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Others

Evaluation of Erectile Dysfunction and Left Ventricular Diastolic Parameters in Lead Exposed Workers

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Background: Lead exposure causes a wide range of vascular diseases through oxidative stress, sympathetic hyperactivity and impairment in nitric oxide bioavailability. In this study, the association between the effects of lead exposure on left ventricular diastolic indices and erectile function were assessed.
Methods: A total of 94 lead-exposed workers without known cardiovascular diseases or risk factors and 30 healthy subjects were enrolled. Systolic and diastolic functions were measured using transthoracic echocardiography. All participants were non-smokers. The International Index of Erectile Function Questionnaire (IIEF-5) was used to diagnose and grade erectile dysfunction (ED). Echocardiographic parameters, IIEF-5 score and blood lead level (BLL) were analyzed.
Results: The mean age and median BLL were 32.3 ± 6.4 years and 19 μg/dL in the workers, respectively. Sixty-five (69.1%) workers and 9 control subjects (30%) had ED. The IIEF-5 score was lower in the workers (17.0 ± 6.1) than in the controls (22.7 ± 2.1). In the workers, E and e' waves and E/A ratio were lower, and A wave, E/e' ratio, and left atrial volume index (LAVI) were higher than in the controls. Additionally, BLL was correlated with IIEF-5 score, e' wave, and E/e' ratio. IIEF-5 score was correlated with e' wave, E/e' ratio and LAVI. BLL was an independent risk factor for a decreased e' wave and IIEF-5 score and increased E/e' ratio in the lead-exposed workers.
Conclusions: Impairment of diastolic and erectile functions, despite a younger age and in the absence of accompanying risk factors, was correlated with increased BLL.

Key Words: Diastolic dysfunction • Echocardiography • Erectile dysfunction • Lead exposure

INTRODUCTION

Lead is one of the most common heavy metals that can cause numerous and serious health effects, and exposure can be both from the environment and work place. Lead exposure can lead to a wide range of cardiovascular diseases including atherosclerosis, ischemic heart diseases and increased diastolic and systolic blood pressure (BP).[1-4] Additionally, it has been demonstrated that long-term low-dose lead exposure can cause morphological and functional changes in the heart.[5] It can also cause negative effects on the cardiovascular system by promoting vascular inflammation via oxidative stress, decreasing nitric oxide (NO) availability, and increasing sympathetic tone.[6-8]

Erectile dysfunction (ED) is defined as the persistent inability to achieve or to maintain an adequate erection for satisfactory sexual performance, and it affects more than half of all males.[9] Various validated questionnaires

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are used to diagnose and grade ED. The short version with five items of the International Index of Erectile Function (IIEF-5) is currently the most widely used, because of its high sensitivity and specificity for the diagnosis of ED.[10] Besides neuronal, vascular and endocrine diseases, life style factors such as smoking and alcohol consumption, and psychological factors, it has been shown that environmental and occupational exposure to lead are important risk factors for the development of ED.[11]

For the left ventricle to function effectively as a pump, it must be able not only to eject but also to fill, which is its diastolic function.[12-14] Increased production of oxidative stress metabolites and endothelial dysfunction characterized by a decreased concentration of NO are the common pathologic processes of lead toxicity, ED and diastolic dysfunction.[8,15] The aim of this study was to evaluate the effect of lead exposure on erectile and diastolic functions, and the relationship between ED and diastolic function in workers exposed to lead at their work place without overt cardiovascular diseases, and to compare them with healthy control subjects.

METHODS

Study population

In this cross-sectional study, we examined 216 male workers who were occupationally exposed to lead and were referred to our clinic, and 30 healthy subjects who worked in our center as hospital staff without known overt cardiovascular diseases between January 2015 and December 2015. A complete medical history and physical examination findings including height (m), weight (kg), body mass index (BMI) calculated as weight/height^2 and BP were recorded on the day of transthoracic echocardiography (TTE). 12-lead surface electrocardiography, laboratory and TTE findings were evaluated. Workers with coronary artery disease, pre-existing hypertension (HT) defined as systolic BP > 140 mmHg and diastolic BP > 90 mmHg and/or taking anti-hypertensive medications, valvular heart disease except for trivial regurgitation, diabetes mellitus (DM), thyroid dysfunction, hyperlipidemia, major pelvic surgery, cigarette smokers and alcohol consumers, obesity (BMI > 30 kg/m^2) and without a regular sexual relationship were excluded. Blood serum levels of testosterone, free testosterone, luteinizing hormone, follicle stimulating hormone, estradiol, and prolactin were measured in the early morning between 8 a.m. and 10 a.m. Workers with any imbalance in these hormones were excluded from the study. Workers with sinus tachycardia, first degree atrioventricular block and atrial fibrillation which affected the mitral inflow pattern, and those who used medications such as central acting sympatholytics and antidepressants that could affect erectile function were also excluded.

After taking into account these exclusion criteria, 122 workers were excluded, and the study was carried out with a total of 94 workers. Of the 94 workers, 62 (66%) were battery production workers and 32 (34%) were metal recycling workers. Most of the workplaces were small and medium-sized enterprises. Therefore, in most of the workplaces, measurements of environmental exposure/toxic substances were not done. In the small number of workplaces where measurements were done, accurate values could not be obtained because of incorrect measurements and inadequate data. All participants were men over the age of 18 years, and all provided informed consent before enrollment. The study protocol was in accordance with the 1975 Declaration of Helsinki and was approved by the local ethics committee.

