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Full Length Research Paper

Effects of cadmium (Cd) and lead (Pb) on the structure and function of thyroid gland

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The present study was carried out to investigate the effects of two heavy metals, Cadmium (Cd) and Lead (Pb), on the structure and function of the thyroid gland. Wistar albino rats were chosen for experimental purpose. The animals were fed on diet mixed with given doses of Cd and Pb salts. Blood serum was taken from treated rats recorded decrease in the thyroxine (T4) and the 3, 3 , 5-triiodothyronine (T3) levels with a concomitant rise in the Thyroid Stimulator Hormone (TSH) levels, while no change in glucose and cholesterol levels was shown. Microscopic examination of the cellular structure of the thyroid glands of treated rat's recorded changes in the follicular cells of the thyroid tissues in the rats exposed to Cd and Pb in a comparison to that of the control animals. Histological results were confirmed by the findings of the serum analyses that recorded inhibition on the production of the thyroid hormones in the presence of Cd and Pb. This indicates that animals exposed to Cd and Pb may be at a risk of thyroid damage.

Key words: Heavy metals, cadmium, lead, thyroid.

INTRODUCTION

Thyroid is an endocrine gland synthesizes and secretes important regulatory hormones: triiodothyronine (T3), tetraiodothyronine (T4) and calcitonin (CT). Iodothyronine (T3, T4), synthesized in follicular cells are necessary for normal growth and development (Zoeller et al., 2002). Parafollicular cells, via CT secretion, play an important role in the regulation of calcium and phosphate metabo-lism (Sakai et al., 2000; Sawicki, 1995). Serum levels of thyroid hormones, including T3, T4 and TSH, are com-monly used as reliable indicators of the thyroid function in humans and experimental animals. Changes in the se-rum concentration of these hormones can reflect distur-bances in their glandular synthesis and/or secretion as well as disorders in their extra-thyroidal peripheral metabolism (Chaurasia et al., 1996; Kelly, 2000; Paier et al.., 1993). The function of thyroid gland is evaluated by measuring the levels of serum thyroid hormones such as T3 and T4, and pituitary TSH. The cellular structure of the thyroid gland can be assessed under a light micro-scope.

In recent years, it has been pointed out that a few exo-genous environmental pollutants have a disrupting effect on the human endocrine system (Jun et al., 2005). Since the beginning of this century, human environment has been undergoing profound changes in the wake of mo-dern scientific and technological development. Increasing use of metals is one measure of man s progress and, accordingly, human population is simultaneously ex-posed to a complex mixture of metals through air, water, and food.

Cadmium (Cd) and Lead (Pb) are heavy metals that can be toxic when introduced into body by ingestion or inhalation in sufficient quantities. They cause various destructive effects (Neathery and Miller, 1975). In human, lead and cadmium cause many serious diseases and dysfunction of organs (Gennart et al., 1992; McGregor and Mason, 1990). Cadmium enters the environment

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through fertilizer application, burning of fossil fuels, mining and other industrial activities (Hayes, 1995). Likewise, Lead can enter the environment through vehicle and Industry exhausts and sewage sledge application in agriculture (Vogiatizis, 2001).

The main purpose of the study was to assess and evaluate the influence of toxicity with Cd and Pb on the structure and function of the thyroid gland. Despite of many reports are available on the effects of Cd and Pb on the thyroid gland, the present study was involved the hormones measurement with histomorphology study of thyroid gland to give more clear idea about the mechanism of effects. Further, the study considers the effects of these metals in glucose and cholesterol levels of the blood serum of experimental animals as measures of the thyroid function.

