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REVIEW ARTICLE

Lead as a Risk Factor for Osteoporosis in Post-menopausal Women

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Abstract Lead exposure is increasingly becoming an important risk factor for osteoporosis. In adults, approximately 80–90 % of absorbed lead is stored in the bones. These bone lead deposits are released into the blood during periods of enhanced bone resorption like menopause, forming a potential endogenous source of lead exposure. Post-menopausal women are at a higher risk for bone lead release because of hormonal and age related changes in bone metabolism. Estrogen deficiency is associated with increase in osteoclasts number and activity leading to both the early and late form of osteoporosis. Hence, high blood lead level coupled with concomitant environmental exposure exposes women in this age group to lead related adverse outcomes like hypertension, reduced kidney and neurocognitive functions as well as increased risk of atherosclerosis and cardiovascular mortality. A few studies have also identified coexisting variates like ethnicity, occupation, residence, education, smoking, alcohol medications, water etc. as significant determinants of bone and blood lead in women, thus increasing the magnitude of postmenopausal bone changes. Hence, interventions focused on reducing the intensity of bone resorption during menopause will help decrease exposure to endogenous lead. This would play a significant role in decreasing the morbidity and mortality associated with menopause. Also, identification of modifiable factors that prevent bone lead release will reduce the risk of chronic lead exposure and improve the health outcomes of post-menopausal women.

Keywords Lead · Osteoporosis · Post-menopausal · Risk

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Bone tissue is constantly undergoing remodelling in the human body due to the activity of osteoblasts and osteoclasts and under normal physiological conditions, a fine balance is maintained between the two. The osteoclasts are responsible for the constant process of bone resorption whereas the osteoblasts are involved in the compensatory phase of bone formation. Estrogen plays a fundamental role in skeletal growth and bone homeostasis. After menopause, the decline in estrogen leads to an increased bone turnover rate, with resorption exceeding formation. This promotes the onset of post-menopausal osteoporosis which predisposes women to increased skeletal fragility and risk of fracture [1, 2]. Though the underlying mechanism is said to be complex and multifaceted, Cervellati et al. [3] in their study showed that oxidative stress and bone resorption interplay could be one of the mechanisms triggering post-menopausal osteoporosis. Another study has focused on estrogens' role on major cytokines [4] in the bone microenvironment that regulate osteoclast function (Box 1, 2).

Lead exposure is an important risk factor for osteoporosis as it is associated with decreased bone density and bone strength [5–7]. Lead is a potent occupational toxin and its non-biodegradable nature is responsible for its prolonged persistence in the environment. So far no safe level of lead exposure has been found. Exposure to lead occurs through various sources like paint, contaminated dust and soil, drinking water, lead glazed ceramics, toys, cosmetics, herbal remedies etc. Though acute toxicity of lead is quite uncommon and mainly related to occupational exposure, chronic toxicity is more common (Table 1). In adults, 80–95 % of retained lead is stored in bone with a half-life of approximately 20–30 years. Due to the slow release of lead from bone, lead levels in bone increase significantly with age [8].

Box 1 Osteoporosis facts

Literally means "porous bones"
Called "silent disease" i.e. bone loss may occur without symptoms
There is decreased bone mass leading to increased skeletal fragility
Effects all the bones of the body
Fractures most common in hip, wrist and spine
Sudden strain or fall may cause fracture
Collapse of vertebrae is noticed when patient complains of severe back pain, loss of height, stooped posture or curved back

Box 2 Common sources of lead poisoning

Water
Paint
Pipes
Brass plumbing fixtures
Soil and contaminated dust
Batteries
Ammunition
Jewellery
Toys
Cosmetics
Traditional medicines
Pigments and pottery
Leaded gasoline

Table 1 Acute and chronic lead poisoning

	Acute poisoning	Chronic poisoning
Prevalence	Uncommon	Common
Duration	High level exposure of shorter duration	Low level exposure of longer duration
Lead levels (μg/dL)	100–120	40–60
Sources	Occupational	Dust, soil, toys, water, ceramics, cosmetics, traditional medicines etc.
Signs and symptoms	Headache, vomiting, abdominal pain, muscle pain, seizures, coma, encephalopathy	Lethargy, loss of appetite, constipation, hyperactivity, attention dysfunction, persistent vomiting, memory loss, kidney dysfunction

