Liver Function Tests in Mine Workers Exposed to Lead: An Occupational Cohort Study

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Research

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Abstract

Background: Operational processes in lead mines cause workers to be occupationally exposed to lead particles, chronic exposure to lead can results innumerous health effects.

Method: To know the effects of chronic lead exposure on liver function, the blood lead levels (BLL) and liver function tests of lead miners for 3- years (2017-2019) were followed and the obtained results were compared with those attained in the non-exposed group.

Results: The BLL levels of the lead-mine workers were higher than with recommended level and the non-exposed group (24.15 and 6.35 μg dL^{-1}, respectively, $p<0.001$). The findings indicated a positive and significant relationship between BLL and lactate dehydrogenase (r: 0.942, $p<0.001$), aspartate transaminase (r: 0.869, $p<0.001$), alkaline phosphatase (r: 0.9679, $p<0.005$), alanine transaminase (r: 0.9779, $p<0.001$), and bilirubin (r: 0.9169, $p<0.001$) levels, while we found a negative and significant correlation between BLL and triglyceride (r: -0.929, $p<0.05$), total protein (r: -0.896, $p<0.001$), albumin (r: -0.941, $p<0.0021$), and globulin (r: -0.863, $p<0.001$) levels. Moreover, no significant relationship was found between BLL and cholesterol, LDL, LDH, and BUN levels ($p>0.05$).

Conclusions: This report showed that the chronic lead exposure is a major occupational hazard in lead mine workers. Despite the fact that the level of liver function parameters was in the normal range, the results of 3- years follow-up show a significant relationship between BLL and alteration of liver function parameters levels of lead miners. The study can be helpful in raising awareness of alteration in liver functions due to occupational exposure to lead.

Highlights

- Occupational exposure to lead can cause alter liver enzymes.
- LDH, AST, ALK, ALT, and bilirubin are increased due to chronic exposure to lead.
- Compare with non- exposure group, exposure group had a lower level of TG.
- Total protein, albumin, and globulin are decreased due to chronic exposure to lead.
- Occupational exposure to lead had no significant effect on BUN levels.

Background

Lead is a high-consumption mineral metal and exposure to lead (Pb: Plumbum) compounds is mainly due to human activities [1]. Although lead toxicity has been considered since ancient times, it is still an important environmental and occupational health problem [2, 3].

Oral and inhalation are the main absorption routs of the inorganic Pb compounds (40% from the respiratory tract and approximately 5–10 % from the gastrointestinal tract). Lead after absorption into the bloodstream is distributed in several organs particularly to the kidney and liver, which then may be

accumulated in the bones and cause hurt to the various organs including the liver, central and/or peripheral nervous system, heart, immune system, kidneys, and male gonads [3, 4]. Chronic exposure may lead to irreversible functional and morphological changes in the liver and renal [5].

Lead can disrupt the normal function of cations and essential enzymes throughout the body's cells, especially calcium; beside Pb poisoning is mostly accompanied by multi-systemic symptoms and signs. Autopsy researches on the humans exposed to Pb showed that the liver is the most important reservoir of lead among soft tissues of the human body (approximately 33%) [3, 6].

Various researchers have demonstrated the effects of lead exposure on the liver function alteration, but still, relationship between lead exposure and lipid metabolism is argumentative [7, 8]. Hand off course, previous studies have reported that chronic exposure to Pb can cause dyslipidemia, hypercholesterolemia, and increase the risk of atherosclerosis. Also, Pb exposure can impair the detoxification of xenobiotics (environmental toxins and drugs), changes tryptophan metabolism, and increases serotonin and 5- hydroxyindoleacetic acid in the brain [9–11]. The affinity of Pb to bind to electron donor groups (such as proteins, glutathione, and sulfhydryl group) disrupts various enzymatic processes [12]. In this way, Pb can weaken the function of the antioxidant defense system, produce reactive oxygen species, interfere with some essential elements of the body, damage or destroy cell membranes and inhibit antioxidant enzymes (dependent on sulfhydryl group) [13].

