

Original Article**Missile-related Lead Exposure and Blood Pressure in Patients with Retained Pellets in the Craniomaxillofacial Region**

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ABSTRACT

Background: Environmental and occupational lead exposures are known to cause an elevated blood pressure but can this concept be applied to missile-related lead exposure?

Methods: We implemented a controlled, cohort study design to examine study samples with long-standing missiles in craniomaxillofacial region using atomic absorption spectrophotometry and standard sphygmomanometry to measure the blood lead levels and blood pressure respectively. The predictor variable was blood lead levels and the outcome variable were blood pressure. Other variables were age, number of pellets, and duration of retention. Descriptive, bivariate and multivariate statistics were computed and the *P*-value was set at 0.05.

Results: There was a significant, strong and positive association seen between diastolic blood pressure ($r = 0.34; P < 0.001$) unlike systolic blood pressure that showed an insignificant, weak and negative associations with blood lead levels ($r = -0.01, P = 0.82$). Binary logistic regression showed that blood lead levels, though less significant, (OR = 1.24, $P = 0.01$, 95%CI = 1.04-1.42) had a higher likelihood to cause hypertension than the age of the patients (OR = 1.03, 95%CI = 1.01-1.04, 0.003).

Conclusion: The results of this study suggest an association between missiles-related lead exposure and the diastolic blood pressure.

Keywords: Blood Lead Levels, Blood Pressure, Hypertension, Missile-Related Lead Exposure.

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INTRODUCTION

The relationship between lead exposure and increased blood pressure has recently received a great deal of attention following the implication that morbidity and mortality from cardiovascular disease might be reduced by lowering the lead pollution in the environment [1]. Most but not all studies [2-5] have indicated that the environmental exposure to lead is associated with an increased risk of hypertension and renal diseases. Cardiovascular disease is known to be the leading cause of mortality and a primary contributor to the burden of disease worldwide [6].

While there are several studies on acute trauma from missiles, there are no reports on their toxic or poisoning effects. Incidence of firearm injury is at the epidemic level in most parts of the world [7]. Most projectiles fired from these weapons contain 95% lead and ultimately it is an avocational or recreational source of lead exposure [8]. Acute and chronic toxicity following gunshot injuries have been reported in the literature [9, 10].

Community studies have suggested that low level of lead exposure is significantly associated with increased blood pressure in the general population [1-5]. Also, cohort studies following occupational exposure have strongly associated chronic lead exposure to cardiovascular diseases, essentially increased blood

pressure [11, 12]. Though several studies have reported elevated blood lead levels following retained lead missiles [9, 10, 13] there is scarcity of studies on the association of blood lead level resulting from retained missiles and hypertension. Therefore, the purpose of this study was to examine the association between blood pressure and blood lead levels in patients with missile pellets in their bodies.

MATERIALS AND METHODS**Study Samples**

The University of Benin's Ethics and Research Committee approved the commencement of this study. Each subject also signed an informed consent form. This is a descriptive cohort study design. The sample size for both the study and control populations was based on convenience sampling method. The recruited subjects were individuals that had treatment in the Department of Oral and Maxillofacial Surgery of the University of Benin's Teaching Hospital in southern Nigeria following gunshot injuries to the craniomaxillofacial region and had lead pellets in their bodies for not less than three years. They were recalled from the hospital's registry using name, home address, telephone number and email address. They were matched individually with control groups for their age bracket within 2 years, weight, gender and socio-economic status [3]. The controls were

individuals treated for craniomaxillofacial fracture(s) with trans-osseous wires or plates and screws following aetiologies other than gunshot injuries. The wires, plates and screws were retained for not less than three years, and patients were living within the same geographic environment.

We controlled for the known and major risk factors for hypertension by matching, restrictions and multivariate analyses. To control for predictive factors, the recruited subjects were excluded if they had hypertension or if they were taking antihypertensive medications prior to injury, the age was greater than 45 years, the body mass index was > 30 , the frequency of exercise was less than once a week, the current use of cigarette was more than 10/day, the current alcohol intake was more than 5 bottles/ day, the glomerular filtration rate (GFR) was less than 90mls/minute, the total cholesterol level was more than 240 mg/dl, and had previous or recent environmental or occupational lead exposure [11]

Radiographic Measurements

The posteroanterior (PA) radiographs of the skulls of the participants were reviewed to verify the presence and approximate number of retained pellets in the body (Figure 1). If there were limitations with the plain radiographs, computed tomography was used for pellets dose assessment.



