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Association of Serum Ferritin Levels and Thyroid Hormones

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Abstract

Thyroid metabolism is orchestrated by the action of various minerals and trace elements including iron, iodine, selenium, and zinc. Iron deficiency, specifically deficiency in serum ferritin levels, is one of the common causes of thyroid dysfunction. Our objective was to evaluate the relationship between serum ferritin levels and circulating thyroid hormones. For this, a retrospective analysis was performed on 16,512 individuals who tested for serum levels of ferritin and thyroid profile at Vibrant America Clinical Laboratories. Subjects were stratified based on the serum levels of ferritin. Age ($p < 0.0001$) was found to be a significant factor in altering serum ferritin levels and also serum ferritin levels were significantly associated with varying levels of thyroid hormones in both males and females, with the levels of T4 ($p < 0.0001$) and RT3 ($p < 0.0001$) being the most significant. The levels of FT4 ($p < 0.0001$) and TSH ($p = 0.0120$) were significantly associated but did not exhibit any change in expression levels. Serum ferritin was found to be positively correlated with free thyroxine ($r = 0.04325$, $p < 0.0001$) and inversely correlated with serum triiodothyronine ($r = -0.03232$, $p < 0.0001$). Analysis of Linear association by Pearson's correlation exhibited a considerable correlation between varying serum ferritin levels with all tested thyroid hormones. The study concludes that serum ferritin levels were associated with thyroid hormone synthesis and metabolism in individuals with optimal levels of circulating ferritin.

Keywords

Ferritin, Thyroxine, Free Triiodothyronine, Free Thyroxine, Thyroid Stimulating Hormone

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1. Introduction

Thyroid metabolism is brought about by the action of various minerals and trace elements. Iron, iodine, selenium, and zinc play a crucial role in the regular synthesis of thyroid hormones. (Siddiqui *et al.* 2014) Iodine is known to have the most vital role in the synthesis of T3 and T4. Selenium serves as an antioxidant defense mechanism and is also involved in the conversion of T4 to T3 through the deiodinase enzyme. Thyroid disorders are the most prevalent endocrine disorders affecting 5% to 6% of the U.S. population [1] [2]. The hypothalamus-pitui- tary-thyroid (HPT) axis controls the auto-regulated feedback loop, which controls the thyroid glands [3]. Thyroid imbalance can result from various factors including iodine deficiency, obesity, surgical history, pregnancy, etc. Nutritional deficiencies are one of the preventable causes of thyroid disorders [4].

Iron deficiency, specifically deficiency in serum ferritin levels, is one of the common causes of thyroid dysfunction. Iron is a vital nutrient and an important cofactor involved in various biochemical processes, including oxygen transport. Although an iron deficiency can alter various physiological functions, elevated levels of iron in the blood can also be toxic [5]. Therefore, iron metabolism is highly regulated by various proteins including transferrin for iron transport and ferritin for iron storage and buffering of excess iron.

Ferritin, an iron storage protein similar to fibrinogen, acts as the most vital marker of body iron. Low levels of ferritin, which is an indicator of iron storage in the body, can have an impact on thyroid synthesis. In addition to affecting thyroid hormone production, low levels of ferritin can also impact the conversion of the inactive thyroid hormone T4 to the active thyroid hormone T3. This conversion takes place primarily in the liver and requires an adequate supply of iron. In turn, extremely high levels of ferritin can sometimes be associated with certain conditions that can have an impact on thyroid function. For example, high levels of ferritin can be a symptom of hemochromatosis, a genetic condition that causes the body to absorb too much iron from the diet [6]. Hemochromatosis can lead to damage to various organs, including the liver, heart, and pancreas, and can also affect thyroid function. Serum levels of ferritin can reflect iron storage in the body and are found to have various clinical significances, as serum levels of ferritin were correlated with the risk of myocardial infarction. Serum ferritin levels can also be a nonspecific tumor marker for liver, spleen, or bone marrow cancer. High serum levels of ferritin were observed in hepatitis, cirrhosis, and various other malignant diseases. A strong correlation was reported between the high serum levels of ferritin in patients with neuroblastoma, leukemia, and various other cancers [7].

Several studies have demonstrated the association of serum ferritin in various clinical pathological conditions such as cardiovascular disorders, tumor markers, etc [8]. However, studies on the association of ferritin with the thyroid gland have been limited. The current study aimed to investigate the relationship between thyroid function and serum ferritin levels in a large cohort of samples.

