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Effects of occupational lead exposure on testosterone secretion

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Abstract

This study aims the determination of the relationship between blood lead levels (BLL) and reproductive hormones in workers with occupational lead (Pb) exposure. 58 workers who visited Ankara Occupational and Environmental Diseases Hospital between 2013 and 2017 and had a BLL of > 5 µg/dL and no infertility problem, were included in the study as the case group. The workers who have a chronic disease and use prescribed or herbal medicine were excluded. 63 healthy office workers with no heavy metal exposure at the workplace were selected as the control group. BLL, total testosterone (TT), free testosterone (FT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), uric acid, creatinine, complete blood count (CBC), prolactin (PRL), follicle stimulant hormone (FSH), luteinizing hormone (LH) levels were examined and the occupational anamnesis of the workers were taken. As a percentage, 47.9 % (n=58) of 121 persons (all males) was the study group with Pb exposure and 52.1 % (n=63) were the control group. While the BLL was 34,20 µg/dL in the exposed group, it was 1,82 µg/dL in the control group (p<0.001). Total and free testosterone levels were 6,35 and 13,57 in the control group; 4,65 and 8,13 in the exposed group (p< 0.001), respectively. LH level was 4,01 in the exposed group while it was 4,58 in the control group (p=0.072). FSH were 4,50 and 3,99 respectively, for the control and exposed group (P=0,220) (Table 1). Our results shows that chronic Pb exposure toxicity on the male reproduction system seems to have a mixt effect, probably on the axial of hypophysis-testis.

Keywords: Testosterone, lead exposure, follicle stimulant hormone (FSH), luteinizing hormone (LH), reproductive dysfunction

Introduction

Lead is a blue-grey colour heavy metal, with a low melting point, which does not occur as a metal by itself. It usually exists as a compound of two or more elements. Metallic lead is rust-free and resistant against water and air [1].

Pb and Pb-alloys are widely used in pipes, batteries, scales, bullets and ammunitions, cable sheaths, anti-radiation sheets, paint production and ceramic glazing. The most frequent use is in batteries of the cars and other vehicles [2,3].

The use of chemicals have increased in parallel with the increasing industrialization today. Similarly, there are many scientific study on the endocrine disrupting effects of industrial chemical, including reproductive system. Recent studies revealed that the chemicals affecting the male hormones and leading to infertility are still worldwide used. Pesticides, heavy metals such as mercury, cadmium, lead and the chemicals such as polychlorinated biphenyls (PCBs) and dioxin are the examples.

The studies, which were conducted in terms of the correlation between Pb exposure and male infertility, focused mainly on the sperm and its functions. Although the evidences are still obscure in the studies carried out, it is stated that fertility problems can be seen in males who have a BLL of 30-40 µg/dL [4].

Even though there are some studies that emphasize the relationship between Pb exposure and loss of fertility [5-8], there are also some other studies indicating no relationship between occupational Pb exposure and loss of fertility, as in the multinational study (Belgium, Finland, Italy and UK) conducted by Joffe et al. [9]. There are other studies that have conflicting results. While one study predicted normal LH, FSH and PRL level, while testosterone decreases (10), the other study presented increased FSH and LH levels in workers who have a BLL of 10-40 µg/dL (11). The spermatogenesis was found to decrease in workers of a battery factory where Pb exposure was severe [12,13]. In the study he

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focused on the effect of the working environment on the male reproduction system, Sheiner et al. found out that the workers who are employed in different industrial sectors had more frequent infertility. The further analysis of this study revealed that the infertility sources were varicocele, sperm anomalies and hormonal imbalance [14].

Also the sperm motility and sperm head morphology disorders are some other parameters that could be correlated with BLL [15]. The workers in molding presented hypogonadism and low testosterone hormone levels, caused by inorganic lead exposure [16]. In an another study, results revealed a correlation between the exposure time and testicular dysfunction [17].

Similarly, animal studies suggested that Pb exposure had harmful effects on male reproduction system, as in humans. The studies carried out on monkeys showed that Pb exposure decreased the LH level and inhibiting/FSH ratio [18]. Similarly, chronic lead exposure in monkeys has been proven to cause dysfunction in Sertoli cells [19]. In his study on monkeys, Foster et al. [20] has pointed out the deformations in Sertoli cells, basal lamina, seminiferous tubule epithelium and spermatids by using electron microscope. Similarly, Bizzaro et al. advocate this outcome, by means of his studies in which he showed a time-dependent increase, in the fraction of damaged mitochondria in the Sertoli cells in mice exposed to Pb acetate intermittently for a period of 4 weeks [21].

A more recent animal study showed that lead blocked dihydrotestosterone binding to the receptor in the prostate and seminal vesicle due to its divalent cation property [22].

Since most of the lead exposure occur at the workplace, semen disorder and lack of libido is observed more distinctively in those with occupational lead exposure [23, 24].

