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ASSOCIATION OF BLOOD LEAD LEVELS IN RELATION TO REPRODUCTIVE HORMONES AMONG HEALTHY POSTMENOPAUSAL WOMEN.

Biochemistry

Dr. Dipankar Bhattacharyya — Consultant, Dept of Obstetrics and Gynaecology, AMRI Hospital, Kolkata

Dr Ipsita Mazumdar* — Associate Professor, KPC Medical College & Hospital, Kolkata, West Bengal, India.*Corresponding Author

Prof Krishnajyoti Goswami — Professor, Lincoln University College, Kuala Lumpur, Malaysia

ABSTRACT

Lead (Pb) is pervasive in the environment and highly toxic for humans, with most adults having measurable levels in their blood. Some epidemiologic studies in peri- and post- menopausal women have suggested that Pb alter hormone levels, as an environment disrupting chemical and reproductive toxin that primarily represent current exposures to Pb through various sources. It has been associated with altered steroidogesis, gonadotrophin binding and decreased serum gonadotrophin levels, altered follicular growth and maturation. It can also stimulate the Estrogen (E2) receptor by interacting with amino acids at the receptor binding site and produce estrogenic changes.

The present study estimates associations between blood Lead level and reproductive hormones among healthy peri- and post- menopausal women. A total of 279 participants were enrolled. Blood was analysed for Pb and hormonal estimation of E2, LH, FSH, TT and SHBG levels. Blood Pb levels were significantly and positively correlated with serum FSH, LH and SHBG, TT and E2 levels in postmenopausal women exposed over a period of time.

KEYWORDS

Lead, Postmenopausal women, LH, FSH, E2.

Introduction

Lead (Pb) is pervasive in the environment and highly toxic for humans and also is ubiquitous in the environment following many years of industrial use, with most adults having measurable levels of this non-essential element in their blood. Exogenous factors may affect hormonal function, and also some epidemiologic studies in peri- and post- menopausal women have suggested that toxic heavy metals alter hormone levels[1]. Pb is an environment disrupting chemical and reproductive toxin. Blood Pb levels in peri- and post- menopausal women primarily represent current exposures to Pb through contaminated food and water, home renovations, Pb-glazed pottery, certain health care products and or folk remedies, as well as bone Pb stores released during bone turnover[2]. Divalent Pb, can stimulte the Estrogen (E2) receptor by interacting with amino acids at the receptor binding site and produce estrogenic changes[3]. Pb bio-accumulate in the body primarily accumulating in the bone where it has a half-life of 12 – 27 years. Pb has been identified in human follicular fluid and ovarian tissue, and have been associated with adverse reproductive outcomes in epidemiologic studies while the biological mechanisms by which this metal may exert adverse reproductive effects have not been fully elucidated, toxicological studies have provided some insights[4].Pb have been associated with altered steroidogesis, decreased gonadotrophin binding and decreased serum gonadotrophin levels[5]. Pb is associated with altered follicular growth and maturation[6].

The objective of the present study was to estimate associations between biomarkers of Pb exposures and patterns of reproductive hormones like, Estradiol (E2), Progesterone, LH, FSH, testosterone (TT) and sex hormone binding globulin (SHBG) among healthy peri- and post- menopausal women. Blood collection was not timed to particular stages of the menstrual cycle and was limited to women aged 55– 60 years of age.

Materials and Methods

A total of 293 participants were enrolled in the study. A woman was considered to be post menopausal if she was more than 55 years of age[7]. The post menopausal women with a history of hysterectomy and oophorectomy and taking hormone replacement therapy were excluded from this study. Finally, the current study was based on a total of 279 post menopausal women. Meticulous history of previous exposure to Pb was collected and the participants were deivided into the Study group and Control group respectively, according to that and their blood Pb levels.

The study was in accordance with Declaration of Helsinki and guidelines on good clinical practice locally available. The study protocol was approved by institutional review board and ethics committee[8].

All participants provided written informed consent before data collection and then were asked to provide a health and reproductive history and lifestyle information (e.g., smoking and alcohol intake) and anthropometric measurements were taken by trained staffs. The usual physical activity questionnaire (IPAQ) and a food frequency questionnaire was used to estimate usual daily total energy, iron, shellfish, fish and vegetable intake during the previous six months.

Weight and height were measured with participants wearing light clothing and no shoes. Body Mass Index (BMI) was calculated as weight in kilogram divided by height in metres square. Blood pressure was measured following standards methods. In accordance with the American Diabetics Association (ADA) 2017 criteria, diabetics as a previous diagnosis by healthcare professionals, fasting plasma glucose (FPG) > 126 mg/dl, or glycated haemoglobin HbA1C $\geq$ 6.5 % Hb or previous diagnosis of diabetics[9].

Venous blood sample were drawn from all subjects after an overnight fast of at least 10 hours. Blood was collected for Pb analysis and hormonal estimation of E2, LH, FSH, TT and SHBG levels.

Blood Pb measurement was done using Lead Care Analyser (ESA, USA, Version 3.3), which includes the Lead Care Kit. 50 µl of whole blood in the EDTA was added to the treatment reagent in special tubes supplied with the kits.

Serum E2, LH, FSH, TT and SHBG were measured by Roche Cobas 6000 Modular System based on ECLIA principle[10]. The minimum detection limit of each hormones was as follows:18.4 pg/ml (E2), 0.1 mIU/ml (LH), 0.1 mIU/ml (FSH), 0.025 ng/ml (TT) and 0.35 nmol/L (SHBG).

