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Nutrition-pollution interaction: An emerging research area

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The impact of environmental pollution, especially chronic low exposures of heavy metals (Pb, Cd, Hg, As, Cr, *etc*.) on nutritional status and health of human and livestock, has become a cause of concern. It is established that malnutrition inhibits enzyme system, alters neurotransmitter levels, degenerate myelin, glial and neural elements, lowering of IQ scores as well as impairment of fine and gross motor coordination. Chronic low-level exposure to heavy metals also results in similar type of deformities at sub-clinical level. However, additive impact of undernutrition and adverse effects of heavy metal exposure is emerging as a serious threat to health in developing countries. High blood Pb/Cd levels and low nutrient levels cause subclinical damage of organ system such as haemopoietic, renal, nervous systems in neonates, children, post-partum women, and occupationally exposed population. This could be due to chronic low-level heavy metal exposures and *vis-à-vis* interaction between pollutants and nutrients. Our studies are focused on the utility of biomarkers for early subclinical detection of haemopoietic and rental toxicity. Lead exposure from non-conventional sources such as toys, pet/glass bottles, *etc*. suggest long-term investigation. The present review compiles result of studies conducted in this area highlighting the importance of pollution-nutrition interaction. This may facilitate policymakers on developing the strategies to counter the heavy metal exposure of humans/livestock and their consequences.

Key words Biotoxicity - blood lead levels - early biomarkers - lead toxicity - pollutants - subclinical lead toxicity

Introduction

The importance of metals in cellular and subcellular functions is well recognized. The physiological role of certain elements such as copper (Cu), iron (Fe), magnesium (Mg), zinc (Zn), *etc*. is well established and these are considered as essential micronutrients. However, in the past five decades, biotoxicity due to exposure of heavy metals such as cadmium (Cd), lead (Pb), aluminium (Al), mercury (Hg), arsenic (As) and their interactions with nutrients has emerged as serious public health concern[1,2]. The current review is prepared keeping in view of the long term impact of environmental pollutants on human health and live stock.

Bioimportance of metals

The metal ions, such as manganese, iron, zinc and magnesium, are classified as major and the elements such as cobalt, copper, nickel, tungsten, molybdenum as minor elements based on their influence on biological pathways through metal-binding proteins and enzymatic reactions in living organisms. The biological role of various elements/metals is summarized in Fig. 1. Iron is an important constituent of haemoglobin, an oxygen

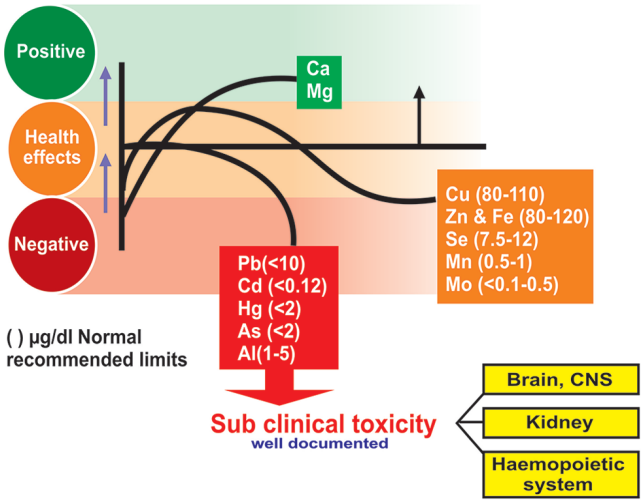

Fig. 1. Essential and non-essential elements. The safe cut-off levels of different heavy metals and their toxic effects on different organ systems are shown in curves. Ca, calcium; Mg, magnesium; Cu, copper; Zn, zinc; Fe, iron; Se, selenium; Mn, manganese; Mo, molybdenum; Pb, lead; Cd, cadmium; Hg, mercury, As, arsenic; Al, aluminium.

carrier protein whereas cytochromes function for energy production and in metabolism of xenobiotics[3]. The elements, such as Cu and Zn, act as cofactors for monoamine oxidase and metalloenzymes. Magnesium is known as macro-mineral, as the body requires it in large amount to perform various activities. Readily utilizable high-energy molecule adenosine triphosphate (ATP) is utilized as MgATP complex[3].

