

# Serum Sex Hormonal Responses to Acute Oral Cadmium Exposure of Male Wistar Rats

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## ABSTRACT

The objective of this study is to investigate the possible effects of cadmium (Cd) exposure on the serum levels of sex hormones in male Wistar rats. Twenty rats were grouped into four and treated with Cd as follows; control (unexposed) and groups 2, 3 and 4 were exposed to 10ppm, 100ppm and 1000ppm Cd respectively for 7 days through contamination of their drinking water. Blood samples were collected for the determination of sex hormones via enzyme immunoassays and the obtained data statistically compared. There was a significant increase in blood Cd level in the 100ppm ( $0.0153 \pm 0.0085$ ppm) and 1000ppm ( $0.0298 \pm 0.0204$ ppm) exposed groups compared to control ( $0.0008 \pm 0.0005$ ppm). The results showed a dose-response increase in serum leutinizing hormone ( $2.10 \pm 0.12$ ;  $2.29 \pm 0.26$ ;  $2.22 \pm 0.37$ ;  $3.18 \pm 0.54$ ) g/L and follicle stimulating hormone ( $1.63 \pm 0.40$ ;  $2.40 \pm 0.32$ ;  $3.09 \pm 0.10$ ;  $3.81 \pm 0.36$ ) g/L but decrease in serum testosterone ( $4.62 \pm 0.490$ ;  $2.87 \pm 0.47$ ;  $2.10 \pm 0.18$ ;  $1.57 \pm 0.32$ ) ng/ml in that order in the unexposed group compared to the Cd-exposed groups. Oral Cd exposure can be a critical determinant of sex hormone homeostasis in male rats and its influence in the animal fertility is not unlikely.

## Introduction

Cadmium (Cd) is a toxic, extensive and persistent metal in the environment and modern civilization processes have contributed to it increase in the environment and has led to its rising occurrence in the food chains [1]. This metal has been placed 7th on the list of substances that pose potential threat to human health due to their known or suspected toxicity [2]. Industrially, Cd is used in a variety of manufactured products resulting in the increased bio-accessibility, and anthropogenic sources are the most significant threat to human health [1,3]. Exposure to Cd can occur through smoking, contaminated food, water and air [4,5]. The European Food Safety Authority (EFSA) estimated between 20.3 and 74.2  $\mu\text{g}/\text{day}$  as the average daily dietary exposure of Cd for a 70 kg person [5] and children and vegetarians have been noted as specific groups at risk of consuming higher dietary Cd than the recognized safe dose [6]. Due to lower concentrations of iron in women, they are thought to be at greater risk of increased Cd accumulation than males [7,8].

Cd accumulates in the kidney, liver and the reproductive organs [9]. For this reason, Cd is categorized as environmental endocrine disruptors because it alters endocrine system function(s) and consequently cause adverse endocrine related health effects [10]. The endocrine disrupting effect of Cd has been extensively investigated but the outcomes are both agonistic [11-14] and antagonistic [14-16]. Chronic Cd exposures has been reported to disturbed reproductive endocrine function, cause testes degeneration, decrease testicular mass [17-19], and decreased spermatozoa mobility [20] in male rats. Studies in female rats showed Cd accumulates in the female reproductive organs [9,14,21-24]. *In vivo* studies have shown Cd administration to cause histopathological alterations in the ovary and uterus that include corpus luteum and granulosa cells degeneration, deceased oocytes population, increased luminal epithelial height and endometrial thickness [1, 25, 26] and disturbances in the concentrations of

circulating steroid hormones and estrous cycle abnormalities [1,21]. On the other hand, Johnson et al. [12] documented Cd exposure to produced uterine hyperplasia, increased mammary glands growth, and hormone-regulated genes induction in ovariectomized rats.

Cd has also been reported to shows androgen-like activities in vitro and in vivo, and it disrupts the male endocrine system in animal models [4]. There are however conflicting results regarding Cd increases or decreases testosterone production in experimental models [27-29], with decreases more commonly seen after a single, large dose injection of cadmium and increases more commonly seen after chronic oral cadmium exposure [30]. In human, studies investigating the association of Cd and sex steroid hormones in men have been inconsistent with either no association [31-33], or a positive association between cadmium and testosterone levels [34-36]. Due to the paucity of literature on the effect of Cd on male sex hormone levels, this study investigates the changes in the reproductive hormones of adult male Wistar rats following acute oral exposure.

## Materials and Methods

### Materials

Cadmium chloride ( $\text{CdCl}_2$ ) was obtained from a Chemical store in Nigeria. All other chemicals were of analytical grade. The rat chow was obtained from a poultry store in Ekpoma, Nigeria. Except otherwise stated, the drinking water supplied was clean tap water.

**Animals:** Twenty male Wistar rats, weighing 140g to 160g were obtained from the Animal House, College of Medicine, Ambrose Alli University, Ekpoma. The rats were transported and kept in their own cages in the physiology laboratory II and maintained in a room with 12-hour light/dark cycle. They were fed standard rat chow and water ad libitum for a two-week period of acclimatization.