2. Materials and Methods

The retrospective analysis was carried out at Vibrant America Clinical Laboratories between January 2018 and October 2021. A total of 16,512 individuals which includes 10,709 females and 5803 males were involved in the study. The subjects were tested for serum levels of ferritin and thyroid hormones thyroxine (T4), triiodothyronine (T3), free T4 hormone (FT4), and thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), Anti-Thyroid Peroxidase (Anti-TPO), and reverse T3 (RT3). Since the study was carried out on remnant deidentified samples and hence was exempted from formal ethical review by Western IRB (Washington USA). The study population comprised free-living individuals who had no clinical indications of iron deficiency or thyroid abnormalities.

2.1. Reference Range of Thyroid Hormones and Serum Ferritin

Thyroid hormones (T4, T3, FT4, FT3, TSH, Anti-TPO, and RT3) and serum ferritin levels were examined in Vibrant America Laboratories. The reference ranges for thyroid hormones and ferritin levels were as per the standard reference ranges followed by commercial test labs and hospital labs.

2.2. Serum Analysis of Thyroid Hormones

Serum FT4 concentrations were determined using a specific anti-thyroxine antibody labeled with a ruthenium complex. The test allows the use of a small number of antibodies approximately 1% - 2% of the total free thyroxine of a normal serum sample, this enables the equilibrium between free T4 and antibody-bound T4 virtually unaffected.

T3, RT3, and FT3 Waters TQ-S Tandem Mass Spectrometer were used for estimation. The analytical standards of thyroid hormones were obtained from Cerilliant Corporation (Round Rock, Texas). This technique is a reliable and LC-MS/MS-based highly sensitive technique.

Serum levels of TSH, FT4, anti-TPO, and anti-Tg tests were measured using a commercial Roche e601 analyzer (Roche Diagnostics, Indianapolis, IN, USA) following the manufacturer's instructions. All reagents were procured from Roche Diagnostics (Indianapolis, IN, USA). The levels of Anti-TPO were measured using recombinant antigens and polyclonal anti-TPO antibody-based Elecsys anti-TPO assay kit.

2.3. Serum Analysis of Ferritin Concentrations

Peripheral blood was obtained from the subjects and immediately processed for serum separation. The invitro quantitative determination of serum ferritin was estimated by electrochemiluminescence immunoassay (ECLIA) and analyzed using Elecsys and Cobas E analyzers.

2.4. Statistical Analysis

The processing of clinical data from deidentified subjects was performed via Java

for Windows version 1.8.161 and statistical analysis was performed using GraphPad Prism version 7.00 (Windows). Descriptive statistics were used to define continuous variables (mean ± SD, median, minimum, and maximum) with statistical significance set at $p < 0.05$. Mann-Whitney U test was used to compare two independent groups without normal distribution. Pearson's correlation analysis was done to find a probable correlation between variables with significance set at $p < 0.005$.

3. Results

To evaluate the association of serum ferritin levels with thyroid functioning a total of 16512 individuals of both sexes were included in the study. The mean age of the population is 48.2 ± 15.7. The sample comprised 5803 males (35.2%) and 10709 females (64.8%) with a mean age of 49.7 ± 16 and 47.4 ± 15.5 respectively (Table 1). A significant ($p > 0.05$) difference was observed in ferritin levels between males and females.

Based on serum ferritin levels the study population was stratified into three groups, which were the study population was stratified into three groups subjects with ferritin levels less than the reference range (≤ 12 ng/mL), within the reference range (males: 12-300, females: 12-150 ng/mL), and greater than reference range (male: ≥300 ng/mL, female: ≥150 ng/mL) (Figure 1). A strong significance was observed between age and varying levels of ferritin through ordinary one-way ANOVA (Table 2). The thyroid hormones such as T4, TSH, and RT3 were found to be significantly associated with varying levels of serum ferritin. Especially, the level of T4 exhibited a significant increase with the increase in serum level of ferritin (<0.0001). Interestingly, the level of RT3 was found to be significantly increased with increased serum ferritin (<0.0001). Although FT4,

Table 1. Baseline characteristics classified by gender.

