Vol: 8 Issue: 2

EDJ

Correlation Between Cadmium Level and Iron Regulatory Markers in Hypothyroid Patients

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ABSTRACT

Background and Objectives: The insufficient production of thyroid hormones (THs) is called hypothyroidism. Thyroid hormone reduction in the blood causes an elevated secretion of thyroid stimulating hormone (TSH). Naturally occurring environmental pollutants, like heavy metals, have numerous effects on ecosystems. Their bioaccumulation results in a variety of harmful consequences on various body tissues and organ systems, including the thyroid gland. The study aimed to evaluate the main relationships between levels of cadmium (Cd) with hepcidin hormone, ferritin and other iron markers in hypothyroid patients.

Methods: The study carried out on 90 female subjects in Galiawa Diabetes and Endocrinology Teaching Center in Erbil city and Kawrgosk laboratory.The data collection for the study was started from November 2024 to February 2025. The study included hypothyroid patients compared with healthy persons by analyzing the samples of blood parameters including hematological, iron regulatory markers and blood Cd level.

Results: There were significant differences in the hematological, iron regulatory markers and cadmium in the patients when compared to controls at ($p < 0.001$). Pearson correlation analysis revealed statistically significant correlations between Cd level and Hb, MCV and ferritin. While there was no statistical correlation between Cd with other iron parameters. ROC curve analysis for Cd indicated that Cd was a risk factor of hypothyroidism.

Conclusion: From the ROC and Pearson correlation analysis we conclude that cadmium is a significant markers in alteration of the studied iron regulatory marker and hematological parameters.

Keywords: Hypothyroidism, ferritin, Cadmium, hepcidin, iron markers

Article Information

Submission Date: 15/6/2025
Revision date: 15/9/2025
Acceptance date: 29/9/2025
Publishing date: Dec 2025

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DOI: doi.org/10.15218/edj.2025.27

INTRODUCTION

Thyroid gland is one of the largest endocrine glands in the body which regulates the body's growth, development, and metabolism, including the basal metabolic rate (BMR).[1] By continuously delivering a consistent amount of THs into the bloodstream, it also promotes both physical and mental development and aids in the regulation of several other bodily processes. Thyroid iron-dependent enzymes are essential for BMR and also play a part in erythropoiesis and iron regulation processes.[2]

Hypothyroidism indicates decreased thyroidal secretion of THs by factors affecting the thyroid gland itself; the fall in serum concentrations of THs causes an increased secretion and elevated serum TSH concentrations.[3]

Many factors raise the risk of thyroid disease determinants, including endocrine disruptors like toxic environmental xenobiotics and exposure to heavy metals, age, smoking status, genetic susceptibility, ethnicity, nutritional deficiencies, and the introduction of novel therapeutics.[4]

Thyroid hormone homeostasis is highly sensitive to environmental chemical insults, particularly exposure to toxic heavy metals. Recent epidemiological studies have increasingly investigated the relationship between exposure to heavy metals such as Cd and thyroid function in both occupational and general populations. Emerging evidence suggests that these toxic metals can disrupt thyroid hormone synthesis and regulatory balance, as well as interfere with iron homeostasis mechanisms, potentially leading to significant endocrine disturbances.[5]

Heavy metals are harmful substances that don't break down naturally. They are now the most significant worldwide issue, negatively affecting people, animals, and plants. which can enter the human body through a variety of routes.[7]

Cadmium is a toxic metal for the human organism and for all ecosystems. Low levels of Cd are found in nature, but human activity causes increased levels of Cd in the environment because it enters the air and water as micropollutants from pollution, industrial operations, waste incineration, and recycling of electronic waste.[8] Due to its poor excretion and lack of metabolic breakdown into less hazardous species, the human body's capacity to react to exposure to Cd is restricted. Because of its incredibly long biological half-life, it is essentially a cumulative poison; prolonged exposure results in negative effects from the metal that is stored in the organs.[9]

