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Determination of Lead Concentration in Human Biological Samples

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Metal induced toxicity is very well reported across the world. Metals like Lead, copper, cadmium, mercury, nickel, iron and arsenic can enters human body through air, dust, food, beverages, ink and smoking, has negative impact on health. Lead does not have any nutritional value in the body even a small amount causes severe toxic effects to all forms of life.
Objectives: Determination of lead concentration in human biological samples and impact of lead in blood on serum creatinine and hemoglobin.
Methodology: The blood samples were analyzed using Lead care II analyzer for determining Lead concentration in blood. Totally 40 subjects were investigated among which 20 were taken as test group and 20 were taken as control for the period of 6 months.
Results and Discussion: The results shows that the Lead concentration varies from 4.1 µg/dl to 19 µg/dl in test group and from 3.3 µg/dl to 12.9 µg/dl in control group, the two tailed spearman's

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correlation coefficient is used to determine the relationship between serum creatinine and haemoglobin with blood Lead concentration, mean value of serum creatinine in test group is found to be 7.61 and the standard deviation is SD 3.84, similarly the mean value of control group is 1.06 and the standard deviation is found to be SD 0.19. The study revealed that the mean value of Haemoglobin is found to be 9.29, 13.37 and the SD 2.92, 0.68 for test and control respectively.
Conclusion: There is a strong correlation between serum creatinine and Lead in blood which is statistically significant (0.001) and there is no correlation between lead in blood and haemoglobin.

Keywords: Lead toxicity; heavy metals toxicity; lead in blood; toxicity studies; acute and chronic toxicity of lead.

1. INTRODUCTION

Metal induced toxicity is very well reported across the world. Metals like Lead, copper, cadmium, mercury, nickel, iron and arsenic have ability to generate reactive radicals, leading to cellular damage, lipid bilayer, DNA and also depletion of enzyme activities. These metals generate reactive species which in turn may cause neurotoxicity, hepatotoxicity, nephrotoxicity and infertility in human beings [1].

Lead is an element that is found to be purely toxic to all forms of life. Elements like manganese, selenium, nickel and molybdenum, although toxic at high levels, are actually required nutrients at lower levels. Lead has no nutritional value or positive biological effect even at lower concentration. Exposure to Lead can produce a negative impact on health of all age groups. Both adults and children can suffer from the effects of Lead poisoning, but in childhood poisoning the damage done is irreversible and is much more frequent and severe [2-6]. In over last two decades, worldwide atmospheric lead concentrations have decreased significantly, because many nations have removed tetra-ethyl lead from gasoline. But still the possibility of human exposure to lead is unavoidable because of the presence of its salts in air, dust, food, beverages, ink and even smoking also one of the factor that increase the amount of lead levels in blood [7]. Although hazardous to our health, it is been extracting and using for over 6000 years, assumed that an average of 150-250 gms of Lead is ingested daily through food, 5-10% is absorbed. The other sources for Lead poisoning may be Lead-solder kettles, cans and Lead-glazed pottery, which releases Lead when acidic fluids are stored or cooked in them [8]. Hence we aimed to determine the lead concentration in human biological samples and to analyse the impact of lead in blood on serum creatinine and hemoglobin in a tertiary care teaching hospital and Research centre, Bangalore.

1.1 Applications

The primary applications of Lead in Lead-acid batteries, which account for approximately 80 percent of the metal usage. Although pure Lead is very reactive its compounds such as Lead oxide can be very stable, making them suitable ingredients as corrosion resistant coating for iron and steel. Lead alloys are still used in some bullets. Lead glasses are considered to have special applications in camera lenses and optical instruments, while Lead crystals are used to create decorative pieces. Other Lead compounds are used in some paint pigments, as well as matches and fireworks [9].

1.2 Distribution of Lead in Different Tissues

Lead enters into the human body by inhalation, ingestion and absorbed through skin [10]. While entering the body, Lead gains access into the circulatory system and can move into various tissues [11].