	Female N = 10,709		Male n = 5803	
	Mean ± SD	Median (min - max)	Mean ± SD	Median (min - max)
Age (years)	47.4 ± 15.5	48 (12 - 100)	49.7 ± 16.0	50 (12 - 95)
Ferritin (ng/mL)	89.5 ± 80.1	67.9 (2.4 - 963.8)	201.3 ± 147.5	169.3 (5.2 - 993.4)
Thyroid markers				
FT3 (pg/mL)	3.0 ± 0.67	2.9 (1.3 - 15.02)	3.2 ± 0.59	3.24 (0.7 - 10.1)
FT4 (ng/dL)	1.2 ± 0.2	1.23 (0.39 - 5.81)	1.2 ± 0.27	1.27 (0.20 - 4.0)
T4 (µg/dL)	7.2 ± 1.5	7.03 (2.4 - 18.8)	6.8 ± 1.3	6.7 (1.2 - 19.5)
T3 (ng/mL)	1.1 ± 0.29	1.06 (0.32 - 4.3)	1.08 ± 0.23	1.07 (0.3 - 3.63)
TSH (µIU/mL)	2.3 ± 3.6	1.8 (0.005 - 160.6)	2.4 ± 2.3	2.03 (0.006 - 51.7)
ATPO (IU/mL)	37.8 ± 101.7	13.07 (5 - 1659)	24.1 ± 83.0	11.8 (5.0 - 2724)
RT3 (ng/dL)	13.3 ± 6.9	12.5 (4.5 - 460.9)	14.3 ± 5.6	13.5 (4.5 - 143.0)

Table 2. Clinical characteristics of candidates with varying serum levels.

Parameters	Ferritin < reference range	Ferritin within the reference range	Ferritin > reference range	p
n	582	13962	2232	
Age	45.5 ± 13.4	47.4 ± 15.8	54.3 ± 13.9	<0.0001
Free triiodothyronine (FT3) 2.3 - 4.1 pg/mL	3.1 ± 0.6	3.1 ± 0.6	3.1 ± 0.6	0.4652
Free thyroxine (FT4) 0.9 - 1.7 ng/dL	1.2 ± 0.3	1.2 ± 0.22	1.2 ± 0.23	<0.0001
Thyroxine (T4) 0.40 - 4.50 mIU/mL	6.9 ± 1.5	7.05 ± 1.4	7.2 ± 1.5	<0.0001
Triiodothyronine (T3) 100 - 200 ng/dL	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.0320
Thyroid-stimulating hormone (TSH) 0.3 - 4.2 mlU/L	2.6 ± 4.7	2.3 ± 2.8	2.4 ± 4.8	0.0120
Antithyroid peroxidase (anti-TPO) < 9.0 IU/mL	40.3 ± 136.2	31.9 ± 88.9	36.4 ± 118.3	0.2794
Reverse T3 (RT3) 9.2 - 24.1 ng/dL	13.18 ± 4.3	13.6 ± 6.7	14.4 ± 7.1	<0.0001

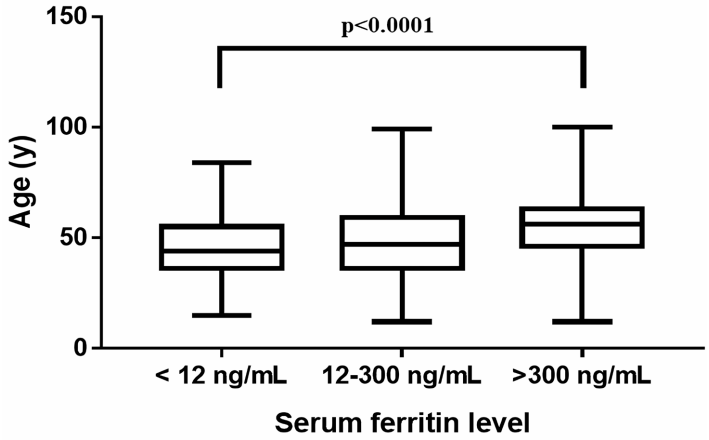

Figure 1. Trends of age along with increasing levels of serum ferritin.

T3, and TSH were found to be significantly associated, they did not exhibit any change in expression levels concerning serum ferritin levels. The impact of serum ferritin on developing abnormities in thyroid functioning was tested by a non-parametric U-test. Serum levels of ferritin are significantly associated with altered levels of serum thyroxine ($p < 0.0001$). The excessive production or low synthesis of TSH ($p = 0.0120$) is not associated with the serum levels of ferritin.

The Person correlation analysis with $p < 0.05$ was performed between serum ferritin levels and thyroid hormones (Table 3). There was a strong positive correlation between FT4($r = 0.04325$, $p < 0.0001$) with serum ferritin (Table 4). In terms of the association between thyroid hormones and serum ferritin, males exhibited a strong positive correlation with T4 ($r = 0.0668$, $p < 0.0001$) (Table 5). The correlation between serum ferritin and thyroid hormones in females exhibited no significant correlation (Table 6). The thyroid hormones FT3 ($r = -0.06034$, $p < 0.0001$) exhibited a negative correlation with ferritin in males. The whole population observed a strong negative correlation between ferritin and thyroid hormones ($r = -0.03232$, $p < 0.0001$) (Figure 2).