Mining is one of the hardest and most harmful occupations posing many health risks to miners [14]. The emission of heavy metals caused by mining and smelting in lead- zinc mines pollutes air, water, and soil, which can have adverse effects on the health of miners and residents around mines [15]. The operation process in lead-zinc mines, involving underground mining, ore mining, transport, crushing, lab examination, grinding, roughing, and smelting, can cause emission of various heavy metals especially the lead (Pb). In Iran, sixty-eight types of minerals including Pb mine are found and this country has the largest reserves of lead and zinc in Asia and the world (approximately 222 million tons) [16, 17].

Although it is well documented in previous literature, but is need to know of the scenario of blood lead level (BLL) and its liver effects on lead-mine workers. So, the object of this cohort study is providing know the blood lead levels among the mine workers and follows its biochemical effects on the liver function at during 3- years in Middle East largest lead- mine (Iran).

Materials And Methods

Study population

This prospective occupational cohort study was performed in the lead mine complex in Iran from 2017 to 2019. Before data and biological specimen collection, all the subjects (n = 250) were well informed about the objectives of the study and health risks of the Pb exposure and its toxicity. This cohort study started with a 2017 self-reporting questionnaire that investigated the personal, occupational, and medical history of the subjects. These factors included age, weight, alcohol, tobacco, employment duration, and average

daily exposure time average to lead sources. The recruitment and selection of study subjects were based on their medical history. Those who had a systemic disease, or were on medication for other reasons, were excluded from this study. Finally, 180 healthy male workers grouped in two sub-cohorts of exposed (n = 100) and non-exposed (n = 80). It should be noted that the food and habits dietary intake of all the entire subjects were the normal states. The consent was taken from the participants of the two groups. Liver function tests were performed annually from 2017 to 2019 in the both groups.

Blood sample collection

In the morning, 15 mL of fasting venous blood was obtained from the subjects in the exposed group before the commencement of the work. Of the blood sample, 10 mL was used for blood lead measurement, and 5 mL for the biochemical analyses. In order to collect blood samples serum, vacuum tubes contained K_3-EDTA (Greiner- Germany) and plain tubes were used. The same amount of fasting venous blood was also obtained from the non- exposed subjects. Then, the blood samples were transferred to a toxicology laboratory and frozen at -20°C until assayed.

Measure of BLL

Determination of blood lead level (BLL) was performed by means of a graphite furnace atomic absorption spectrophotometer (900T, Perkin Elmer).For this purpose, blood samples of five-fold dilution with dilute surfactant solution were used. To eliminate small and non-specific absorption signals from the blood matrix, a simultaneous background correction was used. The lead levels in the blood samples were accurately measured from as little as 20 µL of blood at a wavelength of 283.3 nm.

Measurement of the biochemical parameters

Triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol, lactate dehydrogenase (LDH), aspartate transaminase (AST), alkaline phosphatase (ALK), alanine transaminase (ALT), total serum protein, bilirubin, globulin, albumin, and blood urea nitrogen (BUN) levels were measured by an semi-automated biochemistry analyzer (Roche – Hitachi MODULAR Analytics, Japan) using the Roche kits.

The ALT and AST were determined using the UV-kinetic method by reagent obtained from Roche Ldt. Serum total bilirubin was measure based on the Jendrassik method [18], in which, diazotized sulphanilic acid reacts with serum bilirubin and pink color of azobilirubin is produce. Then azobilirubin catalyzes with dimethyl sulphoxide to give a pink color solution that the serum bilirubin concentration is proportional to the color intensity of the solution (detected at 546 nm).

Determination of serum total proteins (TP) was performed using a Roche Kit based on the Biuret method [19]. This test is based on the reacts of cupric ion with protein at the alkaline pH conditions to give a purple color solution (direct detect at 546 nm).

Serum albumin was measured by the BCG method[20], which is based on the bonds of the serum albumin with the tetrabromocresol sulfonephthalein green (BCG) at pH of 4.2 and production of a blue

green colored solution (detected at 600 nm). Also, the serum globulins and Albumin /Globulin ratio was estimated by using serum albumin and TP values.

The serum ALK was measured according to the King Armstrong method using Roche diagnostics kit [21]. With an alkaline pH, the ALK hydrolyses by disodium phenyl phosphate to form phenol. The produced phenol reacts with 4-aminoantipyrine in the presence of potassium ferricyanide (as an oxidizing agent) to form a red color complex (detected at 510 nm).