Figure 1. A posteroanterior radiograph showing pellets in the craniomaxillofacial region.

Blood Pressure Measurement

The definition and measurements of blood pressure was based on the guidelines for the management of hypertension in Nigeria adopted by the Nigerian Hypertension Society. The guidelines were recommended by consensus groups after examination of the current hypertension guidelines from United States (US), the United Kingdom (UK) and the World Health

Organisation's International Society of Hypertension (WHO/ISH) [13]. Hypertension was defined as an elevated blood pressure (systolic blood pressure (SBP) ≥ 140 mmHg and /or diastolic blood pressure (DBP) ≥ 90 mmHg or on antihypertensive medications in Nigerians, aged 15 years or above [13].

Blood pressure was measured in two consequent visits of one week interval, and the measurement in individuals that smoked or ingested caffeine within 30minutes was deferred. Measurements were commenced after 5minute of rest. Appropriate cuff size was selected as required such that it completely encircled the girth of the patient's upper arm. Subjects were seated with arms bared, supported and at their heart level. A desk-model mercury manual sphygmomanometer and a stethoscope were used. The systolic and diastolic blood pressure were measured and recorded. The diastolic pressure was recorded when the Korotkoff's sound (Phase V) disappeared. Measurements were also done in standing position with arm held horizontally at the level of the base of the heart. An average of two measurements separated by an interval of two minutes was recorded and used for analysis. Additional measurements were taken whenever the first two measurements differed by 10mmHg.

Blood Lead Determination

Sample collection was strictly based on the guidelines from Centre for Disease Control (CDC) for collecting and handling blood lead samples [14]. About 5ml of whole blood was obtained by venepuncture from the cubital vein after skin disinfection with 75% alcohol with a sterile 10ml syringe and subsequently transferred in heparin- containing test tube. It was transported to the laboratory at Nigerian Institute for Oil Palm Research (NIFOR) where lead analysis was performed with atomic absorption spectrophotometry, using Graphite furnace Atomic Absorption Spectrometer, model 210. The readings, after instrument adjustment, were as follows: wavelength of 217nm, band pass of 1.0mm, detection limit of 0.001 μ g/dl, optimum working range 2.5 and hollow cathode lamp. Two analytical chemists were instructed to perform single measurement for standardization. The average of the two measurements was considered for the analysis.

Health and Risk Questionnaires

A health questionnaire was completed by each patient and was used to exclude any previous occupational and recreational lead exposure in both the control and experimental subjects. The purpose was for the selecting the subjects in the study and not for inclusion in the analysis. The usefulness of these instruments has been documented in a previously published study [14].

Glomerular Filtration Rate (GFR) and Total Cholesterol Estimations

The two protocols adopted by our hospital for estimating renal function are the creatinine clearance and

the glomerular filtration rate (GFR) determination. The GFR protocol was chosen because it was more convenient for the recruited subjects since it involves a single measurement of serum creatinine. Upon taking all precautionary measures, venous blood samples were collected according to the Collection of Diagnostic Blood Specimens by Venepuncture guidelines of the Clinical and Laboratory Standard Institute (CLSI) [15]. The blood samples were delivered to the chemical pathology laboratory of the hospital for serum creatinine measurements. The laboratory is known for its routine quality control standard practices before setting instruments for analytical running of sensitive investigative tests. For the standardization of instruments' the calibration was performed according to the manufacturer's specifications and by taking the average of double measurements. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to estimate the GFR from the creatinine values as follows [15].

$$GFR = 141 \times \text{Min} \left(\frac{Scr}{K}, 1 \right) \times \text{Max} \left(\frac{Scr}{K}, 1 \right)^{-1.209} \times 0.993^{\text{Age}} \times 1.02 [\text{if female}] \times 1.159 [\text{if Black}]^2$$

Stage 1: GFR = \geq 90ml/min (Normal kidney function).

Stage 2: GFR = 60 - 89ml/min (Mild decline in kidney function)

Stage 3a: GFR = 45 - 59ml/min (Mild to moderate decline in kidney function)

Stage 3b: GFR = 30 - 44ml/min (Moderate to severe decline in kidney function)

Stage 4: GFR = 15-29ml/min (Severe decline in kidney function)

Stage 5: GFR = $<$ 5 ml/minute (Kidney failure).

