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Altered Serum Lipids and Paraoxonase Activity: A Step toward Atherosclerosis among Lead Exposed Egyptian Workers

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Abstract: A vast amount of evidence during the past decade, has confirmed that lead is associated with lipid and lipoprotein abnormalities which play a major role in the pathogenesis and progression of atherosclerosis and cardiovascular diseases. This study aimed: to investigate the relationship between chronic occupational lead exposure, lipid profile, and serum PON1 activity as one of the mechanisms of atherosclerosis. Male workers (n=100) in lead battery manufactory were recruited for this study. They were compared with 100 male age matched non-lead workers. Serum lipid profile and paraoxonase activity were done to their samples. Serum Lead was determined vsing atomic absorption spectroscopy. There was significant differences regarding triglycerides, total cholesterol, and HDL- c (p=0.01, 0.05 and 0.04, respectively) between both groups. A cumulative effect of blood lead on lipid profile was significantly detected. Multiple linear regression analysis showed that blood lead level was the only negative significant predictors to serum paraoxonase activity (p=0.03) in lead workers. lead exposure is associated with increased triglycerides, total cholesterol and LDL-c and decrease HDL-c. Because of the protective role of PON1 in the development of atherosclerosis, decrease in serum PON1 activity due to lead exposure may render individuals more susceptible to atherosclerosis.

INTRODUCTION

Lead exposure is a well known occupational health hazard. The continuous lead over exposure and lead poisoning remains a serious problem in Egypt especially among workers of battery and recycling factories.(1) Multiple morphological and biochemical changes in the cardiovascular system, various organs and blood are documented with chronic lead exposure.(2) Also it is associated with altered lipid metabolism especially serum cholesterol and lipoprotein levels in

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both humans and animals. [3-6]

Atherosclerosis is a chronic disease that is caused by damage to the arterial wall from inflammation and fibro-fatty deposits.[7] A vast amount of evidence during the past decade, has confirmed that lipid and lipoprotein abnormalities play a major role in the pathogenesis and progression of atherosclerosis and cardiovascular diseases.[8,9]

Cholesterol is a key component in the development of atherosclerosis. An inverse correlation between the serum concentration of HDL-c (high density lipoprotein cholesterol) and the development of atherosclerosis has long been known.[10] Several laboratories have reported that HDL-c protects against LDL-c (low density lipoprotein cholesterol) oxidation.[11,12] which is the main step in initiation and progression of atherosclerosis.[13] The anti-atherogenic properties of HDL-c are partially due to the activity of HDL-associated enzymes, which prevent and/or reverse LDL oxidation. [14] One of those enzymes is the calcium-dependent ester hydrolase paraoxonase (PON1) which is found tightly associated with the HDL particle.[15]

Paraoxonase-1 (PON1) is a protein of 354 amino acids with a molecular mass of 43 kilo Dalton. Multiple factors can affect PON1 levels and thus interfering with its protective function.[16] Previous studies have shown that various metals, including lead even at low concentrations < 1 µg/dl, caused significant inhibition of PON1 activity in vitro.[17,18] and in vivo.[19]

The aim of the present study was to investigate the relationship between chronic occupational lead exposure, lipid profile, and serum PON1 activity as one of the mechanisms of atherosclerosis

SUBJECTS AND METHODS

This cross sectional study was conducted from June 2008 till May 2009.

Subjects

1. Occupational lead exposed group

(group A): 100 male workers in a lead-acid battery manufactory in Cairo, Egypt were recruited for this study. Those with diabetes mellitus, thyrotoxicosis, renal disease, or smokers were excluded from the study.

2. Occupational non lead exposed group (group B): 100 Kasr Al-Aini male workers who are matched with group A as regard age and social class were similarly investigated.

Methods

All patients were informed about the aim of the study and approval by all workers through written consent was obtained before study set up. Both groups were subjected to:

1. History with special emphasis on age, and duration of their occupation.
2. Examination was done for blood pressure measurements (Hypertension was considered as systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg according to American Heart association.[20]
3. Blood lipid as well as blood lead, in addition to PON1 activity were measured for all the sample participants.

