

Relationship Between Blood Lead Level and Elevated Blood Pressure in Hypertensive Patients: Implication of Nitric Oxide

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Abstract: The correlation between the blood lead (B-Pb) levels and the values of blood pressure in hypertensive patients was investigated. Moreover, plasma levels of nitric oxide (NO), total antioxidants (TAOX) and malondialdehyde (MDA) were detected to investigate the correlations between the measured parameters and B-Pb levels in hypertensive patients. Fifty-five hypertensive patients were compared with fifty-three age and sex matched control group. The B-Pb levels were detected by flame atomic absorption spectrometry. The plasma levels of NO, TAOX and MDA were measured by colorimetric methods. In the hypertensive patients, B-Pb levels were significantly higher than controls. Concomitantly, the plasma levels of MDA were significantly increased while the plasma levels of NO and TAOX were significantly reduced in the hypertensive patients in comparison with controls. There were significant positive correlations between B-Pb and each of MDA, systolic and diastolic blood pressure. Conversely, a significant negative correlation was found between B-Pb and NO. Our study indicated that B-Pb level was associated with elevated blood pressure as well as oxidative stress in hypertensive patients. Moreover, the negative correlation between the B-Pb level and NO level may clarify their implication in cardiovascular disease and hypertension.

Keywords: Hypertension, B-Pb, NO, TAOX, MDA.

INTRODUCTION

Lead is a common environmental and industrial pollutant with no beneficial biological role. It has been detected in all phases of environment and biological system. The persistence of lead in the blood of animals and humans and the associated health risk is a topic of current debate and concern [1, 2]. Moreover, rapid industrialization and the continued use of leaded gasoline appear to be increasing lead exposure throughout the developing world [3]. Considerable attention has been paid to the possibility that low levels of lead exposure among adults in the general population can elevate blood pressure and increase the risk for cardiovascular disease morbidity and mortality [4-7].

The notion that lead exposure may influence blood pressure in humans is biologically plausible. Hu *et al.*, [8] reported significantly higher levels of lead in skeletal and blood compartments among men with hypertension. Previously, some investigators reported that lead induces hypertension in rats [9, 10]. Other animal data suggested that lead acts at multiple sites within the cardiovascular system, including direct effects on the excitability and contractility of the heart, alteration of the compliance of the vascular smooth muscle tissue, and direct action on parts of the central nervous system responsible for blood pressure regulation [4]. Evidence in animals also suggested that lead may affect blood pressure through the renin-angiotensin system [9].

Many studies have provided new insights into the mechanisms by which metals can influence vascular

function. Basal vascular tone impairment has been suggested as a possible mechanism of lead-induced hypertension. Thus, studies described by many investigators [11] suggested that low-concentration of lead exposure produced an imbalance of endothelial derived vasoconstrictor and vasodilator factors showed that the vasoconstrictor tone was conducive to hypertension. Moreover, the increased vasoconstriction was also accompanied by a rise in plasma levels of endothelin-3 and a decrease in plasma and urinary cyclic guanosine monophosphate [11]. Moreover, Sanchez-Mendoza *et al.*, [12] have demonstrated that in hypertensive rats, decreased vasodilator tone is associated to increased vasoconstrictor response and that decreased NO production was responsible for this decreased vascular tone.

Oxidative stress is a condition of oxidant / antioxidant disequilibrium, in which increased reactive oxygen species (ROS) generation overwhelms antioxidant defence mechanisms leading to oxidative damage of cellular molecules. Of these, lipids are the most sensitive in that polyunsaturated fatty acids in cell membrane react with free radicals to form peroxidation products. Malondialdehyde (MDA) is the end product and best-known indicator of lipid peroxidation. To deal with harmful effects of ROS, a network of antioxidant defence mechanisms exist. Insufficient antioxidant protection or excess production of ROS can result in oxidative stress [13].

Farmand *et al.*, [14] suggested that lead-induced hypertension is related to an over- production of ROS. ROS may increase blood pressure directly or indirectly by increasing the concentration of calcium in endothelial cells. The release of ROS increases the arterial blood pressure and induces atherosclerotic changes in blood vessels. In

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consequence, it may lead to arterial hypertension and coronary heart disease [15,16].

