Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2, 2175-2186
2025
Publisher: Learning Gate
DOI: 10.55214/25768484.v9i2.5054

Level of chemical element content in serum of thyroid cancer patients as a potential biomarkers for thyroid cancer

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Abstract: The thyroid gland plays a crucial role in regulating metabolism and growth through the production of thyroid hormones. Trace elements are vital for the proper functioning of the thyroid and are implicated in various thyroid disorders, including autoimmune diseases and malignancies. Among these trace elements, iron (Fe), copper (Cu), manganese (Mn), zinc (Zn), and magnesium (Mg) have been closely studied for their impact on thyroid health. The imbalance or deficiency of these elements can interfere with thyroid function and potentially contribute to the development of thyroid pathologies. This study aimed to investigate the serum levels of several trace elements—zinc, copper, iron, manganese, and magnesium—in patients diagnosed with thyroid cancer, specifically comparing these levels with those in healthy controls. The primary objective was to identify any correlations between trace element concentrations and the occurrence of thyroid malignancies to understand their potential role in the development and progression of thyroid cancer. The study included 45 thyroid cancer patients, consisting of 31 individuals with papillary thyroid carcinoma (PTC) and 14 with follicular thyroid carcinoma (FTC), as well as 45 healthy controls. Serum concentrations of zinc, copper, iron, manganese, and magnesium were measured and compared between the two groups. Statistical analyses were performed to assess differences in the concentrations of these trace elements and to determine any significant relationships with thyroid cancer occurrence. The study found a statistically significant increase in the serum levels of copper and manganese in thyroid cancer patients compared to healthy controls ($p < 0.05$). Conversely, levels of zinc, iron, and magnesium were significantly lower in the cancer group. These findings indicate a strong association between altered trace element concentrations and the presence of thyroid malignancy, particularly copper and manganese, which were elevated in the serum of cancer patients. Furthermore, the data suggest that deficiencies in other trace elements, such as zinc, may also contribute to the pathophysiology of thyroid cancer. The results of this study highlight the potential role of trace elements, particularly copper and manganese, in thyroid cancer development. The observed alterations in trace element levels may serve as useful biomarkers for the diagnosis and prognosis of thyroid cancer. Further research is needed to explore the underlying mechanisms connecting trace element imbalances with thyroid malignancies and to develop targeted therapeutic strategies aimed at correcting these deficiencies to improve patient outcomes.

Keywords: *AAS, Blood, Metal, Statistical analysis, Thyroid cancer.*

1. Introduction

Thyroid disorders are among the most common endocrine pathologies, ranking as the second most prevalent in both human and animal studies [1]. Several trace elements are essential for the synthesis and metabolism of thyroid hormones, which are fundamental to the thyroid's normal functioning. It is widely acknowledged that aging significantly impacts the development of thyroid cancer and adenomatous goiter [2]. As individuals age, substantial functional changes occur in the endocrine system, including the thyroid gland, and thyroid dysfunction becomes more prevalent in older

History: Received: 19 December 2024; Revised: 27 January 2025; Accepted: 7 February 2025; Published: 26 February 2025
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populations compared to younger individuals [1]. By the age of 65, about 50% of the elderly population will have thyroid nodules[1]. Moreover, thyroid nodules and cancer affect women at rates two to five times higher than men. Aging is thought to cause the accumulation of molecular damage in DNA, proteins, and lipids, contributing to cellular aging, which is often accompanied by an increase in oxidative stress at the cellular level. The aging process is complex, involving changes in cellular morphology and biochemistry across both individual cells and entire organs, as well as the body as a whole. The oxidative stress theory is widely recognized as one of the most prominent explanations for the molecular mechanisms of aging [3].

Over the 20th century, significant insights have been gained regarding the environmental factors influencing the incidence of thyroid tumors. It has been demonstrated that the development of thyroid goiters and subsequent cancer can be affected by the excess, deficiency, or imbalance of more than twenty chemical elements in the environment. This has been confirmed through epidemiological, clinical, and experimental studies. Besides iodine, other critical elements, such as magnesium (Mg), iron (Fe), zinc (Zn), manganese (Mn), and copper (Cu), are also involved. However, much of the existing data is largely descriptive and does not offer precise insights into the underlying processes of tumorigenesis [4].