Collection of biological samples

Blood samples were drawn in 10 mm tubes with red caps not containing gel for the analysis of biochemical parameters. Lead levels were determined in whole blood samples using Inductively Coupled Plasma Mass Spectrometry (Agilent 7700 series, Tokyo, Japan). Blood samples were digested using the microwave-induced acid digestion method. Standard solutions of lead were prepared by diluting certified standard solutions (High purity Standards, Charleston, SC, USA). Two level quality control materials were used (Seronorm, Billingstad, Norway). The lead calibration curve ranged from 0 to 100 μg/dL. The limit of detection and limit of quantification were 0.02 and 0.1 μg/dL, respectively.

Evaluation of erectile function

Erectile function and severity of dysfunction were assessed according to the National Institutes of Health criteria with the IIEF-5 Questionnaire, which has been widely used in epidemiologic and clinical studies.[10] The IIEF-5 Questionnaire consists of questions about erection confidence, erection firmness, maintenance ability, maintenance frequency, and satisfaction. Each item is scored on a five-point scale with a low score representing poorer sexual status and a higher score indicating better sexual function. The minimum score was 5 and maximum score was 25. Subjects with IIEF-5 scores < 22 were considered as having ED, and those with scores ≥ 22 as having normal erectile function. The workers with ED were further classified into four groups according to the IIEF-5 Questionnaire as severe ED (5-7), moderate ED (8-11), mild-moderate ED (12-16), and mild ED (17-21). The internal consistency of the IIEF-5 Questionnaire was adequate with a Cronbach's alpha of 0.94. In the study population, the test-retest reliability was adequate with an intra-class correlation coefficient for agreement of 0.91.

Transthoracic echocardiography

Standard TTE imaging was performed using an ESAOTE cardiac ultrasound scanner (Indianapolis, IL) by the same physician blinded to clinical information according to the recommendations of the American Society of Echocardiography.[16] Images were obtained using a 2.5-3.5 MHz transducer in the left lateral decubitus position in parasternal and apical views. Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were determined with M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view. Left ventricular (LV) endocardial borders were manually traced at end-diastole and end-systole in apical 2- and 4-chamber views, and left ventricular ejection fraction (LVEF) was calculated according to the modified biplane Simpson's rule. In cases where the Simpson's method could not be used, LVEF was calculated using the Teicholz method. Left atrial (LA) volume was obtained using the biplane area-length method from apical 4- and 2-chamber views at end-systole just prior to mitral valve opening, and was corrected for body surface area and recorded in mL/m^2 (LA volume index, LAVI).

Mitral inflow velocities were measured using pulsed wave Doppler from the apical 4-chamber view positioned at the tips of the mitral leaflets at end-expiration. The peak early filling velocity (E wave), peak filling velocity during atrial systole (A wave), the E/A ratio, and the deceleration time (DT) of the early filling velocity were calculated. The isovolumic relaxation time (IVRT) was derived using pulsed wave Doppler by placing the cursor in the LV outflow and mitral inflow simultaneously, and recorded as the time interval between aortic valve closure and mitral valve opening. The peak early diastolic tissue velocity (e') of the mitral annulus was measured from the 4-chamber view. The sample volume was positioned on the septal (medial) and lateral insertion sites of the mitral valve. At least three consecutive measurements were obtained, and thee' wave was recorded as the average of septal and lateral measurements. The E/e' ratio was calculated as E wave divided by e'.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 20 (SPSS 20) for Windows (IBM SPSS Inc., Chicago, IL). Variables with normal distribution were presented as mean ± standard deviation, and those without normal distribution were presented as median with minimum and maximum range. Categorical variables were presented as number and percentage. Comparisons between groups of continuous variables were performed using the t-test for independent variables showing normal distribution and the Mann-Whitney U test for those not showing normal distribution. Variables showing significant differences between the lead-exposed workers and control subjects were included in correlation analysis. Pearson's correlation analysis was used to test normal distribution, while Spearman's correlation analysis was used for variables not showing normal distribution. In the lead-exposed group, variables showing significant correlations were further included in regression analysis for dedicated parameters (IIEF-5 score, e' wave and E/e' ratio) in order to test whether or not they might be independent risk factors. For this purpose, stepwise linear regression analysis was used for multivariate regression analysis. Before this analysis, logarithmic transformation was performed of parameters that did not show normal distribution. In the lead-exposed group, the Mann-Whitney U test was used to test the significance of multi-group differences using Bonferroni correction to adjust for multiple comparisons. A p value below 0.05 was considered to be statistically significant.

RESULTS

The baseline demographic, clinical, laboratory and echocardiographic parameters of the 94 lead-exposed workers and 30 control subjects are shown in Table 1. There were no statistical differences between the groups in terms of age, systolic and diastolic BP, weight, height, BMI, laboratory findings, LVEDD, LVESD and LVEF. The mean age was 32.3 ± 6.4 years in the lead-exposed workers and 33.1 ± 6.8 years in the control subjects. The mean E and e' waves and E/A ratio were significantly lower in the lead-exposed workers, whereas mean A wave, E/e' ratio and LAVI were significantly higher in the lead-exposed workers. The median blood lead level (BLL) was 19 μg/dL (minimum 3.2 and maximum 89.6 μg/dL) in the workers and 0.5 μg/dL (minimum 0.1 and maximum 1.7 μg/dL) in the control subjects. The mean IIEF-5 score was lower in the workers (17.0 ± 6.1) than in the control subjects (22.7 ± 2.1).