Although the evidence in support of a role of lead-induced hypertension is strong, it is not conclusive, nor is the mechanisms by which lead may act on the vascular system clear. Lead exposure may be more of a risk factor for certain “susceptible populations”, and thus may not be apparent in the general population. Inasmuch as hypertension remains a significant risk factor for other forms of cardiovascular disease, the propensity for environmental exposure actors to contribute to this risk is, potentially, an important public health concern [2].

According to this background, the current study was conducted to determine the blood lead (B-Pb) levels in hypertensive patients and to investigate the correlation between B-Pb levels and the values of blood pressure in hypertensive patients. Moreover, the plasma levels of nitric oxide (NO), total antioxidants (TAOX) and malondialdehyde (MDA) were detected to investigate the correlations between these measured parameters and B-Pb levels.

MATERIALS AND METHODS

In the present study, 55 consecutive hypertensive patients were recruited, during their routine check-up in the OPD clinic, Qassim University, College of Medicine, during January – March, 2010. After approval by the ethics committee of the College of Medicine, Qassim University, Saudia Arabia, an informed consent was obtained from each subject enrolled in the study. The patients were males and their ages ranged from 24 - 59 years. Fifty-three apparently healthy volunteer normotensive controls were matched hypertensive patients in age, sex and body mass index (BMI).

Each patient was subjected to full complete medical history including duration of the disease and details of therapy. Before inclusion, all participants underwent careful physical examination and detailed laboratory investigations to exclude any conditions that may interfere with the disease. Full clinical examination including fundus examination and routine investigations (ECG, ultrasonography, chest X-ray, and complete urine analysis). Also, the BMI (weight, Kg/(height)², m²) was calculated. All patients were examined for any complications. Exclusion criteria included smoking, history of recent acute illness, clinical evidence suggestive of any liver or kidney diseases. We used the mean of three systolic and diastolic blood pressure measurements, all of which were taken by a physician in the Clinical Unit of Qassim University. Patients were categorized as hypertensive if any of the following criteria were met: current user of blood pressure medication (self-report), a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher [17].

Blood sample (10 mL) was collected in two heparinized tubes from each participant. The first tube was centrifuged at 5000 rpm for 10 min for plasma separation. The plasma sample was divided into aliquots and kept at -70°C until biochemical analyses. The second tube contained whole blood was used for B-Pb determination. The lead levels in the blood were determined by employing flame atomic absorption spectrometry according to previously reported methods [18]. Calibration curve was constructed by adding

known amounts of lead standard (E. Merck). Analysis of diluted samples of blood was injected into the atomic absorption spectrophotometer (Perkin-Elmer Model 400, Shelton, CT, USA). Hollow cathode lamp of Pb was used at wavelength of 283.3 nm. The results of B-Pb levels were expressed as µg/dl.

The plasma levels of TAOX capacity were determined according to Koracevic *et al.*, [19] using commercial kit. The plasma level of MDA was determined using 1,1,3,3-tetrahydroxypropane as malondialdehyde standard and mixing equal volumes of the coloring reagent (0.375% thiobarbituric acid, w/v, in 15 % trichloroacetic acid + 0.25% N HCl) and samples or standards and 10 µL of butylated hydroxytoluene (0.8, w/v, in hexane), incubated at 100 °C for 15 min, cooled and centrifuged at 3000 rpm for 10 min. MDA and thiobarbituric acid react to form a pink color. Absorbance at 535 nm of the supernatant was recorded against reagent blank and concentration in µM was calculated from standard curve (0.25 - 20 µM) [20]. The plasma levels of NO was determined as total nitrite after deproteinization with ZnSO₄ (30%), nitrate reduction with cadmium (activated by 2% HCl) and the color developed by the reaction with Griess reagent (1% sulfanilamide/ 0.1% naphthylethylene diamine diHCL, w/v in 2.5% H₃PO₄) was recorded at 550nm against reagent blank using sodium nitrite 10-100 µM as standard [21].

Statistical Analysis

The statistical analysis was performed using Prism Statistical Package version 5.0 (Graphpad, San Diego, CA, USA). Data comparisons were performed by using student *t*-test and ANOVA with Bonferroni's post multiple comparisons test and the correlations among the clinical and biochemical parameters were performed using Spearman's rank correlation coefficient. The levels of significance were accepted with $P < 0.05$ and the results were presented in Tables as mean ± SEM.