MATERIALS AND METHODS

Experimental design

The study was carried out in accordance with national and international laws and Guidelines for the Use of Animals in Biomedical Research. Twenty adult males' albino rats were procured from the Central Veterinary Research Laboratories (150-200 g body weight). These rats were acclimated for two weeks before experimentation in well-ventilated animal cages (45 X 45 X 45 cm.) and under standard laboratory conditions (photoperiod: 14 h light: 10 h dark and temperature 24 ± 1ºC). The persistent rats were divided into three groups .Group (I) represented the control group was fed on diet free from any other additions (0.0 ppm/kg. body weight) daily for 6 weeks. Group (II) was given diet mixed with lead acetate (1000.0 ppm/ kg. body weight) daily for 6weeks. Whereas the group
(III) was given diet mixed with cadmium carbonate (100.0 ppm/ kg. body weight) daily for 6 weeks. The doses of target metals were chosen according to Abaza et al. *(*1996). The experiments were terminated after six weeks. Blood samples were collected from the three groups after the elapse of one week, three weeks and six weeks. The hormones, glucose and cholesterol levels were measured after each intervals. Animals in all groups were dissected by the end of the experiments. Both the thyroid lobes of each rat were collected for histomorphology investigation and assessed microscopically.

Blood sampling and processing

Blood samples were collected from the Retro Orbital Plexus muscle of the eye following Poole (1987). Blood was collected in non-heparinized test tube. Blood samples were left for approximately 20 minutes to allow clotting. Clear sera were obtained by centrifugation at 2000 r.p.m for 15 minutes. Then the separated sera were kept at 4.0°C in the refrigerator for hormones, glucose and cholesterol assay. Thyroid glands removed from all rats under experiment were separated from attached tissues, washed twice with phosphate buffer saline (pH 7.4) prior fixated and processed for histological investigations.

Estimation of T3, T4 and TSH (thyroid-stimulating hormone)

T3, T4 and TSH serum levels were measured radioimmunologically using commercially available kits T3 RIA- kit IMK-422, T4-RIA- kit M IMK-437 (China Institute of Atomic Energy 1994) and TSH RIA-kit IMK-432(Beijing Atom High-Tech Co., LTD) respectively. All assays were performed in the laboratories of Sudan Atomic Energy Commission (SAEC).

Determination of glucose and of cholesterol levels

Glucose in the serum was measured by enzymatic method using Glucose-TR kit (Spinreact), whereas Cholesterol was measured calorimetrical using ferric chloride as indicator (Zarraw et al., 1964).

Statistical analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences Inc, Chicago, Illinois) version 13.0. One- way analysis of variance (ANOVA) was used for some treatments to visualize the interactions effects. The level of significance is the standard.

Histological Studies

The thyroid lobes were fixed in formal saline at room temperature for 24 h before being dehydrated and embedded in paraffin wax (melting point 65^{O}C). The tissues were sectioned at 5 m and routinely stained with haematoxylin and eosin (H&E) . Histological structure of follicular cells of the thyroid was evaluated under a light microscope (NIKON ECLIPSE E 400, USA) and photographed using digital camera attached to the microscope.

RESULTS

Thyroid hormones concentrations

No significant change was observed in 3, 3 , 5-triiodothyronine (T3) concentration of control group after one, three and six weeks (P> 0.05). In the animals' groups given lead acetate (1000.0 ppm/kg. body weight) and cadmium carbonate (100.0 ppm /kg. body weight), the average values of T3 were decreased. The decrease due to Pb was significantly different compared to control since the first week till the end of experiment. However, in the case of Cd, the decrease was become higher only after 3 and 6 weeks from the first dose (Figure 1). These changes were highly significant difference in rats treated by Pb and Cd compared to the control group (P< 0.000).

Thyroxin (T4**)** concentration decreased in the serum of two groups of rats treated with Cd and Pb .The decrease due to Cd and Pb was significantly different since the first week till the end of experiment compared to control group (Figure 2). These changes were high significant difference in rats treated with Pb and Cd compared to the control group (P< 0.003). Thyroid Stimulator Hormone (TSH) concentrations increased in the serum of rats treated with Cd and Pb. These increases were after one and three weeks in Pb group and after 3 weeks in Cd group compared with the control group. However, TSH concentration decreased in the serum of both Cd, Pb rats group after 6 weeks, and reached 0.0 concentrations for rats fed on Pb (Figure 3). There were significant diffe-