Biotoxicity of heavy metals

The heavy metals include Cd, Pb, Hg, As, are natural constituents of the earth crust and most of the time indispensable due to industrial, domestic, medicinal applications. In the last few decades 'biotoxic' phenomenon has emerged globally due to mining, industrial emission, poor disposal practices *etc*. and heavy metals are classified as 'pollutants'[1,2]. The outbreaks of *Itai-Itai* (1912) due to Cd poisoning and *Minamata* (1953) disease due to Hg pollution from rivers of Japan are examples of pollution diseases. Many reports on indiscriminate disposal of several metals resulting in a rise of heavy metals affecting flora and fauna have been published[4]. Several studies drew the attention on low-level chronic heavy metal exposure, which was impairing the enzyme function at cellular level resulting in subclinical damage of organ system, namely, nervous, haemopoietic, renal, cardiovascular and reproductive system[2,5,6].

Among the various heavy metal exposures, the toxicity due to Pb has been extensively investigated since it is indispensable due to versatile applications. Bellinger[7] reviewed an association between early-life exposure and childhood outcomes, which included neuropsychological impairment between concurrent or cumulative lead exposure and adult cognition, kidney function and cardiovascular health. Subclinical damage of organ systems which is slow progressive, most of the time irreversible is more important than the classical signs and symptoms of heavy metal poisoning[5,8].

Nutrient-pollutant interactions

Biotoxicity due to interaction between pollutants (heavy metals) and nutritional status may affect health of neonates, growing children, pregnant women and occupationally exposed population. Kordas *et al*[1] documented increased exposure to environmental chemicals due to; (*i*) food as source for delivering toxicants, (*ii*) toxicant absorption and metabolism by interaction with nutrients, and (*iii*) genetic predisposition. Among the many disorders, iron deficiency anaemia, vitamin A and zinc deficiency were most prevalent and posed serious risk to the human health. Strengthening of industrial health and occupational medicine to detect evidence on interaction of pollutants with nutrients and assess exposure, effect and susceptibility is need of the hour[5].

Biological monitoring of target population

In a joint meeting of EEC (European Economic Community), NIOSH (National Institute for Occupational Safety and Health) and OSHA (Occupational Safety and Health Association), biological monitoring was defined as 'the measurement and assessment of agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risk compared to an appropriate reference'[5]. In the present context, the abnormal clinical signs and symptoms cannot be detected, identifying the biomarkers for assessing the exposure and damage become the prime requirement. Goyer[9] demonstrated early renal damage by histopathological evidence attributing to Pb exposure and this was among the first reports in confirming the subclinical toxicity. Cory-Slechta *et al*[10] demonstrated the impairment of the myelination process during the developmental stages of children leading to neuropsychological dysfunction. There are many challenges to detect early tissue damage of haemopoietic, renal and nervous systems.

The heavy metals are known to cause progressive, irreversible damage of kidney which can be clinically diagnosed after 30-50 per cent of damage based on creatinine clearance. The biomarkers such as N-acetyl-3-D-glucosaminidase (NAG), a lysosomal enzyme and beta-2-microglobulin (β2M), small molecular weight protein have been considered to be the sensitive indicators of early renal damage[11].

The deleterious effects of lead on haemopoietic system and other biochemical activities are well known. In acute exposure, hypochromic microcytic anaemia is well documented due to bone marrow depletion; however, all the patients with elevated lead levels are not anaemic[11]. Lead induces critical derangement in haembiosynthesis, results in the excretion of porphyrins and its precursors into urine[5]. The blood lead levels (BLLs) as low as 30-35 µg/dl are known to inhibit δ- aminolevulinic acid dehydratase (ALAD), a key enzyme involved in the coupling of two molecules of ALA for the formation of porphobilinogen and further synthesis of haemoglobin[5,11].

Since heavy metal exposure is low and chronic, the damage of potential organ system will also be slow, progressive, sometimes irreversible which can be observed at subcellular level only. Therefore, biomonitoring, specially detecting subclinical damage by developing sensitive biomarkers is an important area. Heavy metals exposure from air, water, food and other non-conventional sources affect human and livestock health apart from damaging ecosystem. The target group of such exposure includes neonates, infants, children, reproductive-age men and women, post-partum women and occupationally exposed population.

Studies conducted by National Institute of Nutrition (NIN) of Indian Council of Medical Research

The National Institute of Nutrition (NIN), under the aegis of Indian Council of Medical Research (ICMR), at Hyderabad, India, carried out studies to generate evidence-based information. In addition, an effort was made to assess the exposure of pollutants (heavy metals especially Pb) alone or their interaction with nutrition. Among all heavy metals, studies on lead exposure are concentrated as it is a universal pollutant.