3-1 Ten ml of fresh blood samples were withdrawn and collected on-site during the health examination. Each sample was divided into 2 tubes: one on EDTA (lead free) tube for measurement of blood lead- all samples were stored at −20°C until measurement. The second aliquot was obtained in plain tube. The sera were separated for analysis of lipid profile and PON1 activity immediately on the same day. All lab tests were done in chemical pathology department, faculty of medicine, Cairo university

3-2 Total cholesterol, triglycerides and HDL–c were measured for all workers by an automated enzymatic assay on

Hitachi 917.[21] by a kit purchased from Roche (Roche Diagnostics GmbH, D-68298 Mannheim. Germany). LDL-c was calculated using Friedwald's formula.[22] Regarding the blood lipid, total cholesterol < 200 mg/dl; triglycerides < 150 mg/dl; HDL > 40 mg/dl and LDL < 100 mg/dl, are considered favorable profile according to the guidelines of risk factors for cardiovascular disease given by the American Heart Association.[20]

3-3 Blood lead was analyzed by a Zeeman Effect graphite furnace atomic absorption spectroscopy; PerkinElmer AS 800 auto-sampler (PerkinElmer, Wellesley, MA, USA).[23] According to the U.S. Occupational Safety and Health Administration [OSHA][24] workers were classified into:

Group I: subjects with blood lead level < 40 ug/dl

Group II: subjects with blood lead level 40 - 59 ug/dl

Group III: subjects with blood lead level ≥ 60 ug/dl

3-4 PON1 paraoxonase activity was measured spectrophotometrically[25] using 1.2 mM paraoxon (O, O-diethyl p-nitrophenyl phosphate); in 50 mM Tris/HCl buffer (pH 6.8) containing 1.0 mM CaCl2. These chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA). The rate of generation of p-nitrophenol was monitored at 25°C with a continuously recording spectrophotometer at 405 nm (RA 50, Chemistry analyzer, Bayer, Chemical Heritage Foundation, 315 Chestnut Street, Philadelphia, PA 19106). PON1 activity was expressed as micromoles of hydrolysis product formed per minute per liter.

3-4-1 Calculation:

PON activity (nmol) = $[(\Delta Abs/min) \times (1/\varepsilon)(tv/sv) \times (1/d)] \times 10^9$

Where $\Delta Abs/min$ is blank-corrected change in absorbance/min, ε is the

molar absorbance coefficient, (7480 litre · mol^{-1} · cm^{-1}), tv is the total reaction volume (0.3 ml), sv is the sample reaction volume (0.04 ml), and d is the light path (0.6 cm). The conversion of molar into nanomolar absorbance coefficient (in litre · mol^{-1} · cm^{-1}) was achieved through multiplying by 10^9.

Statistical analysis:

Data obtained from the study was coded and entered using the software SPSS (Statistical package for social science) version11.0. Quantitative parametric data was summarized using mean and standard deviation, while non parametric data was summarized as median and percentiles. Frequency and percentages were used for qualitative variables. Comparison between groups was done using chi square for qualitative variables. For quantitative data t-test and Mann Whitney were used to compare two groups, while ANOVA and Kruskal Wallis test were used to compare multiple groups. The correlation between blood lead level and PON1 activity, as well as blood lead level and serum lipids was assessed by Pearson coefficient of correlation. Multiple linear regression analysis was used to test the association between PON1 activity and blood lead level, age, duration of exposure and total cholesterol, HDL-c and LDL-c, and triglycerides. P-value was considered significantiy $p< 0.05$. and highly significant if <0.01.

RESULTS

A total of 100 occupationally lead exposed male workers (group A) with a mean age of 34.6 ± 11.5 years and 100 workers not known to be exposed occupationally to lead (group B) with a mean age of 32.5 ± 13.9 years were evaluated for their blood lead levels, serum lipids, and PON1 activity.

No significant difference was detected between group A and B as regard age, blood pressure values, although higher

systolic and diastolic values were observed among group A. Concerning blood lipids; in spite of normal values among both groups, the lead exposed group showed higher values than the other group. Those values proved significant differences for triglycerides, cholesterol, and HDL- c (p=0.01, 0.05 and 0.04 respectively), while on the other hand, LDL-c demonstrated no significant difference (p=0 .7), as seen in table 1.