Cadmium exerts significant physiological actions by generating reactive oxygen species (ROS) and disrupting cellular biochemistry. It disrupts the endocrine system and has teratogenic effects in addition to producing nephrotoxicity, ototoxicity, and hepatotoxicity.[10] Cadmium has the potential to cause cancer because it disrupts DNA repair processes and alters cell signaling pathways.[11]

Cadmium, once absorbed through the intestinal tract, is primarily water-soluble and is transported via the circulatory system to various organs throughout the body.[7] We hypothesized that exposure to such heavy metals could be implicated as a risk factor for elucidating hypothyroidism and iron deficiency in our selected studied groups. To determine this, we investigated the main physiological markers related to iron deficiency in hypothyroid patients.

METHODS

Subjects and study design

The case study was carried out on 90 female subjects. The study design included two group subjects :-Group 1: Forty-five healthy females were with normal thyroid function and their age range between (20-45) years.

Group 2: Forty-five female patients with hypothyroid disease, decreased level of T3 and T4 with elevated level of TSH with their age (25-50) years and having a symptom of hypothyroidism.

Inclusion and Exclusion Criteria

Through thorough history taking, physical examination, and standard laboratory testing, hypothyroidism was identified based on the inclusion criteria of reduced thyroid hormone levels accompanied by elevated TSH levels, having hypothyroid disease and must exhibit symptoms of poisoning with heavy metals which included fatigue, muscle pain, and headache that assessed with a standard questionnaire as shown in figure 2. Also, sample collection for the patients collected from the Galiawa Diabetes and Endocrinology Teaching Center in Erbil city and Kawrgosk laboratory.While exclusion criteria were smoking, pregnancy, clinical evidence of diabetes, liver and kidney diseases, cardiac disease. Infections, other chronic disease and history of drug intake that affect liver or kidney function.

Estimation of Serum Thyroid Hormones and Some Biochemical Parameters in hypothyroid patient

Baseline Characteristics:

Name: Phone Number:

Gender: Education:

Age: Marital status: single/married Occupation:

Participant Height & Weight:

Height: cm weight: kg

BMI: kg/m2 Blood Pressure: mmHg

Participant Life Style

Smoking: yes/no

Exercise: yes/no

Profile of Thyroid Disorders:

Family history of a thyroid disorder: Yes/No

Did you measure thyroid hormones previously? Yes/No

Medication for thyroid disease: Yes/No

Other medication: Yes/No

Thank you for your participation

Hope you are in good health

Figure 2. Scientific questionnaire form

Among all sub-groups of the study and other questions included in a scientific questionnaire form list for each participant.

Research Ethics

Approval of the study was obtained from Hawler Medical University/ College of Dentistry/ Basic science Department, Academic Ethical Committee Office with ethics study number (HMUD/2425191)/ date of approval(5.1.2025). All patients were asked to sign an informed written consent for the acceptance of the study project.

Blood Sample Collection

Peripheral blood samples were collected by using standard phlebotomy procedures. Five ml of blood samples were drawn by using a disposable needle and then transfer into two tubes: an EDTA tube for estimation of complete blood count and

DOI: doi.org/10.15218/edj.2025.27

a gel tube for investigating biochemical parameters (TSH, FT3, FT4, hepcidin and other iron markers) and Cd level. The gel tube was incubated and the samples were kept at room temperature for 15 minutes, after which the serum was separated by centrifugation at 1120 ×g for 20 minutes. After that, the serum was transferred into Eppendorf tubes and stored at -50 ºC until assay. The anticoagulated blood that was collected was balanced. The primary CBC parameters were examined when the sample was placed in a Coulter counter (Coulter counter/Hitachi 211Q/ Japan) machine.

Iron regulatory markers

Determination of Hepcidin

Hepcidin was estimated by the Enzyme-Linked Immunosorbent Assay.

Estimation of serum ferritin level

The serum ferritin level was measured using a fully automated immuno-analyzer (Cobas e 411 by Roche Diagnostics, HITACHI, Japan), which operates based on electrochemiluminescence technology.

Detection Of Serum Iron and TIBC

Serum iron and TIBC were measured using the KENZA biochemical analyzer diagnostic kit (4 KENZA 240TX /French).