The study utilised both internal and external quality control procedure and obtained consistently satisfactory results, using quality control sera of BioRad, USA.

The statistical analysis was done using SAS version 9.2 software (Cary, NC, USA), by applying Student's t Test, considering the P value of <0.05 as statistically significant.

Results

The general characteristics of the study populations are summarised in **Table 1.** This study recruited 279 postmenopausal women. Blood Pb levels were significantly and positively correlated with serum FSH, LH and SHBG, TT and E2 levels in postmenopausal women exposed to Pb over a peroid of time.

Table 1 : General characteristics of participants

Parameters	Control Group (N=158)	Study Group (N=121)	P value
Age (in year)	57 ± 3.0 (56 – 63)	58 ± 2.9 (56 – 62)	< 0.5
BMI (in Kg/m2)	24.0 ± 2.1 (22.2 - 26.4)	24.1 ± 1.9 (22.2 – 26.3)	<0.68
TT (in nmol/L)	0.26 ± 0.02 (0.22 – 0.29)	0.48 ± 0.09 (0.42 – 0.54)	<0.0001
E2 (in pmol/L)	26.39±2.23(24.02–28.13)	37.50 ± 3.56 (35.12 – 43.97)	<0.0001
FSH (in IU/L)	33.96 ± 6.78(26.20 – 39.69)	63.50 ± 14.94 (47.10 – 82.76)	<0.0001
LH (in IU/L)	8.12 ± 2.69(5.92 – 11.02)	22.79 ± 4.96 (17.36 – 29.61)	<0.0001
SHBG (in nmol/L)	28.38±14.02(14.67–42.98)	62.30 ± 17.92(42.96 – 86.31)	<0.0001
Blood Pb Level (in µg/dl)	2.23 ± 0.89 (1.60 – 3.97)	16.20 ± 4.32 (12.90 – 21.70)	<0.0001

Values represent Mean ± SD

Thus it was observed that in age and BMI matched postmenopausal women there exists very significant differences in serum reproductive hormone levels depending on Pb exposure.

Discussion

The finding of this study provide some evidence that low levels of Pb may be associated with hormonal variation in healthy postmenopausal women. Blood Pb levels were positively associated with serum FSH, LH and SHBG levels among postmenopausal women. Only a limited number of epidemiological studies have explored the association between blood Pb levels and reproductive hormones. Our results are consistent with several population-based studies conducted in US postmenopausal women[11].

Also, these significant association of blood Pb levels with serum FSH and LH may explain these increases by two possible mechanisms. The Pb can cross the blood-brain barrier and directly disrupt the hypothalamic-pituitary axis[12]. Long-term low-dose Pb exposure has been shown to cause a significant increase in gonadotropin - realising hormone mRNA, which may stimulate the secretion of FSH and LH. Pb could also act directly by elevating homocysteine concentrations. Furthermore, homocysteine serves as an N-methyl D-aspartate agonist and GABA antagonist N-methyl D-aspartate stimulates FSH and LH release and GABA plays a major role in the regulation of gonadotropin - releasing hormone neutron activity and secretion[13].

In addition, the elevated serum FSH levels are independent risk factors for bone loss in postmenopausal women and could be used as indicators in the early diagnosis of postmenopausal osteoporosis[14]. And the elevated levels of serum LH induce changes in adrenal function towards cortisol secretion, which may contribute to an increased incidence of metabolic syndrome in women after menopause[15].

We have also observed, positive association between blood Pb levels and serum TT levels. Studies have been conducted to show positive corelation between blood Pb levels and TT levels in male workers. Though not much data is available about serum TT levels of Pb exposed post menopausal women, our study reflects the results[16]

It is clearly evident that there is no Pb induced oxidative stress in postmenopausal women. Generally Pb induces the generation of reactive oxygen species, increases the level of lipid peroxidation and inhibits the activity of antioxidant enzymes, including glutathione, catalase and superoxide dismutase[13].

This study shows blood Pb levels to be positively associated with serum SHBG levels in postmenopausal women. The serum SHBG is produced and secreted by the liver into the blood where it binds sex steroids and regulates their bio-availability and stimulates albumin–bound testosterone, which is associated with atherosclerosis in postmenopausal women[17].

This study revealed that Pb exposure could increase serum SHBG levels; thus influencing the utility of serum SHBG as a sensitive biomarker or alternatively as a biomarker of the degree of inflammation in metabolic diseases. But the mechanism by which Pb affects serum SHBG is still unknown.

Our study reveals a significant level of increse in E2 in post menopausal women affected with Pb poisoning. Divalent Pb, can stimulte the Estrogen (E2) receptor by interacting with amino acids at the receptor binding site and produce estrogenic changes3.A few studies done on mice have shown that interaction of Pb with hormone action maybe direct, via changes in hormone receptors,[18] or is caused by changes in Prolactin levels which increase in Pb poisoning[19].

In conclusion, blood Pb levels were positively associated with serum FSH, LH and SHBG levels and no clear cut association with serum TT and E2 levels in postmenopausal women.

Limitation of study

The inability to obtain large sample size. This is due to the nature of the cases, which are difficult to find considering all the inclusion and exclusion criteria.

Conflict of Interest

The authors declare no conflict of interest in the present study conducted.

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