According to the IIEF-5 questionnaire, of the 94 lead-exposed workers, 29 (30.9%) had normal erectile function (non-ED workers) and 65 (69.1%) had ED. In the control group, 9 subjects (30%) had ED. In the workers with ED, the BLL [median 25.4 μg/dL (3.2-89.6) vs. 14.4 μg/dL (4.6-71.7), p = 0.001] and LAVI (33.2 ± 3.2 vs. 31.1 ± 3.3 mL/m^2, p = 0.007) were significantly higher than in the non-ED workers. In addition, the IIEF-5 score was lower in the workers with ED than in those without ED (14.1 ± 5.2 vs. 23.5 ± 1.0, p < 0.001). There were no significant differences in the other demographic, clinical, laboratory and echocardiographic characteristic between the workers with and without ED (Table 2).

Of the 65 ED workers, 10 (10.6%) had severe, 13 (13.8%) had moderate, 17 (18.1%) had mild-moderate, and 25 (26.6%) had mild ED. The demographic, clinical and echocardiographic parameters of the five groups

Table 1. Baseline demographic, clinical, laboratory and echocardiographic characteristics of lead exposed workers and control subjects

Characteristics	Lead exposed workers (n = 94)	Control subjects (n = 30)	p value
Age (years)	32.3 ± 6.4	33.1 ± 6.8	0.575
Systolic blood pressure (mmHg)	122.1 ± 9.8	119.5 ± 10.8	0.258
Diastolic blood pressure (mmHg)	73.5 ± 7.0	72.5 ± 7.4	0.483
Weight (kg)	77.2 ± 10.9	74.3 ± 6.8	0.091
Height (m)	1.73 ± 0.07	1.72 ± 0.06	0.267
Body mass index (kg/m^2)	25.5 ± 3.5	25.0 ± 2.4	0.358
Hemoglobin (g/dL)	15.0 ± 1.3	14.8 ± 1.2	0.288
Fasting blood glucose (mg/dL)	91.3 ± 15.5	92.8 ± 14.2	0.638
Total cholesterol (mg/dL)	158.7 ± 34.9	167.9 ± 26.0	0.127
Low density lipoprotein (mg/dL)	83.9 ± 28.0	91.9 ± 16.7	0.142
High density lipoprotein (mg/dL)	45.6 ± 10.5	48.9 ± 11.8	0.182
Triglyceride (mg/dL)	139.0 ± 44.9	143.2 ± 49.5	0.681
LV end diastolic diameter (cm)	4.6 ± 0.4	4.6 ± 0.3	0.671
LV end systolic diameter (cm)	2.8 ± 0.3	2.8 ± 0.4	0.638
LV ejection fraction (%)	64.4 ± 3.1	63.9 ± 3.1	0.446
E wave (cm/s)	102.8 ± 10.3	112.4 ± 7.7	< 0.001
A wave (cm/s)	103.7 ± 15.6	87.5 ± 10.2	< 0.001
E/A ratio	1.00 ± 0.15	1.30 ± 0.19	< 0.001
e' wave (cm/s)	10.8 ± 1.9	13.2 ± 1.0	< 0.001
E/e' ratio	9.7 ± 1.7	8.5 ± 0.8	< 0.001
Isovolumic relaxation time (ms)	83.1 ± 7.9	80.3 ± 6.7	0.072
Deceleration time (ms)	184.2 ± 14.3	180.4 ± 14.7	0.227
Left atrial volume index (mL/m^2)	32.6 ± 3.4	29.2 ± 1.9	< 0.001
IIEF-5 score	17.0 ± 6.1	22.7 ± 2.1	< 0.001
Blood lead level (μg/dL)	19 [3.2-89.6]	0.5 [0.1-1.7]	< 0.001

IIEF, international index of erectile function; LV, left ventricle.
The results shown as mean ± standard deviation or median [minimum-maximum].

Table 2. Demographic, clinical, laboratory and echocardiographic parameters according to the presence of ED in lead exposed workers