RESULTS

The clinical criteria of patients and controls are summarized in Tables 1. Age and BMI did not show significant differences among the comparable groups. The B-Pb levels and the plasma levels of bioindices in hypertensive patients comparing with controls were shown in Table 2. The B-Pb levels were significantly higher in hypertensive patients than controls. The plasma levels of MDA were significantly increased in the hypertensive patients in comparison with controls. Unlikely, the plasma levels of NO and TAOX were significantly lower in hypertensive patients than control group. The correlations between the B-Pb levels and clinical and biochemical indices in hypertensive patients were shown in Table 3. There were significant positive correlations between B-Pb and each of MDA, systolic and diastolic blood pressure. Conversely, a significant negative correlation was found between B-Pb and NO. No significant correlations were found between the B-Pb levels and each of age, TAOX, and BMI in hypertensive patients.

DISCUSSION

There is considerable public health interest in the possible toxic effects of environmental lead exposure on the cardiovascular system, with additional concern regarding the

Table 1. Clinical Characteristics in Hypertensive Patients Compared with Controls

Parameters	Controls (n=53)	Hypertensive Patients (n=55)	P-Value
Age (years)	39.92 ± 1.209	43.16 ± 1.292	P<0.07 NS
BMI (kg/m ²)	28.53 ± 0.541	29.87 ± 0.509	P<0.07 NS
Blood pressure			
Systolic (mmHg)	114.30 ± 0.831	137.60 ± 2.045	P<0.0001
Diastolic (mmHg)	80.26 ± 0.505	90.29 ± 1.063	P<0.0001

Results are expressed as mean± SE; BMI, Body mass index, NS, non significant.

Table 2. Blood Lead and Plasma Levels of Bio-Indices in Hypertensive Patients Compared with Controls

Parameters	Controls (n=53)	Hypertensive Patients (n=55)	P-Value
B- Pb (µg/dL)	1.85 ± 0.132	2.21 ± 0.125	P<0.05
NO (nmol/ml)	27.87 ± 2.443	18.67 ± 0.923	P<0.001
ACE (U/L)			
TAOX (mmol/ L)	1.189 ± 0.017	1.073 ± 0.036	P<0.01
MDA (µmol/L)	1.74 ± 0.036	2.16 ± 0.049	P<0.001

Results are expressed as mean± SE; B-Pb, blood lead; NO, nitric oxide; TAOX, total antioxidant capacity; MDA, malodialdehyde.

Table 3. Correlations of B-Pb Levels with Age, BMI, Systolic BP, Diastolic BP, NO, ACE, TAOX and MDA in Hypertensive Patient

Variables	Correlation Coefficient (r)	P-Value
B-Pb vs		
NO	-0.46	P< 0.01*
TAOX	-0.30	NS
MDA	+0.51	P<0.05*
Age	+0.11	NS
Systolic BP	+0.41	P< 0.01*
Diastolic BP	+0.39	P< 0.05*
BMI	+ 0.12	NS

*significant; B-Pb, blood lead; BP, blood pressure; NO, nitric oxide; TAOX, total antioxidant capacity; MDA, malodialdehyde; BMI, body mass index; NS, non significant.

role of chronic low-level lead exposures in the pathogenesis of hypertension, a leading risk factor for cardiovascular disease morbidity and mortality [7, 2]. Vupputuri *et al.*, [22] suggested that increased levels of B-Pb remain an important environmental risk factor for elevated blood pressure. Many studies [23, 24] but not all [25] have indicated that environmental exposure to lead is associated with an increased risk of hypertension. Martin *et al.*, [26] suggested that lead has an acute effect on blood pressure via recent dose and a chronic effect on hypertension risk via cumulative dose.

In the present study, the B-Pb levels were significantly higher in hypertensive patients than controls and positively correlated with the increase of systolic and diastolic blood

pressure level. In this regard, Dursun *et al.*, [27] found a significant elevation of the mean systolic and diastolic blood pressures in the lead-treated rats when compared to healthy controls. Robles *et al.*, [28] confirmed the hypertensive effect of lead exposure. Vupputuri *et al.*, [22] showed that significant associations between blood lead level and systolic and diastolic blood pressures in black men. Nash *et al.*, [17] found that B-Pb level is positively associated with both systolic and diastolic blood pressure in postmenopausal women. Recently, Kasperczyk *et al.*, [29] found that B-Pb levels were positively correlated with high arterial blood pressure (both systolic and diastolic). Moreover, Afridi *et al.*, [30] reported higher levels of B-Pb as well as a lower level of Zn, correlated well with the consequences of

hypertension. Conversely, Staessen *et al.*, [31] failed to recognize a significant relation between B-Pb and hypertension.