Studies have shown that an imbalance in the concentrations of trace elements can lead to various diseases. While many trace elements are beneficial within specific concentration ranges, both excessive and insufficient amounts can lead to harmful effects [5]. The search for reliable chemical markers for the differential diagnosis of benign and malignant thyroid nodules has become a priority. Despite advancements in iodine deficiency prevention, goiter, especially in its nodular form, remains one of the most common thyroid disorders. Recent studies have reported an increase in thyroid cancer incidences in populations from Israel, the USA, and Scandinavia [6]. Typically, benign euthyroid goiter nodules precede thyroid cancer [7]. Consequently, early detection of benign and malignant thyroid nodules is crucial. Unfortunately, commonly used diagnostic methods, such as needle biopsy and subsequent cytological analysis, often lack sufficient diagnostic accuracy. Given the unique elemental composition of thyroid tissue [6] significant changes in elemental content are expected to occur as tumors progress. Such differences in elemental concentrations between benign and malignant nodules may provide valuable diagnostic information [8].

This study aims to investigate the serum concentrations of magnesium, iron, zinc, copper, and manganese in patients with newly diagnosed papillary and follicular thyroid carcinoma, and compare these levels with those in healthy controls. The goal is to explore the relationship between these trace metals and thyroid cancer, and to assess whether imbalances in these metals could potentially serve as diagnostic biomarkers for thyroid cancer.

2. Materials and Methods

2.1. Study Population

The study involved 45 patients diagnosed with thyroid carcinoma, specifically 31 cases of papillary thyroid carcinoma (PTC) and 14 cases of follicular thyroid carcinoma (FTC), who were undergoing treatment at the Medical Radiological Research Centre's Al Amal Specialized Hospital for Oncology. The patient group included 14 male and 17 female patients with PTC, and 5 male and 9 female patients with FTC. The ages of the patients ranged from 45 to 50 years, with a mean age of 45 ± 5.4 years. Importantly, all patients included in the study had newly diagnosed thyroid cancer and had not yet undergone any prior surgical treatment for the condition. None of the patients had metastases at the time of diagnosis. The control group consisted of 45 healthy individuals, matched for age and gender with the thyroid cancer patients. The control group was selected from individuals with no history of thyroid or other major health issues. The inclusion criteria for the cancer group were newly diagnosed cases of papillary or follicular thyroid carcinoma, and exclusion criteria were patients with other malignancies or prior treatments for thyroid cancer.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 2175-2186, 2025
DOI: 10.55214/25768484.v9i2.5054

2.2. Sample Collection and Processing

We collected blood from all participants into 5 mL of whole blood in vacutainer evacuated tubes. Blood was drawn from the antecubital vein of the patient with 70% isopropyl alcohol used to disinfect the patient's skin with BD syringes. The blood samples were stored immediately after collection at -15 degrees C until they could be processed. They were stored in a controlled environment to prevent any degradation or contamination.

Each blood sample received was weighed using an analytical balance to obtain accurate measurements for further analysis upon arrival at the laboratory. The blood samples were then subjected to wet digestion using a combination of nitric acid (HNO_3) and perchloric acid ($HClO_4$) in a 10:1 volume-to-volume ratio. The digestion was done using a hot plate and temperature of 80°C until white vapors showed that the digestion is complete. They were cooled to room temperature and diluted with 0.1 N nitric acid (HNO_3) to the appropriate volume. Simultaneously processed blank samples containing all reagents but no blood sample were used as control to rule out contamination.

2.3. Analytical Methodology

The trace element concentrations (magnesium [Mg], iron [Fe], zinc [Zn], copper [Cu], and manganese [Mn]) in the blood samples were measured using flame atomic absorption spectrometry (AAS) [9]. The AAS instrument used was a Shimadzu AA-670 spectrophotometer (Japan). The following key operating parameters were optimized for each metal analyzed:

- Detection wavelength: Specific to each metal (e.g., Mg at 285.2 nm, Fe at 248.3 nm).
- Hollow cathode lamp current: Adjusted for each element to ensure accurate detection.
- Slit width: Optimized for each metal to minimize interference from other elements.
- Fuel and oxidant flow rates: Set for each element for optimal sensitivity.
- Flame type: The appropriate flame type (air-acetylene) was used for each element.