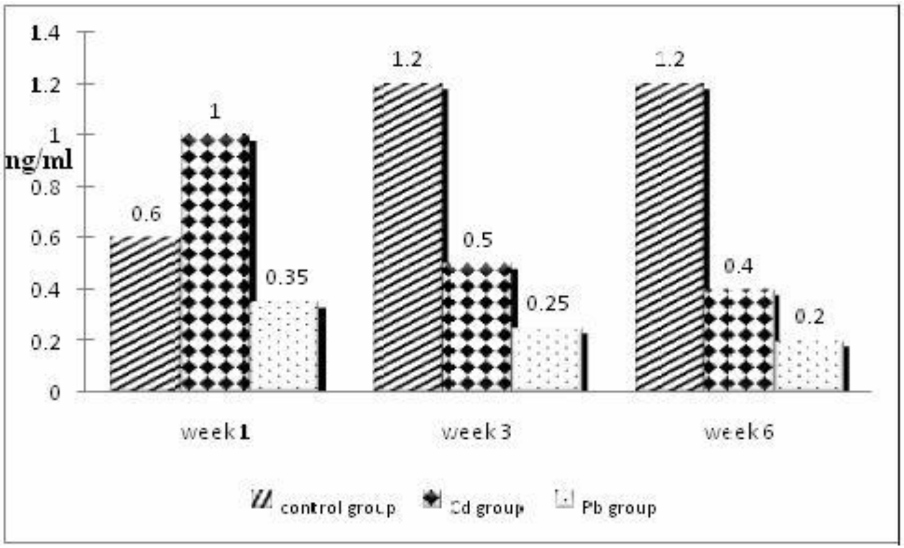

Figure 1. The means of T3concentration in the serum of both rats group treated with Cd and Pb as compared with the control group during the study period.

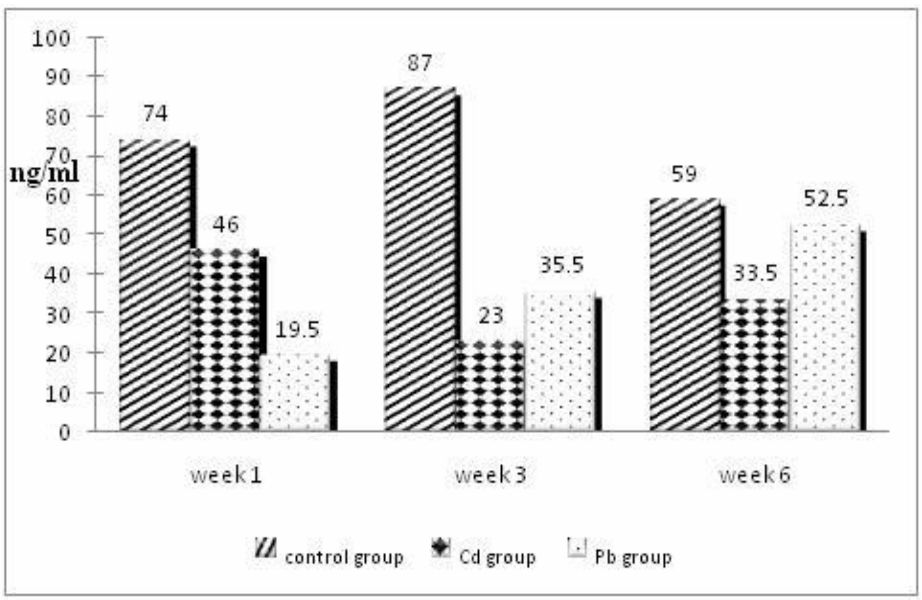

Figure 2. The means of T4 concentration in the serum of both rats group treated with Cd and Pb as compared with the control group during the study period.

rence between treated rats groups with Cd and Pb compared to control group with time of exposure (*P*< 0.020).

Glucose levels

No significant change was observed in the glucose levels between treated groups and the control group **(Figure 4)** (*P*> 0.05).

Cholesterol levels

No significant change was observed in the cholesterol levels between treated groups and the control group **(Figure 5)** (*P*> 0.05).