Characteristics	Without ED (n = 29)	With ED (n = 65)	p value
Age (years)	33.0 ± 6.6	32.0 ± 6.4	0.538
Systolic blood pressure (mmHg)	121.5 ± 11.2	122.3 ± 9.2	0.733
Diastolic blood pressure (mmHg)	72.8 ± 7.6	73.9 ± 6.8	0.511
Weight (kg)	80.4 ± 9.8	77.7 ± 11.1	0.137
Height (m)	1.74 ± 0.06	1.73 ± 0.07	0.849
Body mass index (kg/m^2)	26.5 ± 2.7	25.7 ± 3.7	0.069
Hemoglobin (g/dL)	14.9 ± 1.33	15.1 ± 1.28	0.476
Fasting blood glucose (mg/dL)	92.0 ± 10.6	90.7 ± 17.3	0.707
Total cholesterol (mg/dL)	162.6 ± 27.8	157.0 ± 37.7	0.420
Low density lipoprotein (mg/dL)	86.9 ± 27.1	82.5 ± 28.5	0.480
High density lipoprotein (mg/dL)	46.0 ± 9.1	45.4 ± 11.1	0.802
Triglyceride (mg/dL)	152.4 ± 49	133.0 ± 41.7	0.073
LV end diastolic diameter (cm)	4.6 ± 0.3	4.6 ± 0.3	0.603
LV end systolic diameter (cm)	2.8 ± 0.3	2.8 ± 0.3	0.526
LV ejection fraction (%)	64.3 ± 3.6	64.5 ± 2.9	0.769
Interventricular septum thickness (cm)	0.97 ± 0.14	0.95 ± 0.11	0.457
Posterior wall thickness (cm)	0.90 ± 0.11	0.91 ± 0.13	0.719
E wave (cm/s)	102.0 ± 11.3	103.2 ± 9.9	0.635
A wave (cm/s)	105.1 ± 16.6	103.1 ± 15.2	0.587
E/A ratio	0.98 ± 0.15	1.01 ± 0.15	0.378
e' wave (cm/s)	11.4 ± 2.1	10.6 ± 1.76	0.105
E/e' ratio	9.2 ± 1.8	9.9 ± 1.7	0.070
Isovolumic relaxation time (ms)	82.8 ± 7.9	83.1 ± 8.0	0.842
Deceleration time (ms)	184.5 ± 14.6	184.1 ± 14.3	0.913
Left atrial volume index (mL/m^2)	31.1 ± 3.3	33.2 ± 3.2	0.007
IIEF-5 score	23.5 ± 1.0	14.1 ± 5.2	< 0.001
Blood lead level (μg/dL)	14.4 [4.6-71.7]	25.4 [3.2-89.6]	0.001
Serum testosterone level (ng/dL)	420.5 ± 89.1	408.4 ± 99.1	0.639
Serum prolactin level (ng/dL)	7.1 ± 1.9	7.6 ± 2.1	0.275

ED, erectile dysfunction; IIEF, international index of erectile function; LV, left ventricle.
The results shown as mean ± standard deviation or median [minimum-maximum].

are shown in Table 3. The mean IIEF-5 score was 5.5 ± 0.9 in the severe ED, 10.0 ± 0.9 in the moderate ED, 14.6 ± 1.4 in the mild-moderate ED, 19.5 ± 1.4 in the mild ED, and 23.5 ± 1.0 in the non-ED workers. The median BLL was 42.45 μg/dL (range, 24.4-89.6 μg/dL) in the severe ED, 28.2 μg/dL (range, 9.5-63.9 μg/dL) in the moderate ED, 26.5 μg/dL (range, 10.3-64 μg/dL) in the mild-moderate ED, 17.4 μg/dL (range, 3.2-62.9 μg/dL) in the mild ED, and 14.4 μg/dL (range, 4.6-71.7 μg/dL) in the non-ED workers. The difference in BLL between the groups was statistically significant ($p < 0.001$), mainly driven by the severe ED group in post hoc analysis. With regards to the echocardiographic parameters, E/e' ratio ($p = 0.021$) and LAVI ($p = 0.043$) were found to be different between the groups. In post hoc analysis, most significant differences originated from the severe ED group in terms of E/e' ratio, and the non-ED group in terms of LAVI. There were no significant differences in age, systolic and diastolic BP, BMI and other echocardiographic parameters including LVEDD, LVESD, LVEF, E wave, A wave, E/A ratio, e' wave, IVRT and DT between the groups. Serum testosterone (420.5 ± 89.1 ng/dL vs. 408.4 ± 99.1 ng/dL, $p = 0.639$) and prolactin (7.1 ± 1.9 ng/dL vs. 7.6 ± 2.1 ng/dL, $p = 0.275$) levels were similar between the ED workers and non-ED workers, respectively.

Correlation analysis

In the lead-exposed workers overall, BLL was significantly negatively correlated with IIEF-5 score (r = -0.495, p < 0.001) (Figure 1A) and e' wave (r = -0.402, p < 0.001) (Figure 1B), and positively correlated with E/e' ratio (r = 0.406, p < 0.001) (Figure 1C). In addition, the IIEF-5 score was significantly positively correlated with e' wave (r = 0.329, p = 0.002) (Figure 2A), and significantly negatively correlated with E/e' ratio (r = -0.358, p < 0.001) (Figure 2B) and LAVI (r = -0.301, p = 0.004) (Figure 2C).

In the non-ED workers (IIEF-5 score ≥ 22), there were no significant correlations between IIEF-5 score and BLL, age, BMI, systolic and diastolic BP or any of the echocardiographic parameters. On the other hand, in the workers with ED (IIEF-5 score < 22), IIEF-5 score was negatively correlated with E/e' ratio (r = -0.404, p = 0.001) and BLL (r = -0.435, p < 0.001), and positively correlated with e' wave (r = 0.359, p = 0.003). In this group, BLL was positively correlated with E/e' ratio (r = 0.322, p = 0.009), and negatively correlated with e' wave (r = -0.381, p = 0.001).