Estimation Of Transferrin Saturation (TS %)

Transferrin saturation is calculated according to Brittenham et al., (2014) as follow:

$$TS\ \% = (\text{serum iron} \div TIBC) \times 100$$

Determination Of blood Levels Of Cadmium

First the blood sample must be digested before using the ICP method which is a sophisticated instrument used in determination of Cd and iodine concentrations in blood samples based on atomic spectrometry, after due pretreatment. Blood samples were digested by using microwave method: Precisely 0.5 ml of whole blood was collected into a separate Pyrex flask. Then, 8 ml of a freshly prepared mixture of concentrated nitric acid and hydrogen peroxide (65%–68%) [HNO_3-H_2O_2] was added, and the mixture was left to stand for 10 minutes. The flasks were covered with watch glasses and heated at 150 °C for 10 minutes for digestion. Afterward, 2 ml of nitric acid and a few drops of hydrogen peroxide were added to the digested samples, and heating was continued on a hot plate at approximately 190 °C until a clear solution was achieved. The excess acid mixture was evaporated to a semi-dry residue, then allowed to cool and diluted with 0.1 ml of nitric acid. The contents were transferred to a 100 ml volumetric flask and brought up to volume with distilled water. A blank extraction, using distilled water instead of the sample, was performed following the same procedure.[15]

Thyroid hormones determination

Serum level of T3, T4 and TSH were determined by fully automated immunoanalyzer (Cobas e 411 Roche Diagnostics, HITACHI, Japan) based on the electrochemiluminescent (ECL) technology.

Statistical Analysis

All statistical test and analysis were performed in GraphPad Prism 10 and MS-Excel 2025 using descriptive statistics. Categorical data were expressed as percentages, continuous variables were shown as mean ± SD. Normality and lognormality tests were done to analyze the parameters that are either parametric or non-parametric data. Parametric data were examined using the t-test, while for non-parametric data, the Mann-Whitney test was used. The measured parameters and Cd level were also correlated using Person's Correlation coefficient (r). To determine that Cd is a risk factor in the hypothyroid patient group, the Receiver Operating Characteristic (ROC) curve was used to show sensitivity on the y-axis and (100 – specificity) on the x-axis.

RESULTS

Hematological Parameters

The results of the current study indicated that there were statistical differences in most of the parameters between hypothyroid and control subjects. In hypothyroid patients RBC(10^6/L), Hb (g/dL), HCT(%), MCV(fl), MCH(pg) and MCHC(gm/dl) were significantly decreased (4.14 ± 0.41), (10.50 ± 1.15), (34.40 ± 2.97), (79.89 ± 5.74), (22.60 ± 2.25) and (30.49 ± 2.84) respectively in comparison to the control groups, (4.32± 0.37) at($p<0.05$), (11.68 ± 1.08) at($p<0.001$), (36.34 ± 2.57) at ($p<0. 01$), (84.04 ± 6.97) at ($p<0.01$), (26.92 ±2.08) at($p<0.001$), (32.10 ± 1.83) at($p<0.01$), while high significant increase was observed in RDW-SD(fl) patient group (67.99 ± 12.23) compared to control group (55.96 ± 6.30) at ($P<0.001$) as shown in the table (1).

Table 1. Hematological parameter changes between hypothyroid and control groups (Mean ± SD)

Parameters	Patient N = 45 Mean ± SD	Control N = 45 Mean ± SD	P-value
RBC 10^6/L	4.14 ± 0.41	4.32 ± 0.37	0.05
Hb g/dl	10.50 ± 1.15	11.68 ±1.08	0.001
HCT %	34.40 ± 2.97	36.34 ± 2.57	0.01
MCV fl	79.89 ± 5.74	84.04 ± 6.97	0.01
MCH pg	22.60 ± 2.25	26.92 ± 2.08	0.001
MCHC gμ/dl	30.49 ± 2.84	32.10 ± 1.83	0.01
RDW-SD fl	67.99 ± 12.23	55.96 ± 6.30	0.001

*RBC: Red blood cell count, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW-SD: Red cell distribution width-standard deviation. Differences between the patient's subjects compared to control subjects are shown with star sign (*P<0.05, **P<0.01, ***P<0.001).