Investigational reports

***Epidemiology finding*:** Bhat and Krishnamachari[12] reported the neurological diseases in cattle suspecting of lead toxicity at mining area of Guntur district, Andhra Pradesh, India. This study revealed higher Pb levels in effluents at the site of discharge (~75 ppm), dung of cattle (4.7-38.3 ppm) and milk (0.05-0.15 ppm) compared to controls. The further investigations confirmed that source of drinking water to cattle and raise of forage was from the river where mining effluents were discharged into open area connected through canals.

***Investigation in livestock*:** A study in 2014 showed about 2.5 times higher Pb in blood and milk samples of lactating buffalos housed in university facility as compared to buffaloes from local shandies[13]. An inverse correlation between BLL with serum elements (Fe, Zn and Mg) and positive association with creatinine, alanine aminotransferase and ALP was also recorded. The most alarming finding was significant association between the lead levels of blood and milk samples, as 'lacto-ferritin' bound form of Pb has highest bioavailability. It was speculated that high lead levels in milk and blood samples of buffalos housed in university area might be due to exposure to environment having high Pb levels due to emissions from battery manufacturing units, active military shooting and potentially with high vehicular traffic[13].

Occupational lead toxicity

The potential population includes auto mechanics, monocasters, smelters, battery employees, and traffic police personnel, as they are constantly exposed to lead fumes. These were screened for clinical signs and symptoms such as abdominal discomfort, metallic taste, nausea, vomiting, headache, *etc*., BLL and biomarkers of haemopoietic and renal toxicity. Lead line, tremors, sensory and motor disturbances in 36 per cent of automechanics. The BLL was higher in auto-mechanics (24.3-62.4 µg/dl) compared to non-occupational group (19.4-30.6 µg/dl) whereas haemoglobin, serum albumin, creatinine and creatinine clearance were in normal range. The most alarming finding in the study was 5-7 fold elevation of urinary NAG activity and β_2M levels, respectively, which has demonstrated early renal tubular damage. This study has emphasized that the biomarkers such as NAG and β_2M must be included during the screening of BLL of the target group who are at risk of environmental exposure[11].

The monocasters were employees, occupationally engaged in the minting of printing blocks with Pb metal till 1990s, were screened for BLL, urinary NAG, δ-ALAD[8]. The employees with two times higher

BLL were enrolled for supplementation of thiamine (vitamin B1) as it was reported to have beneficial effect in reducing the risk of lead toxicity[14].

The routine clinical parameters were not significantly different whereas characteristic features of Pb poisoning were around 80 per cent in monocasters. The mean BLL among mono-casters (41.9±7.0 µg/dl) was two times higher compared to controls (23.3±3.3 µg/dl) along with inhibition of δ-ALAD activity (40-50%) and increase in urinary NAG levels (~3-4 fold). There was also a significant correlation between BLL and δ-ALAD (r=−0.65; $P<0.001$) and urinary NAG activities (r=0.76; $P<0.001$), demonstrating biomarkers utility in detecting early subclinical organ damage of haemopoietic and renal system (Fig. 2A & B).

The thiamine treatment reduced BLL significantly from fourth month and continued till the end of 12th month. The maximum BLL reduction was approximately 20 per cent (Fig. 3A). The biomarkers such as δ-ALAD activity were increased significantly (Fig. 3B) by the end of second month of treatment along with significant decrease in urinary NAG activity from fourth month of post-treatment. The results suggested that thiamine could be a potential candidature for prevention of Pb toxicity[14].

The employees in battery industries have different level of exposure as the unit has melting, plate making, assembly, dispatch and administrative wing. The studies were conducted based on the requirement of the local pollution control department during 1997-2010. The study results (1997-1998) showed

