Hypothyroidism and its effect on serum vitamin D and iron among adult female: A review from Middle East perspective

Hossameldin Fatthy Eldosouky1, Wan Salman Wan Saudi1, M Tanveer Hossain Parash1, Sadia Choudhury Shimmi1

1Department of Biomedical Science and Therapeutics, Faculty of Medicine and Health science, Universiti Malaysia Sabah (UMS), Kota Kinabalu 88400, Sabah, Malaysia

Abstract
Hypothyroidism is a pathophysiological phase in which insufficient hormones are produced, leading to an imbalance in basal metabolic rate and inefficiency in the physiological role of body systems. Vitamin D affects thyrocytes by decreasing thyroid-stimulating hormone (TSH) stimulated iodide uptake and cellular development. In hypothyroidism, hypovitaminosis D is due to malabsorption from the intestine and inactivation of vitamin D. Thyroid hormones induce erythropoietin gene expression causing an increase in the secretion of erythropoietin. Iron deficiency decreases the activity of the thyroid peroxidase enzyme. Hypothyroidism can cause microcytic anaemia due to malabsorption of iron and menorrhagia. Hypothyroidism is a common but under-recognized and under-diagnosed condition in the Persian Gulf countries. Moreover, the evaluation of the effect of hypothyroidism on vitamin D and iron levels is inadequate. Identifying this bi-deficiency is essential so that doctors can identify and treat them earlier and reduce the deficiency-related complications, and supplements can be given to prevent further health complications like osteoporosis and iron deficiency anaemia.

Introduction
Hypothyroidism is a global endocrine disorder that affects about 5% of the population, 99% of whom have primary hypothyroidism, mainly due to iodine deficiency in the environment, which causes Hashimoto disease.1 Among the female population in the United States of America and Europe, where there is plenty of iodine source, the rate of hypothyroidism is ranged from 1% to 2%, and it mainly affects older females with a ratio of 10 compared to males. In Northern Europe, Japan, and the USA, the hypothyroidism rate ranges from 0.6 up to 12 per 1000 females and 1.3 up to 4.0 per 1000 in males.2

In United Arab Emirates females, the prevalence of hypothyroidism in the last ten years is 6.5%.3 Also, in Libya and Saudi Arabia, the prevalence of hypothyroidism is 6.18% and 47.34%, respectively.4 In the Bahraini female population, the high-risk age group is 20–40 years old.5 However, in the Jordan population, both sex is at risk for hypothyroidism comparing with global statistics.6

Hypothyroidism has a pathophysiological effect on body systems with manifestations depending on the level of hormone deficiency. Also, abnormal basal metabolism, including hyponatremia and anaemia, is common in hypothyroidism.7,8

Vitamin D
About 50% of the world population with different races and age groups suffer from hypovitaminosis D. Many factors are related to the lifestyle and environment that reduce sunlight exposure. For example, black individuals who have more melanin in the skin need greater sunlight exposure. Recent research has shown vitamin D’s vital role in cancers, heart disorders, fractures, and falls, autoimmune disorders, influenza, type-2 diabetes, and mood disorder.9

About 40 to 57% of the United States of America and European elderly male and female have hypovitaminosis D. Young adults and children are also not away from the risk of hypovitaminosis D. In Maine, about 48% of young girls, in Boston about 52% of Hispanic and black adolescents, and Europe, 60% of children and adults, are at high risk of hypovitaminosis D, and the percentage increases to 90% during winter and spring.10

Causes of Hypovitaminosis D can be classified into:
A) Ultraviolet B deficiency10
- Elderly individuals having a low concentration of skin 7-dehydrocholesterol (primary source to form calciferol).
- Individuals with rich melanin, which take part with 7-dehydrocholesterol for UVB photons absorption in
Iron is vital for haemoglobin. Iron is also a vital function in maintaining a healthy immune system. According to British Dietetic Association, adult females need 14.8 mg/d on average.

Iron deficiency reasons
- Blood loss: menstruation, peptic ulcer, a hiatal hernia, hookworm infestation, a colon polyp, or colorectal cancer
- Low iron diet
- Iron malabsorption
- Pregnancy/ repeated childbirth

Over 800 million females over the world are suffering from anaemia. In India, anaemia is a substantial public health issue. About 52% of the female population of reproductive age in India are suffering from iron deficiency.13 In Egypt, the health indicator shows the mean haemoglobin value for mothers is about 11.9 g/dL with an anaemia prevalence of about 47.2%. Among adolescents, the mean haemoglobin is 12.5 g/dL, with anaemia prevalence of 35.7%.14 In Jordan, 35.2% of the female reproductive population, had iron deficiency anaemia (19.6%) due to excessive blood loss during menstruation.15 In the United Arab Emirates, in 2016, the prevalence of anaemia was about 27.8% among 15–49 years old females, which has been increased compared to a prevalence of 26% in 2007.16