Table 3. Demographic, clinical and echocardiographic characteristics according to the IIEF-5 score groups

Characteristics	Severe ED (Score 5-7) (n = 10)	Moderate ED (Score 8-11) (n = 13)	Mild-moderate ED (Score 12-16) (n = 17)	Mild ED (Score 17-21) (n = 25)	Non-ED group (Score 22-25) (n = 29)	p value
Age (years)	28.3 ± 4.3	31.7 ± 6.0	32.6 ± 7.0	33.4 ± 6.5	33.0 ± 6.6	0.285
IIEF score	5.5 ± 0.8	10.0 ± 0.9	14.6 ± 1.4	19.5 ± 1.4	23.5 ± 1.0	< 0.001
Systolic BP (mmHg)	126.7 ± 9.8	122.0 ± 9.0	120.7 ± 9.7	121.8 ± 8.8	121.5 ± 11.2	0.636
Diastolic BP (mmHg)	75.7 ± 5.1	75.6 ± 5.5	70.1 ± 8.0	74.8 ± 6.5	72.8 ± 7.6	0.129
BMI (kg/m^2)	23.7 ± 4.0	25.3 ± 3.6	25.5 ± 3.6	25.3 ± 3.9	26.5 ± 2.7	0.255
Blood lead level (μg/dL)	42.45 [24.4-89.6]	28.2 [9.5-63.9]	26.5 [10.3-64]	17.4 [3.2-62.9]	14.4 [4.6-71.7]	< 0.001
LV EDD (mm)	4.7 ± 0.2	4.8 ± 0.2	4.5 ± 0.2	4.6 ± 0.3	4.6 ± 0.3	0.096
LV EDD (mm)	2.7 ± 0.3	2.7 ± 0.4	2.8 ± 0.2	2.8 ± 0.3	2.8 ± 0.3	0.638
LV EF (%)	65.4 ± 2.7	63.8 ± 3.2	65.1 ± 3.4	64.1 ± 3.4	64.3 ± 3.6	0.629
E wave (cm/s)	107.4 ± 10.3	102.4 ± 9.1	101.0 ± 8.9	103.3 ± 10.9	102.0 ± 11.3	0.619
A wave (cm/s)	98.0 ± 21.5	100.6 ± 19.0	105.1 ± 12.3	105.1 ± 12.0	105.1 ± 16.6	0.671
E/A ratio	1.12 ± 0.16	1.04 ± 0.18	0.96 ± 0.10	0.99 ± 0.14	0.98 ± 0.15	0.070
e' wave (cm/s)	9.7 ± 1.3	10.1 ± 1.7	10.7 ± 1.9	11.2 ± 1.6	11.4 ± 2.1	0.079
E/e' ratio	11.1 ± 1.5	10.3 ± 1.7	9.6 ± 1.8	9.4 ± 1.4	9.2 ± 1.8	0.021
IVRT (ms)	80.2 ± 6.9	84.0 ± 8.5	82.3 ± 9.1	84.5 ± 7.4	82.8 ± 7.9	0.652
DT (ms)	181.6 ± 15.6	181.3 ± 16.6	187.5 ± 12.5	184.1 ± 14.0	184.5 ± 14.6	0.788
LAVI (mL/m^2)	33.9 ± 2.4	34.1 ± 3.8	32.6 ± 3.7	32.8 ± 2.8	31.1 ± 3.3	0.043

BMI, body mass index; BP, blood pressure; DT, deceleration time; ED, erectile dysfunction; EDD, end-diastolic diameter; EF, ejection fraction; IIEF, international index of erectile function; IVRT, isovolumic relaxation time; LAVI, left atrial volume index; LV, left ventricular. The results shown as mean ± standard deviation or median [minimum-maximum].

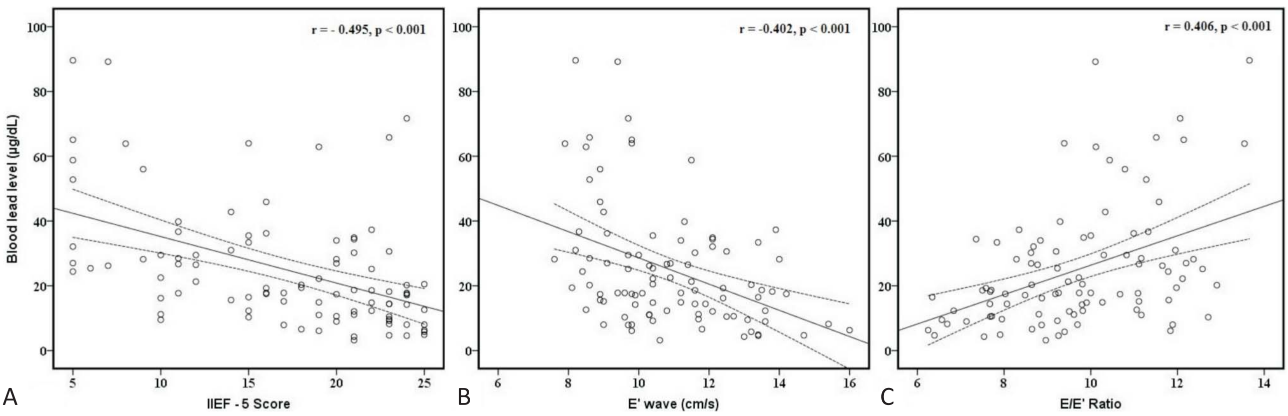

Figure 1. *Correlation of BLL with (A) IIEF-5 score, (B) e' wave and (C) E/e' ratio.*

Regression analysis

Multivariate stepwise linear regression analysis (Table 4) showed that BLL was an independent risk factor for decreased e' wave (β = -1.142, p < 0.001) and increased E/e' ratio (β = 1.053, p < 0.001) in all lead-exposed workers. Additionally, a higher BLL (β = -3.732, p < 0.001) and increased LAVI (β = -0.386, p = 0.019) were found to be independent risk factors for lowering the IIEF-5 score in all lead-exposed workers. On the other hand, a higher BLL (β = -3.470, p < 0.001) and decreased e' wave (β = 0.804, p = 0.010) were found to be independent risk factors for lowering the IIEF-5 score in the workers with ED.