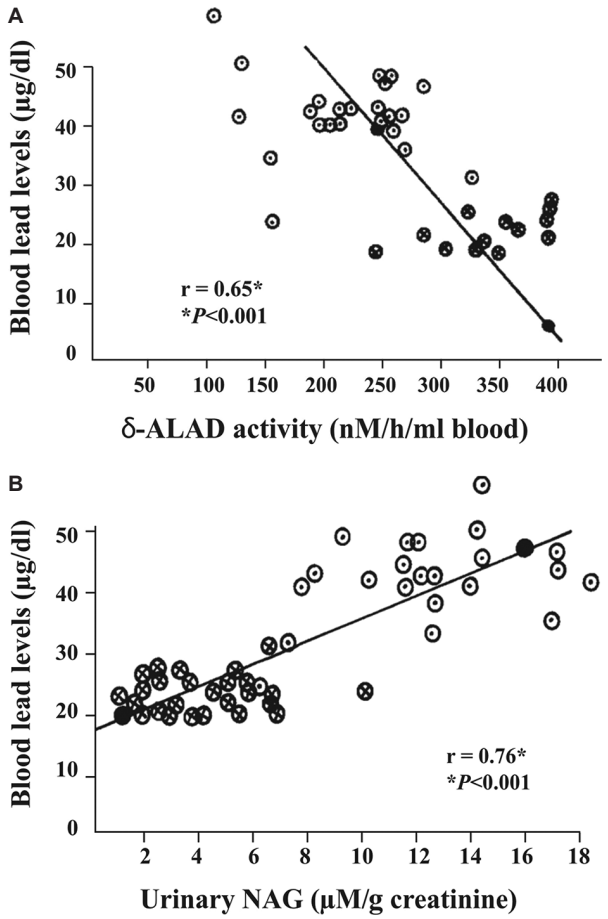

Fig. 2. Blood lead levels (BLL) correlations with δ-ALAD and NAG. The BLL of monocasters was significantly correlated inversely with δ-ALAD activity (**A**) and positively with NAG activity (**B**). ALAD, amino levulinic acid dehydratase; NAG, N-acetyl-3-D-glucosaminidase. *Indicates a significant correlation at $P<0.001$. *Source*: Reproduced with permission from Ref. 8.

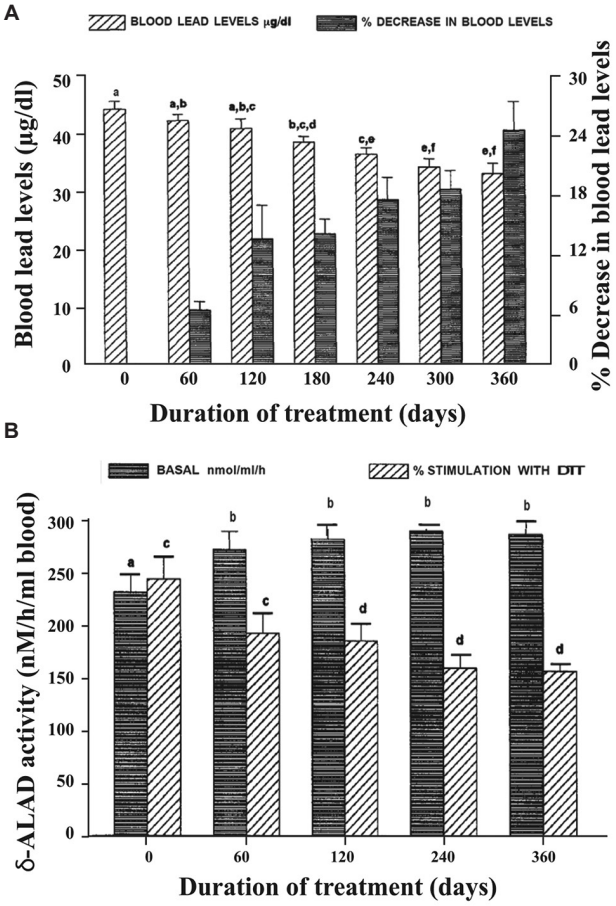

Fig. 3. Thiamine treatment effect on blood lead levels (BLL) (**A**) and ALAD activity (**B**) in monocasters. Bars represent mean±SD of BLL and per cent decrease of BLL during the course of experiment. A significant decrease in BLL of monocasters on supplementation with thiamine as the treatment regimen continues. Different superscripts represent significant difference at $P<0.05$. ALAD, amino levulinic acid dehydratase; SD, standard deviation. *Source*: Reproduced with permission from Ref. 14.