Total cholesterol determination was also performed in the same laboratory following same principle of CLSI. This was performed using automated machine and information on total cholesterol estimation. The two sets of data were used for selection of patients and were not included in the analysis.

Body Mass Index

Body mass index (BMI) was obtained from the physical examination and calculated as weight in kilograms divided by the square of height in meters. Weight was measured with a stadiometer attached-manual scale with a capacity of 250kg. It was adjusted to the 0.1kg precision. The weights of subjects wearing light cloth were measured barefooted while standing at the centre of the scale. The height was measured with the head of the patients in Frankfurt plane and the arms relaxed at the side of the body, with the palms facing the thighs. The height was recorded when the movable part of the stadiometer touched the vertex of the head in neutral position. Precision was set at 0.1 meter. This measurement was also used for the selection of patients and was not included in the analysis in the results.

Data Analyses

The data collected were age, sex, cigarette smoking, alcohol use, body mass index, level of exercise, total cholesterol levels, GFR, blood lead levels (BLLs), number of retained pellets and duration of retention, hypertension, diastolic blood pressure (DBP) and systolic blood pressures (SBP). The outcome or dependent variables were hypertension, diastolic and systolic blood pressures while the predictive or independent variable was BLLs. Age of the patients was covariate. Other measured data were used in study sample selection.

In the univariate analysis, continuous data were summarized in means, standard deviations and the categorical data were in proportions and percentages. The data were entered into a computer and analysed using the statistical package for social sciences (SPSS, Version 17). In the bivariate analysis, mean difference of continuous variables were tested with two samples *t*-tests. In multivariate analysis, associations, predictions and causal relationship between predictors and outcome variables were determined with Pearson's correlations, two- models simple linear regressions and binary logistic regression, respectively. The statistical analyses were subjected to assumption testing to determine the data fitness. Using a two tailed-test, a P-value of $<$ 0.05 was and 95% confidence level considered as being significant.

Ethics Statement

The institution's Ethics and Research Committee approval was obtained and each of the participants gave their signed informed consent.

RESULTS

Out of the 30 patients contacted through the hospital's record information data, only 24 agreed to participate and duly gave their consent, thus giving a response rate of 89.3%. There were 19(79.3%) males and 5(20.7%) females (male: female ratio 3.8:1). The males patients had a higher blood lead levels than their female counterparts with a value of 0.21 μ g/dl, which was statistically insignificant (95% CI = - 0.17- 0.21, P = 0.83). Data concerning the age, diastolic and systolic blood pressure, and hypertension of the recruited subject are shown in Table 1.

As expected, the control group presented with lower blood lead concentrations than those patients in the experimental group, and this was strongly significant as seen in Table 1. The patients who had retained 10 or greater number of pellets (\geq 10) had their BLL greater than those with lesser than 10 pellets ($<$ 10) with a value of 0.23(95% CI = -1.00 -1.47, P = 0.68). The BLLs was 1.39 μ g/dl higher in the individuals who had pellets retention for ten or more years (\geq 10 years) than those with retention less than ten years ($<$ 10 years). The difference was statistically significant (95% CI=0.55-2.34, P = 0.01). The duration of pellets retention and the number of pellets retained were strongly associated with

the blood lead levels of the patients, which were highly significant (Table 2).

The result of independent or unpaired *t*-test showed that the patients presenting with hypertension had a blood levels of 1.10 $\mu\text{g}/\text{dl}$ higher than those without hypertension and the differences were significant (95% CI = 0.22 - 1.98, $P = 0.02$). The mean lead level in the venous blood samples of patients with hypertension was 4.67 $\mu\text{g}/\text{dl}$ while that in the controls was 1.02 $\mu\text{g}/\text{dl}$. The mean difference of 3.65 $\mu\text{g}/\text{dl}$ could not be tested statistically by paired *t*-test since the weight case was equal to one and no deviation was observed.

