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Impact of Thyroid Cancers on Thyroid Hormones among Patients Attended Tripoli University Hospital

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ABSTRACT

Thyroid cancer is one of the most common endocrine system malignancy, accounting for 3.8% of new cancer cases in the US and ranking ninth overall. The number of people diagnosed with thyroid cancer has increased dramatically over the last three decades, indicating the disease's global severity. The purpose of this study was to determine the effect different types of thyroid cancers on thyroid hormones (TSH, T4 and T3). This study was conducted in the Oncology and Endocrinology departments of Tripoli University Hospital (TUH). A total of 70 thyroid cancer patients were targeted, and data was collected using patient record file. TSH, T4 and T3 levels monitored and analyzed in biochemistry laboratory using Cobas e411 Fully Automated Machin. Thyroid cancer struck most females than males. Thyroid cancer incidence has increased among people aged 20 to 40. Most thyroid cancer cases are papillary thyroid carcinoma. Thyroidectomy was done with an 87.14% success rate. The level of TSH hormones increased in thyroid cancer patients. Also, the percentage of T4 hormone levels was mostly increased, whereas thyroid cancer had no proven effect on T3. Papillary thyroid carcinoma was the most common thyroid cancer. There was pronounced effect of thyroid cancer on the TSH and T4 hormone, however T3 hormone remained unchanged.

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INTRODUCTION

The Endocrine System is a network of glands spread throughout the body that produce hormones [1]. Hormones are chemical signals that coordinate a variety of biological activities, and endocrine illnesses result when glands generate insufficient or inappropriate quantities of hormones [2]. Endocrine system composed of: Thyroid gland, Parathyroid glands, Pineal gland, Pancreas, Pituitary gland, Gonads (Ovaries, Testes) and Adrenal glands [3].

Thyroid gland is a butterfly-shaped gland located in the anterior region of the lower neck, in front of the trachea [4]. Normal thyroid adult weight is 15 - 20 g (M>F), increase over 50 g and grows in size during pregnancy and menstruation in females [5,6]. Thyroid gland is enveloped by two capsules (true and false), which the true capsule is formed by condensation of fibro-elastic connective tissue of the gland and the dense capillary plexus is located deep to the capsule and the false capsule is derived from pretracheal layer of deep cervical fascia true capsule [7]. Thyroid gland consists of two lobes, namely the right and left lobe, which connected by a thin structure (isthmus) and each lobe superior and inferior pole and usually the superior pole is narrower than the inferior pole giving a pear-like shape to each lateral lobe [8,9].

The primary functional unit of the thyroid gland is made up of irregularly shaped spherical structures called follicles [10]. A single layer of epithelial cells (thyrocytes), which are specialized for producing and secreting T4 and T3 hormones are surround the central lumen of the thyroid follicles, which is filled with a uniform, pink material called colloid [11-13]. There are small C cells, also known as Parafollicular cells, that generate calcitonin in between these thyroid follicles or within the thyroid follicle walls [14].

Thyroid cancer is the most common endocrine neoplasm and represents approximately 0.5-1% of all human malignancy, and classified into differentiated thyroid cancers, papillary, follicular cell thyroid cancers, medullary thyroid cancers, and anaplastic thyroid cancer [15-17].

Papillary thyroid carcinoma is accounting for 70-90% of well-differentiated thyroid malignancies usually diagnosis in adult 45 years old could be occur in children [18]. Follicular thyroid carcinoma is more aggressive than papillary thyroid carcinoma and accounts for about 14% of thyroid cancers. Medullary thyroid carcinoma is a cancer of non-thyroid cells found in the thyroid gland that accounts for about 3% of thyroid cancers and is frequently associated with multiple endocrine neoplasia. Anaplastic thyroid carcinoma accounts for about 2% of all thyroid cancers and is the most dangerous type of thyroid cancer because it spreads quickly to nearby lymph nodes and distant sites [18,19]. Its global prevalence is steadily increasing, while the mortality rate has remained stable in recent years. In both sexes, incidence rates in high and very high Human Development Index countries [20].