The AAS instrument was used with automated background correction to eliminate interference. The samples were analyzed in triplicate to ensure precision, and the average concentration of each metal in every sample was calculated. Standard Reference Materials (SRMs) were used to verify the accuracy of the measurements, with recoveries ranging from 94% to 101%. In addition to the primary laboratory analysis, all samples were also analyzed at an independent laboratory to verify consistency. The results from both laboratories showed a variation of only ±2%, confirming the reliability of the findings.

For the preparation of working standards, stock standard solutions (1000 mg/L) of trace elements were prepared by diluting the 1000 ppm stock solutions in deionized distilled water (DDDW). Blood samples containing copper, zinc, and iron were diluted by a factor of 10 in DDDW, while the serum for magnesium analysis was diluted 1:100 due to its higher concentration. Manganese was analyzed by diluting the serum 1:5 in DDDW. The conventional addition method was employed for all elements analyzed, ensuring accuracy in the determination of trace metal levels. The aforementioned elements were analyzed using atomic absorption spectrophotometry – Flame (AAS; Varian Spectra AA 300/400) which is accessible in Medicine City, Iraq [10].

Statistical Analysis

The data were analyzed using SPSS software (version 26). Prior to statistical analysis, the data were tested for normality using the Kolmogorov-Smirnov test. For normally distributed data, the Student's t-test was used to compare the mean concentrations of trace elements between thyroid cancer patients and healthy controls. A significance threshold of $p < 0.05$ was considered statistically significant. In addition, multivariate analysis was performed to evaluate the effects of potential confounding variables such as age, gender, smoking status, and diet on trace metal concentrations. The p-value for all analyses was set at 0.05.

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Table 1.
Acomparesion of the morphological characteristic of thyroid cancer patients and control group.

		Thyroid cancer		Healthy control		P value
		No	%	No	%	
Age (years)	<45years	6	12.8	-	-	0.0001*
	30---39	7	14.4	13	43.3	
	40---49	22	44.5	17	56.7	
	=>50years	26	42.8	-	-	
	Mean±SD (Range)	45.0±9.1(25-59)		39.1±3.5(31-45)		0.0001#
Gender	Male	19	31.7	13	43.3	0.276
	Female	**41**	**68.3**	**17**	**56.7**	

Note: *Significantdifference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.
#Significantdifference between two independent means using Students-t-test at 0.05 level.

3. Results

The results in Table 1 present a comparison of the morphological characteristics between thyroid cancer patients and healthy controls, focusing on variables such as age, gender, and the distribution of cancer types.

In terms of age, the thyroid cancer patients had a mean age of 45.0 ± 9.1 years, with an age range between 25 and 59 years. In comparison, the healthy control group had a mean age of 39.1 ± 3.5 years, with ages ranging from 31 to 45 years. The difference in age between the two groups was statistically significant, with a p-value of 0.0001, indicating that thyroid cancer patients in this study were generally older than the control group.

Looking at the gender distribution, the thyroid cancer cohort consisted of 31 females (68.3%) and 14 males (31.7%), while the control group included 17 females (56.7%) and 13 males (43.3%). The gender difference between the cancer and control groups showed a higher proportion of females in the thyroid cancer group, which aligns with the well-established observation that thyroid cancer predominantly affects women. The p-value for gender was 0.276, indicating that the gender distribution between the two groups was not statistically significant.

Regarding the age group distribution, the thyroid cancer patients were divided into the following categories:

- 12.8% were under 45 years of age
- 14.4% were between 30 and 39 years
- 44.5% were between 40 and 49 years
- 42.8% were 50 years or older.

This age distribution shows a predominance of thyroid cancer patients in the 40-49 and 50+ age groups, which is typical of the age distribution for thyroid cancer, especially for the more common papillary carcinoma. These proportions highlight that thyroid cancer is more frequently diagnosed in individuals over 40 years of age, with a significant number of cases in the 50+ age group.

Overall, the results in Table 3 show significant age-related differences between the thyroid cancer and control groups, with thyroid cancer patients being older on average. The gender distribution indicates a higher proportion of females in the thyroid cancer group, consistent with known demographic patterns for thyroid malignancies. The detailed age breakdown reveals that a large proportion of thyroid cancer cases occur in individuals aged 40 and above.