sequential elevated BLL based on their exposure level to Pb fumes in the respective divisions with mean BLL (41.9±8.76 µg/dl) as compared to the administrative employees (25.8±3.10 µg/dl). The clinical signs specific to the Pb toxicity were present in 80 per cent of the screened individuals, In spite of normal Hb, an inhibited δ-ALAD activity (30-40%) was noted among the employees. The most alarming observation was mild to severe hypochromia in 30 per cent of employees in peripheral examination of blood smear[15]. Studies conducted during 2007-2008 to screen the employees (n=110) of acid battery manufacturing industry, for BLL, serum elemental levels and routine biochemical investigations showed that 30 per cent employees had high BLL (>100 µg/dl) and the rest had 40 µg/dl (Table). The essential elements, namely Fe, Zn, Cu, Mg and Ca in serum were deficient among 12-18 per cent of the screened employees. The serum creatinine and cholesterol levels were significantly higher among occupational group compared with controls[16]. The screening process continued in 2009-2010 at one of the leading battery manufacturing units in two regions of Telangana and Andhra Pradesh States in India. A total of 198 employees, broadly from administrative (98) and from different manufacturing area (100) were screened for BLL and Hb levels. The levels of Pb in the blood were between 34 and 55 µg/dl; as these employees were exposed to Pb at the workplace. The administrative staff had blood level between 8 and 20 µg/dl and is 2-3 folds less than industrially exposed subjects. The mean Hb levels were comparable among all the groups.

A study was conducted in traffic police personnel who were constantly exposed to lead. The mean BLL of traffic personnel was within the safe limits with further evidenced by lower zinc protoporphyrin (ZPP) levels (30 µg EP/100 ml blood). One of the reasons attributed was that in India traffic personnel are frequently transferred to civil stations therefore, exposure levels were not at risk[17].

Neonate, children & pregnant/post-partum women

The lead is a potential toxicant in neonates, children and pregnant women as it affects the developmental activity. It accumulates in skeleton and has long half-life and comes into equilibrium between mother and foetus.

Neonate & pregnant/post-partum women

A pilot study[18] in urban and rural neonate, pregnant and post-partum women was conducted to monitor Pb, Fe, Zn, Cu and Mg levels in blood, chord and placenta. The results revealed that the prevalence of anaemia and trace element deficiency was high. The BLL was significantly higher among urban post-partum women (16.1±8.14 µg/dl) compared to rural (10.9±4.37 µg/dl). Similarly, the mean BLL was higher in urban neonates (7.5±5.15 µg/dl) than the rural (5.9±3.01 µg/dl)

Table. Distribution of blood lead levels of screened employees into categories with percentage of subjects

BLL categories (µg/dl)	Number of subjects	BLL mean±SD (µg/dl)	Percentage of subjects	Cumulative percentage
<25*	3	20.3±2.23	2.7	2.7
25.01-30.00§	3	27.7±1.82	2.7	5.4
30.01-40.00†	1	36.1	0.9	6.3
40.01-50.00‡	3	45.6±0.49	2.7	9.0
50.01-60.00	6	56.4±1.73	5.5	14.5
60.01-70.00	10	65.7±2.73	9.1	23.6
70.01-80.00	15	75.7±3.13	13.6	37.2
80.01-90.00	18	85.7±3.43	16.4	53.6
90.01-100.00	15	96.2±2.73	13.6	67.2
>100.01	36	136.2±38.22	32.7	100

*Cut-off levels (<25.0 µg/dl) for workplace exposure specified by CDC-NIOSH-ABLES (Centre for Disease Control and Prevention-National Institute for Occupational Safety and Health-Adult Blood Lead Epidemiology and Surveillance), §Cut-off levels (<30.0 µg/dl) for workplace exposure specified by ACGIH-BEI (American Conference of Governmental Industrial Hygienists-Biological Exposure Indices), †Cut-off levels (<40.0 µg/dl) for workplace exposure specified by CDC; OSHA (Occupational Safety and Health Administration); WHO (World Health Organization), ‡Cut-off levels (<50.0 µg/dl) for workplace exposure specified by the United Kingdom health and safety executive. SD, standard deviation; BLL, blood lead level.

Source: Reproduced with permission from Ref. 16

counterpart. There was a significant correlation (r=0.354; $P<0.01$) between maternal and neonatal BLL, whereas significant inverse (r=−0.969; $P<0.05$) relationship was observed between placental Pb and cord BLL. The mean placental and cord BLLs were comparable between urban and rural post-partum women.