**Study Design:** After acclimatization, the rats were randomly assigned to four experimental groups, ( $n = 5$ ) as follows: Group 1; served as the control group and was supplied clean tap water throughout the experiment. Group 2, 3 and 4 served as test groups and were served drinking water contaminated with cadmium

chloride in the concentration of 10ppm, 100ppm, and 1000ppm, respectively. All animal had access to normal meal and drinking water throughout the study period.

**Sample Collection:** At the end of the 7th day, blood sample (3ml) was collected into two separate plain containers (each containing 1ml and 2 ml) via cardiac puncture after animals were cervically decapitated after ketamine/ zylazine anesthesia. The 1 ml blood samples were digested with  $\text{HNO}_3$  and blood Cd level determined by atomic absorption spectrophotometer as documented by Goncalves et al. [37]. The 2 ml blood samples were spin at 5000rpm for 15 minutes and the serum obtained placed in plain containers and refrigerated until assay. FSH, LH and testosterone concentrations were measured using ELISA kits (Biocheck, Inc, USA) and according to manufacturer's instructions.

**Statistical Analysis:** Statistical analyses were performed using "tools" from the SPSS version 20.0 programme. The data was subjected to one-way analysis of variance (ANOVA) and LSD post hoc test was used for multiple comparisons and expressed as mean  $\pm$  standard deviation;  $p < 0.05$  was considered significant.

### Results

Table 1 shows the effect of Cd exposure in drinking water on blood Cd-level of the experimented animals. The exposure to varying concentration of Cd caused a dose-dependent increase in blood Cd levels and significant in the 100ppm ( $0.0153 \pm 0.0085$ ppm) and 1000ppm ( $0.0298 \pm 0.0204$ ppm) groups compared to the control ( $0.0008 \pm 0.0005$ ppm). Figures 1- 3 shows the effect of Cd exposure in drinking water on serum FSH, LH and T respectively. There was a dose dependent significant increase in serum FSH ( $1.63 \pm 0.40$  g/L vs  $2.40 \pm 0.32$  g/L vs  $3.09 \pm 0.10$  g/L vs  $3.81 \pm 0.36$  g/L) but only the 1000ppm dose significantly increase serum LH ( $2.10 \pm 0.12$  g/L vs  $2.29 \pm 0.26$  g/L vs  $2.22 \pm 0.37$  g/L vs  $3.18 \pm 0.54$ g/L) compared to the control. Also, there was a dose dependent decrease in serum T compared to the control ( $4.62 \pm 0.49$  ng/ml vs  $2.87 \pm 0.47$  ng/ml vs  $2.10 \pm 0.18$  ng/ml vs  $1.57 \pm 0.32$ ng/ml) following vary doses of Cd exposure.

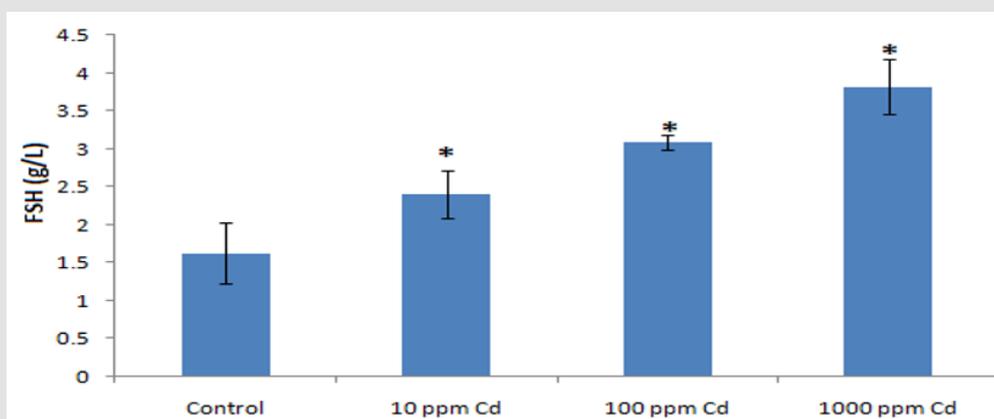
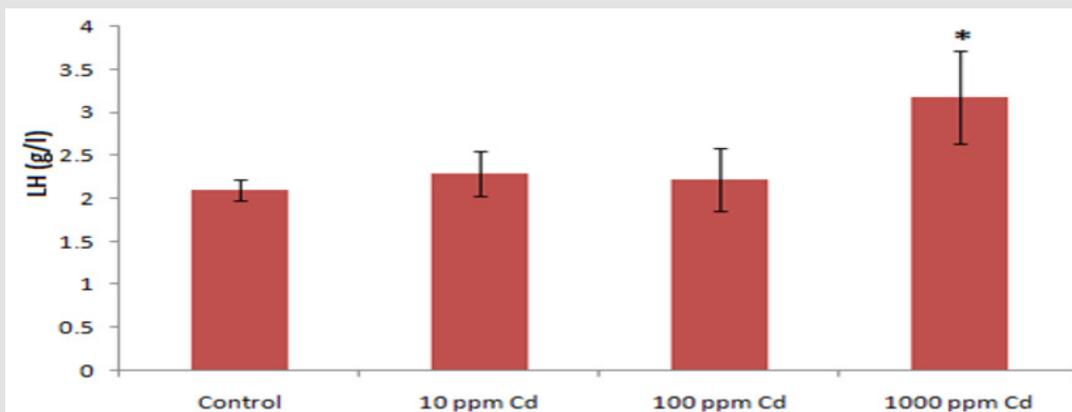
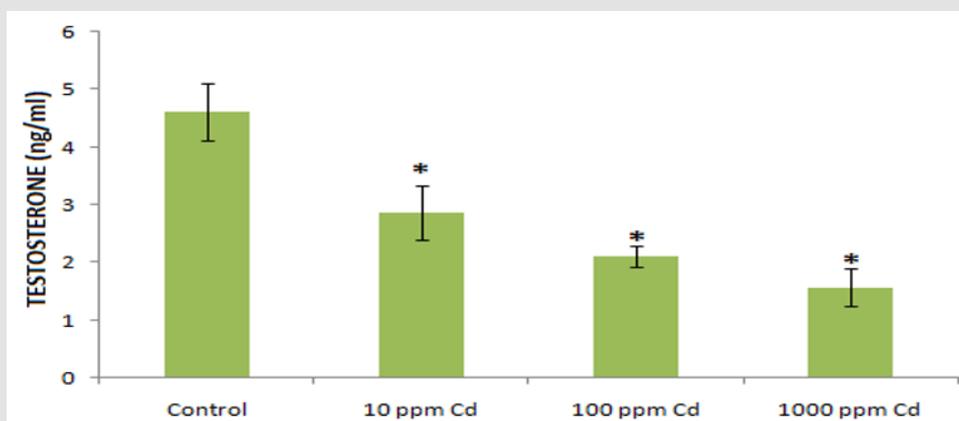