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Table 2.
Serum level of trace elements in different types of thyroid cancer (μg/L) compare with control patients.

Trace elements	Thyroid cancer patients	Control	High/low
Zinc	860 ± 26	1008 ± 156	
Copper	1634 ± 155	1442 ± 35	
Iron	1256 ± 456	1420 ± 75	
Magnesium	17200±146	17600 ± 400	
Manganese	1.4 ± 0.35	1.15 ± 0.0	

The results from Tables 2 and 3 demonstrate notable differences in the serum concentrations of several trace elements between thyroid cancer patients and healthy controls, which may have significant clinical implications. In particular, zinc levels were found to be significantly lower in thyroid cancer patients (860 ± 26 μg/L) compared to healthy controls (1008 ± 156 μg/L). Zinc is a vital trace element involved in many cellular processes, including immune function, DNA synthesis, and thyroid hormone metabolism. Zinc deficiency has been associated with various thyroid dysfunctions, including hypothyroidism, and may contribute to the development of cancer by impairing immune response and promoting oxidative stress. The lower zinc levels observed in thyroid cancer patients suggest that zinc deficiency might play a role in the pathogenesis of thyroid cancer. Clinically, this indicates the potential value of monitoring zinc levels in patients with thyroid cancer. Zinc supplementation could be considered as an adjunct therapy to restore immune function, reduce oxidative damage, and potentially improve thyroid hormone metabolism.

Copper levels were significantly higher in the thyroid cancer group (1634 ± 155 μg/L) than in the healthy controls (1442 ± 35 μg/L). Copper is an essential element involved in enzymatic reactions related to cellular growth, energy production, and angiogenesis, which is the formation of new blood vessels. In cancer, elevated copper levels are often observed due to the enhanced angiogenesis needed to support tumor growth. The significantly higher copper levels in thyroid cancer patients suggest that copper may play a role in supporting the rapid growth and spread of the tumor. Elevated copper levels have been linked to tumor progression in various cancers, and this finding suggests that copper could be a marker of cancer aggressiveness. Clinically, copper may not only serve as a biomarker for thyroid cancer but also as a therapeutic target. Copper chelation therapies, which aim to reduce copper levels, could potentially slow tumor growth by limiting angiogenesis and depriving the tumor of necessary nutrients.

Iron levels were lower in thyroid cancer patients (1256 ± 456 μg/L) compared to healthy controls (1420 ± 75 μg/L), but this difference was not statistically significant. Iron is crucial for thyroid hormone synthesis and plays an important role in cellular respiration and energy production. Iron deficiency in cancer patients is often linked to anemia, a common comorbidity in malignancy due to systemic inflammation and poor iron absorption. While the difference in iron levels was not significant in this study, it may still have clinical relevance. Iron supplementation in thyroid cancer patients, especially those exhibiting signs of anemia, might be necessary to maintain proper thyroid function and overall health. Monitoring iron levels in these patients could also help guide treatment decisions and address the risks of anemia, which could complicate their overall management.

Magnesium levels in thyroid cancer patients (17,200 ± 146 μg/L) were slightly lower compared to the controls (17,600 ± 400 μg/L), but this difference was not significant. Magnesium is involved in many cellular functions, including DNA repair, protein synthesis, and cell division. Magnesium deficiency has been linked to increased oxidative stress and a higher risk of cancer due to impaired DNA repair mechanisms. Although the decrease in magnesium levels was not statistically significant, it is clinically relevant because magnesium is essential for maintaining cellular integrity, particularly in cancer patients who experience high levels of oxidative stress. Magnesium supplementation may help improve cellular function, mitigate the effects of oxidative damage, and support overall cancer therapy.

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ISSN: 2576-8484
Vol. 9, No. 2: 2175-2186, 2025
DOI: 10.55214/25768484.v9i2.5054

Therefore, monitoring and maintaining adequate magnesium levels in thyroid cancer patients could contribute to better disease management and treatment outcomes.