In approximately half of the female university students of the United Arab Emirates, the rate of anaemia profile indicators (Haemoglobin less than 12 g/dL) was 26.7%, and largest part (88.4%) had mild anaemia, and 7.2% were moderately anaemic, and 2.3% were severely anaemic, with haemoglobin less than 7 g/dL. About 15.9% of the anaemia cases were microcytic (MCV < 80 fL) and 1.6% were macrocytic (MCV > 96 fL). The most prevalent detected anaemia was microcytic with mild severity.17 In Yemen, female university students, the main reasons for anaemia were malnutrition and lifestyle.18

Among Saudi female university students, 64% of students were found to be anaemic. The rate of mild anaemia (hemoglobin 10 up to 11 g/dL) was 45%, moderate anaemia (hemoglobin 7 up to 10 g/dL) was 49%, and severe anaemia (haemoglobin less than 7 g/dL) was 6%. Among the anaemic students, 81% showed microcytic (MCV < 80 fL) and 1.6% had macrocytic (MCV > 96 fL) anaemia.19

Thyroid relation with iron
Thyroid hormones induce erythropoietin gene expression, causing increased secretion of erythropoietin.20 Thyroid peroxidase (haeme-dependent) is the main enzyme in the production of thyroid hormones. Iron deficiency anaemia decreases the activity of thyroid peroxidase in rats.21 Hypothyroidism can cause different forms of anaemia, including microcytic anaemia due to malabsorption of iron and menorrhagia, and macrocytic anaemia due to abnormality in absorption of cobalamin, folacin, vitamin B12 deficiency (pernicious anaemia), and vitamin A nutritional deficiency. Also, abnormal thyroid function alters blood index, white blood cell (WBC) count, and platelet count.22
In 2018, Taylor et al commented that there was a paucity of data regarding the epidemiology of hypothyroidism in the Middle Eastern population. Since then, numerous research of Arab countries has focused on the prevalence, diagnosis, and management of hypothyroidism. Yet, according to Alzahrani et al, “Hypothyroidism is a common but under-recognized and under-diagnosed condition in the Persian Gulf countries.” Al Shahriani conducted a systemic review in the Middle East region to highlight and consolidate the prevailing data on thyroid disease. They aimed to “present the aggregated burden, risk factors and prognosis of various thyroid diseases prevalent in Arab countries.” Amouzegar et al evaluated the “progression in time from euthyroidism to subclinical or overt hypo- or hyperthyroidism.” However, the effect of hypothyroidism on vitamin D and iron levels was inadequately evaluated as a bi-deficiency. Therefore, this article is exploring the scopes for study on the bi-deficiencies status of the hypothyroid population.

Discussion

Studies about the relation of hypothyroidism with vitamin D
Fawzy et al tested TSH, FT4 (Free T4), TPO Abs (thyroid peroxidase antibodies), and 25-OH Vit D (25 hydroxyvitamin D3) for study group (65 females and 14 males) and control group (14 normal individuals). The study group was sub-grouped into subclinical and hypothyroid depend on TSH level. For the subclinical group, TSH level was (6.80±1.86 μIU/mL), and for the hypothyroid group, it was (55.20±34.39 μIU/mL), showing a significant increase in TSH compared to the control group (1.86±.99 μIU/mL), (P<0.001). For the subclinical group, 25-OH Vit D was (28.80±12.25 nmol/L), and for the hypothyroid group, it was (11.57±3.70 nmol/L), showing a significant decrease in 25-OH Vit D compared to the control group (90.86±12.60 nmol/L), (P<0.001). A negative correlation was detected between TSH, TPO, and 25-OH Vit D levels (P<0.001), but a positive correlation was detected between 25-OH Vit D and FT4 levels (P<0.001), and a positive correlation was detected between TSH and TPO levels (P<0.05). The study concluded that 25-OH Vit D deficiency relates to hypothyroidism.

Mackawy et al conducted a study in thirty hypothyroid patients and thirty healthy individuals. They measured serum vitamin D levels, and the vitamin D was reduced below 20 ng/mL and showed a significant reduction in the hypothyroid group compared with the healthy group (t = -11.128, P = 0.000); and it was more reduced in females than male individuals (t = -1.32, P<0.05). Calcium levels were reduced significantly in hypothyroid individuals compared to healthy individuals (t = -5.69, P = 0.000). The study concluded that hypothyroidism is associated with hypovitaminosis D and hypocalcaemia.