Histological studies

Microscopic examination of the thyroid follicular cells of

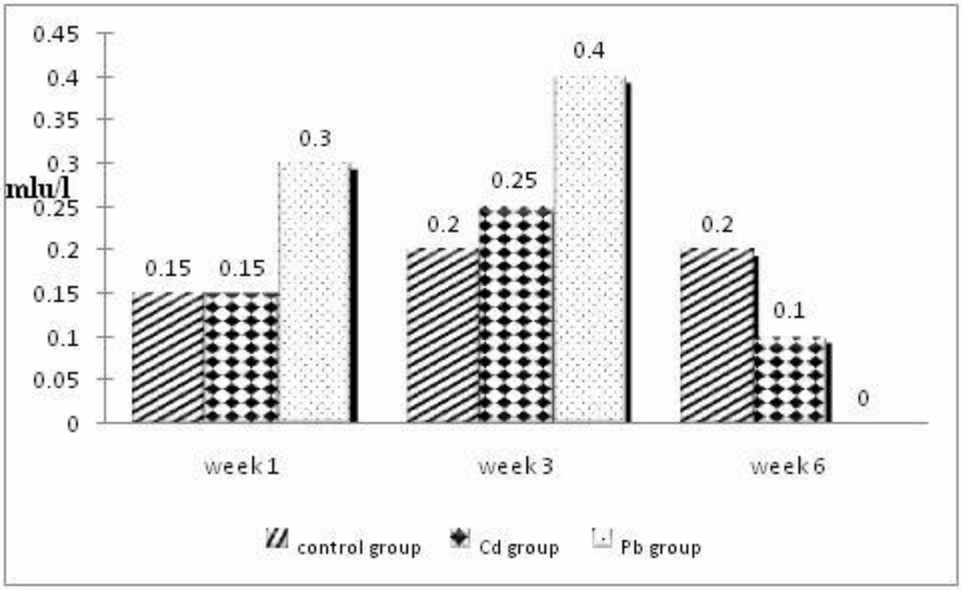

Figure 3. The means of TSH concentration in the serum of both rats group treated with Cd and Pb as compared with the control group during the study period.

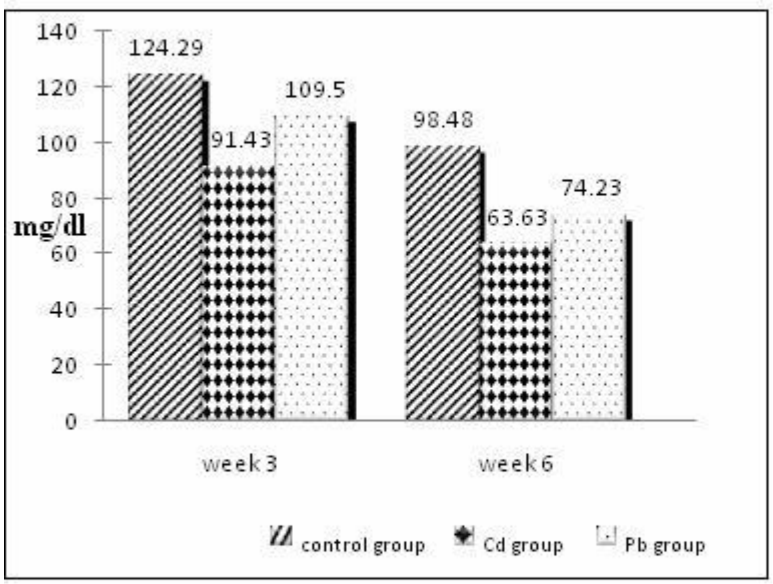

Figure 4. The means of glucose levels in the serum of both rats group treated with Cd and Pb as compared with the control group during the study period.

rats exposed to Cd and Pb differed from the normal structure observed in the control animals (Figure 6). Sections of the thyroid of rats in Control group (I) follicles lined with cubic epithelium lie on the periphery of the gland. A group (II) exposed to Cd for 6 week revealed presence of desquamated epithelial cells inside the follicles, cell infiltration of follicles in connective tissue and follicles lined with high-toned epithelium and light cytoplasm (Figure 7). There was an increase of the size of the thyroid follicles and they were filled with colloids. Changes of a similar kind were observed in the rats fed on Pb diet (group III). These were seriously advanced. The thyroid follicles were turgid with colloids resulting in desquamated epithelial follicles lining (Figure 8).