Materials and Methods

Study population

In this case-control study, 58 workers who visited the occupational diseases outpatient clinic at Ankara Occupational and Environmental Diseases Hospital, were included as the case group. Case group had a BLL > 5 µg/dL and no infertility problem. The workers who have a chronic disease and use prescribed or herbal medicine were not included in the study. 63 healthy office workers with no heavy metal exposure at the workplace were selected as the control group. The Decision of the Ethics Committee, Ankara Keçiören Training and Research Hospital, is available for the study.

Measurements

Demographic data of the study and control group was collected from occupational anamnesis. Cell-Dyn Emerald Hematologic Analysis device was used for the haematological analyses; Inductively Coupled Plasma – Mass Spectrometer (ICP-MS) Agilent 7.700 device was used for the blood lead analyses and Abbott Architect i 2000 Immunoassay device was used for FSH, LH, PRL, TST analyses of the blood samples taken into tubes containing Ethylene Diamine Tetra-Acetic acid (EDTA).

Statistical Analysis

The participants were divided into two groups: those with and without a lead exposure based on the severity of Pb exposure. Statistical analysis was performed using SPSS 22,0 software in order to assess the occupational anamnesis and laboratory results. Data distribution was determined with Kolmogorov-Smirnow test. In the study, the statistical significance level of which was accepted as 0.05, the difference between the averages of two independent variables was evaluated with t-test; the difference between more than two variables was evaluated with ANOVA (analysis of variance) and additionally with Pearson Correlation analysis. The averages are given with the standard deviations.

Results

A total of 121 male workers were included in the study. 47,9 % (n=58) was the study group while 52,1 % (n=63) was the control group. The average age of the exposed group was 37,9 while it was 40,4 in the control group. The average work duration of the control group was 8,68 ±8,02 years and 4,94 ±1,64 years in the exposed group. While the BLL was 34,20 µg/dL in the exposed group, it was 1,82 µg/dL in the control group (p<0.001). Total and free testosterone levels were 6,35 and 13,57 in the control group; 4,65 and 8,13 in the exposed group (p< 0.001), respectively. LH level was 4,01 in the exposed group while it was 4,58 in the control group (p=0.072). FSH were 4,50 and 3,99 respectively, for the control and exposed group (P=0,220). PRL levels were 12,00 and 12,17 respectively (P=0,880), (Table 1).

Tablo 1. Means of continuous variables of the control group and exposure group

	Group	N	Mean	Std. Deviation	p
Age	Control Group	63	40.4127	9.40939	.138
	Exposed Group	58	37.9828	8.46767	
BLL (µg/dL)	**Control Group**	**63**	**1.8292**	**1.07345**	**.000**
	Exposed Group	**58**	**34.2016**	**22.64164**	
FT (ng/ml)	**Control Group**	**63**	**13.5752**	**2.94580**	**.000**
	Exposed Group	**58**	**8.1331**	**1.70954**	
TT (ng/ml)	**Control Group**	**63**	**6.3570**	**2.28270**	**.000**
	Exposed Group	**58**	**4.6522**	**1.80194**	
TSH (µıu/ml)	Control Group	63	1.5924	.90275	.631
	Exposed Group	58	1.6926	1.32333	
T3 (pg/ml)	Control Group	63	2.9952	.41452	.828
	Exposed Group	58	3.0122	.44444	
T4 (ng/dl)	Control Group	63	1.0313	.16621	.149
	Exposed Group	58	1.0743	.15985	
FSH (mlu/ml)	Control Group	63	4.5087	2.79870	.220
	Exposed Group	58	3.9907	1.73847	
LH (mlu/ml)	Control Group	63	4.5871	1.85395	.072
	Exposed Group	58	4.0110	1.64034	
PRL (mlu/ml)	Control Group	63	12.0056	5.05628	.880
	Exposed Group	58	12.1747	6.96578	

In the analysis carried out according to BLL of the study group (group-1: 5-10 µg/dL, group-2: 10-40 µg/dL, group-3: >40 µg/dL), FT levels were significantly high in the control group compared to the exposed group (p<0,001). While the highest FT level of the study group was in group-2, the lowest FT level was seen group-3. However, this finding was not significant statistically. For LH and FSH levels, the highest levels were found in group-2 while the lowest was found in group-1. Nevertheless, no significant difference was found in terms of the LH and FSH levels between the control group and the groups classified according to the BLL (Table 2, Figure 1-3).

The strongest negative correlations were between BLL and FT (r= -0,576, p < 0,01) and between LH and FSH (r= 0,527, p < 0,01) (Table 3). It was found that there was a negative correlation between BLL and TT (r= -0,262, p < 0,01) and a positive correlation between TT and FT (r= 0,461, p < 0,01).