Cadmium level and iron regulatory markers

Statistical analysis for the results in table (2) revealed that serum hepcidin, iron, transferrin saturation (TS) and ferritin are markedly decreased in hypothyroid patients (43.90 ± 12.26), (36.25 ± 9.79), (11.77 ± 3.55), (50.14 ± 12.67) respectively, when compared to control (52.18 ± 9.28), (65.76 ± 19.29), (22.38 ± 7.55) at P<0.001, (58.20 ± 18.33) at (P<0.05). Conversely, TIBC is non-- significantly elevated in hypothyroid subject (314.2 ± 48.37) when compared to the control subject (308.2 ± 79.61). Regarding heavy metal for both groups, patients showed an elevated level of cadmium (0.47 ± 0.40), when compared with control (0.05 ± 0.07) at p<0.01.

Table 2. Iron regulatory markers and cadmium level changes between patient and control groups (Mean ± SD).

Iron regulatory markers	Patient N=45 Mean± SD	Control N=45 Mean ± SD	P- value
Hepcidin ng/μL	43.90 ± 12.26	52.18 ± 9.28	0.001
Ferritin ng/μL	50.14 ± 12.67	58.20 ± 18.33	0.05
TS %	11.77 ± 3.55	22.38 ± 7.55	0.001
Serum iron μ/dL	36.25 ± 9.79	65.76 ± 19.29	0.001
TIBCμ/dL	314.2 ± 48.37	308.2 ± 79.61	NS
Cd μg/L	0.47 ± 0.40	0.05 ± 0.07	0.001

* TS: Transferrin saturation, TIBC: Total iron binding capacity., NS: non-significant.

DOI: doi.org/10.15218/edj.2025.27

Estimation of serum thyroid hormones profile and iodine concentrations between hypothyroid patient and healthy individual

Table (3) illustrates that there was a significant decrease in the level of iodine, free triiodothyronine (T3) and free thyroxin (T4) in hypothyroidism groups (4.84 ± 1.54), (0.87 ± 0.41), (58.21 ± 10.55), respectively, as compared to its level in healthy group (7.10 ± 1.30), (1.97 ± 0.62), (109.1 ± 28.81) at($P<0.001$). The level of TSH is highly elevated among hypothyroid patients (6.44 ± 1.77) as compared with healthy individuals (2.19 ± 1.02) at ($p< 0.001$).

Table 3. Levels of iodine and serum thyroid hormones changes in hypothyroid group and healthy group (mean ± SD)

Parameters	Patient N=45 Mean ± SD	Control N=45 Mean ± SD	P-value
Iodine µg	4.84 ± 1.54	7.10 ± 1.30	0.001
TSH ulU/µl	6.44 ± 1.77	2.19 ± 1.02	0.001
T3 nmol/l	0.87 ± 0.41	1.97 ± 0.62	0.001
T4 nmol/l	58.21 ± 10.55	109.1 ± 28.81	0.001

* TSH: Thyroid stimulating hormone, T3: free triiodothyronine, T4: Thyroxine

Correlation coefficient (r) between data variables

Pearson's Correlation between serum cadmium level and blood parameters

Table (4) provided the results obtained from correlation analysis in hypothyroidism patients in which a non-significant correlation was found between RBC ($r= 0.080$, $p= 0.600$), HCT ($r = -0.073$, $p = 0.630$), MCH ($r = 0.241$, $p = 0.110$), MCHC ($r = -0.128$, $p = 0.401$) and RDW-SD ($r = 0.023$, $p = 0.877$). A significant correlation existed between Cd level with Hb concentration ($r = -0.301$, $p = 0.043$) and MCV ($r = 0.381$, $p = 0.009$).