DISCUSSION

Decreased T3 and T4 serum concentrations according to

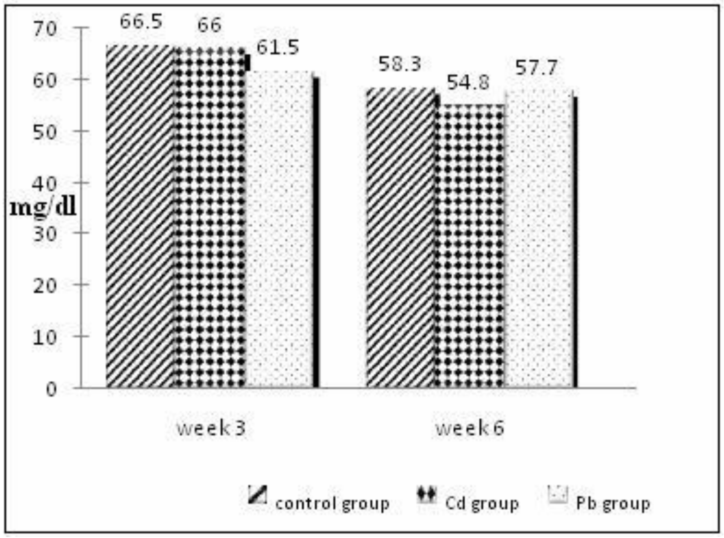

Figure 5. The means of cholesterol levels in the serum of both rats group treated with Cd and Pb as compared with the control group during the study period.