Lead being a bone seeking element, its exposure during the lifetime of an individual leads to its accumulation in the skeletal compartment. Mobilization of lead from the skeleton to the blood compartment occurs during periods of increased bone demineralization such as pregnancy, lactation, menopause and old age [1]. This high level of endogenously released lead coupled with exposure to exogenous sources of lead causes a number of adverse outcomes including raised blood pressure [9–12], decreased kidney function [13], derangements in neurocognitive function [14, 15] and high risk of atherosclerosis and cardiovascular mortality [16]. Thus, post-menopausal women are at great risk not only because of hormonal and age related changes in bone metabolism but also due to the release of decades old stored lead from bone.

Campbell and Auinger [17] did a secondary analysis of the National database of the Third National Health and Nutritional Examination Surgery (NHANES III) and explored the association between lead exposure and osteoporosis in a large number of adults. They found a significant inverse association between lead exposure and bone mineral density (BMD) among white subjects. However, this association lacked significance among the African-American subjects, which was probably due to the considerably smaller sample size. Nash et al. in 2004 using NHANES III data, too, had found an inverse association between bone mineral density and blood lead levels in peri and post-menopausal women in the United States. They concluded that lead stored in bone significantly increases blood lead level and that menopause and bone status are predictors of blood lead levels (BLL) among women aged 40–59 years. They also observed that the magnitude of post-menopausal change in BLL depends on a number of other factors like time since menopause and different ethnic groups on the basis of prior exposure [18]. Silbergeld et al. examined the lead status in women using the NHANES II data set compiled for the period 1976–1980. They observed that bone lead is not an inert storage site for absorbed lead and that it may interact with other factors like Vitamin D, dietary calcium and several regulatory aspects of bone cell functions, to aggravate post-menopausal osteoporosis [19].

The hypothesis, that estrogen decline aggravates bone resorption which promotes bone lead release into the blood, was supported by Korrick et al., who studied correlates of bone and BLL among middle aged and elderly women. They postulated that post-menopausal women not taking estrogen had higher BLL than those women of the same age group who were using estrogens. They specifically demonstrated an interaction between bone lead and estrogen status as bone lead positively associated with blood lead only in post-menopausal women not using estrogens and not in pre-menopausal women or post-menopausal women using estrogens [20].

Since bone turnover depends on the balance between osteoclast mediated bone resorption and osteoblast mediated bone formation, biochemical markers of bone remodelling offer a dynamic analysis of the skeletal

Table 2 Bone formation markers

Marker	Source	Sample type	Assay
Bone alkaline phosphatase	Osteoblast plasma membrane	Serum/EDTA plasma	Automated/manual
Osteocalcin	Osteoblasts	Serum/EDTA plasma	Automated/manual
Procollagen type I C terminal propeptide (PICP)	Proliferating osteoblasts and fibroblasts	Serum/EDTA plasma	Automated/manual
Procollagen type I N terminal propeptide (PINP)	Proliferating osteoblasts and fibroblasts	Serum/EDTA plasma	Automated/manual

Table 3 Bone resorption markers

Marker	Source	Sample type	Assay
(a) Collagen derived			
Carboxy terminal cross linked telopeptides of Type I collagen (CTX)	Osteoclastic hydrolysis of collagen	Urine/serum/EDTA plasma	Automated/manual
Amino terminal cross-linked telopeptides of Type I collagen (NTX)	Osteoclastic hydrolysis of Type I collagen	Urine	Automated/manual
Deoxypyridinoline	Type I collagen (mature)	Urine	Automated/manual
Pyridinoline	Type I and II collagen (mature)	Urine	Automated/manual
(b) Osteoclastic enzymes			
Tartrate Resistant Acid Phosphatase Isoform 5b (TRAP 5b)	Osteoclasts	Serum	Automated/manual
Cathepsin K	Osteoclasts	Serum/EDTA plasma	Manual

changes. There are several clinically useful markers of bone formation and resorption, and serial assessment of these markers at regular intervals provides a relatively accurate picture of bone turnover. The most sensitive markers of bone formation in post menopausal osteoporosis are bone alkaline phosphatise (BAP), osteocalcin and N-terminal propeptide of protocollagen type I (PINP). For bone resorption, the markers of choice are serum C terminal telopeptides of Type I collagen (CTX) and urine N-terminal telopeptide of collagen type I (NTX) [21]. The Expert group from the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) has recommended that the reference markers for bone formation and resorption respectively are serum PINP and serum CTX. Some of the markers of bone turnover are mentioned in Tables 2 and 3.