Age and BMI are very strong factors that induces hypertension but they seem to be independent of lead effect. Kasperczyk *et al.*, [29] did not find a correlation between B-Pb and BMI or age. Our study showed similar finding. Unlikely, Harlan, [23] found that BMI has an inverse relation to B-Pb in the US population. deQueiroz *et al.*, [32] found that BMI is significantly correlated with the increase in blood pressure levels.

There are many reports in the literature proposing possible physiological and cellular mechanisms of lead -induced hypertension based on animal and *in vitro* studies. Lead may cause enhanced sympathetic nerve activity with increases in circulating epinephrine and norepinephrine levels in conjunction with decreased density of vasodilating beta 2 adrenergic receptors [33]. Chronic low-level exposure to lead results in increased activity of angiotensin converting enzyme activity and increases in plasma renin, angiotensin II, and aldosterone levels [34]. Plasma kininase I and II levels are higher during Pb exposure. This can lead to decreases in plasma bradykinin levels resulting in a reduction in endothelial NO production [35].

There is very strong evidence that lead decreases the functional availability of the potent vasodilator NO, most likely through direct or indirect mechanisms involving oxidative stress [34]. In the current study, the plasma levels of NO were significantly lower in hypertensive patients than controls. The B-Pb levels were negatively correlated with NO levels in hypertensive patients. In this regard, Dursun *et al.*, [27] showed that exposure to low lead results in a marked decrease of plasma NO levels. Robles *et al.*, [28] suggested that decreased NO synthesis or increased NO catabolism are present in the hypertensive animals. ROS are logical candidates to mediate NO modulation; moreover, Robles *et al.*, [28] demonstrated that lead treatment was associated with increased ROS production and inactivation of NO. Thus, high ROS levels after lead-exposure may increase the presence of superoxide anion, raising the probabilities of an interaction between NO and ROS to produce a peroxynitrite, highly deleterious molecule.

Peroxyntirite is a strong, relatively long-lived oxidant which has been implicated in tissue injury. It is known to initiate lipid peroxidation and might lead to irreversible tissue damage, and impaired vascular function [36]. Robles *et al.*, [28] suggested that NO production or release is impaired as a result of lead-exposure. Taken together, the data suggest that upon lead exposure, a higher production of ROS is generated, inactivating NO.

Many reports have suggested that lead-induced hypertension is related to an over production of free radicals and/or a decrease of the antioxidative mechanisms in the body [14,37]. The release of ROS increases the arterial blood pressure and induces atherosclerotic changes in blood vessels. In consequence, it may lead to arterial hypertension and coronary heart disease [15,16].

In the current study, plasma levels of TAOX were significantly lower but plasma levels of MDA were significantly higher in hypertensive patients than controls.

The B-Pb concentrations were positively correlated with MDA levels in hypertensive patients. In this regard, many studies [38,39] have proven that the exposure of human to lead compounds results in increased peroxidation of lipids in blood, due to changes in the activity of antioxidant enzymes. Moreover, Kasperczyk *et al.*, [29] found a positive correlation between B-Pb and MDA among human exposed to lead. Conversely, Dursun *et al.*, [27] showed that lead administration results in hypertension and a nonsignificant rise in plasma concentration of lipid peroxides.

Previous reports have shown that lead-induced hypertension could be related to an increase in ROS [15,16]. In addition, it is widely accepted that oxidative stress may contribute to the generation of hypertension and endothelial dysfunction via the inactivation of NO [35]. Robles *et al.*, [28] demonstrated that rats exposed to lead had a higher production of ROS, such that coadministration of lead with antioxidant treatment was able to prevent the oxidative stress and the hypertensive effect of lead treatment.

CONCLUSION

The blood lead level is significantly and positively correlated with blood pressure among hypertensive patients. Lead exposure may increase blood pressure through increase the oxidative stress and NO reduction. Further biochemical and epidemiological researches are needed, especially in the field of metal exposure -induced hypertension, to determine the pathological; clinical significances and the mechanisms of the adverse effects as well as to support our findings and to study their direct impact on cardiovascular outcomes.

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