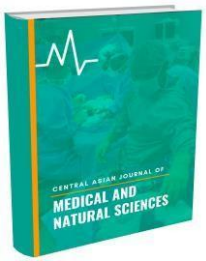

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*Article*

# Biochemical Assessment of ACE Expression and Progranulin, Sphingosine levels in Overactive Thyroid with Malignant Nodule Patients

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**Abstract:** Background: Thyroid nodules are a common finding in clinical settings, with their occurrence ranging approximately from 19% to 68% in the general population when assessed using ultrasonography. Thyroid-stimulating hormone (TSH) is a crucial regulator of thyroid growth and function, acting through TSH receptor activation. Elevated TSH levels have been linked to an increased risk of thyroid cancer, according to several studies. Materials and methods: A total of sixty blood samples were obtained from the laboratories of Kirkuk Hospital between (September 2024 and January 2025). The samples were subsequently categorized into two primary groups: a control group and a group comprising patients with malignant thyroid nodules and hyperthyroidism. Determination of TSH and anti-TPO by one-step sandwich enzyme immunoassay method. Determination of the concentrations of ACE , Progranulin, and Sphingosine by ELISA kit. Results; When comparing to the control group, the patient malignant nodule hyperthyroidism group's TSH and anti-TPO levels significantly increase ($P<0.01$). The findings indicated that, in comparison to the control group, the group's ACE activity (IU/L) had significantly increased ($P<0.01$) and FC had significantly increased ($P<0.05$). When comparing to the control group, the levels of progranulin pg/ml in the malignant nodule hyperthyroidism group were significantly higher ($P<0.001$). Conclusion:- The study revealed a significant elevations in current study biomarkers among thyroid cancer patients compared to the control group, TSH and Anti-TPO levels were markedly increased suggesting underlying thyroid dysfunction and autoimmune involvement. ACE activity possibly linked to tumor-associated inflammation, fibrosis, or angiogenesis. Progranulin levels indicating its potential role as a biomarker for aggressive thyroid cancer.

**Keywords:** ACE Expression , Progranulin, Sphingosine.

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## Introduction

Thyroid nodules are common in clinical practice, with ultrasonography (USG) detecting them in 19%–68% of the population. The morbidity of the malignancy is 5-15 percent, and it depends upon the iodine status, geography, and personal factors. The USG, fine-needle aspiration cytology (FNAC), and molecular testing are the better methods of standard evaluation but FNAC results are inconclusive in 15 per cent to 30 per cent of instances, which underscores the need to identify supplementary predictors of malignancy [1]. Thyroid-stimulating hormone (TSH) is an important hormone that regulates thyroid growth and activities by stimulating TSH receptors. A number of studies have put forward a correlation between high levels of TSH and high risks of thyroid cancer. It is

hypothesized that an increase in TSH will cause an increase in thyrocyte proliferation, which may involve neoplastic transformation. Other studies have however concluded that there is no significant relationship between TSH and the risk of malignancy. With this contradicting evidence, additional studies are necessary to show whether preoperative TSH levels can be used as a reliable indicator of malignancy in thyroid nodules [2]. An important enzyme involved in the production of thyroid hormone is thyroid peroxidase (TPO). Through the actions of TPO, tyrosine residues found in thyroglobulin become iodinated as well as coupled with both triiodothyronine (T3) and levothyroxine (T4). Antibodies against TPO are commonly used as a major marker for autoimmune disease of the thyroid; these antibodies are frequently elevated in cases of Hashimoto's thyroiditis and Graves' disease [3,4].

ACE (Angiotensin-converting enzyme) was first identified in the 1950's as a hypertensin-converting enzyme. In humans there are two forms of ACE, a somatic form of ACE found in many different tissues and a smaller germinal isoenzyme also known as germinal ACE which is located in the testes. Both somatic and germinal ACE are ectoenzymes which act on the surface of cells to hydrolyze circulating peptides. In body fluids, ACE is also present as a soluble form produced by secretase cleavage of the membrane-bound enzyme. The newly discovered homolog for ACE has been named ACE2 and is the most recent addition to the ACE family. ACE is a peptidyl dipeptidase or endopeptidase (e.g., of cholecystokinin), which removes the carboxy-terminal dipeptide of its substrates, including angiotensin I and bradykinin, whereas ACE2 is a carboxypeptidase, which cleaves the carboxy-terminal hydrophobic or basic residues of its These data indicate that the role of ACE in cell surface peptide metabolism can be wider than had ever been realized. [5,6].