Table 3. Association of serum ferritin with hypo and hyperthyroid subjects.

		n	Ferritin (mean ± SD)	p
Hyperthyroidism (Pirahanchi *et al.*, 2023)	Thyroxine > 4.50 mIU/mL	661	120.7 ± 126.1	0.0097
	Thyroid-stimulating hormone < 0.3 - 4.2 mIU/L	286	116.7 ± 95.0	0.9222
Hypothyroidism (Pirahanchi *et al.*, 2023)	Thyroxine < 0.4 mIU/	299	138.4 ± 125.3	0.0398
	Thyroid-stimulating hormone > 4 mIU/L	826	146.6 ± 293.1	0.1282
Subclinical hyperthyroidism (Pirahanchi *et al.*, 2023)	Thyroid-stimulating hormone < 4 mIU/L	286	116.7 ± 95.0	0.9222
Subclinical hypothyroidism (Pirahanchi *et al.*, 2023)	Thyroid-stimulating hormone > 4 mIU/L	826	146.6 ± 293.1	0.1282

Table 4. The correlation between ferritin and thyroid hormones.

Thyroid marker	Ferritin	
	r	p
T4	−0.01226	0.1124
FT4	0.04325	<0.0001
FT3	0.02343	0.0024
T3	−0.03232	<0.0001
TSH	0.008865	0.2509
ATPO	−0.002012	0.7944
RT3	−0.008697	0.26

Table 5. The correlation between serum ferritin and thyroid hormones in male subjects.

Thyroid marker	Ferritin	
	r	p
T4	0.06686	<0.0001
FT4	0.03317	0.0109
FT3	−0.06034	<0.0001
T3	−0.04373	0.0008
TSH	0.002117	0.8709
ATPO	0.004187	0.748
RT3	−0.01273	0.3286

Table 6. The correlation between serum ferritin and thyroid hormones in female subjects.

Thyroid marker	Ferritin	
	r	p
T4	0.003299	0.7307

Continued

FT4	0.01072	0.2633
FT3	−0.006527	0.4959
T3	−0.009849	0.3042
TSH	0.007784	0.4168
ATPO	−0.008038	0.4017
RT3	0.005843	0.5422

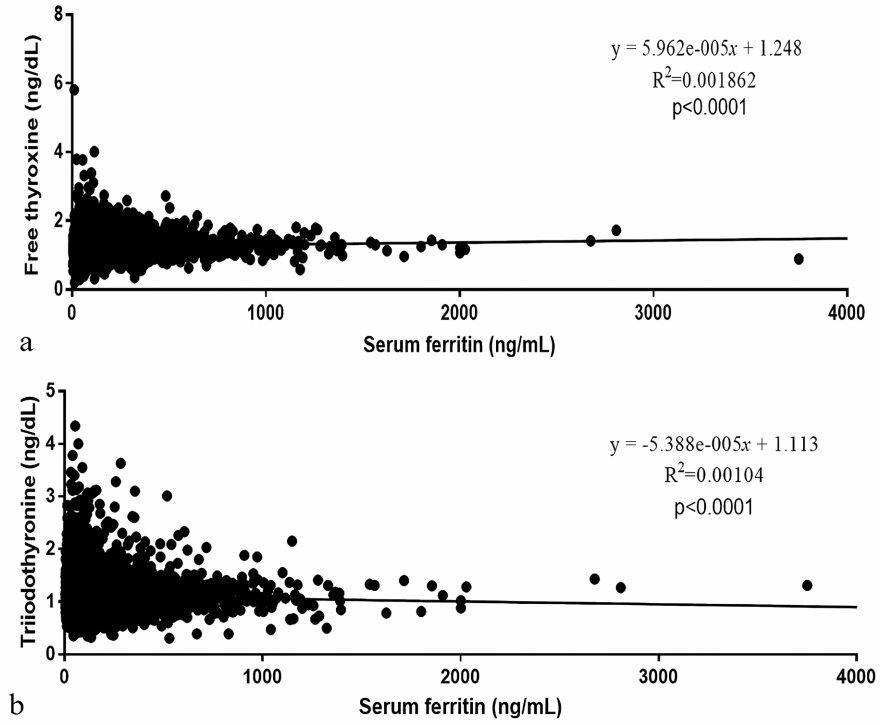

Figure 2. Relationship between thyroid hormones and serum ferritin. (a) Free thyroxine, (b) Triiodothyronine.