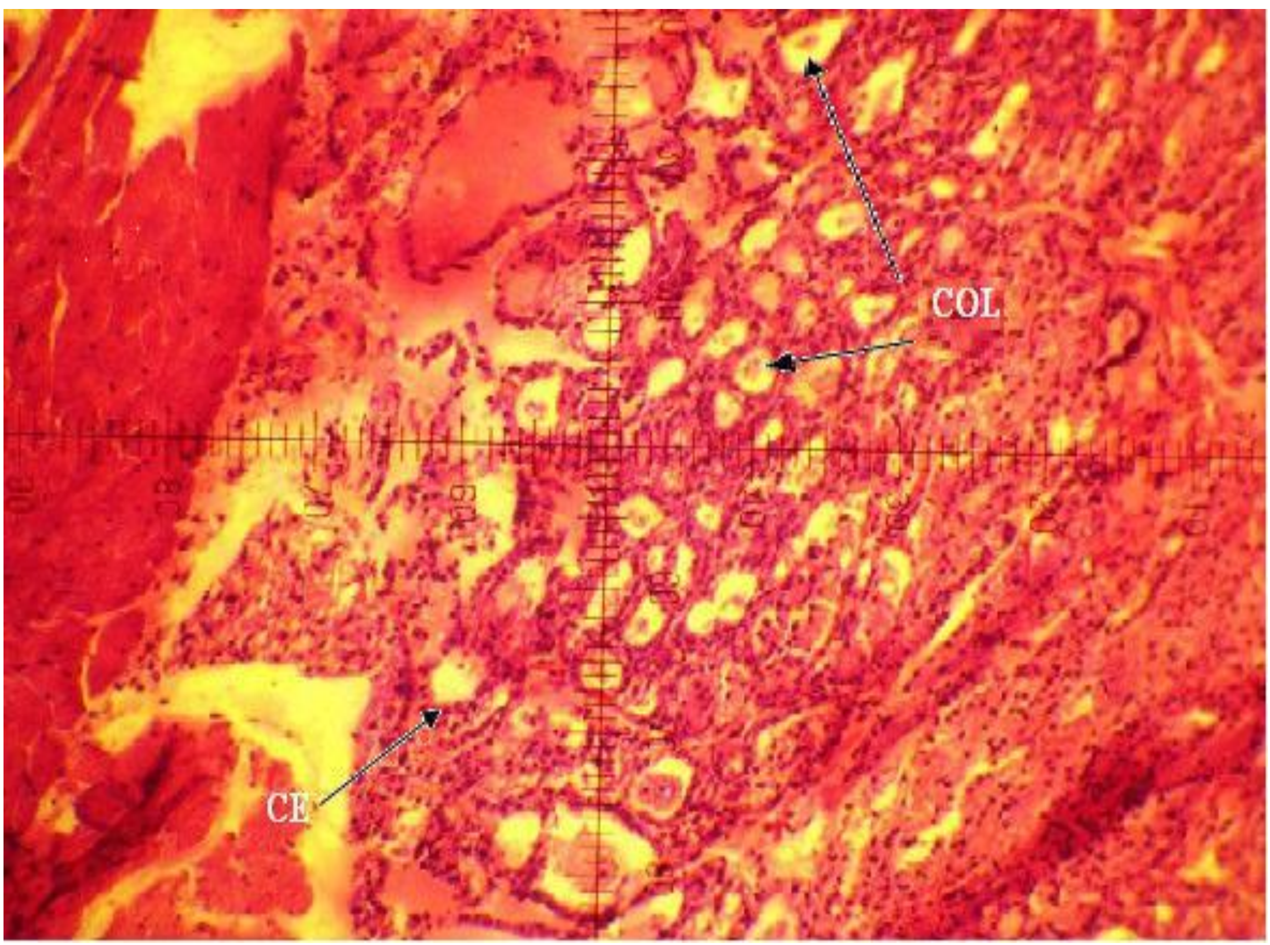

Figure 6. Thyroid sections of the control group rats (Group 1) that show follicles lined with Cubic Epithelium (CE) lie on the periphery of the gland and colloids (COL) concentrated in the centre. (10x10).

