pre -exposure Mean ± SD	N	Post-exposure Mean ± SD	Difference Mean ± SD	*P**
Lead (µg/dl)	29	10.3±2.3	30	18.9±3.6	8.8±2.6	0.0001
ZPP (µg/dl)	29	42±7.5	30	42.9±8.1	0.03±6.5	NS
Hemoglobin (g/dl)	30	15±0.7	30	14.8±0.9	0.2±0.7	NS
MCV (fl)	30	88.7±2.5	30	89±2.7	0.4±2.6	NS
Iron (µg/dl)	29	108.5±43.6	30	77.4±24.4	-30.4±41.2	0.0005
Ferritin (µg/L)	27	58.1±27.7	16	51±19.9	-6.1±10.7	0.0625

SD = standard deviation

*P value for the *t*-test

ZPP = zinc protoporphyrin, MCV = mean corpuscular volume

Discussion

This study demonstrates the interactions between iron metabo-lism and lead intoxication among young adults. This has been suggested previously, mainly by cross-sectional studies and stud-ies of the pediatric population. We demonstrated a mean blood lead level increase (8.8 ± 2.6) with a mean iron decrease (-30.4 ± 41.2) and mean ferritin decrease (-6.1 ± 10.7) simultaneously after 6 weeks of lead dust exposure among young and healthy adults. Soldiers in the study were at twice the risk for lead poisoning and iron depletion independently (to be discussed below) and a synergistic effect between these two should therefore be of concern. It is shown that even within a relatively short period of exposure (i.e., 6 weeks) the whole group doubled its blood lead levels (*P* = 0.0001). Five soldiers had levels above 20 µg/dl and two soldiers above 25 µg/dl. When blood lead levels are above 30 µg/dl, according to international occupational regulations, these individuals should be released from work [9]. Regardless of the "occupational regulations," the U.S. Centers for Disease Control recognized blood lead levels of ≥ 25 µg/dl in adults and ≥ 10 µg/dl in children aged ≤ 6 years as levels of concern and recommended a new set of guidelines for treatment of lead levels ≥ 15 µg/dl [4]; no similar level has been set for older children
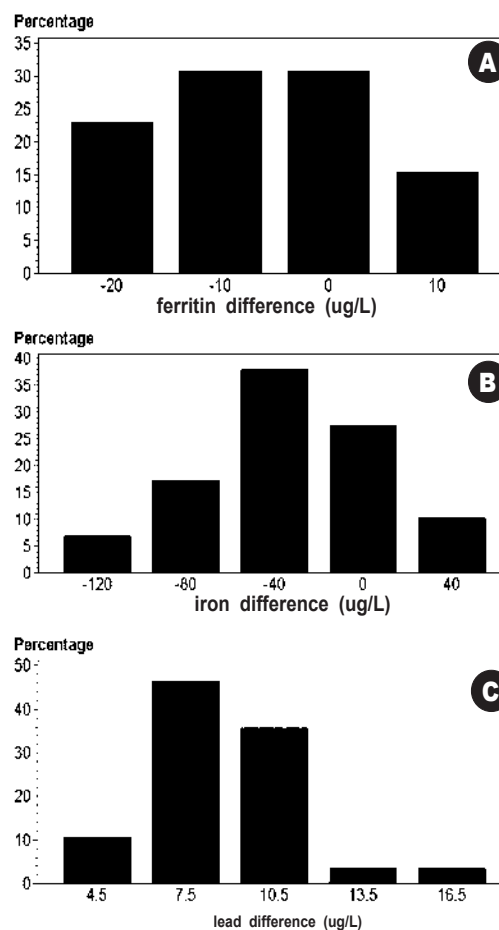
Figure 1. Group distribution differences of pre- and post-exposure levels. ferritin **[A]**, iron **[B]** and lead **[C]**
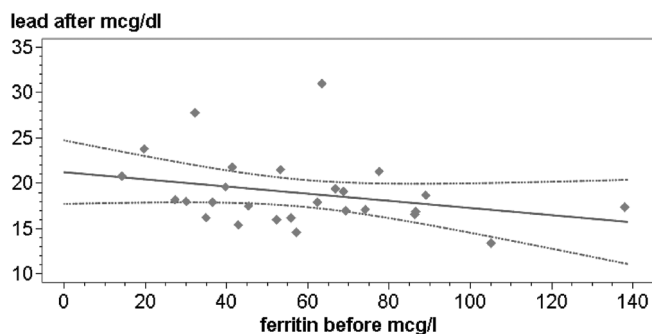
Figure 2. Correlation between pre-exposure ferritin levels and post-exposure lead level (Pearson's correlation coefficient = -0.28, r = 0.14, number of observations = 27)

and adolescents [10]. Even though our findings are considered to be sub-clinical levels among adults, and none of the soldiers were symptomatic, these findings should not be underestimated, as it was previously shown that these blood lead levels are associated with an increased risk of hypertension and neurological deficit [11]. Furthermore, the strict definition for toxic blood lead levels in children [4] raises the question about the appropriate definition for this group of soldiers, some of whom are still in their late adolescent period (the group's age ranges between 19 and 21).