DISCUSSION

In this study, the effects of lead exposure on the prevalence and severity of ED and diastolic function were analyzed, and a close relationship was observed

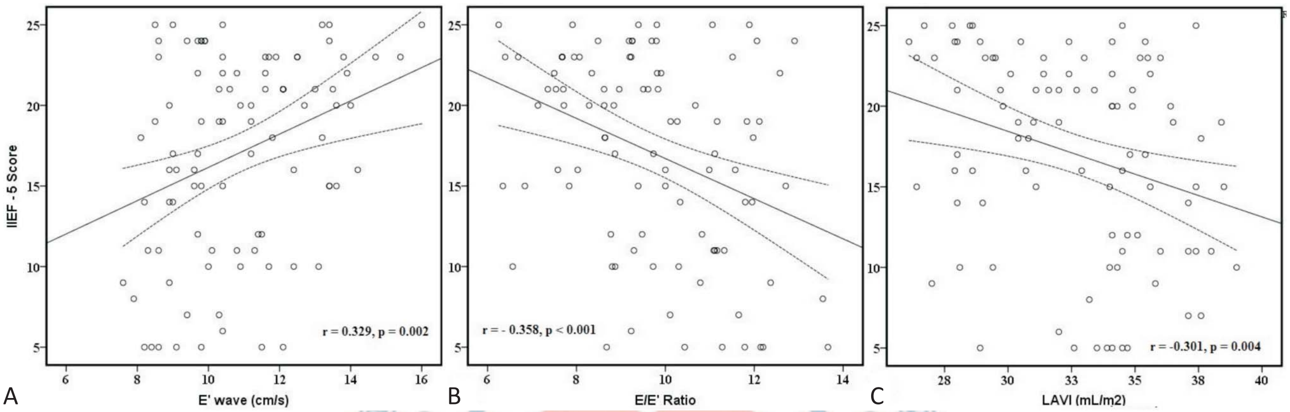

Figure 2. *Correlation of IIEF-5 score with (A) e' wave, (B) E/e' ratio and (C) LAVI.*

Table 4. Multivariate stepwise linear regression analysis results for determination of predictors of e' wave, E/e' ratio and IIEF-5 score in lead exposed workers

	β ± SE	95% CI		p value
		Lower	Upper	
e' wave[a]				
Blood lead level (μg/dL)*[#]	-1.142 ± 0.244	-1.627	-0.658	< 0.001
		R^2 = 0.192, Adjusted R^2 = 0.184, p < 0.001		
E/e' ratio[a]				
Blood lead level (μg/dL)*[†]	1.053 ± 0.224	0.607	1.498	< 0.001
		R^2 = 0.223, Adjusted R^2 = 0.206, p < 0.001		
IIEF-5 Score [a]				
Blood lead level (μg/dL)*[‡]	-3.732 ± 0.752	-5.227	-2.237	< 0.001
LAVI (mL/m^2)[‡]	-0.386 ± 0.161	-0.706	-0.066	0.019
		R^2 = 0.337, Adjusted R^2 = 0.315, p < 0.001		
IIIEF-5 Score [b]				
Blood lead level (μg/dL)*[§]	-3.470 ± 0.766	-5.004	-1.937	< 0.001
e' wave (cm/s)[§]	0.804 ± 0.303	0.197	1.411	0.010
		R^2 = 0.514, Adjusted R^2 = 0.464, p < 0.001		

CI, confidence interval; IIEF, international Index of Erectile Function; LAVI, left atrial volume index; R, model fit; SE, standard error; β, regression coefficients.

Regression analysis ([a]) in lead exposed workers and ([b]) in workers with erectile dysfunction. *, Logaritmic transformation was applied to blood lead level in order to obtain normal distribution.

Regression analysis was performed in parameters among [#] E/e' ratio, IIEF-5 score and blood lead level; [†] E wave, e' wave, IIEF-5 score and blood lead level; [‡] E/e' ratio, E/A ratio, e' wave, LAVI and blood lead level; [§] blood lead level, E/e' ratio and e' wave.

among BLL, IIEF-5 score and diastolic function. The diastolic function parameters in the lead-exposed workers were worse, the IIEF-5 score was lower and BLL was higher than those in the control subjects. In the workers with ED, BLL and LAVI as important diastolic function parameters were significantly higher than in the non-ED workers. Moreover, increased BLL and LAVI values were observed with increasing severity of ED. In addition, BLL and LAVI in all of the lead-exposed workers and BLL and e' wave in the workers with ED were independent risk factors for the prediction of IIEF-5 score.