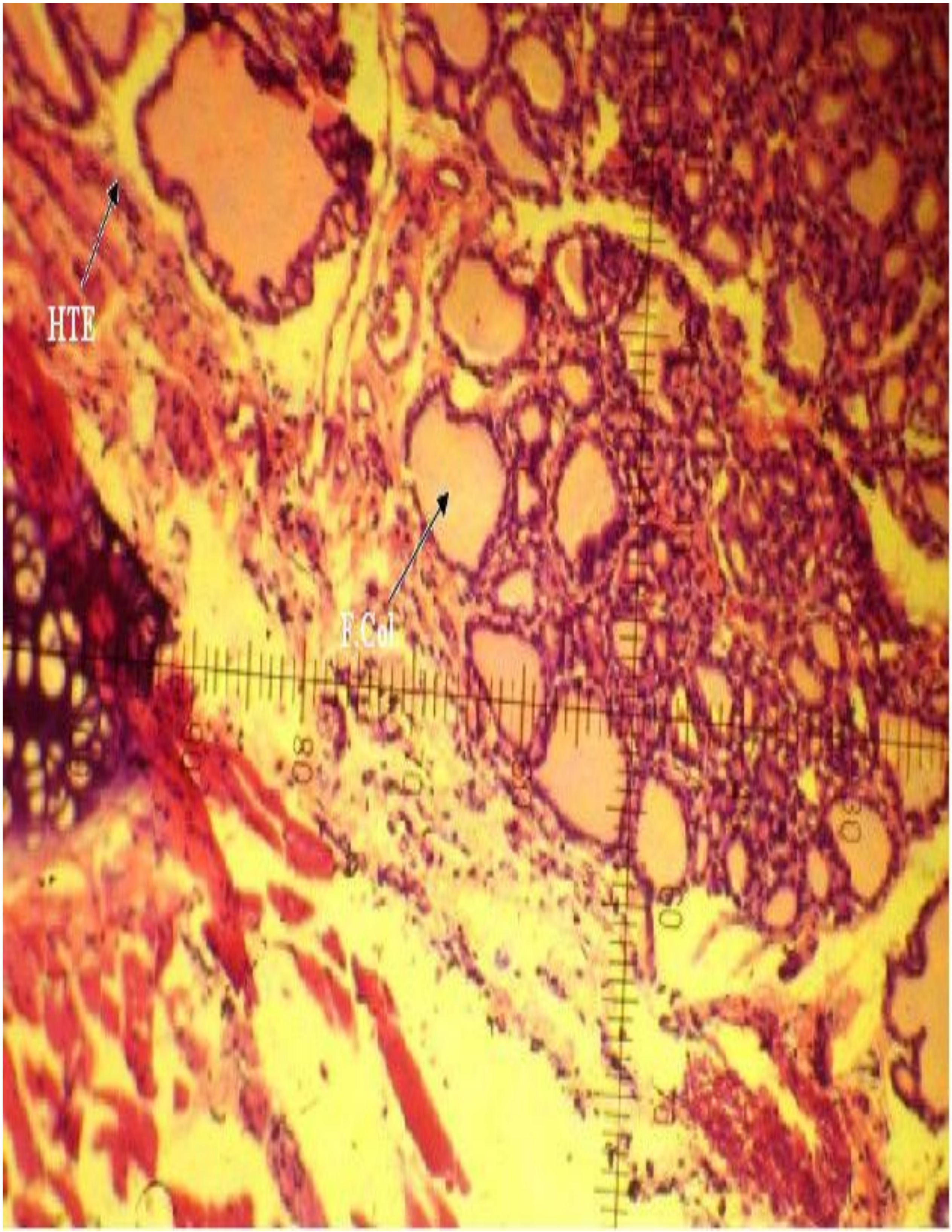

Figure 7. Results of light microscopy examination of the structure of thyroid follicular cells in rats given diet-containing Cd for 6 weeks (group II). Some follicles of the thyroid were lined with high-toned epithelium (THE). Some of the follicles were lined with desquamated epithelial cells and filled with the colloid (F.Col). (10x10)