1.3 Lead in Blood

Lead inhibits certain enzymes necessary for haeme production of delta-aminolevulenic acid dehydratase (ALAD), co-proporphyrinogen and ferrochelotase. Crystal studies of Progesterone binding proteins show all ALADs to be homo-octamers that purify with 8 Zn (II), of which 4 has sulphur ligands. In the presence of Pb (II), strong binding interaction is seen preferentially between these sites and Lead. In second step of haeme synthesis ALAD catalyses the asymmetric addition of 2 molecules of alpha-linolenic acid (ALA) to form porphobilinogen [12]. Even less than 10 µg/L lead levels can be detected in urine and blood due to displacement of Zn at the metal

binding site by Lead thereby increasing ALA levels in blood and plasma [12,13,14]. Many studies have concluded that chronic exposure to Lead leads to decrease in erythrocyte membrane permeability which is due to decrease in membrane transfer protein [15,16]. As Lead displaces zinc from its position an increase in the amount of zinc protoporphyrin in blood is also a biological marker for Lead poisoning [17]. Red blood cells (RBC's) has high affinity for Lead and contains 95-99%. One third of the Lead absorbed by the body reaches to systemic circulation in 2-3 minutes of which three-fourth of blood Lead is present in RBC's [18-22]. Within a week, Lead is lost from the RBC's with a net half-time of 15-20 days. Lead moves from diffusible plasma to Extra Vascular Fluid (EVF) which in turn moves to the retention sites in the tissues in a time and concentration dependent process [23,24]. This movement of Lead is treated as if it passed directly from the diffusible plasma to the retention sites in the tissue and therefore, is regarded as passing instantaneously through the EVF [23,25]. The EVF is three times the size of plasma pool and therefore, it contains three times as much Lead as in diffusible plasma [18,26].

1.4 Lead in Liver

Lead rapidly gets absorbed by the liver from systemic circulation and accumulated around 10-15% and removes within a week [27-31]. This is a time bound activity which is important in understanding the process of Lead chelation. Considering liver as consisting of 2 compartments: Liver 1 which has high Lead uptake from plasma and short half-time, Liver 2 which has low Lead uptake but with high retention time it gradually builds up Lead content over time [32,33]. Of all the Lead entering the liver from the diffusible plasma around 4% gets deposited in liver 1 and the removal half-time from liver 1 is 10 days. 45% of the Lead from liver 1 enters the small intestine as biliary secretions, another 45% returns to the diffusible plasma and 10% of the Lead in liver 1 is transferred to liver 2 where it is stored for a long time where the removal half-time is about 1 year. All the Lead leaving the diffusible plasma is assumed to return to the diffusible plasma over time. Liver may contain 2-3% of total body Lead [34,35].

1.5 Lead in Kidney

15-20% of Lead from the exchangeable blood plasma enters kidney within 1-2 hours. A substantial amount of the Lead that enters the kidney is excreted as urine or reabsorbed into the blood within few hours [36,37]. Comparison of the decline in renal and hepatic activity over the first two months indicates a half-time in the kidneys that would be roughly one-half of that in the liver [38]. The kidney is viewed as containing two compartments, urinary path and kidney tissue. The urinary path has relatively high Lead deposition but short retention time. The kidney tissue has relatively low Lead deposition but high retention time. Both these compartments receive Lead from the blood plasma. Lead in the urinary path compartment moves to bladder, through glomerular filtration, tubular absorption and tubular secretion after which it is excreted [36]. Around 2% of plasma Lead is said to enter the urinary path compartment and 0.02% of plasma Lead enters the other kidney tissue which has tenacious Lead retention ability. The removal half-time from the other kidney tissue to the diffusible plasma is about 1 year.

1.6 Lead in Brain

Brain is extremely sensitive to Lead and distributed unevenly in the brain, depends on the amount of Lead exposure. At low levels, the Lead concentration in different regions of the brain is significantly correlated with the potassium concentration, indicating that Lead is mostly accumulated in the cell rich parts of the brain like hippocampus [39-41]. Lead enters the cell gets accumulated in mitochondria and calcium rich centers, at high concentrations there will be change in blood-brain barrier and enters neuronal tissues. In young children Lead poisoning is very common, sometimes the concentration in the brain even exceeds than that of liver and kidneys. The brain has low Lead uptake capacity, but it has high tenacious Lead retention capacity [42]. It can accumulate up to 0.1% of body Lead with a half-time of 2 years in children and up to 0.15% in adults with a half-time of 6 months.