Finally, manganese levels in thyroid cancer patients (1.4 ± 0.35 μg/L) were significantly higher than in healthy controls (1.15 ± 0.05 μg/L). Manganese is an essential cofactor for several enzymes involved in antioxidant defense and cellular protection. Elevated manganese levels have been observed in various cancers, possibly reflecting a compensatory mechanism to counteract oxidative damage. The increase in manganese levels in thyroid cancer patients may suggest a response to the increased oxidative stress present in tumor cells. This finding raises the possibility of using manganese levels as a biomarker for thyroid cancer, particularly in monitoring the oxidative environment of cancerous tissues. In clinical practice, manganese chelation therapy could be explored as a potential therapeutic approach to reduce oxidative stress and limit cancer progression.

Overall, the results of this study suggest that trace elements such as zinc, copper, iron, magnesium, and manganese play significant roles in the development and progression of thyroid cancer. Alterations in the serum concentrations of these metals may not only serve as biomarkers for diagnosis and prognosis but also as targets for potential therapeutic interventions. Clinically, the findings highlight the importance of monitoring trace element levels in thyroid cancer patients, as correcting deficiencies or imbalances in these metals could improve patient outcomes. Future studies are necessary to further elucidate the mechanisms through which these metals influence thyroid carcinogenesis and to evaluate the potential benefits of trace element supplementation or chelation in the management of thyroid cancer.

45 patients had preoperative testing for (Mg, Fe, Zn, Mn, and Cu). in the therapeutic phase of thyroid cancer The mean values of each serum factor examined were used to calculate the parameter levels, which are summarized in Table 4.

Table 3.
Zinc, Copper, Iron, Magnesium, Manganese in **(μg/dL)**

	Thyroid carcinoma	**Healthy control**	
Zinc	0.519±1.174	0.664±1.206	0.0001#
Copper	10.380±3.483	6.967±2.221	0.0001#
Iron	0.466±16.119	1.286±1.168	0.036#
Magnesium	1.828±0.725	2.663±0.985	0.0001#
Manganese	145.243±180.945	46.441±27.874	0.006#

#Significantdifference between two independent means using Students-t-test at 0.05 level.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
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DOI: 10.55214/25768484.v9i2.5054