The BUN was measured by colorimetric method viaa Spectrophotometry UV-Vis (Lambda 950. Perkin Elmer) set at 520 nm.

Statistical Analysis

To analyze the collected data, we used appropriate descriptive and analytical statistics such as mean, standard deviation, Mann-Whitney U test, Kolmogorov Smirnov (KS), Friedman test and chi-square test. In order to compare quantitative variables, we first examined the data for normal distribution, for this purpose; Kolmogorov Smirnov test was used. The results showed that except for a few cases, most variables did not follow the normal distribution, thus, non-parametric tests were used to analyze the collected data. Mann Whitney U test was used when comparison of demographic variable, BLL and liver function tests of both groups. Fried man test was used to compare of the trend of average change BLL and liver function tests of healthy over three years. Chi-square test was also used when comparison of qualitative variable ratio of tobacco smoking in two groups. Data analysis was performed using SPSS software version 16.0 and maximum alpha error of 0.05 was considered as acceptable cut-point for significance.

Results

The demographic characteristics of the exposure and non-exposure groups are shown in Table 1. Mann-Whitney nonparametric test was used to compare the demographic variables between the exposure and the non-exposure groups. The results of this test showed that there was a significant difference in the mean of daily exposure in the exposure and non-exposure groups ($p = 0$), which is logical because the exposure in the control group was zero. Based on chi-square test, the proportion of smokers in the exposure groups was slightly higher than that of the non-exposure groups, but this difference was not significant ($p = 0.058$).

Table 1
Comparison of demographic variables between the exposure and the non exposure groups

Demographic characteristics	Exposure group (N = 100) mean ± SD	Non-exposure group (N = 80) mean ± SD	p-Value
Age(year)	33.76 ± 4.82	33.46 ± 5.30	0.80
BMI	23.19 ± 1.51	23.56 ± 1.80	0.22
Work experience (year)	8.64 ± 4.53	7.66 ± 3.82	0.17
Tobacco smoke (%)	22.00%	11.30%	0.058

BMI: body mass index, **SD**: Standard deviation.

The three- years average of BLL and liver function parameters in exposed and Non- exposed workers presented in Fig. 1.

BLL and liver function tests of healthy exposure and non-exposure groups are shown in Table 2. The mean of BLL and liver function tests of the two groups by different years was compared based on Mann-Whitney U test. The results showed that the mean of the BLL in the exposure groups in all years (2017–2019) was much higher than this scale in the non-exposure groups and this difference was statistically significant ($p < 0.001$). Biological exposure index (BEI) 2019 for BLL recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) is 20μg dL^{-1}. Thus, the BLL of the exposure group in all years exceeded the normal level.

Table 2
Comparison of changes in blood lead levels and liver function in exposed and non-exposed groups

Biochemical Parameters	Mean ± SD	Normal range	years				p-Value……
			Y_{17}	Y_{18}	Y_{19}	**p-Value**……	
BLL	Exposure Group	20	24.16 ± 8.36	24.05 ± 8.17	24.24 ± 8.25	0.402	< 0.001
	Non Exposure Group		6.05 ± 1.93	6.48 ± 1.86	6.51 ± 1.64	0.001	
	p-value…	–	< 0.001	< 0.001	< 0.001	–	
TG	Exposure Group	30–200	90.7 ± 41.2	91.5 ± 41.2	91.3 ± 41.3	0.854	0.013
	Non Exposure Group		102 ± 12.3	104 ± 12.3	102 ± 12.3	0.066	
	p-value	–	0.013	0.007	0.007	–	
LDL	Exposure Group	100–130	89.99 ± 24.50	90.02 ± 23.64	87.90 ± 21.87	0.253	< 0.001
	Non Exposure Group		75.15 ± 10.68	77.79 ± 11.05	75.77 ± 12.20	0.195	
	p-value	–	< 0.001	< 0.001	< 0.001	–	
HDL	Exposure Group	Up of 60	73.05 ± 14.6	74.45 ± 14.32	75.02 ± 13.61	0.018	< 0.001
	Non Exposure Group		92.18 ± 6.34	89.76 ± 7.95	91.82 ± 6.02	< 0.001	
	p-value	–	< 0.001	< 0.001	< 0.001	–	
Cholesterol	Exposure Group	110–200	163.04 ± 31.7	164.47 ± 30.22	162.92 ± 29.06	0.186	0.228
	Non Exposure Group		167.33 ± 7.35	167.43 ± 8.39	167.6 ± 9.71	0.350	