1.7 Lead Poisoning

Over the past 40 years, greater awareness about the negative health effects of Lead has resulted in many countries banning numerous of Lead products. Leaded fuel, which was widely used for much in the 20th century is now banned in most of the developed countries. Similar bans exist for paints with Lead pigments, Lead fishing sinkers and Lead piping [43,44].

1.8 Acute Poisoning

In acute poisoning, typical neurological signs are pain, muscle weakness, paraesthesia, and rarely symptoms associated with encephalitis [45]. Abdominal pain, nausea, vomiting, diarrhoea and constipation are acute symptoms. Lead effect on the mouth includes astringency and metallic taste. Gastrointestinal problems, such as constipation, diarrhoea, poor appetite and weight loss are common in acute poisoning. Absorption of large amounts of Lead over a short time can cause shock due to loss of water from the gastrointestinal tract. Haemolysis due to acute poisoning can cause anaemia and haemoglobin. Damage to kidneys can cause changes in urination such as decreased urine output. People who survive acute poisoning often go on to display symptoms of chronic poisoning [46].

1.9 Chronic Poisoning

Chronic poisoning usually presents with multiple systems [47] associated with gastrointestinal, neuromuscular and neurological symptoms. Central nervous system and neuromuscular symptoms usually results from the intense exposure, while gastrointestinal symptoms results from exposure over longer periods [46]. Signs of chronic exposure include loss of short-term memory or concentration, depression, nausea, abdominal pain, loss of coordination and numbness and tingling in the extremities [48]. Fatigue, sleeplessness, headache, stupor, slurred speech and anaemia are also found in chronic Lead poisoning [49]. A "Lead hue" of the skin with pallor is another feature [50]. A blue line along the gum, with bluish black edging to the teeth, known as “Burton line” is another indication of chronic Lead poisoning [49]. Children with chronic poisoning may refuse to play or may have hyperkinetic or aggressive behaviour disorders [45].

1.10 Lead and Cancer

IARC had been classified lead as a “possible human carcinogen”. The most commonly cancers caused by lead are lung cancer, stomach cancer and gliomas [51].

1.11 Lead and Gout

Hyperuraemic gout, apparently resulting from increased reabsorption of uric acid by the tubular cells is a third metabolic correlate of lead induced renal impairment [52].

1.12 Lead and Hypertension

Lead has also been suspected of increasing the risk for hypertension. Studies shows that statistically significant linear association between blood Lead concentrations and elevation of blood pressure among males and females aged 12-74 years. Lead can inhibit renal tubular reabsorption of sodium directly, probably by acting on Na^+/K^+-ATPase to alter intracellular concentrations of sodium and calcium ions. A change in cellular volume may elevate plasma renin activity. Lead may also affect cytosolic free calcium ion in juxtaglomerular cells and finally Lead may alter renal vascular reactivity to CY adrenergic agents [53].

1.13 Neurological Toxicity

In the peripheral nervous system the motor axons are the principal target of Lead [54]. Extensor muscle with "wrist drop" or "ankle drop" is the fatigue and short term memory loss in smelter workers exposed to Lead, the prevalence of these abnormalities increased with blood Lead concentrations [55].

1.14 Reproductive Toxicity of Lead

First half of the century, reproductive toxicity is described in lead workers of both sexes with high exposure of Lead incidence of spontaneous abortion was reported in female Lead workers and in the wives of male Lead workers decreased sperm counts and an increased prevalence of morphologically abnormal sperm have been reported. Lead causes irreversible neurological damage in the foetus of blood at low (15-20 µg/dl) concentration levels substantially across the placenta [56].

Lead is associated with many toxicities such as Cancer, Gout, Hypertension, Neurological toxicities, abnormal kidney function and reproductive system as well [51-55] and also associated with inhibiting of certain enzymes which are necessary for production of Haeme [57]. Similar studies were carried out on lead and other heavy metals like Cadmium, Mercury, Arsenic, aluminium. Increased lead levels of blood accumulate in the renal cortex causes Nephrotoxicity/Chronic Kidney Disease and neurologic effect [58,59].

2. MATERIALS AND METHODS

2.1 Method and Collection of Data

The Patients undergoing dialysis at KIMS Hospital and Research Centre, Bangalore were selected for the study and informed consent was taken and blood samples were collected (2ml) from the patients who have fulfilled inclusion criteria using a specially selected disposable plastic syringe (DispoVan) and stored in EDTA tubes under 10°c -30°c until blood sample is subjected to analysis, blood samples were analysed within 24 hours.