The mean ± SD blood lead level of lead exposed group was 45.7 ± 15.3 µg/dL, with a minimum of 17 µg/dL and a maximum of 80 µg/dL, while the blood lead level of non exposed group was 12.5 ± 3.3 µg/dL with a minimum g 5 µg/dL and a maximum of 20 µg/dL. A highly significant difference (p<0.01) was detected between both groups (Table 1). The median value of the paraoxonase activity was highly significantly higher among group A than among group B (987 vs 367.2 umol/ min/L respectively).

Lead exposed workers were divided into 3 groups according to their blood lead levels: group 1 (blood lead ≤ 40 µg/dL), group 2 (blood lead 40–59 µg/dL), and group 3 (blood lead≥ 60) µg/dL). The clinical and biochemical parameters of the studied workers are presented in table 2.

Blood pressure: Systolic and diastolic blood pressures of the subjects were in the normotensive range. The workers in group 3 had a borderline high systolic blood pressure (134.3 ± 24.4 mmHg). However, statistical analyses revealed no significant difference in both the systolic and diastolic blood pressures between the three groups (p > 0.05).

Plasma lipid profiles: Table 2 demonstrated that, with a few exceptions, the values of the lipids were within the reference ranges prescribed by the American Heart Association. Total cholesterol showed gradual increase among groups reaching its highest (normal) level in group 3 with significant

differences between group 1 and the other two groups as well as between groups 2 and 3. HDL-c showed gradual decrease as the blood lead level increases with a significant difference between groups 2 and 3. LDL-c was above the reference range in group 3, meanwhile significant differences were detected between group 1 and group 3. On the other hand, triglyceride concentrations were not significantly different between the three groups ($p > 0.05$). A positive significant correlations were observed between blood lead and total cholesterol ($r = 0.3$; $p=0.05$) and blood lead and LDL cholesterol ($r = 0.3$; $p = 0.04$), while, non significant negative correlation was found between blood lead and HDL-c($r=-0.2$; $p=0.1$)

Paraoxonase activity: A significant difference was observed between the three groups regarding the paraoxonase activity. Gradual decrease in the enzyme activity was obvious as the lead level increased. The activity reached a minimum median value of 300 (100.6-1087 umol/min/L) when lead level was ≥60ug/dl (Table 2). A negative significant correlation was detected between blood lead level and paraoxonase activity as shown in figure 1 ($r=-0.2$; $p=0.03$).

Table 3 represents the prediction of paraoxonase activity. Only the lead level was the significant predictors ($p=0.03$). An increase in the blood lead of 1ug/dl was found to be associated with 5.7 umol/min /L decrease in the paraoxonase activity (Table 3).

DISCUSSION

The present study showed that positive significant correlations existed between blood lead and both, total cholesterol and LDL cholesterol as well as a negative non significant correlation with HDL cholesterol among chronically lead exposed workers (Table 2). Also it illustrated the role of blood lead as the only significant predictor of PON1 activity (Table 3).

The findings of the present study support the findings of others.[1,5,6] and indicate that exposure to lead alters significantly the lipid levels as demonstrated by comparing lead exposed (group A) and non lead exposed (group B) workers (Table1).

Plasma lipoprotein includes four groups (cholesterol, triglycerides, HDL and LDL). HDL and LDL are responsible for lipid metabolism and the exchange of cholesterol and triglycerides between tissues.[9,26]

Numerous population studies have shown an inverse correlation between plasma HDL levels and risk of cardiovascular disease, implying that factors associated with HDL protect against atherosclerosis.[27,28] The cholesterol requirements of most extra-hepatic tissues are supplied by LDL. A major function of HDL cholesterol is to enhance removal of excess cholesterol from peripheral tissues followed by esterification and delivering it to the liver for eventual elimination from the body.[29,30] This role of HDL has been shown to be responsible for its atheroprotective properties. In this study, although all the values of lipid profile were within the reference range, the total cholesterol levels in group A were 1.4 times higher than group B (Table 1). Also a significant difference between both groups were detected in triglyceride level and HDL