Y: Year, **BLL**: Blood lead level, **TG**: Triglyceride, **LDL**: Low density lipoprotein, **HDL**: high density lipoprotein, **Ch**: Cholesterol, **LDH**: lactate dehydrogenase, **AST**: Aspartate transaminase, **ALK**: Alkaline phosphatase, **ALT**: Alanine transaminase, **A/G**: Albumin/ Globulin, **BUN**: Blood urea nitrogen, ●: µg dL^{-1}, *: mg dL^{-1}, **: Unit/ L, ***: g dL^{-1}, …: Based on comparisons between the two groups by year. ……: Based on comparing the trend of annual changes in each group. ……: Based on compare the trend of annual changes by two groups.

	p-value	–	0.620	0.432	0.279	–	
Ch/HDL	Exposure Group	< 4	2.26 ± 0.39	2.24 ± 0.35	2.19 ± 0.33	0.616	< 0.001
	Non Exposure Group		1.82 ± 0.17	1.88 ± 0.19	1.83 ± 0.17	0.028	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
LDH	Exposure Group	140–280	223.07 ± 40.7	226.99 ± 41.51	231.25 ± 42.84	< 0.001	< 0.001
	Non Exposure Group		159.85 ± 12.6	159.92 ± 10.1	162.32 ± 12.0	0.017	
	p-value	-	< 0.001	< 0.001	< 0.001	–	
AST	Exposure Group	8–38	35.17 ± 10.15	35.79 ± 9.36	36.07 ± 9.67	0.224	< 0.001
	Non Exposure Group		28.72 ± 2.68	28.73 ± 2.32	29.71 ± 2.15	0.032	
	p-value	–	< 0.001	< 0.001	< 0.001	–	
ALK	Exposure Group	30–140	152.85 ± 52.53	153.56 ± 51.70	152.85 ± 53.76	0.168	< 0.001
	Non Exposure Group		124.57 ± 5.02	125.1 ± 5.34	126.35 ± 4.56	0.026	
	p-value	–	0.004	0.005	< 0.001	-	
ALT	Exposure Group	10–55	38.6 ± 8.42	38.57 ± 8.66	38.44 ± 8.43	0.831	< 0.001
	Non Exposure Group		29.02 ± 2.7	29.05 ± 2.65	29.86 ± 2.36	0.117	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
Protein	Exposure Group	6.6–8.3	7.038 ± .698	7.031 ± 0.7	7.041 ± 0.68	0.829	< 0.001

Y: Year, **BLL**: Blood lead level, **TG**: Triglyceride, **LDL**: Low density lipoprotein, **HDL**: high density lipoprotein, **Ch**: Cholesterol, **LDH**: lactate dehydrogenase, **AST**: Aspartate transaminase, **ALK**: Alkaline phosphatase, **ALT**: Alanine transaminase, **A/G**: Albumin/ Globulin, **BUN**: Blood urea nitrogen, ●: µg dL^{-1}, *: mg dL^{-1}, **: Unit/ L, ***: g dL^{-1}, …: Based on comparisons between the two groups by year. ……: Based on comparing the trend of annual changes in each group. ……: Based on compare the trend of annual changes by two groups.

	Non Exposure Group		7.5 ± 0.249	7.31 ± 1.33	7.58 ± 0.28	0.090	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
Bilirubin	Exposure Group	0.5-1	1.12 ± 0.24	1.23 ± 0.88	1.17 ± 0.25	< 0.001	< 0.001
	Non Exposure Group		0.81 ± 0.085	0.83 ± 0.081	0.82 ± 0.089	0.119	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
Globulin	Exposure Group	2.8–3.2	3.13 ± 0.28	3.10 ± 0.28	3.05 ± 0.3	< 0.001	< 0.001
	Non Exposure Group		3.23 ± 0.047	3.22 ± 0.051	3.24 ± 0.063	0.223	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
Albumin	Exposure Group	3–5	3.77 ± 0.5	3.76 ± 0.5	3.73 ± 0.8	< 0.001	< 0.001
	Non Exposure Group		4.01 ± 0.17	4.12 ± 0.78	4 ± 0.14	0.951	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
A/G	Exposure Group	1.5-2	1.19 ± 0.088	1.19 ± 0.093	1.23 ± 0.2	0.014	0.005
	Non Exposure Group		1.24 ± 0.058	1.27 ± 0.24	1.23 ± 0.048	0.350	
	p-value	–	< 0.001	< 0.001	< 0.001	-	
BUN	Exposure Group	8–24	14.3 ± 3.29	15.26 ± 3.5	14.91 ± 3.37	< 0.001	0.575
	Non Exposure Group		14.57 ± 3.27	14.46 ± 3.46	14.87 ± 3.22	0.236	
	p-value	–	0.510	0.100	0.846	-	