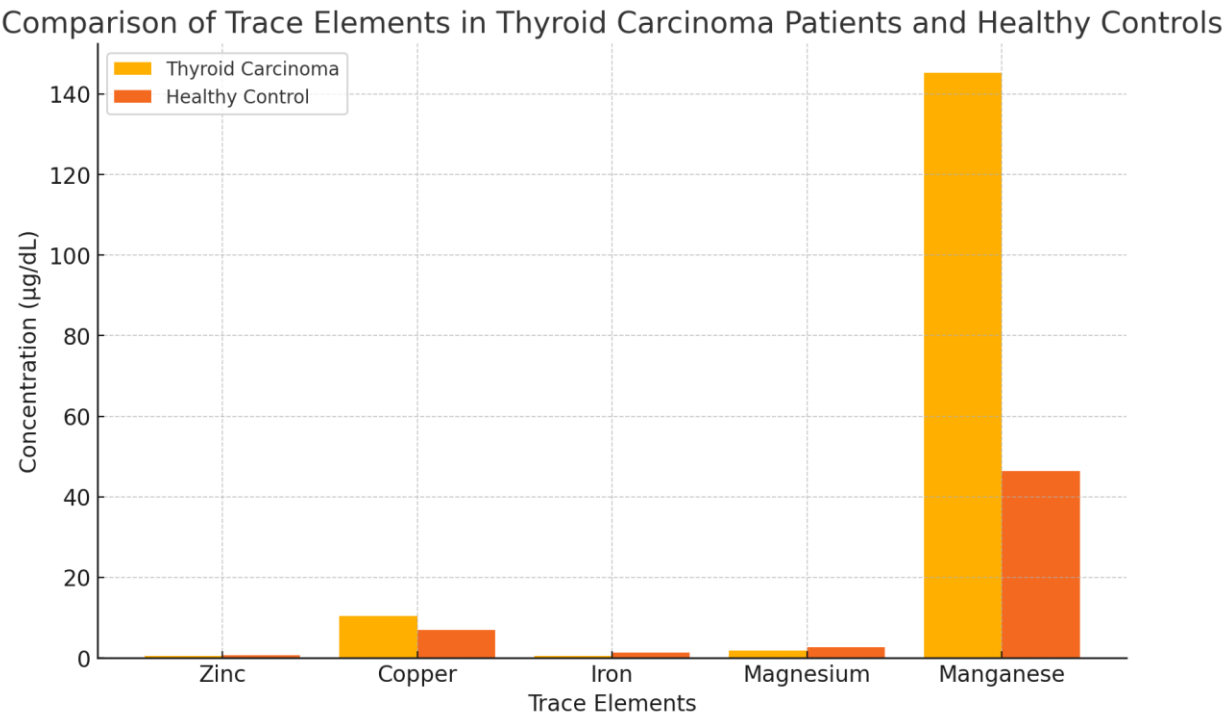

Figure 1.
Comparison of trace elements in thyroid carcinoma patients and healthy controls

4. Discussion

Thyroid cancer is one of the most prevalent forms of endocrine malignancies worldwide, with its incidence steadily rising in recent years. The etiology of thyroid cancer remains complex, with genetic, environmental, and hormonal factors contributing to its development. Previous studies have suggested that trace elements play a significant role in the onset and progression of thyroid cancer. These elements, which include magnesium, zinc, copper, iron, and manganese, are essential for normal cellular function, and their imbalances may influence thyroid health and cancer pathogenesis. The involvement of trace metals in thyroid cancer despite a growing mass of evidence is not sufficiently studied.

This study aimed to investigate the serum concentration of some trace elements, Mg, Fe, Zn, Cu, and Mn in patients with thyroid cancer in order to compare that with the same in healthy controls. The study sought to identify potential biomarkers for thyroid cancer, and to understand the role of these trace metals in the pathophysiology of the disease, by studying them. A cohort of 45 thyroid cancer patients, 31 papillary thyroid cancer and 14 follicular carcinoma cases were compared with an age and gender matched control group. Results from this investigation suggest possible utility of these trace elements as diagnostic markers of thyroid cancer and as potential pathogenetic factors involved in the disease at the molecular level.

The zinc concentrations (µg/L) in patients with papillary and follicular cancer were respectively 1008 ± 156 and 934 ± 175 for the patients with papillary and follicular cancer. Zinc (Zn) is essential to human health because it is required in performing gene expression, cellular division and development, and it is implicated in multiple enzymes that support immunological and reproductive functions. Zinc deficiency can prevent physical growth in children and increase susceptibility to many diseases [11]. Numerous studies have been made to determine if zinc relationates to thyroid hormone levels and it has been found that both hypothyroidism and hyperthyroidism plays an essential role in decreasing zinc levels [12]. In general, too little zinc seems to be associated with hypothyroidism and too much is associated with hyperthyroidism [13]. Research has also shown an extremely close positive correlation

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 2175-2186, 2025
DOI: 10.55214/25768484.v9i2.5054

between the level of zinc and thyroid autoantibodies in people who have autoimmune conditions in the thyroid gland [14]. Zinc also relations to thyroid size sell there is a positive relations between zinc and thyroid volume [15, 16]. As with other malignancies, serum zinc levels are vastly reduced in patients with thyroid cancer [17] Zinc levels in papillary thyroid carcinoma (PTC) and follicular carcinoma compared to healthy individuals are markedly lower. The variations of serum trace element levels indicate that zinc is critically important for proper thyroid function and suggest a link of zinc to cancer. As such, micronutrient deficiencies must be evaluated and addressed in order to enable targeted nutritional interventions in thyroid cancer patients. Supplementing the diet with zinc, initially aimed at restoring immune function, has also been shown to improve thyroid function by lowering TSH levels.