This study exhibited the cumulative effect of blood lead level and strengthened the dose response relationship between it and altered lipid profile. Increasing the duration of lead exposure and consequently gradual increase in the blood lead level was associated with a significant increase in cholesterol, LDL-c and a significant decrease in HDL-c. Although correlations do not imply causality, the observation of a significant positive relationship between lead and total cholesterol on one hand, and a significant positive correlation between lead and LDL

cholesterol on the other hand (Table 3), seems to support these findings. These are in accordance with the results of other studies. [1,5,6,19,31]

One of the most important mechanisms by which HDL can prevent atherosclerosis is inhibition of oxidation of LDL as well as the atherogenic effects of oxidised LDL.[30] The paraoxonase enzyme (PON1) resides on high-density lipoprotein (HDL, 'good cholesterol') and is involved in the prevention of atherosclerosis by protecting against LDL-c oxidation.[15] It is to be mentioned that a significant decrease in PON1 activity between lead exposed and non exposed workers was obvious in this study (Table 1). As the blood lead increased, a steady significant decrease in PON1 activity was observed. This represents a reduced protection against LDL oxidation, thereby increasing the accumulation of lipid peroxides and, eventually, promoting atherosclerosis. This was consistent with studies previously performed by Ito et al.[3], Debord et al.[18] and Li et al.[19]

The mechanism by which heavy metals including lead inhibit serum PON1 activity was discussed by Gonzalvo et al.[32] They suggested that metal ions, such as lead, copper and mercury, bind to the free sulfhydryl group of the enzyme and this will reduce not only the hydrolytic activity of PON1 but also its antioxidant function.

According to OSHA rules,[24] workers with blood lead levels greater than 40 µg/dL, must be notified and should be provided with a medical examination. If a worker's blood lead level reaches 60 µg/dL (or averages 50 µg/dL or more on three or more tests), the employer is obligated to remove the employee from excessive exposure, with maintenance of seniority and pay, until his lead level falls below 40 µg/dL. The most striking observation in this study was that workers exhibited blood lead levels greater than 60 µg/dL and they

were still working in their position.

In conclusion, lead exposure is associated with increased triglycerides, total cholesterol and LDL-c and decreased HDL-c. However, the association of these findings with profound cardiovascular damage in lead workers needs to be explored. Also, lead exposure is associated with decreased serum PON1 activity, which is more profound with increased duration of exposure to lead. Because of the protective role of PON1 in the development of atherosclerosis, decrease in serum PON1 activity due to lead exposure may render individuals more susceptible to atherosclerosis. From the above we recommend that enforcement of strict adherence to OSHA rules. Additional researches are required particularly about nutritional and pharmacological effects on serum PON1 activity that might lead to intervention trials to enhance its activity.

Table 1: Compaction between age and blood profile of lead exposed (Group A) and non- exposed (Group B) workers.

Variable	Workers [Mean (SD)]		P value
	Group A (n=100)	Group B (n=100)	
Age (year)	34.6(11.5)	32.5(13.9)	0.3
Blood pressure (mmHg) SBP	132.2(12.9)	130.9(13.9)	0.9
DBP	80.4(10.1)	78.8(9.5)	0.5
Blood Lipid (mg/dL) Triglycerides [a]	101(32-325)	75(64-160)	0.01*
Total cholesterol	167.1(35.7)	115.4(21.3)	0.05*
HDL –c	44.9(6.9)	47.2(6.1)	0.04*
LDL – c[a]	99.9(28.4)	78.3(32.6)	0.7
Blood lead (ug/dl)	45.7(15.3)	12.5(3.3)	0.0001**
Paraoxonase[a] (µmol/min/L)	367.2 (200.3-1645.6)	987(600-2576)	0.001**

DBP: diastolic blood pressure; SBP: systolic blood pressure
[a]Median (25thpercentile-75th percentile)
* Significant of p <0.05
** highly Significant of p<0.01

Table 2: companion between age, duration of work and blood profile of lead exposed workers.