Mazokopakis et al conducted a study in 218 hypothyroid patients with a mean age of 35.3±8.5 years (180 females and 38 males). One hundred and 86 patients (37.3±5.6 years) in the study group showed vitamin D<30 ng/mL. This group was administered cholecalciferol orally, 1200-4000 IU, daily for 4 months. Biochemical analysis (25-OH Vit. D, TSH, FT4, TPO antibodies, TG antibodies [thyroglobulin antibodies], Ca, Ph) were tested before and after cholecalciferol administration. In hypothyroid patients, a negative correlation was detected between 25-OH vitamin D and TPO antibodies. TPO antibodies in hypothyroid patients with hypovitaminosis D (186) was 364 ± 181 IU/mL, and in hypothyroid patients with normal vitamin D (32), it was 115.8 ± 37.1 IU/mL, showing a significant correlation (P<0.0001). Also, the study demonstrated supplementation of cholecalciferol in 186 hypothyroid patients with hypovitaminosis D, showed reductions in serum anti-TPO antibody levels by 20.3%, body mass index by 2.2%, TG antibodies by 5.3%, and TSH by 4%. The study concluded that hypovitaminosis D might be related to hypothyroidism pathogenesis.

Kim evaluated vitamin D in 776 individuals and found that 369 patients (46.1%) had hypovitaminosis D with autoimmune thyroid disease compared with 407 normal individuals. Among hypothyroid patients, 221 (prevalence ratio 48.9%) showed hypovitaminosis D than the healthy individuals (37.1%). Overt hypothyroidism (60.4%) showed more hypovitaminosis D than subclinical hypothyroidism (21.7%) within the hypothyroid group. Kim concluded that vitamin D negatively correlates with TSH and hypovitaminosis D and is associated with autoimmune thyroid disease and hypothyroidism, especially overt hypothyroidism.

Prasad et al in their study observed thyroid profile (TSH, FT3 [Free T3], FT4, anti TPO antibodies) and calcium, vitamin D in 104 individuals (52 study group with age 39.05±6.83 years, and 52 control group with age 39.07±6.05 years). Hypovitaminosis D was detected by level ≤20 ng/mL. In the hypothyroid group, TSH increased significantly compared to the euthyroid group with P<0.0001. Anti TPO in the hypothyroid group was 50.55±98.95 μIU/mL and for the euthyroid group was 6.86±9.26 μ IU/mL. TPO antibodies increased significantly (P=0.002) in the hypothyroid group compared to the euthyroid group. Vitamin D was reduced significantly (P<0.0001) in a hypothyroid group compared to the euthyroid group. In hypothyroid patients, calcium level was 7.67 ± 1.04 mg/dL, and in the euthyroid group, it was 10.16 ± 0.74 mg/dL. So, the calcium level was reduced significantly (P = 0.0344) in the hypothyroid group. The study concluded that autoimmune hypothyroidism causes a low level of vitamin D and calcium.

Patni et al conducted a study on 138 individuals, including newly detected female cases diagnosed with Hashimoto’s thyroiditis and Grave’s disease and 46 healthy females. Vitamin D, parathyroid hormone, calcium, and anti-thyroid peroxidase antibody levels were measured. Decreased vitamin D was found in Hashimoto’s thyroiditis...
Eldosouky et al
J Res Clin Med, 2022, 10: 1

The study showed that vitamin D has a negative correlation with TPO antibodies (r = -0.32, P = 0.0001) and parathyroid hormone (r = -0.27, P = 0.0049). Correlation of vitamin D with TSH (r = 0.04, P = 0.07) and with FT4 levels (r = 0.02, P = 0.6) was not significant. Hypothyroid patients showed higher anti-TPO levels than normal group and the control group. Also, the study showed hypovitaminosis D is higher in Grave's disease patients compared to hypothyroid patients. A negative correlation was detected between TPO antibodies and vitamin D.

Solhjoo et al\textsuperscript{34} in their study measured vitamin D and TSH in 80 individuals (40 hypothyroid patients and 40 healthy individuals). The difference in vitamin D between the study group and the control group was significant. Mean vitamin D in the subclinical group was 18.3 ng/mL. In autoimmune hypothyroidism, Hashimoto's hypothyroidism was 5.52 ng/mL, showing a statistically significant correlation, but no significant difference between vitamin D and TSH was found in the control and study groups. The outcome of the study showed that there is a relation between hypovitaminosis D and Hashimoto's thyroiditis.