Recently, two studies have shown that BAP and NTx are related to changes in bone density and are predictors of rate of bone loss after menopause [22, 23]. In a study published in 2010, the associations between bone formation and resorption, micronutrient intake and BLLs were studied in women between 20 and 86 years who had participated in NHANES 1999–2002. It was observed that both bone formation (measured as serum BAP) and bone resorption (measured as creatinine adjusted urinary NTx) were significantly associated with higher mean BLLs in peri and post-menopausal women. Also, calcium and vitamin D were associated with lower BLL in post-menopausal women. This may reflect the fact that new bone formation closely follows bone resorption in any segment of the bone and led the researchers to conclude that women with increased bone formation and resorption may be at greater risk for lead associated morbidity and mortality [24]. In another study, beta type I collagen C telopeptide (β-CTx) and osteocalcin were measured to assess bone turnover and to determine their relationship with bone density and age in post menopausal women. They concluded that measurements of both these markers was useful for determining bone remodelling and were also predictors of osteoporosis on post menopausal women [25]. Another study recently concluded that all the four collagen type I derived markers of bone resorption (urinary NTX, serum CTX, urine CTX by ELISA and RIA) are significantly increased in osteopenic/osteoporotic post menopausal women [26].

Some studies have also examined the role of covariates like race/ethnicities, smoking, residence, income, occupation, menopausal status and alcohol intake as important determinants of BLL [27–30]. Jackson et al. in their study, observed that among post-menopausal women, calcium and vitamin D intake were associated with lower mean BLL [21]. This observation contrasted with the results of Korrick et al., who observed that neither blood nor bone lead were significantly associated with dietary intake of micronutrients. However, alcohol intake, especially wine,

positively associated with blood lead. This therefore represented at least one potentially modifiable risk factor for raised BLL [20]. Higher BLL have also been associated with increasing age, smoking, lower parity, use of lead glazed pottery and occupational lead exposure [31–33]. Occupation assumes great importance, as women who had been exposed to lead in the workplace and at home throughout their lives, are more susceptible to the adverse health effects of lead. One study analysed the impact of menopause and lifestyle factors on blood and bone lead levels among female former smelter and mining workers of the Bunker Hill area in the United States. Their findings reinforced the view that exposure throughout life resulted in higher blood lead levels during menopause [34].

Though measures to control lead pollution in developed countries have led to a decline in the BLL there, it still remains a serious public health concern in the developing countries. In India, it is only recently that we have become aware of the health hazards caused by lead and are developing nationwide programs to prevent lead poisoning. Few studies have attempted to investigate the factors associated with raised BLL in Indian children [35–39]. Their data suggests that nearly half of the children have elevated BLL. However, the sample size of these studies is relatively small and not much is known about the risk factors for the elevated BLLs. To the best of our knowledge, there is no data available in the Indian scenario regarding any study on the risk predictors of BLL in the adult population especially in the post-menopausal age group. Therefore, given the adverse ill effects of high BLL, especially with a diverse set of risk factors as found in our population, the toxic effects of lead exposure may be more important than was previously expected.

Since post menopausal women are particularly susceptible to endogenous lead exposure and there is paucity of data available in this context in the Indian population, large scale studies are required urgently to address this issue. Interventions focused on reducing the intensity of bone resorption during menopause will help decrease exposure to endogenous lead. This would play a significant role in decreasing the morbidity and mortality associated with menopause. Also, identification of modifiable factors that prevent bone lead release will reduce the risk of chronic lead exposure and improve the health outcomes of post-menopausal women.

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