The main thyroid hormones are thyroxineT4 and triiodothyronine T3, and they play critical roles in cellular processes such as proliferation, differentiation, apoptosis, metabolism, also have metabolic effects on multiple organs, including the heart, bones, brain, liver, thyroid gland, kidneys, and skeletal muscles [21]. They are stimulated by the anterior pituitary gland (thyroid stimulating hormone, TSH) and an excess of T3 and T4 production combined with a compensatory decrease in TSH causes hyperthyroidism, whereas a decrease in T3 and T4 production combined with a compensatory increase in TSH causes hypothyroidism [22].

Given the strong evidence for the tumor-promoting effects of thyroid hormones and their receptors, which are thought to be mediated by phosphatidylinositol-3-kinase and MAPK and involve activating angiogenesis via αvβ3, thyroid hormones may play a role in conditions other than hyperthyroidism and hypothyroidism [23]. The transmembrane TH receptor αvβ3 has been shown to have two distinct binding sites for the hormone, S1 and S2, of which only the S1 site binds to physiological levels of T3 and the second site S2 binds to T4 [24].

Preclinical research has demonstrated that a variety of tumor cells multiply in response to physiological T4 concentrations. Integrin αvβ3 with its T4 receptor on the integrin is overexpressed by cancer cells and commonly activated in tumor cells. Preliminary clinical data shows that reducing systemic T4 levels while maintaining a normal metabolic state with T3 (euthyroid hypothyroxinemia) inhibits the development of various kinds of solid tumors. Clinical hypothyroidism has been shown in multiple studies to specifically slow the clinical course of cancers, and this evidence confirms that T3 has minimal activity on thyroid hormone analogue integrin receptors [25,26].

Adenocarcinomas thyroid are among the solid cancer cells whose proliferation was stimulated in vitro by T4, and these tumors are usually thyrotropin-dependent (TSH), as it is a major host growth factor for differentiated papillary and follicular thyroid cancers [27,28].

Thyroid hormones and cancer were originally linked more than a century ago. Later, Hercbergs and Leith proposed that TH deficiency may influence cancer outcome. Numerous clinical trials have shown that hypothyroidism slows tumor development whereas hyperthyroidism has the opposite effect [25]. Therefore, the purpose of this study is to determine the effect different types of thyroid cancers on thyroid hormones (Thyroid stimulating hormone (TSH), Tetra-iodothyronine (T4) and Tri-iodothyronine (T3)) in Tripoli University Hospital (TUH).

METHODS

This work was conducted in two departments, Oncology department and Endocrinology department at TUH. A total of 70 patients with thyroid cancer were targeted to study the effect of different types of thyroid cancers on thyroid hormones (TSH, T3 and T4).

Typically, thyroid cancer is diagnosed in Histopathology Department using needle biopsy or fine-needle aspiration (Cytology), or through a blood sample for Thyroid Function Test (TFT) and or CT Scan or MRI. The needle biopsy was examined under a microscope to determine if cancer cells are present. This test is a common method for confirming or ruling out thyroid cancer. Cytology also is the most widely used screening and diagnostic method for thyroid nodules (Fine-needle Aspiration). Papanicolaou stain and Hematoxylin and Eosin stain used as a tool to stain and diagnose thyroid cancers [29].

Thyroid Function Tests (TFTs) is a blood tests measure the levels of thyroid hormones (T3 and T4) and thyroid-stimulating hormone (TSH). While TFTs don't directly diagnose cancer, but used to evaluate overall thyroid function.

Cobas e411 Fully Automated Machin usually used to monitor and analyze the thyroid hormones (TSH, T3 and T4) in biochemistry laboratory [30].
The normal range of Thyroid stimulating hormone (TSH) is 0.27-4.2ulU/ml, Tetra-iodothyronine (T4) is 4.8-12.2 µg/ml and Tri-iodothyronine (T3) is 0.6-1.85 g/ml. Microsoft Office 2019 Plus (Word and Excel) was used for data analysis, tables, and figures.