Table 2. Means of continuous variables of the control group and 3 different lead levels

	Group	N	Mean	Std. Deviation	Minimum	Maximum	P
Age	Non-exposed	63	40.4127	9.40939	24.00	63.00	.319
	1	16	38.9375	10.40172	25.00	61.00	
	2	15	35.6667	8.74779	22.00	48.00	
	3	27	38.7037	7.02641	24.00	52.00	
	Total	121	39.2479	9.01599	22.00	63.00	
BLL (µg/dL)	Non-exposed	63	1.8292	1.07345	.20	4.04	**.000**
	1	16	7.5181	1.53796	5.60	9.82	
	2	15	27.8600	9.32231	10.50	40.00	
	3	27	53.5370	15.03711	41.40	101.00	
	Total	121	17.3465	22.53498	.20	101.00	
FT (ng/ml)	**Non-exposed***	63	13.5752	2.94580	10.11	20.90	**.000**
	1	16	8.2025	1.42498	6.14	10.28	
	2	15	8.7327	1.72136	3.96	10.42	
	3	27	7.7589	1.81227	4.16	10.12	
	Total	121	10.9666	3.65032	3.96	20.90	
TT (ng/ml)	**Non-exposed***	63	6.3570	2.28270	2.34	12.52	**.000**
	1	16	4.1800	1.50090	2.00	6.90	
	2	15	5.2413	1.75832	3.84	11.00	
	3	27	4.6048	1.95300	2.01	9.77	
	Total	121	5.5398	2.22842	2.00	12.52	
TSH (µıu/ml)	Non-exposed	63	1.5924	.90275	.49	4.57	.787
	1	16	1.9062	2.07537	.30	9.04	
	2	15	1.5700	.87582	.12	2.96	
	3	27	1.6341	.94916	.57	4.31	
	Total	121	1.6404	1.12045	.12	9.04	
T3 (pg/ml)	Non-exposed	63	2.9952	.41452	2.14	3.82	.791
	1	16	2.9344	.40735	2.19	3.76	
	2	15	2.9953	.41595	2.18	3.80	
	3	27	3.0678	.48687	2.18	4.20	
	Total	121	3.0034	.42740	2.14	4.20	
T4 (ng/dl)	Non-exposed	63	1.0313	.16621	.72	1.73	.073
	1	16	1.1188	.14165	.97	1.48	
	2	15	.9967	.09116	.88	1.21	
	3	27	1.0911	.18703	.88	1.68	
	Total	121	1.0519	.16394	.72	1.73	
FSH (mlu/ml)	Non-exposed	63	4.5087	2.79870	1.93	20.40	.504
	1	16	3.7269	1.45311	1.34	7.46	
	2	15	4.4793	2.18212	1.76	7.87	
	3	27	3.8756	1.62764	1.01	7.67	
	Total	121	4.2604	2.35585	1.01	20.40	
LH (mlu/ml)	Non-exposed	63	4.5871	1.85395	1.93	9.32	.301
	1	16	3.7519	1.28470	1.98	6.42	
	2	15	4.1460	1.79398	1.91	9.05	
	3	27	4.0896	1.77637	1.41	7.13	
	Total	121	4.3110	1.77129	1.41	9.32	
PRL (mlu/ml)	Non-exposed	63	12.0056	5.05628	4.34	32.82	.840
	1	16	11.0531	6.35232	5.89	25.82	
	2	15	12.9227	4.07498	6.35	20.42	
	3	27	12.4237	8.54358	3.80	34.32	
	Total	121	12.0866	6.02198	3.80	34.32	

The group that caused the difference

Table 3. Pearson correlations of continuous variables

N=121	Age	Lead	FT	TT	TSH	T3	T4	FSH	LH	PRL
Age	1	-.070	-.029	-.008	.191*	-.226*	.025	.335**	.146	-.089
Lead		1	-.576**	-.262**	-.009	.018	.141	-.099	-.142	.037
FT			1	.461**	-.150	.062	-.162	-.058	.094	.126
TT				1	-.106	.120	-.091	-.052	.152	.002
TSH					1	-.056	-.053	.060	-.130	-.134
T3						1	.188*	-.166	-.128	-.203*
T4							1	-.031	.027	-.182*
FSH								1	.527**	.007
LH									1	.225*
PRL										1