Figure 1: Effect of varying concentrations of Cd exposure in drinking water on serum FSH level in adult Wistar rats (\*  $p < 0.05$ ).



**Figure 1:** The effect of varying concentrations of Cd exposure in drinking water on serum LH level in adult Wistar rats (\* p<0.05).



**Figure 3:** The effect of varying concentrations of Cd exposure in drinking water on serum testosterone level in adult Wistar rats (\* p<0.05).

**Table 1:** Effect of varying concentrations of Cd exposure in drinking water on blood Cd level in adult Wistar rats.

	Control	10ppm Cd-exposed	100ppm Cd-exposed	1000ppm Cd-exposed
Blood Cd-level (ppm)	0.0008±0.0005	0.0021±0.0013	0.0153±0.0085*	0.0298±0.0204*

**Discussion**

Direct and indirect evidences exist on Cd-induced deleterious health effects through reactive oxygen species following acute overload and chronic toxicity in animals [38] and an early catabolic damage [39]. Blood Cd level is a measure of acute exposure [40] and in the present study, exposure to 100ppm and 1000ppm Cd for 7 days significantly increase blood Cd level. Other studies have also documented increase blood Cd level following oral exposure. In this instance, Adegoke et al. [41] reported increased blood Cd level higher than those reported in this study following 28 days exposure to 100ppm. However, the increased blood Cd level in the present study showed adequate exposure in the test groups as earlier affirmed by [42,43].

In this study, acute Cd-exposure was observed to be linked with increased production of FSH and LH and inhibition of

serum Testosterone. The observed alterations in sex hormones as compared to the control were dose dependent and significant even at the lowest dose except for LH where only the 1000ppm was. In support of these findings, several studies have documented hormonal alterations following Cd-exposure. Cd has the potential to affect reproduction and development in several mammalian species [44]. Compared to animal studies, it is claimed that cadmium decreases density, volume, and number of sperms, and increases immature sperm forms [45]. These problems are followed by a defect in spermatogenesis, sperm quality, and secretory functions of accessory glands. Besides, it decreases libido, fertility, and serum testosterone level [46].

This study showed blood Cd level to correlates negatively with serum testosterone but positively with serum LH and FSH. These findings disagree with the studies on Croatian men who had never been occupationally exposed to cadmium [34, 36] and in a study

of Chinese male smelter workers [35] where blood cadmium was positively associated with testosterone. However, in US adult men study, a marginally significant association between cadmium and total testosterone among never smokers and free testosterone among current smokers was observed [4]. The increase stimulation of serum FSH and LH by Cd could indicate Cd effect on the pituitary gland gonadotrophine hormones and the hypothalamus gonadotropes. However, the stimulated pituitary hormones did not result in the increase in testosterone. This observation showed that though Cd may stimulate pituitary sex hormones, it inhibits sex organ hormone, testosterone. This observation agrees with the report by Chandel and Chand [46] that Cd decrease serum testosterone and may decrease libido and fertility in men. The perceived effect of Cd on the overall virility of the male should be of grave concern to Health Practitioners and Fertility experts.

Cd exposure induces a dose depended alterations in male sex hormones. Oral Cd exposure has demonstrated to be a critical determinant of hormone in males. The relationship found between Cd exposure and reduced serum T levels may be of importance for male fertility and continuing investigations will be worthwhile.

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