RESULTS

Thyroid cancer, like other cancers, has shown an increase over the last years (2004 - 2021) in the Oncology and Endocrinology department at TUH (Fig. 1).

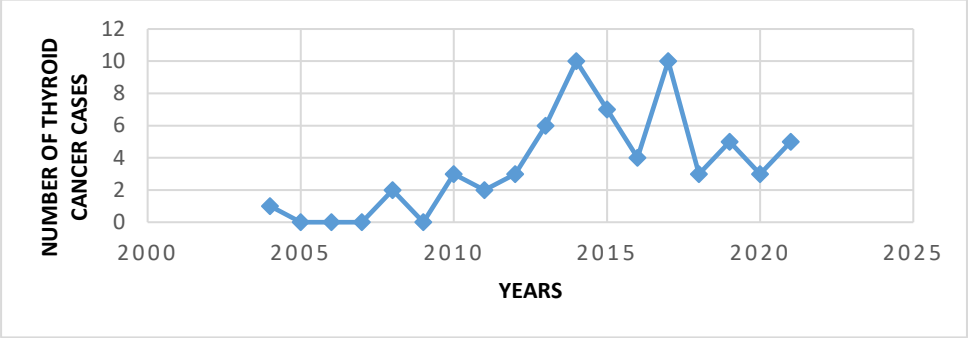

Figure 1. Thyroid cancers over the last years from 2004 to 2021 at the Oncology and Endocrinology departments at TUH.

Among the cases, 61 (87.1%) were females, and 9 (12.8%) were males. Data analysis based on patient files revealed that the incidence of thyroid cancer was higher among patients aged between 20 and 40 years old and lower among those aged between 50 and 80 years old.
Recorded data files reveal the performance of various types of biopsies for diagnosing thyroid cancer. Thyroidectomy biopsies (complete remove thyroid gland) were the most common, followed by fine needle biopsies, and hemithyroidectomy biopsies (partial remove of thyroid gland) were less common. Papillary thyroid cancer emerged as the most prevalent type, constituting 84% of thyroid cancer cases. The second most common type of thyroid cancer was follicular thyroid cancer at 13%, while medullary thyroid cancer accounted less common for 3%. This study identified that, 63 (90%) of thyroid cancer not-metastasized and only 7 (10%) were metastasized.
Out of 70 cases of thyroid cancers, THS hormone results were available for 53 cases, T4 hormone results for 35 cases, and T3 hormone results for 20 cases. Among the 53 cases with THS hormone results, 13 had low levels of TSH hormones, 15 had normal levels, and 25 had high levels (refer to Table 1).
For the 35 cases with T4 hormone results, 2 had low levels of T4 hormones, 14 had normal levels, and 19 had high levels. Additionally, among the 20 cases with T3 hormone results, 1 had low levels, 15 had normal levels, and 4 had high levels of T3 hormones (Table 1).
The average of TSH hormone level for the 53 cases was 21.14 uIU/ml, with a standard deviation of 24.97. For the 35 cases with T4 hormone results, the average of T4 hormone level was 72.48 ng/ml, with a standard deviation of 58.66. Furthermore, the average of T3 hormone level for the 20 cases was 1.56 µg/ml, with a standard deviation of 0.86 (Table 1).

Table 1. TSH, T4 and T3 results for 70 thyroid cancer cases.

Hormones	Range	Frequency	Percentage	Average	Median	St. Deviation	St. Error Mean
TSH	<0.27	13	25%	**21.1417**	**9.47**	**24.21470908**	**3.609758111**
	0.27-4.2	15	28%				
	>4.2	25	47%				
T4	<4.8	2	6%	**72.48926**	**72.03**	**58.66707114**	**12.23292996**
	4.8-12.2	14	40%				
	>12.2	19	54%				
T3	<0.6	1	5%	**1.561429**	**1.535**	**0.860022702**	**0.226571538**
	0.6-1.85	15	75%				
	>1.85	4	20%				

For the 25 thyroid cancer cases which, had high levels of THS hormone, the range was from a minimum of 5.8 uIU/ml to a maximum of 77 uIU/ml, with a main average of 40.71 uIU/ml. For the 19 cases with high level of T4 hormone, the range was from a minimum of 14.1 ng/ml to a maximum of 209 ng/ml, with a main average of 85.89 ng/ml (Figure 2). The main average for the T3 hormones was 1.56µg/ml.