Table 4. Correlation between serum cadmium level and blood parameters represented by correlation coefficient (r) and P-value

Parameters	Cadmium mg/L N=45	
	r	p-value
RBC 10^6/L	0.080	0.600
Hb g/dl	-0.301	0.043
HCT%	-0.073	0.630
MCV fl	0.381	0.009
MCH Pg	0.241	0.110
MCHC gµ/dl	-0.128	0.401
RDW-SD fl	0.023	0.877

r= Correlation coefficient

Correlation between cadmium level and iron regulatory markers

As seen in the table (5), the correlation coefficient between serum Cd with iron regulatory markers showed a positive non-significant correlation between Cd level with serum iron (r = 0.159, p=0.295), TS (r = 0.113, p = 0.457) and TIBC (r= 0.071, p=0.640).

While the statistical analysis demonstrated an inverse non-significant correlation between Cd level with hepcidin (r = -0.098, p = 0.518). On the other hand, serum ferritin was statistically and negatively correlated with Cd.

Table 5. Correlation between Cd level and iron regulatory markers: hepcidin, ferritin, TS, serum iron and TIBC.

Iron regulatory marker	Cadmium mg/L N=45	
	r	P-value
Hepcidin ng/µL	-0.098	0.518
Ferritin ng/µL	-0.316	0.034
TS %	0.113	0.457
Serum iron µ/dL	0.159	0.295
TIBCµ/dL	0.071	0.640

Association between serum cadmium with thyroid hormone profile and iodine concentration

Pearson's correlation analysis showed that concentration of Cd non significantly correlated with the iodine (r =-0.027, p=0.857), T3 (r=-0.193, p=0.202), T4(r = 0.102, p = 0.503) and TSH (r = 0.037, p = 0.808) as seen in the table (6).

Table 6. Association between blood level cadmium with iodine concentration and thyroid profile

Parameters	Cadmium mg/L N=45	
	r	P- value
Iodine	-0.027	0.857
TSH	0.037	0.808
T3	-0.193	0.202
T4	0.102	0.503

Receiver operating characteristics curve (ROC study) for Cd level in hypothyroid and control group.

According to ROC curve analysis, the Area under the curve (AUC) of Cd was equal to 0.725 in hypothyroidism patients for P= 0.0003 as shown in figure (1), which indicates Cd as a good marker in the studied groups.

DOI: doi.org/10.15218/edj.2025.27

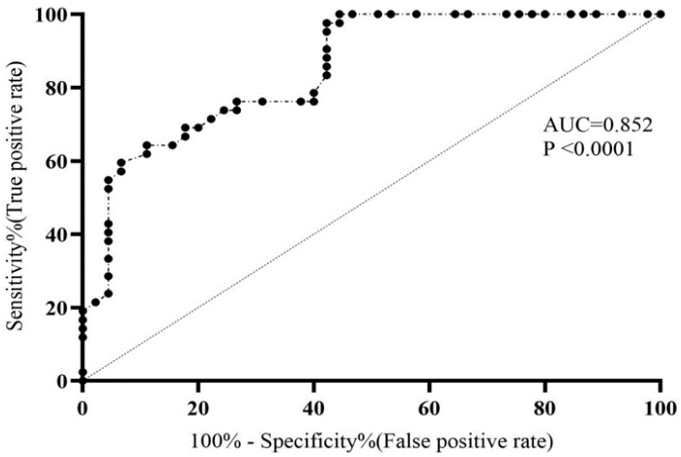

Figure 1. ROC curve shows the sensitivity and specificity of Cd concentration during hypothyroidism AUC: Area under the curve

DISCUSSION

The present study showed a significant decrease in RBC, Hb, HCT, MCV, MCH and MCHC for patients with hypothyroidism compared to the control group. This is in agreement with a previous study, which showed that hypothyroid patients had a significant decrease in RBC, Hb, HCT, MCV, MCH and MCHC. These findings collectively indicate the presence of microcytic and hypochromic anemia in hypothyroidism conditions.[12] Furthermore, this study demonstrated that RDW-SD was significantly increased in hypothyroid patients compared to control. Red cell distribution width is a quantitative measure of anisocytosis. High RDW-SD reflects size and shape variability in red cells of our patients.[13] Reduced thyroid hormone production, which is essential for erythropoiesis, is one of the physiological changes linked to hypothyroidism, which is also linked to a decrease in RBC and hemoglobin levels. Red blood cell deformability and hemoglobin which impair oxygen metabolism and affect cytokines involved in erythropoiesis, leading to anemia and decreased red blood cell indices and changes in the morphology of the erythrocytes.[14]