According to the Israeli occupational safety and health regulations [12], a "lead worker" is defined as anyone who is occupationally exposed to lead for at least 2 months a year. Recommendations for screening and prevention measures include: a) measurement of air lead levels every 6 months, b) workers' education regarding lead exposure hazards and protection measures, and c) physician examination and laboratory tests (including complete blood count, tests for lead and zinc protoporphyrin, and urine sample) every 6 months. Although monitoring for exposure among lead workers in the Israel Defense Force is required only for shooting instructors, we looked for other soldiers at potential risk.

We found a marginally significant relation between pre-exposure ferritin levels and post-exposure blood lead levels. Iron deficiency and lead poisoning are common in many parts of the world and are often associated. Furthermore, it has been shown in children that these two problems can exacerbate each other [5-7]. The observed mean reduction of iron and ferritin can be attributed to several mechanisms. Iron deficiency is a common nutrient deficiency among soldiers [8], and is particularly noticeable among soldiers in elite units who are involved in intensive physical training. Consequently, they often suffer from sports anemia, which is a common finding among athletes engaging in strenuous physical activity [13-15]. While the major contributing factor to sports anemia has traditionally been thought to be dilutional pseudoanemia, recent research indicates that the contribution of iron deficiency may have been previously underestimated [8]. Moreover, it has been reported that iron deficiency without anemia reduces athletic performance, and periodic evaluation of iron stores

is recommended during intensive physical training [16]. It is highly unlikely that the observed reduction in iron and ferritin will be attributed to this mechanism since the specific period under discussion (i.e., indoor firing training) is characterized by relatively low physical intensity. Furthermore, the fact that we found an inverse proportional trend between the initial ferritin level and the amount of post-exposure blood lead levels suggests a direct influence of iron depletion on lead poisoning.

The co-existence of environmental lead poisoning, iron and hemoglobin status has been reported previously [5-7]. The best understood toxic effects of lead involve heme synthesis, as lead inhibits enzymes participating in the process [3]. Lead clearly inhibits normal hematopoiesis, producing microcytic hypochromic anemia. More relevant to our study is the mutual mechanism between iron and lead absorption. Divalent metal transport-1 (formally called Nramp2 or DCT1) is a protein that transfers iron across the apical membrane and into the cell through a proton-coupled process. DMT1 is not specific to iron; it can transport a wide variety of divalent metal ions, including manganese, cobalt, copper, zinc, cadmium and lead [2]. This biological mechanism suggests an increased lead absorption among iron-deficient patients and was demonstrated in numerous studies among children [5-7]. Furthermore, iron supplements were suggested as an option for treatment and prevention of lead poisoning [6]. This phenomenon was also demonstrated among lead workers in whom high blood lead levels were associated with significantly lower hemoglobin, hematocrit and iron levels and lower percentage of transferrin saturation [7].

In addition, experiments in animals suggest that the levels of the apical transporter, DMT1, are altered in response to change in body iron stores [2], thus creating a vicious cycle where high blood lead levels and low iron levels intensify each other. This mechanism is based on lead absorption via the gastrointestinal tract, which probably plays a major role in lead intoxication in addition to respiratory absorption. Intoxication via the gastro-intestinal tract is attributed to poor hygiene and low awareness among our group, as they were not considered a group at risk for lead poisoning and they ate their meals within the district of the range.

Our study has several limitations that warrant consideration. It lacks a control group since it was a retrospective study in a unique clinical constellation. The iron and ferritin reduction was within the normal range and one can argue about its negligible significance. Based on preliminary data on the mutual influence of iron and lead and the statistical significant reciprocal changes, we can assume that continuous exposure to lead would result in a linear reduction of iron stores and consequently would cause iron depletion and iron deficiency.

The strength of this study is the homogenous group of young soldiers who spent the entire period together, and therefore had exactly the same lead exposure, physical activities and nutrition.

DMT1 = divalent metal transport-1

Conclusion

The study's findings suggest that lead poisoning can cause iron depletion and vice versa. This synergistic effect should come readily to every physician's mind, especially when treating patients with a potential risk for each problem separately. This is particularly true in the military, where highly trained soldiers engage in firing activity in closed firing ranges or urban areas. Awareness and prevention are the key elements for dealing with these two problems. We therefore propose the following recommendations: a) firing ranges should be appropriately ventilated and cleaned, b) patients should receive personal hygiene education and behavior instructions (eating and smoking avoidance) when exposed to lead, c) periodic medical assessment including blood tests according to the patients' specific exposure risk should be conducted, and d) iron-depleted patients should be treated prior to lead-exposure activities.

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