*.p<0.05 **. P< 0.01

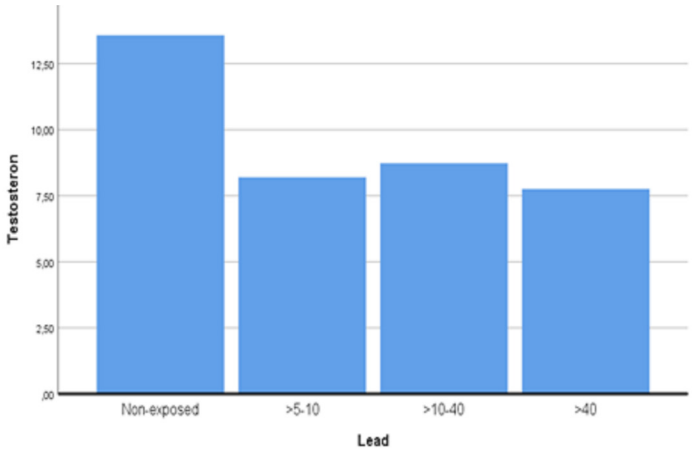

Figure 1. Free testosterone levels for control group and three different lead levels group

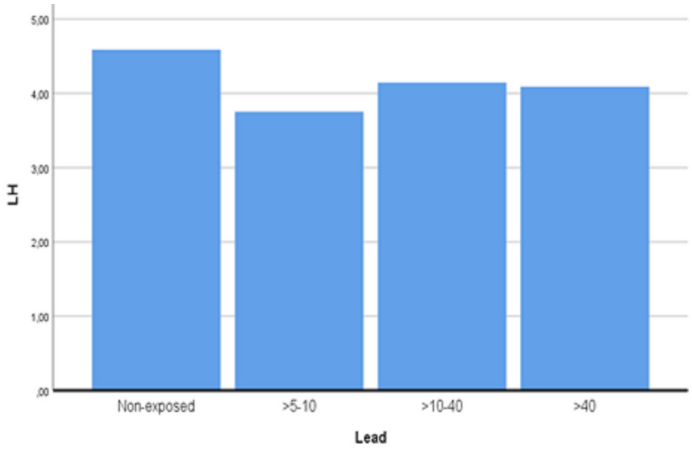

Figure 2. LH levels for control group and three different lead levels group

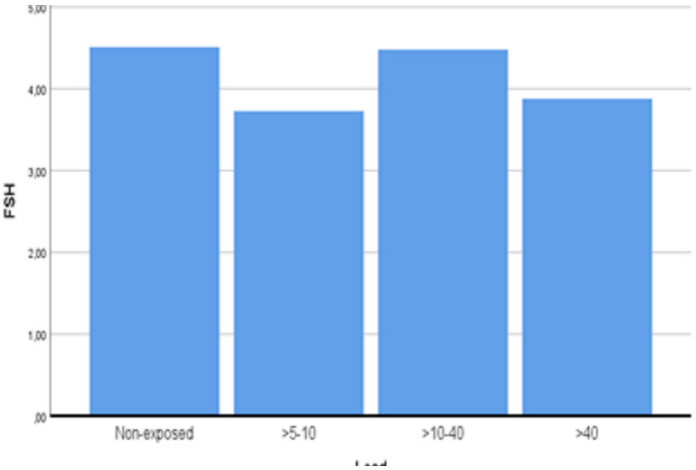

Figure 3. FSH levels for control group and three different lead levels group

Discussion

In our study that we carried out in the workers with a lead exposure of 4,94 ±1,64/year on an average, we observed that free and total level were statistically low in each group. Although FSH and LH levels have been found to be lower than the control group, it was not statistically significant. After we have sliced the exposed workers three groups according to their BLL, significantly low testosterone levels have been found in the first group. This result seems to be a consequence of deteriorated testosterone secretion in the testicle due to Pb exposure. In the second group, FSH and LH levels tend to increase although lead levels are higher than the first group (10-40 µg/dL) (table 2). These increases are estimated to be related to testicle Sertoli and Leydig cell insufficiency. As seen in the table, TT and FT levels increase like FSH and LH levels. However, FSH and LH levels have been found to decrease remarkably like testosterone levels in the severely exposed group (40 µg/dL).

These findings indicate that Pb exposure initially causes testicular damage due to direct toxic effect and decreases the testosterone synthesis. This decrease seems to induce an increase in FSH and LH concentrations. There are similar results in the literature [16, 17]. In cases where BLL remains above 40 µg/dL, testosterone synthesis reduces parallel to FSH and LH synthesis. This result supports the idea regarding the secondary effect of lead on hypophysis, in the studies conducted. It was seen that the lead levels above 40 µg/dL caused adverse effects on the hypothalamic hypophyseal system. These studies points out that FSH and LH levels decrease in the long-term exposure [19, 25-28].

It has been found that lead exposure reduces thyroidal hormonogenesis [29-31]. However, this result is only caused by extremely high lead levels. This aspect should be addressed in exposure groups in higher levels.

Conclusion

The data we obtained in our study indicate that lead exposure causes damage to testicular Sertoli and Leydig cells and causes a decrease in testosterone levels. Additionally high BLL seems to suppress the hormone secretion in hypophysis.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

Ethical approval
Before the study, permissions were obtained from local ethical committee.

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