The results showed that there were significant decreases in serum iron which reported in the study[15] Iron deficiency might be linked to reduced levels of thyroid hormones. This study has similar findings as with the present study. However, transferrin saturation, hepcidin and ferritin levels were also significantly lower in patients, these observation of low hepcidin and ferritin alongside low serum iron and transferrin saturation indicates a more complex iron dysregulation, potentially indicating an absolute iron deficiency in these patients. The connection between hypothyroidism and anemia is thought to result from a lack or deficiency of thyroid hormones, which impairs the stimulation of erythropoiesis. Normochromic normocytic anemia is a condition marked by a deficiency or insufficient production of erythropoietin. Hypothyroidism results in reduced red blood cell production and the onset of anemia because the decreased levels of thyroid hormones limit bone marrow function.[16] TIBC showed no significant difference, which can occur in mixed anemias or if transferrin levels are not significantly altered.

Regarding accumulation of Cd which was significantly elevated in the patient group, this toxic heavy metal is known to interfere with various physiological processes, including hematopoiesis and iron metabolism. Its accumulation can lead to oxidative stress, impair erythropoiesis, and potentially disrupt the balance of iron regulation, possibly by competing with essential metals for binding sites or interfering with enzymes.[9]

Furthermore, the study demonstrates that the patient group exhibits significantly elevated TSH and reduced T3 and T4 as compared to the control group. Also, iodine concentration in hypothyroid patients decreased. This is supported by the study of,[17] who has observed that Iodine deficiency is one of the main risks to develop hypothyroidism. Again, recent studies indicated that high Cd levels in hypothyroid patients has a role as an endocrine disruptor, affecting thyroid hormone synthesis and function. It is linked to thyroid dysfunction through various mechanisms, including oxidative stress and interference with thyroid hormone regulation. These disruptions can lead to altered thyroid hormone levels, contributing to hypothyroidism.[18]

Pearson's correlation analysis showed that there was non-significant correlation found between Cd levels with RBC, HCT, MCH, MCHC and RDW-SD this increasing of Cd associated with a decrease in the oxygen-carrying capacity of the blood, providing direct evidence for a potential detrimental effect of Cd on red blood cell.[19] Despite the observed differences in iron regulatory

markers between both patients and control groups, no significant correlations were found between Cd and hepcidin, TS, serum iron, or TIBC, a significant negative correlation was found between Cd and ferritin. Furthermore, no significant correlations were observed between Cd levels with iodine concentration and thyroid hormones profile. Another study indicated a neutral or poor association between Cd exposure and thyroid hormones.[20]

CONCLUSION

From the ROC and Pearson correlation analysis we conclude that cadmium is a significant marker in alteration of the studied iron regulatory markers and hematological parameters.

It was observed from the study that elevated cadmium levels in the patient group, coupled with its negative correlation with hemoglobin and hematocrit, suggest that Cd exposure could be a contributing factor to the observed anemia. The study revealed that individuals with hypothyroidism had significantly lower mean serum ferritin and iron levels compared to the control group, while TIBC was higher, though not to a statistically significant extent. Furthermore, the ROC analysis confirmed Cd, as a potential risk factor for iron dysregulation and hypothyroidism.

ACKNOWLEDGMENTS

The author would like to thank the private Hemn laboratory Mr. Hemn Salh Kareem and to Dr. Ahmad Hassan for his continuous advises and assistances.

CONFLICT OF INTEREST

There no conflict of interest in this work. This study has not been supported by any individual and/or organizations.

FUNDING

No funding.

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DOI: doi.org/10.15218/edj.2025.27