Variable	Workers [Mean (SD)]			P value	Correlation r (P)
	Group 1 BPb < 40 ug/dl (n=39)	Group 2 BPb 40-59 ug/dl (n=42)	Group 3 BPb ≥ 60 ug/dl (n=19)		
Age (year)	33.3(10.6)	34.7(12)	37.1(12.4)	0.3	
Duration of work (year) †	5(2-24.2)	7(5.6-34)	14(7.5-40.3)	0.4	
SBP (mmHg)	131.3 (12.9)	130.7(16.5)	134.3(24.4)	0.9	
DBP (mmHg)	80(7.2)	80(11.8)	81.1 (9.6)	0.5	
Triglycerides (mg/dL) †	85(32-190)	101(65.4-248.9)	102.3(54.7-352)	0.5	
Total cholesterol (mg/dL)	124.4(22.3)[a]	170.5(26.1)[b]	180.3(53.2)[c]	0.01**	0.3(0.05)
HDL–c (mg/dL)	46.1(7.7)[a]	45.2(5.3)[a]	41.7(7.4) [b]	0.02*	0.2(0.1)
LDL–c† (mg/dL)	97.4(27.4)[a]	98 (32.9)[a]	112 (43.1)[b]	0.01**	0.3(0.04)*
BPb (ug/dl)	30.6(5.8)[a]	49.8(6.6)[b]	68.9(4.8) [c]	0.0001**	
Paraoxonase (µmol/min/L) †	634.6 (200.3-1654.6)[a]	366(170-1420.8)[b]	300 (100.6-1087)[c]	0.001**	0.2(0.03)*

BPb: blood lead level; DBP: diastolic blood pressure; SBP: systolic blood pressure

† Median (25thpercentile-75th percentile)

† † correlations between Bpb and each of total cholesterol, HDL-C, LDL.C and PON1 activity

Means within rows having the same superscripts are not significantly different.

*Significant of P<0.05

**Highly Significant of P<0.01

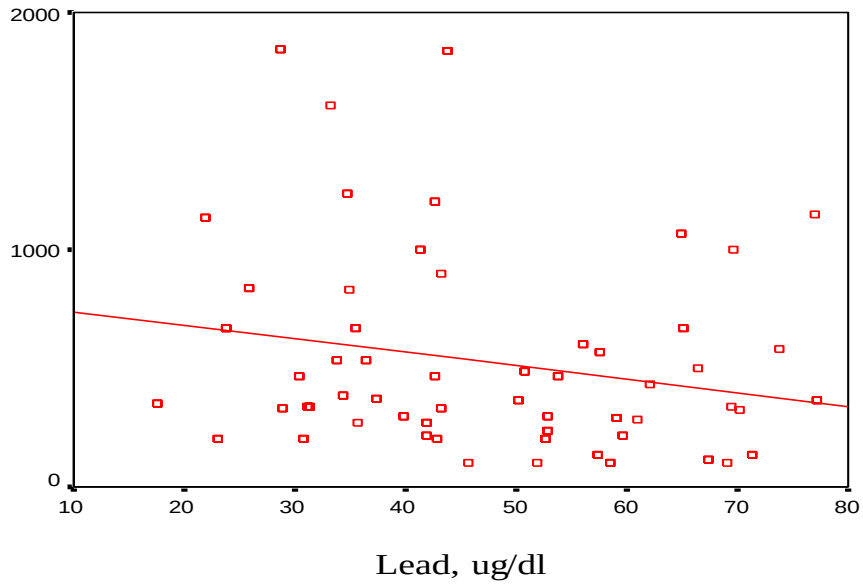

Figure 1: Correlation between paraoxonase activity and blood lead level

Table 3: Prediction of paraoxonase activity using multiple linear regressions

Predictor	Paraoxonase activity		
	B	**SE**	**P value**
Lead	- 5.7	2.7	0.03*
Exposure duration	-10.6	11.9	0.4
Age	-19.6	12.1	0.1
Cholesterol	4.4	2.7	0.1
HDL-c	6.3	7.9	0.4
LDL-c	-5.3	3.1	0.8
Triglycerides	-1.1	.8	.2
Intercept	1552.2	514.2	0.03
R^2	0. 38		

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