Idiculla et al\textsuperscript{35} studied vitamin D in primary hypothyroidism (female and male aged 18 years and above with TSH > 5.1 mIU/L) and involved 115 individuals (same age and sex) with euthyroid TSH < 5 mIU/mL and 120 individuals as the control group. TSH, FT4, vitamin D, and TPO antibody was tested for all groups. In the hypothyroid group, about 96% (110/115) had hypovitaminosis D compared to 90% (108/120) in the control group. A significant decrease in mean vitamin D in the hypothyroid group (12.6 ± 9.04 ng/mL) and Grave's disease (10.6 ± 5.4 ng/mL) compared to the control group (22.8 ± 6.4 ng/mL). Also, the study showed that vitamin D has a negative correlation with TPO antibodies (r = -0.32, P = 0.0001) and parathyroid hormone (r = -0.27, P = 0.0049). Correlation of vitamin D with TSH (r = 0.04, P = 0.07) and with FT4 levels (r = 0.02, P = 0.6) was not significant. Hypothyroid patients showed higher anti-TPO levels than normal group and the control group. Also, the study showed hypovitaminosis D is higher in Grave's disease patients compared to hypothyroid patients. A negative correlation was detected between TPO antibodies and vitamin D.

Zare Ebrahimabad et al\textsuperscript{37} in their study measured vitamin D, calcium, TSH, total T4 (TT4), and FT3 in 175 hypothyroid individuals (75 males and 100 females) and 175 euthyroid controls (85 males and 90 females). In hypothyroid individuals, both vitamin D and Calcium were significantly lower (P < 0.0001). FT3 and calcium showed a significant difference among hypothyroid individuals based on vitamin D level (P < 0.0001). Free T3 was in a positive correlation with vitamin D (r = 0.337, P < 0.0001) and calcium (r = 0.361, P < 0.0001) levels. The study concluded that hypovitaminosis D is related to thyroid profile.

Islam et al\textsuperscript{38} measured vitamin D and TSH for 45 females (hypothyroid individuals aged 25-65 years). Vitamin D decreased significantly in hypothyroid individuals (19.2 ± 1.40 ng/mL) compared to the control group (28.4 ± 1.36 ng/mL, P < 0.001). Vitamin D and TSH levels were in a negative, significant correlation (r = -0.45, P < 0.001). The study mentioned that hypothyroid patients have lower vitamin D levels.

Khan et al\textsuperscript{39} measured vitamin D3, TSH, and FT4 in the hypothyroid group (24 females, 14 males 37.82 ± 7.95 years) and euthyroid group (34.84 ± 8.61 years). The mean level of vitamin D for the euthyroid group was 17.11 ± 5.62 ng/mL, and for the hypothyroid group it was 13.16 ± 4.29 ng/mL. Hypothyroid patients showed significantly lower vitamin D than control individuals (P = 0.037, P < 0.05). In the hypothyroid group, TSH and vitamin D were in a negative correlation (r = -0.119, P = 0.034), and FT4 level and vitamin D level showed a moderate positive correlation (r = 0.457, P = 0.01, P < 0.05). The study concluded that females showed more decrease in vitamin D than males, and there is a relation between hypothyroidism and decreased vitamin D levels.

ElRawi et al\textsuperscript{40} studied VDR polymorphism in 35 Egyptian patients with hypothyroidism. They measured vitamin D levels, TSH, TG antibodies, and TPO antibodies. It was observed that vitamin D is reduced in the hypothyroid group more than in the control group. Also, vitamin D had an inverse relation with TSH, anti-TG, and anti-TPO. Both groups found no relation between VDR polymorphism (Fok1 and Apa1) and TSH or vitamin D. Hypovitaminosis D was affiliated with increased thyroid vascularity and nodularity. Vitamin D was inversely correlated to the thyroid gland volume. The study concluded that hypovitaminosis D was detected in hypothyroidism, thyroid autoimmunity, increased volume, nodularity, and vascularity of thyroid gland in hypothyroid patients. Also, no evidence was found for the relation between VDR polymorphisms (Fok1 and Apa1) and vitamin D levels or TSH levels.

Obaid et al\textsuperscript{41} studied the correlation between vitamin D and hypothyroidism in 100 patients (50 men and 50 women, age 10-80 years, bodyweight of 21-98 kg). The study included three groups according to FT4 level...
(control group with normal FT4 and study group with high, low FT4). All individuals were tested for FT3, FT4, TSH, and vitamin D3. They observed that the mean vitamin D3 level for the study group (low and high FT4) is lower than the control group. Concerning age and body weight, there was no significant negative correlation with vitamin D3 levels. Also, they observed a significant negative correlation coefficient between TSH, FT3, and vitamin D3 (P<0.01) and a positive correlation coefficient between vitamin D3 and FT4. The study concluded that hypothyroid patients have hypovitaminosis D.