***Children*:** In view of the vulnerability and availability of scanty data in children, the studies were conducted in various groups of children. To understand the magnitude of impact of leaded gasoline through automobile emission on children, 600 children aged between 7 and 14 yr residing/going to schools located in low, moderate and high traffic congestion areas in Hyderabad city were enrolled. In addition, rural children of same age group were taken as very low exposure group. All children were screened for BLL, ZPP and Hb levels[17]. The results suggested that about 20-30 per cent of heavy/moderate traffic zone children had the BLL above 15 µg/dl. The mean BLL in children of heavy traffic zone were 16 µg/dl whereas in moderate and light traffic areas, the BLL was 11 µg/dl and in rural children 9 µg/dl. Although the Hb levels were comparable between rural, moderate and heavy traffic areas, the ZPP levels were above 40 µg EP/100 ml blood in 20-41 per cent of the children from different traffic zones.

The mean BLL of children aged around 12-16 yr working in petrol pumps was 39.3±3.7 µg/dl as compared to 23.1±0.5 µg/dl of the children of non-petrol bunk area. Although Hb was normal, microcytic hypochromic anaemia, anisocytosis and basophilic strippling was noted among both the groups[19].

In one of the investigations on children (n=77) with confirmed anaemia and admitted in hospital for blood transfusion showed pale conjunctiva (99%) and fever (61%) with significantly low Hb (8.3±0.92 g/dl), serum Fe (87.0±48.65 µg/dl) and Zn (82.0±40.17 µg/dl) levels[20]. However, serum Cu levels were significantly higher in anaemic children compared to controls[20]. The mean BLL was higher among the anaemic children (4.91±7.45 µg/dl) compared to control (2.42±2.12 µg/dl); but within the safe cut-off limits (<10 µg/dl).

In Hyderabad, the handicraft work of making bangles is famous and children (n=96) aged 10-15 yr are involved in embeding the jewels merged in lead[21]. These children were enrolled for estimation of BLL, Hb, serum Fe, Zn, Cu levels in blood and their effect on cognitive and neuropsychological functions. In 39 per cent of children, BLL was above 25 µg/dl and the rest had >10 µg/dl. It was alarming that 51 per cent of children were anaemic.

The neuropsychological test results suggested that irrespective of BLL, children involved in lead-handling occupations scored significantly higher on performance quotient, picture completion, block design and object assembly compared to children in the non-lead occupations. The children with BLL ≥25 µg/dl in the non-lead occupations had significantly ($P<0.05$) better (lower scores) mean Z scores on the neuropsychological test (Bender-Gestalt) than the lead-handling occupation group. These results were contrary to the evidence regarding the effects of lead toxicity on IQ[19].

Another study conducted on a group of children (n=41) with positive history of pica eating showed BLL 30.0±8.20 µg/dl[19]. In addition, seven children from this group were mentally retarded and had an elevated BLL of 36.8±5.3 µg/dl.

Impact of unleaded petrol on children blood lead level

In a cross sectional study conducted at NIN, Hyderabad, BLL were measured in children (n=600) during 1998-1999. During the early phase of 2000 when leaded gasoline existed, the distribution of BLL was >25, 10-25 and <10 µg/dl in 54, 36 and 10 per cent children, respectively. However, the BLL was changed to 28 (>25 µg/dl), 38 (10-25 µg/dl) and 34 per cent (<10 µg/dl) in two years after the introduction of unleaded gasoline. A cross sectional study was conducted in same age group of children after 7-8 yr of the introduction of unleaded gasoline and found that the BLL of >25 µg/dl was reduced to 3 per cent whereas <10 µg/dl in 58 per cent of children[22]. However, there was no change in BLL ranged from 10 to 25 µg/dl in 38 per cent of children screened, and it was an indication of other sources of Pb exposure which were still continuing.

Studies in experimental animals

The experimental studies were conducted with an objective to understand the effect of lead toxicity on organ system, immunity and to assess the potential benefits with thiamine.

***Lead toxicity & intervention*:** The effect of Pb toxicity along with intervention with thiamine was studied in rat model. The animal model was developed to mimic