Erectile dysfunction affects more than half of all males between the ages of 40 and 70 years.[9] Its prevalence increases with age, and it has similar risk factors of cardiovascular diseases such as DM, HT, and smoking.[17] Although the pathophysiologic process may originate from different neurogenic, endocrinological and psychosocial etiologies, it is emerging as a process of vascular origin. Vasodilatation of the corpus cavernosa, which is necessary for sexual intercourse, decreases with increasing inflammation and oxidative stress and cannot take place sufficiently due to endothelium dysfunction caused by NO synthesis.[18,19] Lead exerts negative effects in the body with similar mechanisms due to its toxicity as a heavy metal. Several studies have reported that the inflammatory process, oxidative stress, endothelial dysfunction and sympathovagal imbalance induced by lead exposure give rise to ED.[11,20] In this study, the prevalence of ED was 69.1% in the 94 lead-exposed workers, and the ED prevalence was 30% in the control group with a similar age and risk profile. The BLL was an independent predictor of IIEF-5 score in the lead-exposed workers overall and the workers with ED. In addition, a significant correlation was observed between ED severity and BLL in the workers with ED. Such a high ED prevalence in these workers with an average age lower than 40 years and low risk profile is a significant finding regarding the negative effects of lead on erectile function.

As a toxic agent, lead has severe negative effects on the human body, primarily on the cardiovascular system after occupational or environmental exposure. The leading negative effects of lead on the cardiovascular system are in BP profile and the atherosclerotic process in the arterial system. Only a few studies have performed echocardiographic examinations on workers exposed to lead. In our study, the E and e' waves and E/A ratio were lower in the lead-exposed workers in comparison to the control subjects, whereas the A wave, E/e' ratio and LAVI were higher. A negative correlation between BLL and e' wave and a positive correlation with the E/e' ratio were observed in the lead-exposed workers overall and the workers with ED. Similarly, Poreba et al.[5] demonstrated worsened systolic and diastolic functions on TTE in patients with occupational exposure to lead. The DT and E/e' ratio in these patients were higher compared to the control subjects, whereas the E/A ratio and e' wave were lower. Additionally, high blood zinc protoporphyrin concentration, which is an indicator of lead exposure, was demonstrated to be a negative independent risk factor for e' wave. In contrast, our study did not show a significant difference between the lead-exposed workers and control subjects regarding systolic function. Although there were significant differences between groups, LAVI, E/e' and e' were still in normal range.

As in many other cardiovascular diseases, a relationship exists between diastolic dysfunction and ED.[15,21] In a study by Uslu et al.,[22] ED patients with no known cardiovascular diseases were compared with a control group, and the E wave, e' wave, and E/A ratio were observed to be significantly lower in the ED patients, whereas the A wave, DT, IVRT and E/e' ratio were significantly higher. Similarly, the IIEF-5 score was positively correlated with e' wave and negatively correlated with E/e' ratio in all workers and the workers with ED in our study. Additionally, LAVI was an independent predictor for the IIEF-5 score in the lead-exposed workers overall, whereas e' wave was an independent predictor for the IIEF-5 score in the workers with ED. It is very important that the average age of the ED patients in our study was 32 years in contrast to the 50-year age average in the aforementioned studies. The negative effects of lead on diastolic and erectile function were demonstrated in addition to the fact that lead can be a risk factor equivalent to HT, DM and smoking.

Lead exposure mediates tissue damage through inflammation and oxidative stress.[23] Oxidative stress is known to produce proinflammatory mediators and reactive oxygen species and inhibit NO, which can initiate inflammatory processes by causing damage to cell membranes through lipid peroxidation and cause an increase in sympathetic and a reduction in vagal activity.[24,25] All of these processes also have an adverse influence on diastolic and erectile function. Thus, endothelial dysfunction characterized by NO inhibition and inflammation and sympathovagal imbalance may play a key role on the relationship between lead exposure, diastolic dysfunction and ED.[26,27]

The cut-off value of BLL that indicates lead intoxication is still under debate.[28,29] No cut-off value was used in our study. The workers were evaluated with regards to their "lead exposure" independent from their BLL. Even though many people are exposed to lead in their daily and occupational lives, the presumption of a "normal value" for lead, which is a toxic and heavy metal is controversial. The cut-off values specified in the literature are used for the determination of exposure severity. Therefore, the investigation of individuals in regard to their clinic outcomes in respect to exposure might be a more correct approach than investigating BLL.

Limitations of the study

Nearly 95% of the total body lead burden is located in bone.[30] In this study, we only analyzed BLL which reflects only relatively recent exposure. Bone and urine lead levels, which may better predict long-term lead toxicity than BLL, were not measured. To control for possible confounding factors, strict exclusion criteria were applied at the beginning of the study, and only the effects of BLL were evaluated. Eventually, an extremely homogeneous group was obtained, and this restricts the real world applicability and reduces the generalizability of the findings. The small sample size and cross-sectional design are other limitations of our study. Furthermore, more precise methods such as strain and strain rate were not evaluated. Finally, it is important to note that the relationship between left ventricular diastolic dysfunction and ED cannot be inferred from this cross-sectional study alone.

CONCLUSIONS

Erectile and diastolic functions were closely associated with lead exposure. Disruption of diastolic and erectile functions, despite a low average age and in the absence of accompanying cardiovascular diseases or risk factors, were shown to be correlated with increased BLL. In addition, this is the first study to report a close relationship between diastolic dysfunction and ED in a population exposed to lead. Subjects exposed to lead should be closely screened for cardiac and reproductive functions.