High levels of TSH and T4 hormone were found in most cases of metastasized thyroid cancer. 13 of the 70 thyroid cancer cases with metastasis had elevated TSH values, averaging 30.13 uIU/ml, with a median of 23.83 uIU/ml and a standard deviation of 24.28. Among the 13 thyroid cancer cases with metastasis, 10 had elevated T4 values, average 96.39 ng/ml, with a standard deviation of 76.23 and a median of 85 ng/ml. Interestingly, T3 hormone levels was low in metastasis thyroid cancer cases.

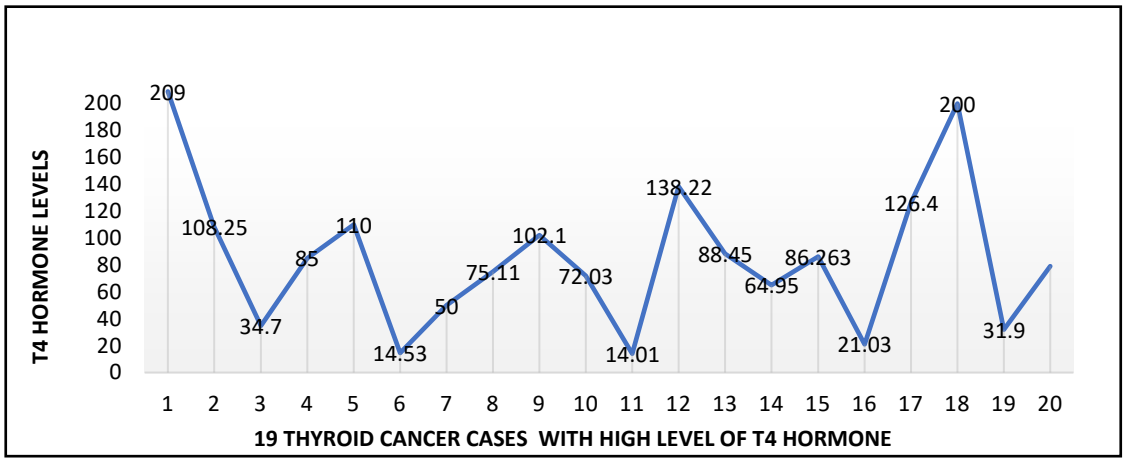

Figure 2: T4 hormone levels for the 19 thyroid cancer cases characterized by a high T4 hormone level, ranging from a minimum of 14.1 ng/ml to a maximum of 209 ng/ml.

DISCUSSION

The results of this study and several previous studies and cancer statistics programs such as Robert Koch Institute report, International Agency for Research on Cancer (IARC) and Epidemiology and End Results (SEER) indicts that thyroid carcinoma clearly significantly higher in females than males [31]. This disparity could potentially be attributed to the impact of sex hormones, which are known to contribute to tumor development in breast and prostate cancer. Sex hormones act through specific nuclear receptors to regulate gene expression and tumor cell biology; thus, polymorphism of the estrogen receptor may be a risk factor for differentiated thyroid cancer (DTC) in females [32, 33].

This study and other studies reveled that thyroid cancer increase particularly among individuals aged 20 to 40 over the last years in worldwide. The causes of thyroid cancer epidemic remain unknown [34,35]. Furthermore, the findings from this study and others have shown that papillary thyroid carcinoma is the most common differentiated thyroid cancer but follicular cancer thyroid cancer is more aggressive than papillary thyroid cancer but still less aggressive than medullary thyroid cancer [18,19].