The serum copper concentrations (μg/L) in papillary and follicular carcinoma patients were measured at 1163 ± 153 and 1231 ± 116, respectively. Copper (Cu) plays a vital role as a catalyst in oxidation-reduction reactions and is essential for maintaining thyroid function and lipid metabolism [18]. Cobalt (Co), similarly, inhibits the excessive absorption of T4 and helps regulate calcium levels. Research has documented a significant correlation between cobalt and thyroid function, with multiple studies indicating that cobalt can stimulate the synthesis of thyroid hormones [19]. A decrease in carbon monoxide (CO) levels could potentially increase oxidative stress within thyroid cells, which may lead to a reduction in thyroid hormone production and lower circulating levels of these hormones [20]. Conversely, thyroid hormones also appear to influence the concentration of carbon monoxide in the bloodstream. A clinical study demonstrated that the administration of radioactive iodine to patients with hyperthyroidism resulted in a decrease in thyroid hormone levels, which subsequently lowered serum cobalt levels. Despite these findings, the connection between cobalt and thyroid autoimmune disorders remains less understood. However, it has been established that elevated cobalt levels in the blood correlate with the presence of thyroid autoantibodies. Furthermore, cobalt is believed to play a role in initiating angiogenesis in tumor cells [21] promoting the growth, proliferation, and development of cancer by generating harmful hydroxyl radicals that can damage DNA [22]. Interestingly, the concentration of cobalt in healthy thyroid tissue is significantly higher than in benign thyroid tissue. Several studies suggest that the level of cobalt in the blood serum of individuals with benign thyroid conditions decreases markedly following surgery, indicating a potential link between cobalt levels and thyroid disease progression [23].

The serum iron concentrations (Fe) in patients with papillary and follicular carcinoma were found to be 1420 ± 284 μg/L and 1357 ± 480 μg/L, respectively. Iron (Fe) is a critical element for overall health, playing an active role in oxidation-reduction processes and facilitating oxygen transport throughout the body. Insufficient iron levels can adversely affect cognitive development, immune function, and pregnancy outcomes [24]. A significant deficiency in iodine can lead to a decrease in thyroid peroxidase (TPO) activity, which in turn disrupts the production of thyroid hormones [25]. There is a vast amount of research both in animals and humans that dietary iron deficiency can alter thyroid metabolism profoundly. This may lead to lower levels of total T4 and total T3 in blood and reduced conversion of peripheral tissue T4 to peripheral tissue T3, and elevated TSH [26]. Thyroid function can be altered even in the absence of anemia. About 23-25% of school age children with goiter and iron deficiency anemia had these thyroid related changes [26]. Additional studies have proposed a relationship between thyroid dysfunctions, including hypothyroidism and hyperthyroidism, and abnormalities of hemoglobin. In particular, iron deficiency anemia is a known entity with 'hyperthyroidism,' although iron metabolism and utilization could be adversely predisposed to because of the former. It increases oxidative stress and speeds hemolysis, increasing the lifespan of red blood cells [27]. Concurrent hypothyroidism and iron deficiency anemia are presumed to reflect a common etiology, for example induced by chronic inflammatory disease, malnutrition, or malabsorption, since hypothyroidism frequently occurs as an adaptive response to energy deprivation. Additionally, if iron, vitamin B 12, folic acid, or iodine are not taken in or absorbed adequately, red blood cell production and thyroid function can be impaired. In addition, iron deficiency may decrease the function of thyroid peroxidase (TPO) and hence thyroid gland and anemia. Anemia may partially follow from biological factors: hypothyroidism decreases the demand

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 2175-2186, 2025
DOI: 10.55214/25768484.v9i2.5054

of peripheral tissues for oxygen transport. Lack of knowledge as to the exact mechanisms by which iron deficiency affects thyroid metabolism has lead to further research to elucidate this connection [28].

The decline in serum magnesium levels was notably more pronounced in patients with papillary carcinoma, with a p-value of less than 0.001 (Table 2, Fig. 4). Magnesium (Mg) is an essential element for the proper development and progression of thyroid diseases. It plays a vital role in maintaining the structural integrity of nucleic acids and is actively involved in key processes such as DNA replication, transcription, and repair. A deficiency in magnesium can lead to DNA mutations, which may contribute to the development of cancer [21]. The relationship between thyroid cancer and serum magnesium levels is well-documented, with malignant tumors frequently exhibiting higher magnesium levels compared to normal tissues [29]. However, individuals diagnosed with thyroid cancer generally show lower serum magnesium levels compared to healthy individuals [30]. Magnesium may influence cancer progression by its association with inflammation and/or free radicals, which can lead to oxidative DNA damage and cancer formation. Additionally, there is evidence to suggest that supplementing with magnesium can improve thyroid function. A deficiency in dietary magnesium may also affect thyroid activity. These findings provide strong evidence for the significant correlation between magnesium levels and thyroid function [31].