The correlation between the varying levels of serum ferritin with thyroid hormones as assessed by Person coefficient revealed that the low levels of serum ferritin were positively correlated with circulating levels of free triiodothyronine (FT3) ($r = 0.2567$, $p < 0.0001$) and were also found to be negatively correlated with serum levels of T4 ($r = -0.1995$, $p < 0.0001$) (Table 7). The present study exhibited no significant correlation between TSH and serum ferritin. The study relived that all the thyroid hormones are correlated with normal levels of serum ferritin. Free thyroxine (FT4) ($r = 0.07755$, $p < 0.0001$), free triiodothyronine (FT3) ($r = 0.04519$, $p < 0.0001$), thyroid-stimulating hormone (TSH) ($r = 0.01966$, $p < 0.0202$) and reverse T3 (RT3) ($r = 0.07044$, $p < 0.0001$) were found to exhibit strong positive correlation with normal levels of serum ferritin whereas, thyroxine (T4) ($r = -0.07096$, $p < 0.0001$), triiodothyronine (T3) ($r = -0.07983$, $p < 0.0001$), antithyroid peroxidase (anti-TPO) ($r = -0.04811$, $p < 0.0001$) were found to be negatively correlated with the serum ferritin at average circulating levels. High

Table 7. Correlation of varying levels of serum ferritin with thyroid hormones.

	r	p
Ferritin < reference range		
T4	−0.1995	<0.0001
FT4	0.05936	0.1527
FT3	0.2567	<0.0001
T3	−0.01078	0.7953
TSH	−0.0631	0.1284
ATPO	−0.1229	0.003
RT3	0.112	0.0069
Ferritin within the reference range		
T4	−0.07096	<0.0001
FT4	0.07755	<0.0001
FT3	0.04519	<0.0001
T3	−0.07983	<0.0001
TSH	0.01966	0.0202
ATPO	−0.04811	<0.0001
RT3	0.07044	<0.0001
Ferritin > reference range		
T4	−0.01877	0.3758
FT4	−0.00169	0.9363
FT3	0.0236	0.2653
T3	−0.00898	0.6718
TSH	−0.00345	0.8705
ATPO	−0.0421	0.0468
RT3	0.1606	<0.0001

levels of serum ferritin were found to have a strong positive correlation with reverse T3 (RT3) ($r = 0.1606$, $p < 0.0001$).

4. Discussion

The relationship between iron and thyroid hormone metabolism has become a focus of research in recent years. Iron and thyroid hormone metabolism are interrelated, and both play important roles in the proper functioning of the body. Iron is necessary to produce thyroid hormone, and thyroid hormone, in turn, affects iron metabolism. Iron in the form of ferritin plays a crucial role in the body's energy metabolism, including the regulation of oxygen consumption and heat production. Dundas *et al.* [9] discovered a significant rate of iron deficiency in women with subclinical hypothyroidism in 1999 and were able to show a small increase in T4, as well as a proportionally lower TSH, in response to therapeutic iron supplementation. In a randomized, double-blind, controlled study published

in 2002 by Zimmermann *et al.* [10] adding iron microcapsules to iodized salt treatment resulted in a significant increase in thyroid hormone levels and a significantly lower incidence of hypothyroidism and thyroid gland enlargement in children aged 6 - 15 years with goiter when compared to iodine treatment alone.

The present study reveals the significant role of serum ferritin in the regular synthesis and healthy functioning of thyroid hormones [11]. The role of iodine and selenium in thyroid health is well-studied. Serum levels of ferritin also play a vital role in thyroid metabolism as the initial synthesis of thyroid hormones is catalyzed by heme-containing thyroid peroxidases [12]. Ferritin is an important component of the enzymes involved in the production of thyroid hormones. For instance, iron is a component of the enzyme peroxidase, which is involved in the iodination of tyrosine residues to form T3 and T4. A lack of iron can lead to a decreased production of thyroid hormones, which can result in an enlarged thyroid gland (goiter) and hypothyroidism, a condition characterized by low levels of thyroid hormones in the blood. In 2012, Akhter S *et al.* [13] reported a significant change in thyroid hormone production in iron-deficient people, where a drop in serum iron affects heme-dependent TPO activity and hence alters thyroid metabolism. They also reported that serum FT4 level was found to be substantially lower in cases than in controls. Our findings are also in line with those of Etekhari *et al.* [14] (2009) who had reported that the depletion of circulating serum ferritin can cause a drop in serum-free T4. The population was categorized in this investigation based on serum ferritin levels, which were found to be strongly linked with age and T4, TSH, and RT3 synthesis. Male ferritin levels are known to be higher than female ferritin levels, and serum ferritin levels vary greatly with age and other conditions [15]. The current findings back this up, with a substantial correlation between blood ferritin levels and age (**Table 2**). In general, ferritin levels tend to decrease with advancing age which can result in iron deficiency anemia. In addition, no significant association was found between blood ferritin levels and thyroid hormones in female individuals (**Table 5**). This supports Macaron and Macaron's [16] discovery in 1982, in which they found a substantial difference in serum levels between sex-matched patients.