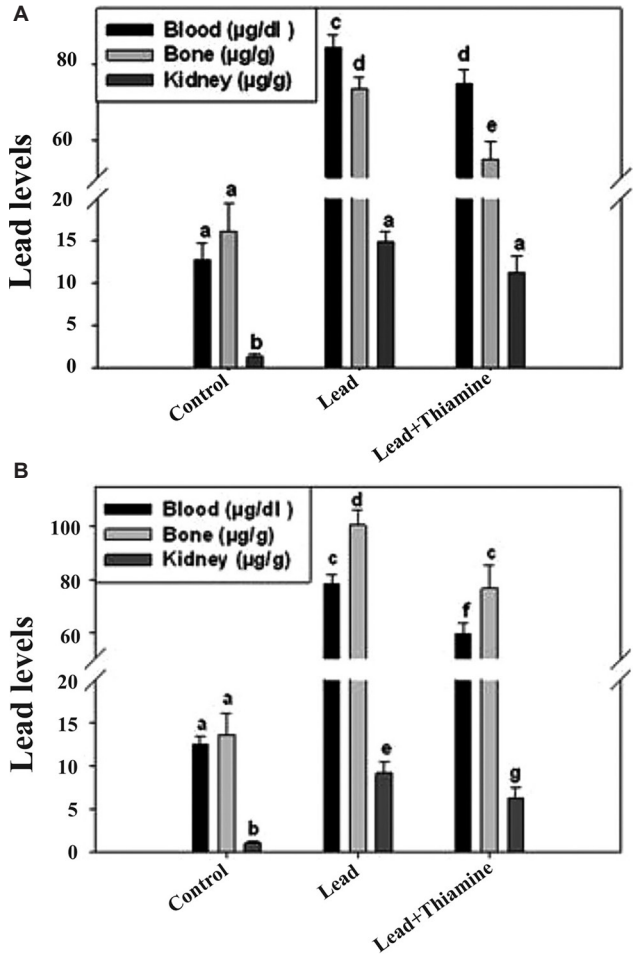

Fig. 4. Rats exposed to Pb through oral gavage and treated with thiamine either simultaneously (**A**) or post-Pb exposure (**B**). The Pb levels of blood, bone and kidney were measured at the end of treatment. Bars indicate mean±SD and bars that do not share common superscripts differ significantly ($P<0.05$). SD, standard deviation; Pb, lead.
Source: Reproduced with permission from Ref. 23.

the exposure status to lead in population. The data showed increased Pb levels with inhibited δ-ALAD and increased urinary NAG levels. The supplementation of thiamine (25 mg/4 ml/kg body weight) reversed the lead levels in blood, bone, kidney and other tissues (Fig. 4A & B). It is good to note that simultaneous administration of thiamine significantly reduced the accumulation Pb in various tissues. In addition, the early biomarkers, such as δ-ALAD and NAG activities, were normalized on both the treatment regimens with thiamine[23].

***Lead toxicity - microflora & immune response*:** In recent years, there has been a growing interest on pre- and probiotics. A study on Pb toxicity and nutritional Fe deficiency on gut microflora and immune response was conducted in experimental rat model[24]. The results of the study suggested that the lactobacilli population was significantly decreased in iron-deficient rats compared to control. Further, a significant decrease in the lactobacilli population was observed in Pb exposed rats irrespective of the dietary regimen. An additive effect of dietary Fe deficiency and oral Pb exposure resulted in greater reductions in the intestinal lactobacilli population compared to either treatment alone whereas no such effect was noted on yeast and *Escherichia coli* populations[24]. The immune response study results indicated no impact of any regimen on total or vaccine-specific IgG levels whereas a significant decrease in mucosal IgA and tetanus toxoid (TT)-specific IgM levels were noted in iron-deficient rats exposed to lead[25]. The CD4+ cell levels were not impacted by treatment regimens, but CD8+ levels were increased significantly in all iron deficient/Pb-exposed rats. *Ex vivo* proliferation of splenocyte was only significantly altered by a dual iron deficient/Pb status, and only in the absence of vaccine stimuli. Cytokine formation in all cases was highly variable[25]. The results indicated the additive effect of Pb exposure and nutritional Fe deficiency leading to compromised immune response and reduced gut microflora.

Conclusion

Studies in various group of populations including children demonstrated that low-level chronic exposure to heavy metals induced slow progressive sub-clinical organ damage and suggested the use of sensitive biomarkers to detect sub-clinical damage. Thiamine as a safe, effective, economically viable agent for reducing heavy metal (Pb, Cd) burden can be one of the choice of recommendation in occupational and vulnerable population. An aggravation of Pb toxicity was evidenced in undernutrition as part of nutrient-pollutant interaction. The deficiency of essential elements such as Fe, Ca, Zn, Cu, Mg and vitamins, *etc*. aggravates the toxicity of heavy metals. Findings on lead exposure from non-conventional sources indicate further investigations.

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***Conflicts of Interest*:** None.

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