Lead care II blood analyser received market clearance from Food & Drug Administration (FDA) in USA and is classified under the Clinical Laboratory Improvement Amendment (CLIA) of 1988 as a moderately complex medical device (Federal register, 1997). It has been used elsewhere with success for paediatric screening [56].

It is chosen for the determination of Lead concentration in blood which employs the method of analysis based on Anodic Stripping Voltammetry (ASV). It delivers quantitative blood Lead concentration as a result, equivalent to those reported by reference laboratories, with only 2 drops of blood in just 3 minutes. It works by electroplating certain metals in solution onto an electrode, this concentrates the metal. The metals on electrode are then sequentially stripped off, which generates a current that can be measured. The current (milliamps) is proportional to the amount of metal being stripped off. The potential (voltage in millivolts) at which the metal is stripped off is characteristic for each metal. This means the metal can be identified as well as quantified [60]. It relies on electrochemistry (ASV) and a unique sensor to detect Lead in whole blood. Most Lead is carried within RBC's, when a sample of whole blood is mixed with treatment reagent, the RBC's are broke down and the Lead becomes available for detection. When a test is run, the analyser applies an electrical potential that causes the Lead to collect on the sensor. After 3 times, the analyser measures the amount of Lead on the sensor and displays the result in micrograms.

3. RESULTS AND DISCUSSION

The study includes 40 subjects who have fulfilled study criteria of which 20 were considered test samples in which 10 were male and 10 were females who were aged above 18 years and underwent dialysis. Similarly 20 healthy subjects were included for controls in which 10 were male and 10 were females. The results taken as shown in the Tables – 1 and 2.

Table 1. Concentration of lead in test group

Sl. no.	Age in years (male and female)		Blood pressure		Haemoglobin (g/dl)	Serum creatinine (mg/dl)	Concentration of lead in blood (µg/dl)
			Systolic (mmhg)	Diastolic (mmhg)			
1	M	50	170	96	9.3	7	7.1
2	M	60	150	100	10.3	1.7	12.9
3	M	38	160	90	9.8	15.2	5.7
4	M	36	116	76	7.5	12.9	4.8
5	M	74	240	120	7.7	9.3	8.1
6	M	49	180	100	8.1	7.3	5.7
7	M	85	140	80	9.2	5.5	19
8	M	68	150	90	10.4	2.2	9.2
9	M	55	190	110	8.5	5.2	6
10	M	23	160	100	5.8	14.9	4.1
11	F	48	160	120	6.5	10.7	6.4
12	F	62	126	82	9.1	3.2	8.1
13	F	55	102	70	18.1	4.5	10.8
14	F	60	180	100	11.9	4.2	11.6
15	F	42	110	80	3.8	8.7	9.2
16	F	60	136	86	9.4	6.2	8.5
17	F	50	120	80	9.6	7.3	11.2
18	F	45	100	70	11.3	6.8	5.8
19	F	45	130	80	12.3	9.1	5.9
20	F	58	150	90	7.3	10.3	6.4

Table 2. Mean and standard deviation of test group

Variables of test group	Mean value	Standard deviation
Age	53.15	13.90
Systolic BP	148.5	33.94
Diastolic BP	91	14.67
Haemoglobin	9.29	2.92
Serum creatinine	7.61	3.84
Lead concentration in blood	8.32	3.49

Table 3. Concentration of lead in control group

Sl. no.	Age		Blood pressure		Heamoglobin (g/dl)	Serum creatinine (mg/dl)	Concentration of lead in blood (µg/dl)
	M	F	Systolic (mmhg)	Diastolic (mmhg)			
1	M	25	120	80	12.2	1.2	3.3
2	M	39	125	80	13.5	0.9	4.6
3	M	38	128	83	14.1	1.2	5.7
4	M	49	127	86	13.8	1	12.9
5	M	30	122	80	13.8	1	8.1
6	M	40	124	84	13.7	1.3	5.9
7	M	50	129	87	13.3	1.3	7.1
8	M	39	122	86	15	1.3	5.9
9	M	24	124	84	14	1.2	3.5
10	M	26	122	85	14	1	6.7
11	F	40	124	83	12.6	0.7	4.4
12	F	25	126	86	13.5	0.9	7
13	F	50	125	85	12.7	1	9.2
14	F	68	129	86	13.7	0.8	7.1
15	F	35	122	85	13	0.9	6.4
16	F	49	126	85	12.7	1	8.5
17	F	38	128	86	12.9	0.9	3.9
18	F	40	120	80	12.4	0.9	5.6
19	F	32	121	84	13	1.3	3.9
20	F	27	125	80	13.5	1.4	5