Nar et al conducted a study on 1197 individuals (age 18-45 years) and measured vitamin D, TSH, FT3, FT4 to find the relation between vitamin D and thyroid panel. The study included three groups: euthyroid (n=940), hypothyroidism (n=206), and hyperthyroidism (n=51). The mean vitamin D level for participants was 18.3±14.53 ng/mL. Mean vitamin D level for females (n=921) was 16.01±14.37 ng/mL, and for males (n=276) was 26.04±12.26 ng/mL (P<0.001). In the euthyroid group, the mean vitamin D level was 18.79±15.04 ng/mL, and in the hypothyroidism group, it was 15.72±11.71 ng/mL, and in the hyperthyroidism group was 20.4±14.23 ng/mL. The study showed a statistically significant (P<0.05) difference between vitamin D and hyperthyroidism and hypothyroidism groups. Vitamin D deficiency was more common in females than males. They concluded that hypovitaminosis D is associated with hypothyroidism.

Shankar and Singh investigated vitamin D, FT3, FT4, and TSH levels in 90 females (45 hypothyroid and 45 control groups). Both the control group and study group were the same age. They observed that patients with elevated TSH showed reduced FT4, but FT3 levels had no difference in both groups. Men's vitamin D levels showed a significant difference between the hypothyroid and control groups (15.44±4.65 vs. 20.91±7.98, P=0.000). The correlation between vitamin D and TSH was significantly negative in the hypothyroid group (r=-0.060, P=0.695).

**Studies about the relation of hypothyroidism with iron**

Ferritin and thyroid profile (TSH, TT3, TT4, and FT4) were measured by Sachdeva et al for 50 hypothyroid individuals to find the relation between ferritin and hypothyroidism. They observed that ferritin levels were significantly lower in hypothyroid patients than in the control group (P<0.001). The study concluded that ferritin level is decreased in hypothyroid patients.

Dahiya et al studied thyroid profile and iron level for 50 hypothyroid patients (age 20-40 years) and compared the result with the control group (euthyroid, age 20-40 years, same-sex as the study group). Iron profile (iron, ferritin, total iron binding capacity) and thyroid profile (TT3, T4, TSH, FT3, and FT4) were analysed for study and control groups. They observed that ferritin was in negative correlation with TSH (r=-0.278, P=0.178), and iron was in negative correlation with TSH (r=-0.121, P=0.657) but total iron binding capacity showed insignificant positive correlation with TSH (r=0.063, P=0.623).

Both iron and ferritin were significantly decreased, but total iron binding capacity was significantly increased in the study group compared to the control group. The study concluded that hypothyroidism causes a decrease in iron levels.

Banday et al evaluated iron profile, ferritin, total iron-binding capacity, and percentage saturation in 70 (50 females and 20 males) hypothyroid patients with age 18-65 years. 14 patients (20%) were anaemic (Haemoglobin (HB)<12 g/dL), 34.2% had iron deficiency (anaemic or non-anaemic), among whom 28.5% were females and 5.70% were males. The study concluded that iron deficiency was found in a significant percentage of hypothyroid patients.

None of the studies considered vitamin D and iron bi-deficiencies in hypothyroid female patients in different countries of the world or the Middle Eastern region. Untreated hypothyroidism leads to chronic conditions like dyslipidaemia, hypertension, cognitive impairment, infertility, and neuromuscular dysfunction. Presence of bi-deficiencies will worsen the situation even more.

**Conclusion**

Hypothyroidism is a common but under-recognized and under-diagnosed condition in the Persian Gulf countries. Moreover, the effect of hypothyroidism on vitamin D and iron levels was inadequately evaluated. This is important to identify whether hypothyroid female patients suffered from vitamin D and iron deficiencies so that doctors can treat them earlier and can reduce the deficiency-related complications. Hence, there are plenty of scopes for studying the status of bi-deficiencies in the hypothyroid population.

**Acknowledgments**

The authors are grateful to the post-graduate committee of the Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah.

**Authors’ contributions**

HFE, SCS, MTHP, and WSWS contributed to the conception, planning of writing, and literature review. HFE and SCS drafted the first manuscript. MTHP wrote the rationale of this manuscript. All authors reviewed and approved the final version of the manuscript.

**Conflict of Interest**

The authors declare no competing interests in this study.

**Funding**

There was no funding for this study.

**References**

3. Alameri M, Wafa W, Moriarty M, Lessan N, Barakat MT.


Serum vitamin D and iron status in hypothyroid female population

61: 965-7. doi: 10.18410/jebmh/2019/203