Y: Year, **BLL**: Blood lead level, **TG**: Triglyceride, **LDL**: Low density lipoprotein, **HDL**: high density lipoprotein, **Ch**: Cholesterol, **LDH**: lactate dehydrogenase, **AST**: Aspartate transaminase, **ALK**: Alkaline phosphatase, **ALT**: Alanine transaminase, **A/G**: Albumin/ Globulin, **BUN**: Blood urea nitrogen, **●**: μg dL^{-1}, *****: mg dL^{-1}, ******: Unit/ L, *******: g dL^{-1}, …: Based on comparisons between the two groups by year. ……: Based on comparing the trend of annual changes in each group. ……: Based on compare the trend of annual changes by two groups.

The findings indicated that the TG level of both groups was within the normal range, but TG level in the exposure group was significantly lower than that of the non- exposure ($p < 0.05$). This is why the TG level in the exposed subjects did not have significant changed during the three years (See Table 2).

The results showed that the LDL levels in the workers with lead exposure were higher than those in the non-exposure subjects ($p < 0.001$), however, the HDL levels in the exposure group were lower than those in the non-exposure group ($p < 0.001$). Also, the means of the LDL and HDL levels for the both groups were within the normal range. Furthermore, the LDL levels of the exposure subjects decreased for the three years; this is while, and the HDL concentration increased over the period (Table 2).The cholesterol level of the both groups was within the normal range, and no significant difference was observed between the both groups ($p > 0.05$). Also, the cholesterol level in exposure subjects did not change significantly during the three years (See Table 2). Moreover, the cholesterol/ HDL ratio in the exposed subjects was significantly higher than that of the non-exposure subjects ($p < 0.001$). Though cholesterol/ HDL ratio in the two groups was in the normal range; this ratio increased in the exposed group during the three years.

The results indicated that the serum LDH, AST, ALK, ALT, and bilirubin of the exposure subjects were significantly higher than those of the non-exposure group ($p < 0.001$), even though, these parameters in the both groups were within the normal range (See Table 2). As shown in Table 2, the serum LDH, AST increased in the exposed group during the three years, while the serum ALT decreased during the three years. Also, the ALK and bilirubin values did not have significant change during in the period.

Following investigation of other liver function tests, the results showed that total serum protein, albumin, globulin and albumin/ globulin levels were lower in the exposed group than those in the non-exposed group ($p < 0.002$), and these parameters had a decreasing trend during the three years follow-up. On comparison of the exposed with the non-exposed subjects, no significant difference was found in term BUN value and this parameter in both groups within in the normal range.

As shown in Table 3, the trend of changes of the HDL, LDH, bilirubin, globulin, albumin, albumin/ globulin ratio, and BUN levels during three years follow- up in the exposure group was significant. Table 3 presents the Spearman correlation coefficient between the BLL and liver function parameters.

Table 3
Comparison of the trend and correlation between average changes BBL and liver function tests of exposure group over three years (p-Value and Spearman R-value)