Though the patients with systolic blood pressure of 140 mmHg or greater were just 5(20.8%), their blood lead levels were 4.09 $\mu\text{g}/\text{dl}$ while those with systolic blood pressure less than 140mmHg were 19 (79.2%) individuals but they had a lower lead level of 3.49 $\mu\text{g}/\text{dl}$. The observed differences were not significant (95% CI = -1.94 - 3.13, $p = 0.55$). Similarly, those with a diastolic blood pressure greater than 90mmHg were just 4 (16.7%) individuals but their mean blood lead level was 1.37 $\mu\text{g}/\text{dl}$ greater than those with diastolic blood pressure greater lesser than 90mmHg whose percentage were 83.3%. However, this observation was not significant (95% CI = - 0.68-3.42, $p = 0.12$). The systolic blood pressures of 12.5% of patients presenting with greater or equal to 5 $\mu\text{g}/\text{dl}$ were 5.67mmHg greater than that of 87.5% patients with blood lead levels less than 5 $\mu\text{g}/\text{dl}$; however, the difference was not significant (95% CI = -1.92-3.21, $p = 0.09$). A similar event was observed with that of diastolic blood pressure,

where 8.33% of patients with greater or equal to 5 $\mu\text{g}/\text{dl}$ had 144mmHg and the remaining 91.7% group with less than 55 $\mu\text{g}/\text{dl}$ had 134mmHg. The mean difference was also not significant (95% CI = -91.1-112, $p = 0.43$).

In the multivariate analysis, the ages and the blood lead concentrations of the patients demonstrated a strong and positive association with diastolic blood pressure, but only age showed a strong and positives association with systolic blood pressures. Although there was no association between systolic blood pressure and blood lead levels, this was not significant while all other associations were statistically significant (Table 2), and they were included in our linear regression analyses. In these two models, there was a striking contribution of the blood lead levels to the variations seen in the diastolic blood pressures than that contributed by the ages. These contributions were highly significant as shown in Table 3. The changes seen in the systolic blood pressure still was far more due to blood lead levels than other risk factor, i.e., age of patients. But this contribution was not significant but the lesser contribution by the patient's age was highly significant as seen in Table 3. Finally, in the age-adjusted binary logistic regression, blood lead levels had a higher likelihood to cause hypertension (OR =1.24, 95%, CI =1.04-1.47, $p = 0.01$) than the patient's ages (OR =1.03, 95%CI =1.01-1.04, $p = 0.003$). Despite that blood lead levels had a greater predictive power but it was less significant than age, which had a higher predictive power for the prediction of hypertension.

Table 1. Characteristics of the study participants, overall and by blood lead levels.

Variables	Measurements	Patients	Controls	Mean difference	95% CI	t-value	P-Value
Age (years)	Range	17-45	19-45				
	Means (SD)	36.7(8.64)	37.1(8.74)	0.39(1.58)	0.28 - 0.50	7.07	<.001
SBP (mmHg)	Range	116-160	112-150				
	Mean (SD)	128(10.5)	123(4.4)	4.78(9.7)	4.14-5.41	14.8	<.001
DBP (mmHg)	Range	72-94	70-91				
	Mean (SD)	83.1(5.53)	79.9(4.87)	3.20(4.53)	2.90-3.50	20.1	<.001
BLL ($\mu\text{g}/\text{dl}$)	Range	0.98-5.03	0.21-3.02				
	Mean (SD)	3.42(1.14)	1.51(0.69)	1.90(0.84)	1.84-1.95	67.0	<.001

BLL = Blood lead levels

SBP = Systolic blood pressure

DBP = Diastolic blood pressure

Table 2. Correlation among blood pressure, lead exposures and risk factors.

	Age (years)	BLL ($\mu\text{g}/\text{dl}$)	DPB (mmHg)	SBP (mmHg)	A	B
Age (years)	1*					
BLL ($\mu\text{g}/\text{dl}$)	- 0.24**					
DBP (mmHg)	0.12**	0.34**				
SBP (mmHg)	0.15**	- 0.01	0.65			
	0.19**	0.55**	0.44**	0.02		
A						
B	0.05	0.24**	0.14**	0.04	0.19**	1*

*No correlation; ** $P < 0.001$, A = Duration of pellets retention; B = Number of pellets retained

Table 3. Regression coefficients of patients' BLL, DBP and SBP.

	B (SE)	95% CI	P-Value
DBP, Regression coefficient (SE)			
BLL ($\mu\text{g}/\text{dl}$)	0.87(0.19)	0.49-1.25	< .001
Age (years)	0.05(0.02)	0.02-0.08	< .001
SBP, Regression coefficient (SE)			
BLL ($\mu\text{g}/\text{dl}$)	0.44(0.41)	-0.37 – 1.24	0.29
Age (years)	0.15(0.03)	0.08-0.21	< .001

DISCUSSION

The current reference value of blood lead level established by CDC (14) and WHO 5 $\mu\text{g}/\text{dl}$ is for both adults and children. The challenge with lead is linked to the absence of an identified threshold for its toxicity, therefore, the ideal acceptable lead level should be zero (0 $\mu\text{g}/\text{dl}$) [15].