Table 4. Mean and standard deviation of control group

Variables of control group	Mean value	Standard deviation
Age	38.2	11.12
Systolic BP	124.45	2.85
Diastolic BP	83.75	2.4
Haemoglobin	13.37	0.68
Serum creatinine	1.06	0.19
Lead concentration in blood	6.23	2.28

The demography of the subjects included into the study was all farmers and the age of the test and control subjects are above 23 years. The mean age of the patients was found to be 53.15, the standard deviation of the test group found to be 13.90 as shown in Table 2.

The 20 samples were grouped as control in which 10 males and 10 females and their mean age is found to be 38.2 and SD 11.12 as shown in the Table 4.

The normal value of blood pressure is taken as 120/80 mmHg as per Joint National Committee (JNC) guidelines, elevated value of lead in blood found to have impact on increasing blood pressure by directly inhibiting the renal tubular reabsorption of Na^+ and also acts on Na^+/K^+ ATPase to alter intracellular concentration of Sodium and Calcium ions.

Systolic and diastolic blood pressure is measured using sphygmomanometer. The mean systolic blood pressure test group was found to be 148.5 with ± 33.94 SD as shown in Table 2. Similarly, the mean diastolic blood pressure was found to be 91 with ±14.67 SD, As well for control group the mean systolic blood pressure is found to be 124.4 with 2.85 SD which is shown in Table 4.

Serum Creatinine is taken as the standard laboratory marker for the detection of kidney disease. The third National Health and Nutrition Examination Survey quoted a mean serum creatinine of 0.96 mg/dl in women and 1.16 mg/dl in men. The present study revealed that the mean value of serum creatinine in test group is found to be 7.61 and the standard deviation is 3.84, similarly the mean value of control group is 1.06 and the standard deviation is found to be 0.19. By using IBM SPSS version 19.0 software a Spearman's Rank Order correlation was run to determine the relationship between 20 test respondents for Lead in Blood and levels of serum creatinine, there is a strong correlation which is statistically significant (0.001) (2 tailed).

The Fig. 1 shows that serum creatinine levels and blood lead levels in tests samples, similarly for control group as shown in Fig. 2, the sample size is on X axis and serum creatinine and Concentration of Lead in blood on Y axis are taken.