Parameters		years			
		Y_{17}	Y_{18}	Y_{19}	Mean
TG	R	-0.930	-0.921	-0.936	-0.929**
	p-Value	0.001	0.001	0.001	–
LDL	R	-0.001	0.148	0.108	0.085
	p-Value	0.990	0.142	0.283	–
HDL	R	0.118	0.51	0.112	0.093
	p-Value	0.243	0.616	0.112	–
Cholesterol	R	0.047	0.123	0.127	0.099
	p-Value	0.644	0.223	0.208	–
Ch/HDL	R	-0.104	0.039	0.004	0.049
	p- Value	0.304	0.70	0.969	–
LDH	R	0.970	0.932	0. 945	0.949*
	p-Value	0.001	0.001	0.001	–
AST	R	0.824	0.888	0.869	0.869*
	p-Value	0.001	0.001	0.001	–
ALK	R	0.985	0.947	0.969	0.967*
	p-Value	0.001	0.001	0.001	–
ALT	R	0.983	0.972	0.977	0.977*
	p-Value	0.001	0.001	0.001	–
Protein	R	-0.920	-0.889	-0.881	-0.896**
	p-Value	0.001	0.001	0.001	–
Bilirubin	R	0.937	0.891	0.920	0.916*
	p-Value	0.001	0.001	0.001	–

BLL: Blood lead level, **TG**: Triglyceride, **LDL**: Low density lipoprotein, **HDL**: high density lipoprotein, **Ch**: Cholesterol, **AST**: Aspartate transaminase, **ALK**: Alkaline phosphatase, **ALT**: Alanine transaminase, **A/G**: Albumin/ Globulin, **BUN**: Blood urea nitrogen, ***Correlation coefficient positive and significant, ****Correlation coefficient negative and significant.

Globulin	R	-0.886	-0.850	-0.853	-0.863**
	p-Value	0.001	0.001	0.001	–
Albumin	R	-0.949	-0.940	-0.935	-0.941**
	p-Value	0.001	0.001	0.001	–
A/G	R	-0.771	-0.734	-0.678	-0.707**
	p-Value	0.001	0.001	0.001	–
BUN	R	0.140	0.163	-0.150	0.151
	p-Value	0.164	0.150	0.880	–

BLL: Blood lead level, **TG**: Triglyceride, **LDL**: Low density lipoprotein, **HDL**: high density lipoprotein, **Ch**: Cholesterol, **AST**: Aspartate transaminase, **ALK**: Alkaline phosphatase, **ALT**: Alanine transaminase, **A/G**: Albumin/ Globulin, **BUN**: Blood urea nitrogen, ***Correlation coefficient positive and significant, ****Correlation coefficient negative and significant.

Discussion

This prospective occupational cohort study evaluated changes in liver function due to occupational exposure to lead among the lead- mine workers. The blood lead level (BLL) and liver function parameters including TG, LDL, HDL, cholesterol, cholesterol/ HDL, LDH, AST, ALK, ALT, total protein, bilirubin, globulin, albumin, albumin/ globulin, and BUN in the exposed and non-exposed subjects were followed during 2017–2019.

The BLL during the three years in the lead- mine workers exceeded the BEI level recommended by the ACGIH (20 μg dL^{-1}) [22], which is much higher than that in the non-exposure subjects ($p < 0.001$), showing that the lead-miners were significantly occupational exposure to Pb and its health risks [23, 24]. Various operations at the mine studied including the extraction, crushing, roughing, purification, lab examination, and transportation of lead ore caused the emission of lead-containing dust into the inhaled air of miners. Despite the provision of control measures and the use of personal protective equipment (mouth mask), the BLL in the exposed workers was still higher than the BEI and control subjects. In addition to respiratory exposure, contact of lead-containing dust with the oral mucosa of miners in the workplace can cause gastrointestinal exposure to lead [3, 25].

TG and HDL levels of the exposed group were lower than those of the non-exposed group, while the LDL levels of the exposed subjects were higher than those of the non-exposed group. There was a negative and significant correlation between the BLL and TG level of the lead miners, however, a significant correlation was not found between BLL and cholesterol, LDL and HDL levels. Previous studies have acknowledged that chronic exposure to lead (battery workers) has no significant effect on cholesterol levels and the age of workers can interference with the TG, LDL, LDH, and cholesterol levels [26, 27].

AST, ALK, ALT, LDH, total protein, bilirubin, and albumin can be used for the comprehensive assessment of the liver function. We found that the levels of serum LDH, AST, ALK, ALT, and bilirubin level increased significantly ($p < 0.001$) in the lead- mine workers as compared with the non-exposed subjects, while serum protein in the exposure group was lower than that in the non-exposure group and a negative and significant correlation between BLL and total protein was observed (r: 0.896, $p < 0.001$).