The serum manganese levels in patients with papillary and follicular carcinoma were measured at 1.3 ± 0.35 µg/L and 1.4 ± 0.39 µg/L, respectively (Table 2, Figure 1). Manganese (Mn) is a trace element that acts as a co-factor for several enzymes and is involved in a variety of biological functions. It plays a critical role in modulating the binding, transportation, and activity of thyroid hormones at the cellular level [32, 33]. Manganese deficiency is relatively rare in humans due to the body's ability to regulate and maintain stable manganese levels in tissues [34]. Despite its importance, the precise effects of manganese on thyroid function are not fully understood. Research has demonstrated a clear relationship between serum manganese concentrations and thyroid hormone levels. Elevated manganese levels have been associated with a decrease in the levels of free T3 and free T4, which can lead to hypothyroidism [34, 35]. Manganese influences thyroid hormone levels by modulating the activity of deiodinases, the enzymes responsible for converting thyroxine (T4) into the more active form, triiodothyronine (T3) [36]. In patients with Hashimoto's thyroiditis, manganese levels in both the blood and thyroid tissues are found to be significantly higher compared to individuals with normal thyroid function [37].

While manganese deficiency primarily impacts thyroid hormone metabolism, it also affects other physiological processes, including the development of the nervous system. Manganese has been shown to interfere with dopamine production, which is essential for regulating thyroid-stimulating hormone (TSH) release. This disruption can lead to the destruction of dopaminergic neurons and result in neurodevelopmental disorders. The increasing incidence of thyroid cancer has been linked to several micronutrient imbalances, including manganese [38]. Patients with thyroid cancer tend to have elevated manganese concentrations in their thyroid tissues when compared to individuals with benign thyroid conditions [39]. The potential role of manganese in cancer development may be attributed to its ability to contribute to oxidative stress, which can lead to genetic mutations and tumor formation [40].

The results demonstrated a statistically significant increase ($p < 0.05$) in the average levels of Copper and Manganese activity in patients with thyroid cancer when compared to the control group. In contrast, Zinc, Iron, and Magnesium showed a significant decrease, consistent with findings from several previous studies. This investigation highlighted a significant correlation between the concentrations of Copper and Manganese and the presence of thyroid cancer. Cytokines are of particular interest in cancer research due to their dual role as both promoters and inhibitors of cell proliferation, which may influence tumor and cancer cell growth. Recent clinical studies have established a strong link between hypothyroidism and an increased risk of developing hepatocellular carcinoma [41]. However, hypothyroidism has also been associated with a reduced risk of breast cancer [42] and a longer survival rate in patients with glioblastoma multiforme [43]. The clinical behavior of thyroid malignancies is

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ISSN: 2576-8484
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thought to be influenced by the transcriptional activity of mutated genes, as well as the stimulating effects of circulating pituitary thyrotropin (TSH) on tumor growth. L-thyroxine (T4), a key thyroid hormone, has been shown to promote cancer cell proliferation through various mechanisms. This article provides a brief overview of the role of T4 as a circulating trophic factor in differentiated thyroid cancers, particularly in terms of its capacity to stimulate cancer growth.

5. Conclusions

Several trace elements are integral to the metabolism and functioning of the thyroid gland, and they are linked to thyroid autoimmunity and malignancies, as outlined in Table 4. Strong evidence supports a close association between elements like iron (Ir) and copper with thyroid metabolism. Additionally, research has shown that the concentrations of blood copper (Cu) and manganese (Mn) can influence thyroid hormone levels. Furthermore, there is evidence suggesting that zinc (Zn), magnesium (Mg), and iron (Ir) may interact with each other, and imbalances in these trace elements could interfere with the thyroid's ability to absorb iodine. Maintaining adequate levels of these trace elements not only helps reduce the prevalence of disorders associated with their deficiencies but also enhances the effectiveness of other trace elements. Deficiencies in trace elements can undermine the success of public health initiatives due to the complex interactions between them. Further research is needed to explore the trace elements linked to thyroid function, with the goal of improving clinical diagnosis and treatment strategies for thyroid diseases in the future.

Transparency:

The author confirms that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 2175-2186, 2025
DOI: 10.55214/25768484.v9i2.5054