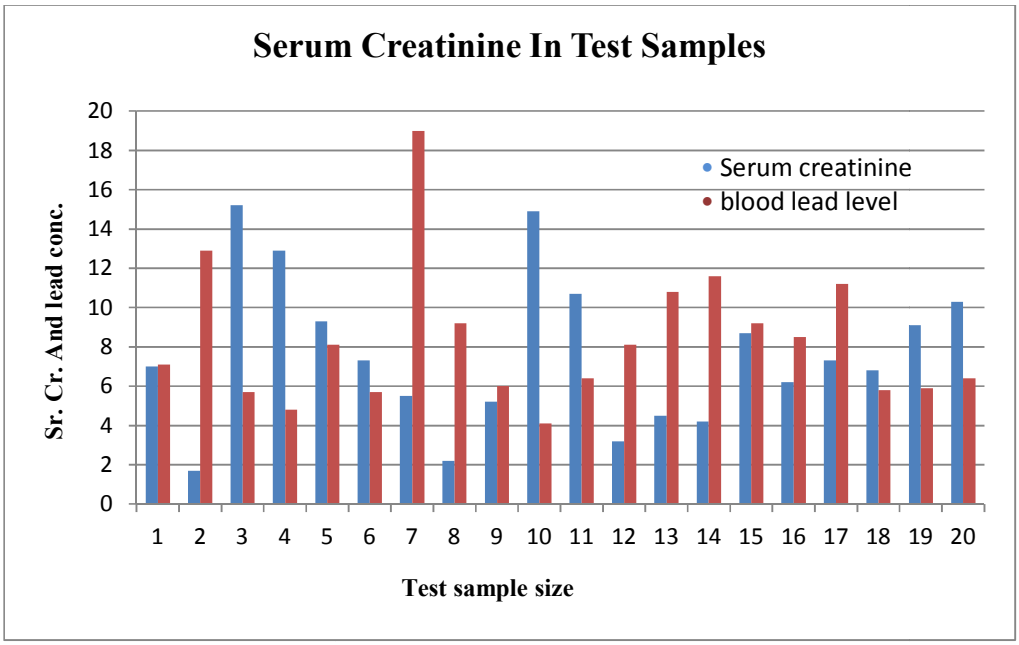

Fig. 1. Test group

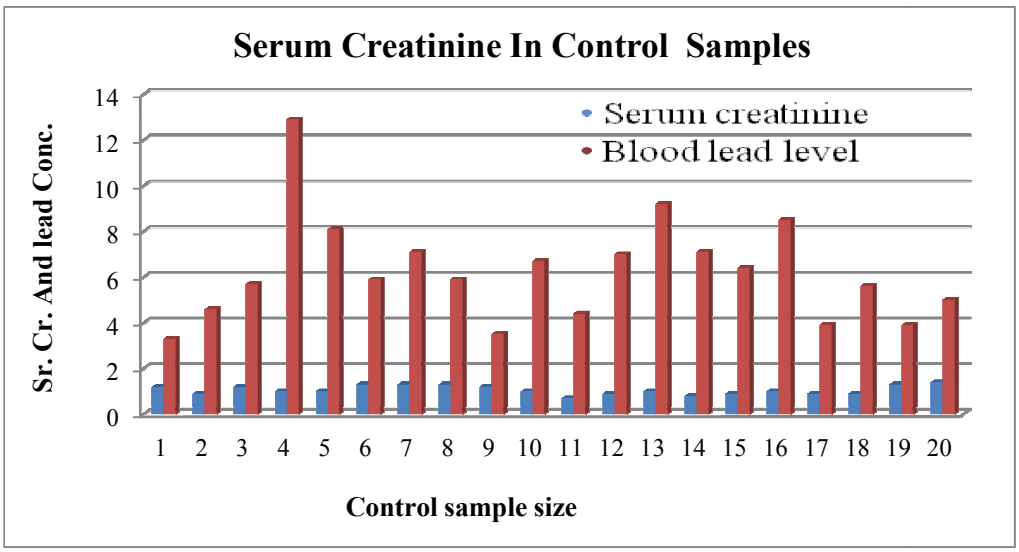

Fig. 2. Control group

Haemoglobin consists of a protein component with two α and two β chains, each chain is linked to a haeme group consisting of a porphyrin ring structure with an iron chelated at its centre, which is capable of binding oxygen under normal conditions, the body produces approximately 6.25 g of Haemoglobin every day. The normal life span of RBCs is 120 days but the lead toxic anaemic patients were found to be 18 to 20 days.

The study revealed that the mean value of Haemoglobin is found to be 9.29, 13.37 and the SD 2.92, 0.68 for test and control respectively. The spearman's correlation coefficient is been adopted to determine the relationship between the Lead in blood and the Haemoglobin and found that significant value of 0.135, which shows that there is no correlation between blood lead level and haemoglobin.

4. CONCLUSION

The determination of Lead concentration in blood and impact of Lead in blood on serum creatinine and hemoglobin shows that there is a strong relationship exists between Lead in Blood and Serum creatinine and also strong positive correlation between Lead in Blood and Serum creatinine, which is statistically significant [rs(20) = 0.683, p = 0.001] in test group. There is a strong, negative correlation between Lead in Blood and levels of Hemoglobin, which is statistically not significant [rs(20) = 0.346, p =0 .135] in test group. There is a strong, negative correlation between Lead in Blood and levels of Serum creatinine in controlled group which is statistically not significant [rs(20) = 0.113, p = 0.635].

There is a strong, negative correlation between Lead in Blood and levels of Hemoglobin, which was statistically not significant [rs(20) = 0.204, p =0 .388] in control group.

Lead is found to be toxic to all forms of life, so it is important to determine its concentration in blood as well as in other tissues to prevent accumulation and further its toxicological effects on different tissues and organs.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

Ethical approval was taken from Vissveswara ours institute of pharmaceutical sciences ethics committee before conducting the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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