The increased in level of LDH in the worker population might have been resulted from damage to the skeletal or cardiovascular system [28–30]. Chronic lead exposure can cause slowing intermediary metabolism, which leads to an increase in LDH level. However, chronic exposure to Pb can result in elevated serum ALP and LDH levels due to liver-kidney damages [8, 31]. Furthermore, chronic exposure to lead can interfere with heme synthesis, then cause hemolysis and release hemoglobin containing more LDH, and ultimately increases serum LDH levels [32].

Lead can accumulate in the liver tissues and have toxic effect through per-oxidative damage to liver cell membranes and then increase serum ALT and AST levels. Previous studies have shown that long-term occupational exposure to Pb causes an increased level of serum transaminase enzymes [33–36]. ALT (r: 0.977, $p < 0.001$) and AST (r: 0.869, $p < 0.001$) levels during three years of follow-up in the exposed lead-mine workers significantly increased as compared with the non-exposure subjects, which illustrates the occurrence of hepatocellular injury. Previous studies have suggested that elevated serum AST and ALK levels may be due to mitochondrial degradation after the destruction of liver cells [37–41].

Bones contain high levels of the ALK, which chronic exposure to lead can cause damage to bone structure (replacement of lead with bone calcium) and then leads to elevated serum ALK levels. A direct and significant correlation between BLL and serum ALK level in the exposed group (r: 0.967, $p < 0.005$) confirms this hypothesis [42]. Moreover, ALK is usually present in the walls of the biliary ducts. An increase in serum ALK level may indicate hepatobiliary or hepatocellular damages [33, 43]. Liver damage can lead to impaired transport functions of the biliary tree ducts or of the hepatocytes, which ultimately increases serum ALK levels[5, 44]. Lead can cause interference and breakdown of cell membranes. On the other hand, phosphate is known as an intracellular anion that increases serum ALK levels when the cell membrane is damaged or destroyed. Thus, chronic exposure to lead can lead to elevated serum ALK levels [37, 38, 45, 46].

A high BLL level results in morphological changes and hemolysis of red blood cells (RBC), which can cause an increase in the serum bilirubin levels. In the present study, the results indicated a positive and significant relationship between the BLL level and bilirubin level of the exposed group (r: 0.916, $p < 0.001$), which is consistent with results of similar previous studies [24, 33, 34, 47].

The serum total protein reflects the important changes the liver function and is an indirect assessment of protein status[33]. It was found that an increase in BLL, decreased the levels of total protein (r: -0.896, $p < 0.001$), globulin (r: -0.863, $p < 0.001$), albumin (r: -0.941, $p < 0.001$) and subsequently decreased the albumin/ globulin ratio (r: -0.707, $p < 0.01$). The increased BLL can leads to decreases in the synthesis of serum proteins reported in various earlier studies [27, 33, 48]. Experimental animal studies show that

chronic exposure to lead can inhibit globulin synthesis in animal bone marrow, therefore, serum protein levels can be used to detect liver injuries due to occupational exposure to lead [27, 49, 50].

The results of the present study demonstrated that occupational exposure to lead had no significant effect on BUN levels. These observations suggest that the BUN levels may not be a good indicator to evaluate renal injuries due to chronic occupational exposure to lead, which is consistent with the results of previous similar studies [37, 51].

Conclusions

The average BLL levels of the lead mine workers during the 3 years of follow-up was higher than the recommended level and therefore it may lead to health risks associated with Pb. Although the level of liver function tests was in the normal range, their changes were statistically significant based on the blood lead level. Our results indicated that chronic exposure to lead can increase serum LDH, AST, ALK, ALT, and bilirubin, and decrease serum total protein, albumin, and globulin levels, but there was no evidence of major hepatic impairment in lead miners. The study can be helpful in raising awareness of alteration in liver functions due to occupational exposure to lead.

Abbreviations

Pb
Plumbum; BLL:Blood lead level; Triglyceride:TG; High density lipoprotein:HDL; Low density lipoprotein:LDL; Cholesterol:Ch; Lactate dehydrogenase:LDH; Aspartate transaminase:AST; Alkaline phosphatase:ALK; Alanine transaminase:ALT; Urea nitrogen:BUN; BEI:Biological exposure index; ACGIH:American conference of governmental industrial hygienists.