We documented a mean blood lead level of 3.42 $\mu\text{g}/\text{dl}$ though we observed few sporadic cases greater than the reference value. Several other missile-related blood lead levels reported in the literature are 9.01 $\mu\text{g}/\text{dl}$, 5.1 $\mu\text{g}/\text{dl}$, 6.71 $\mu\text{g}/\text{dl}$ and 8.78 $\mu\text{g}/\text{dl}$ by Araujo et al [10], McQuiter et al. [16], Nguyen et al. [17] and Farrell et al [18], respectively. The possible explanation for the variation in blood lead levels could be due to the type of lodged missiles and the region of the body involved. While the present study specifically studied missiles in the head and neck region other studies examined other parts of the body. The higher vascularity of the head and neck regions may explain the variations. Further, no case of bullet wound was seen in the course of our study while bullets were the missiles in the previous studies. Evidently, lead content in bullets is 75% higher than in missile pellets.

Association and causal relationship between occupational or environmental lead exposures and hypertension has been extensively studied [1-5, 11, 12, 19, 20]. Our study demonstrated high and significant association between missile-related lead exposure and diastolic blood pressure, but not with systolic blood pressure. We also demonstrated a positive causal relationship between lead exposures and hypertension. Several other reports had similar findings while some others found association with both the diastolic and systolic blood pressure, with only systolic blood pressure, or found no association with either diastolic or systolic pressure.

Almeida et al., in their population-based study in Brazil, reported a geometric mean blood lead levels of 1.97 $\mu\text{g}/\text{dl}$ and strong association between blood lead levels and systolic and diastolic blood pressure. They also reported a positive, causal relationship between hypertension and blood lead concentrations. Bushnik et al. (19) who reported a geometric mean of 1.64 $\mu\text{g}/\text{dl}$, also demonstrated an association between environmental lead exposure and systolic and diastolic blood pressure, but also a negative causal relationship with hypertension. Also, a population study in china [3] reported a geometric mean of 15.2 $\mu\text{g}/\text{dl}$ and an association between diastolic and systolic blood pressure

and did not focus on the causal relationship between lead and hypertension. Parkinson et al. [11] in their occupational study, reported no association between diastolic and systolic blood pressure despite the higher blood lead levels, 39.9 $\mu\text{g}/\text{dl}$, reported in the exposed workers. They; however, did not perform a causal relationship analysis. Vupputuri et al. [20] reported a geometric mean of 4.05 $\mu\text{g}/\text{dl}$ among the Black and White populations in the U.S. They reported association between lead exposure and both systolic and diastolic blood pressure in Blacks, but the association in Whites was seen only with diastolic blood pressure. They reported a positive causal relationship between hypertension and lead exposures in both black and white women, and a marginally significant relation in black men. However, there was no causal relationship in white men.

The reason for the disagreement seen between the present study and that reported by Parkinson et al. [11], may be that the higher blood lead level in the latter study could be due to errors in measurements. It could also be that occupational exposure was an intermittent source while the source of lead in the present study was continuous, due to lodged lead-containing pellets in the body. Further, the latter study failed to analyze the causal relationship between blood lead and hypertension.

Limitations: Lack of reports on missile-related exposure and abnormal changes in blood pressure makes the comparison of our data with those reported by environmental and occupational studies difficult. Another limitation of our study was the fact that we recruited fewer subjects than those of other studies.

CONCLUSION

This study found a strong and positive association between blood lead concentration and diastolic blood pressure but not with systolic blood pressure in human subjects. There was also a positive causal relationship between these variables. We suggest that serial blood pressure monitoring should be considered in patients with retained lead pellets of ≥ 10 and the blood lead levels greater than 5 $\mu\text{g}/\text{dl}$. We also suggest the consideration of chelation therapy and/or surgical pellets extraction as treatment options in the event that blood lead levels exceed 20 $\mu\text{g}/\text{dl}$.

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CONFLICT OF INTEREST

There was no conflict of interest declared by the authors.

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