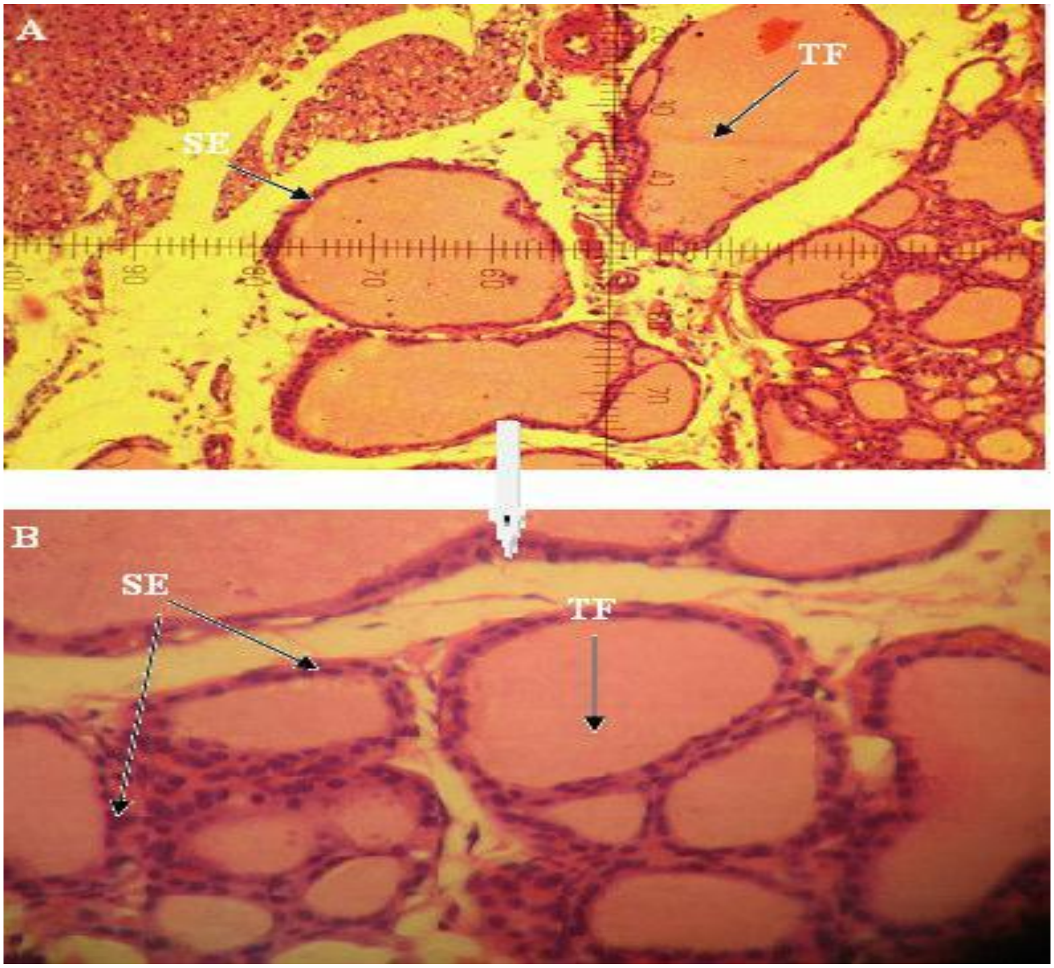

Figure 8. Results of light microscopy examination of the structure of thyroid follicular cells in rats given diet containing Pb for 6 weeks (group III). Some follicles of the thyroid were lined with desquamated epithelium cells (SE). Some of the follicles were turgid with colloid (TF). (**A**: 10 x 10, **B**: 10 x 40).

treatment with metals corroborate earlier reports (Der et al., 1977; Yoshizuka et al., 1991; Nishjio et al., 1994; Pavia et al., 1997; Gupta and Kar, 1997, 1998, 1999). Declined concentration of serum T3 in Cd and Pb treated rats might be due to decreased of transformation rate from T4 to T3 according to inhibition of type-I iodothyronine 5 - monodeiodinase(5 -D) activity, being a selenoenzyme containing a selenocysteine residue as its active site (Shyam et al., 1997; Chaurasia et al., 1996; Paier et al., 1993). Cd and Pb can inhibit 5'-D activity through binding to sulfhydryl groups of this enzyme. Since the thyroid gland is the only organ involved in T4 synthesis, the decrease of this hormone level in the serum of the Cd and Pb-exposed rats, may suggest that Cd and Pb influences the production and/or secretion of T4 by follicular cells (Yoshizuka et al., 1991). The probability of Cd and Pb interference in the synthesis and/or secretion of T4 by the thyroid follicular cells are supported by the results of morphological examinations. These revealed a damaging action of Cd and Pb on the structure of follicular cells of thyroid gland. A tendency towards an increase in the serum TSH concentration observed at exposure to Cd and Pb is a likely response to decreased serum T4 and T3 level. The lack of significant response of TSH to decreased serum T4 and T3 level may suggest Cd and Pb interference with pituitary regulation of thyroid hormones production and secretion (Pavia et al., 1997). One of the more interesting results in our present study that TSH was reached to zero in rats treated with Pb after 6 week and this result has been suggested that Pb interference in synthesis and /or secretion of TSH by the pituitary gland or TRH by the hypothalamus gland, thyroid releasing hormone (TRH) is responsible for regulation the secretion of TSH from the pituitary gland. Although the glucose level seem to be decrease in treated rats with Cd and Pb compared to control group as shown in the Figure 4. But our data revealed there was no significant change in serum glucose level among control group and treated groups, and this result disagreed with result that was obtained previously (Ashour, 2002; Ashour et al., 2007). There was no change between animals treated with Cd and Pb and control group in cholesterol level in serum, indicating that Cd and Pb exposure did not modify cholesterol metabolism as observed in previous study (Boyd et al., 1998).

In summary, the observations made in this study, indicate that Cd and Pb damages the structure and function of the thyroid gland. We suggest that the mode of action or mechanism of Cd and Pb were by interference in the synthesis and/or secretion of T4 by the damage of thyroid follicular cells, decrease transformation rate of the T4 to T3 in peripheral tissue by inhibit the activity of (5 -D) and interference with pituitary gland or hypothalamus gland. Severity of the disturbances increases with the time of exposure. We have obtained important data on Cd and Pb interference in the thyroid gland, yet this problem requires further studies since mechanisms of this action are still poorly recognized.

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