Declarations

Acknowledgment

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Competing of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors Contributions

Conceive and design the study was done by AF, and RR. Drafting of the manuscript was done by AR and AP. Critical revision of the manuscript for important intellectual content was done by SR and AF.

Statistical analysis was also done by AA. SR and RR conceived and supervised entire study and edited the manuscript. All authors approved final version of manuscript.

Availability of data and materials

The data and materials supporting the conclusions of this article is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent to workers and for publication of the results was obtained from the workers in this study. They were also assured of confidentiality and all the samples and questionnaires were kept anonymous. The present study was reviewed and approved by the Institutional Review Board and ethics committee of Larestan University of Medical Sciences (Ethical code: IR.LARUMS.REC.1396.223).

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Figures

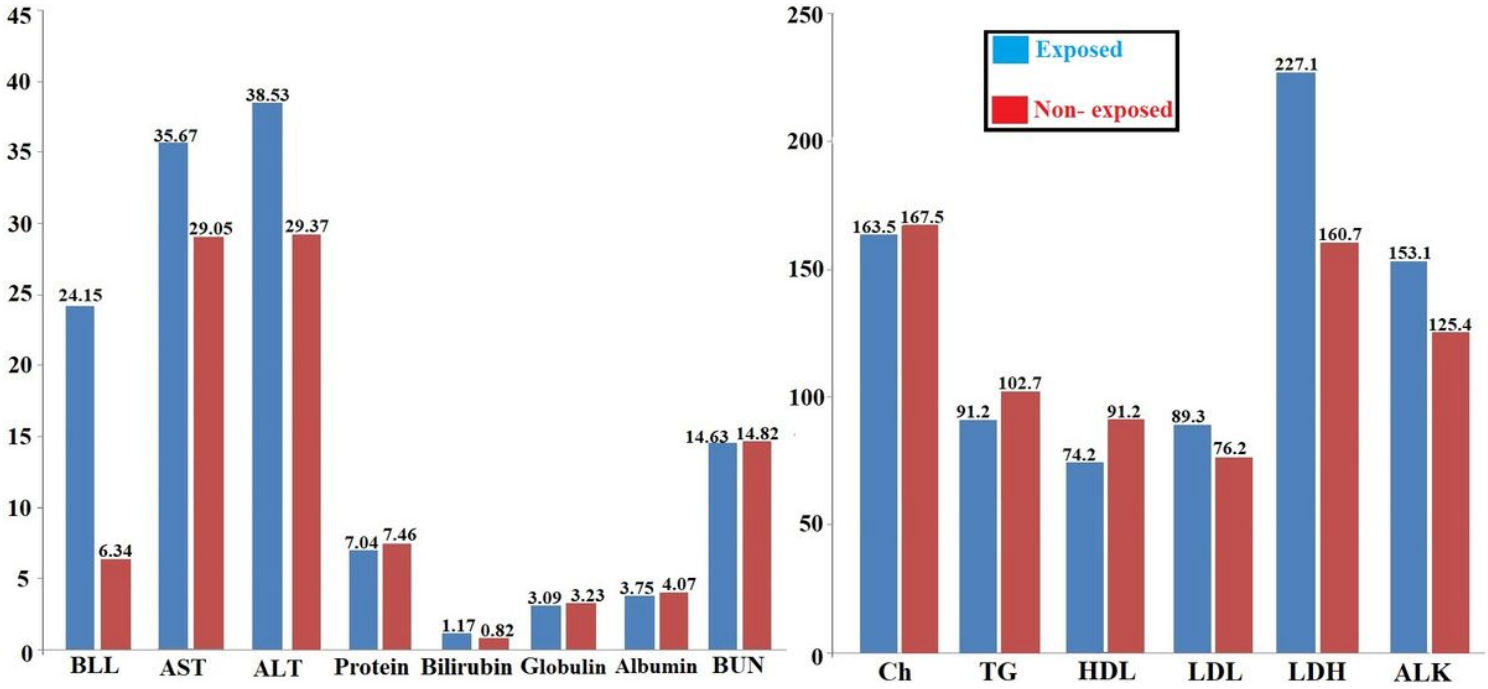

Figure 1

Three- years average level of BLL and liver function parameters in exposed and non- exposed groups

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