REFERENCES

1. Jain NB, Potula V, Schwartz J, et al. Lead levels and ischemic heart disease in a prospective study of middle-aged and elderly men: the VA Normative Aging Study. *Environ Health Perspect* 2007; 115:871-5.
2. Lee TH, Tseng MC, Chen CJ, Lin JL. Association of high body lead store with severe intracranial carotid atherosclerosis. *Neurotoxicology* 2009;30:876-80.
3. Nomiyama K, Nomiyama H, Liu SJ, et al. Lead induced increase of blood pressure in female lead workers. *Occup Environ Med* 2002; 59:734-8.
4. Tsaih SW, Korrick S, Schwartz J, et al. Lead, diabetes, hypertension, and renal function: the normative aging study. *Environ Health Perspect* 2004;112:1178-82.
5. Poreba R, Gac P, Poreba M, Mazur G. Echocardiographic assessment of myocardial function in workers occupationally exposed to lead without clinically evident heart disease. *Environ Toxicol Pharmacol* 2013;36:522-8.
6. Chang HR, Tsao DA, Yu HS, Ho CK. The change of beta-adrenergic system after cessation of lead exposure. *Toxicology* 2005;207: 73-80.
7. Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. *Am J Physiol Heart Circ Physiol* 2008;295:H454-65.
8. Dursun N, Arifoglu C, Suer C, Keskinol L. Blood pressure relationship to nitric oxide, lipid peroxidation, renal function, and renal blood flow in rats exposed to low lead levels. *Biol Trace Elem Res* 2005;104:141-9.
9. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
10. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11:319-26.
11. Gonulalan U, Hayirli A, Kosan M, et al. Erectile dysfunction and depression in patients with chronic lead poisoning. *Andrologia* 2013;45:397-401.
12. Yuksel IO, Koklu E, Kurtoglu E, et al. The association between serum ferritin level, tissue doppler echocardiography, cardiac T2* MRI, and heart rate recovery in patients with beta thalassemia major. *Acta Cardiol Sin* 2016;32:231-8.
13. Yu HP, Jen HL, Yin WH, Wei J. Circulating adiponectin levels following treatment can predict late clinical outcomes in chronic heart failure. *Acta Cardiol Sin* 2017;33:139-49.
14. Lin YS, Liu PH, Chu PH. Obstructive sleep apnea independently

increases the incidence of heart failure and major adverse cardiac events: a retrospective population-based follow-up study. *Acta Cardiol Sin* 2017;33:656-63.
15. El-Sakka AI, Morsy AM, Fagih BI. Severity of erectile dysfunction could predict left ventricular diastolic dysfunction in patients without overt cardiac complaint. *J Sex Med* 2011;8:2590-7.
16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
17. Rosen RC, Fisher WA, Eardley I, et al. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. prevalence of erectile dysfunction and related health concerns in the general population. *Curr Med Res Opin* 2004;20:607-17.
18. Bahouth Z, Zreik R, Graif A, et al. Endothelial function assessment in patients with erectile dysfunction. *Isr Med Assoc J* 2015; 17:682-6.
19. Agarwal A, Nandipati KC, Sharma RK, et al. Role of oxidative stress in the pathophysiological mechanism of erectile dysfunction. *J Androl* 2006;27:335-47.
20. Anis TH, ElKaraksy A, Mostafa T, et al. Chronic lead exposure may be associated with erectile dysfunction. *J Sex Med* 2007;4:1428-34.
21. Zengin K, Ede H, Tanik S, et al. Cardiac factors affecting the success of vardenafil in erectile dysfunction. *Turk J Med Sci* 2015; 45:751-7.
22. Uslu N, Eren M, Gorgulu S, et al. Left ventricular diastolic function and endothelial function in patients with erectile dysfunction. *Am J Cardiol* 2006;97:1785-8.
23. Iavicoli I, Carelli G, Stanek EJ 3rd, et al. Below background levels of blood lead impact cytokine levels in male and female mice. *Toxicol Appl Pharmacol* 2006;210:94-9.
24. Sirivarasai J, Wananukul W, Kaojarern S, et al. Association between inflammatory marker, environmental lead exposure, and glutathione S-transferase gene. *Biomed Res Int* 2013;2013:474963.
25. Vaziri ND, Khan M. Interplay of reactive oxygen species and nitric oxide in the pathogenesis of experimental lead-induced hypertension. *Clin Exp Pharmacol Physiol* 2007;34:920-5.
26. Ma LN, Zhao SP, Gao M, et al. Endothelial dysfunction associated with left ventricular diastolic dysfunction in patients with coronary heart disease. *Int J Cardiol* 2000;72:275-9.
27. Uslu N, Gorgulu S, Alper AT, et al. Erectile dysfunction as a generalized vascular dysfunction. *J Am Soc Echocardiogr* 2006;19: 341-6.
28. Lustberg M, Silbergeld E. Blood lead levels and mortality. *Arch Intern Med* 2002;162:2443-9.
29. Moreira Mde F, Neves EB. Use of urine lead level as an exposure indicator and its relationship to blood lead. *Cad Saude Publica* 2008;24:2151-9.
30. Barry PS, Mossman DB. Lead concentrations in human tissues. *Br J Ind Med* 1970;27:339-51.