Study confirms a connection between elevated TSH levels and more aggressive thyroid cancer characteristics, such as advanced stage and lymph node spread. Measuring TSH levels can predict which patients are at a higher risk for more aggressive forms of thyroid cancer [36]. Higher T4 levels were associated with a higher risk of any solid cancer [27]. The results of this study also revealed that TSH levels increased in thyroid gland cancer patients. Whereas, T4 hormone levels was fluctuated (increased and normal) between thyroid gland cancer patients, while T3 hormone levels remained unaffected in individuals with thyroid cancer.

Previous study showed that TSH is major host growth factor in differentiated papillary and follicular thyroid cancers and T4 is the most active iodothyronine at receptor site in differentiated thyroid cancer cells [28]. Thus, thyroid cancer metastasis may affect by the availability of T4 to thyroid tumor cells.

CONCLUSION

This study revealed that the percentage of thyroid cancer was greater in females aged 20-40 years old than males and the most thyroid cancer cases were papillary thyroid carcinoma. Different types of thyroid cancer effect and increasing TSH hormone level and T4 hormone level, however T3 hormone remained unchanged.

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Conflicts of Interest
There are no financial, personal, or professional conflicts of interest to declare.

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تأثير سرطانات الغدة الدرقية على هرمونات الغدة الدرقية لدى المرضى المترددين على مستشفى جامعة طرابلس

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المستخلص

سرطان الغدة الدرقية هو أحد أكثر أمراض الغدد الصماء شيوعًا، حيث يمثل 3.8% من حالات السرطانات الجديدة في الولايات المتحدة ويحتل المرتبة التاسعة على إجمال السرطانات. خلال العقود الثلاثة الأخيرة لقد ارتفع أعداد حالات تشخيص سرطان الغدة الدرقية بشكل كبير، مما يشير إلى خطورة المرض على مستوى عالمي. هدفت هذه الدراسة إلى تحديد تأثير سرطانات الغدة الدرقية على مستوى هرمونات الغدة الدرقية (TSH ، T4، T3). تمت هذه الدراسة في قسمي الأورام والغدد الصماء في المستشفى الجامعة طرابلس، طرابلس، ليبيا. استهداف الدراسة 70 مريضًا بسرطان الغدة الدرقية، ولقد تم جمع البيانات باستخدام ملفات وسجلات المرضى. ولقد تم مراقبة وتحليل مستويات TSH ، T4، وT3 في مختبر الكيمياء الحيوية باستخدام جهازCobas e411 Fully Automated. أثبتت الدراسة أن معظم مرضى سرطان الغدة الدرقية من الإناث مقارنة بالذكور، وأن اغلب المصابين بسرطان الغدة الدرقية تتراوح أعمارهم بين 20 و40 عامًا. أغلب حالات سرطان الغدة الدرقية من النوع سرطان الغدة الدرقية الحليمي. وصل عدد حالات استئصال كامل للغدة الدرقية بنسبة 87.14%. إرتفاع مستوى هرمون TSH عند مرضى سرطان الغدة الدرقية وكذلك إرتفاع نسبة مستوى هرمون T4، في حين أنه لم يُثبت تغير أو إرتفاع مستوى T3 لدى مرضى سرطان الغدة الدرقية. أظهرت هذه الدراسة أن نسبة الإصابة بسرطان الغدة الدرقية كان أعلى في الإناث من الذكور، وأكثر شيوعًا في الفئة العمرية من 20 إلى 40 عامًا. كما أن سرطان الغدة الدرقية الحليمي هو الأكثر شيوعًا. علاوة على ذلك، أظهرت نتائج هذه الدراسة أن تأثير سرطان الغدة الدرقية على مستوى هرمون TSH وهرمون T4 وكان مرتفع بشكل ملحوظ، مع عدم التأثير على هرمون T3 .

الكلمات الدالة. سرطان الغدة الدرقية، هرمون الغدة الدرقية، رباعي يودوثيرونين، ثلاثي يودوثيرونين.