In our study a positive correlation was observed between serum ferritin and FT4 and a negative correlation with T3, there was no significant correlation among other thyroid markers. In the case of male subjects T4 was found to have a strong positive correlation and FT3 had a strong negative correlation with serum ferritin. This signifies the altering concentration of serum ferritin highly influences the vital thyroid hormones FT4, T4, T3, and FT3. TSH was found to be unaffected by the serum ferritin levels this result coincides with a report by Eftekhari *et al.* [17] 2006 where they stated that the supplementation of iron-to-iron deficient adolescents did not alter the concentration of TSH.

The present study also details the effects of varying concentrations of serum ferritin, the subjects with serum levels below the reference range were found to have a strong negative correlation with T4. This might result from an iron deficiency which significantly reduces the TPO activity thereby inhibiting the con-

version of T4 to T3 and increasing the circulating levels of T4 resulting in hyperthyroidism. The subjects with normal ferritin exhibited a correlation with all thyroid markers except TSH, this again supports the observation reported by Eftekhari *et al.*, 2006 [17]. A study by Sachdeva *et al.* [2015] [18] also reported low ferritin levels in hypothyroid individuals compared to healthy individuals. The current observations also exhibit a negative correlation between TSH and altered levels of serum ferritin whereas in subjects with ferritin levels with reference range did not exhibit any correlation. However, the association between ferritin and TSH remains unclear. For instance, a study of postmenopausal women found no significant association between ferritin levels and TSH levels, and another study of adults with subclinical hypothyroidism found no significant association between ferritin levels and TSH levels. A strong positive correlation was observed with FT4, FT3, and RT3. Since ferritin is an acute phase reactant the negative correlation of T4, T3, and ATPO with ferritin might result from various other conditions such as infection, autoimmunity, malignancy, or renal disorders. High serum levels of ferritin are positively correlated with RT3, high ferritin might result from any of the above-mentioned reasons and result in a decrease in T3 which increases the serum levels of RT3. Tantiworawit *et al.* [19] (2021) have stated that elevated levels of serum ferritin are an early predictor of the development of diabetes, hypothyroidism, and various cardiovascular events.

The retrospective nature of the deidentified serological data is a limitation of this study. The study population involved more than 50% of female subjects and data such as serum iron levels were not taken into consideration which can be considered a discrepancy. However, the study was carried out in a huge population with subjects in diverse age groups and the study significantly highlights the association of serum levels of ferritin in thyroid metabolism.

5. Conclusion

Our study revealed the strong association of serum ferritin levels with the synthesis and metabolism of thyroid hormones in healthy individuals. Abnormal levels of serum ferritin alter the healthy functioning of thyroid hormones due to the abnormal functioning of the heme-dependent enzyme TPO essential for the synthesis of thyroid hormone. The outcomes of the study have considerable clinical significance, such as the monitoring of serum ferritin levels which might predict various chronic disorders including thyroid problems, cardiovascular events, and diabetes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Author Contributions

Hari Krishnamurthy, Karthik Krishna, and Tianhao Wang performed the research. Hari Krishnamurthy, John J. Rajasekaran, Karenah Rajasekaran, and Vasanth Jayaraman designed the study. Qi Song, Kang Bei, and Swarnkumar Reddy analyzed the data. Hari Krishnamurthy and Swarnkumar Reddy wrote the article.

Institutional Review Board Statement

The study comprises a retrospective analysis exempted by Western Institutional Review Board.

Conflicts of Interest

Krishnamurthy, Jayaraman, Krishna, Wang, Bei, and Rajasekaran are employees of Vibrant Sciences LLC. Reddy, Song, and Rajasekaran are employees of Vibrant America LLC.

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