Sphingolipids dominate biological membranes , which are made up of a ceramide base that has a very hydrophobic component and a very hydrophilic portion called the head group that typically contains a phosphate group (phosphorylcholine). Beyond providing structural integrity to membranes, sphingolipids also play key roles in cellular processes such as signaling, activation of cells, responding to stress and programmed cell death [7]. The relationship between sphingolipids and autoimmune diseases such as arthritis and multiple sclerosis has been proven through extensive research. The two sphingolipid synthesis processes are associated with the pathophysiology of autoimmune diseases, and they are the sphingolipid de novo pathway and the sphingomyelinase pathway [8,9,10,11].

Progranulin (PGRN) is a multifunctional, growth factor–like protein released by numerous cell types, contributing to several physiological and pathological processes, including inflammation, tissue repair, and fibrosis. Mechanistically, PGRN exerts anti-inflammatory effects by competitively binding to tumor necrosis factor-alpha (TNF-$\alpha$) receptors, thereby attenuating TNF-$\alpha$-mediated proinflammatory signaling. Dysregulated PGRN activity, however, may contribute to excessive tissue repair during chronic inflammation, ultimately promoting fibrotic progression. PGRN (granulin-epithelin precursor, acrogranin, proepithelin, GP88, or PC-cell-derived growth factor) is an autocrine growth factor composed of 593 amino acids that has a molecular weight of approximately 75−80 kDa. PGRN exhibits several pleiotropic functions, including regulating cell proliferation, aiding in tissue repair and regeneration, and affecting multiple phases of inflammatory pathways [12,13,14]. The GRN gene (the gene for PGRN) is located on the 17q21.32 region of chromosome 17 [15,16][17][18][19][20][21][22][23][24].

**Materials and Methods**

- Specimens collection : A total of sixty blood samples were obtained from the laboratories of Kirkuk Hospital between (September 2024 and January 2025). The samples were subsequently categorized into two primary groups: a control group

and a group comprising patients with malignant thyroid nodules and hyperthyroidism.

- Determination of TSH: TSH levels were determined utilizing a one-step sandwich enzyme immunoassay incorporating a final fluorescent detection step (ELFA). The VIDAS system completed all assay processes automatically. After samples were added to wells containing antibodies tagged with alkaline phosphatase, the device computed the findings using the calibration curve that had been stored and then printed.
- Serum levels of Progranulin, sphingosine, and ACE were measured using a sandwich ELISA kit supplied by SunLong Biotech Technology. Optical density (OD) was read at 450 nm using a spectrophotometer, and the analyte concentrations were calculated based on the standard OD-concentration relationship.
- Genetic analysis: Depending on the technique, genomic DNA is separated from the entire blood. [25], Complementary DNA (cDNA) Synthesis is manufactured from RNA using RT master mix, , then estimates concentration DNA. Total RNA isolation by trans Zol Up kit from Promega. The multi- version of the ACE gene were found utilizing PCR technique by specific Primers (Table 1) as described [26]. Expression levels were measured using relative quantification. The difference in cycle thresholds (ΔCt) and fold changes were examined between the treatment groups and the calibrators of each gene [27].

**Table 1.** Primers used for PCR amplification of the ACE gene.

| | Name of Primer | Sequence |
|---|---|---|
| Primer | Forward primer | AGTGGCTGCTGCTCTTCCT |
| | Reverse primer | TCAGGAGTGTCTCAGCTCCA |
| Housekeeping | Forward primer | TGCCACCCAGAAGACTGTGG |
| | Reverse primer | TTCAGCTCAGGGATGACCTT |

Microarray methods are available to measure expression of DE genes. Therefore, sometimes, while it is biologically significant and more repeatable to assess differential gene expression using a FC analysis, the majority of studies use an analysis of variance method (i.e., statistical tests of significance) that accounts for variability in gene expression [17].

## Results & Discussion

### A. TSH and Anti-TPO levels

The mean and standard deviation values of serum levels of both TSH (mIU/L) and anti-TPO (IU/mL) are shown in Table 2 as well as Figures 1 and 2. The level of both TSH and anti-TPO were statistically significantly elevated ($P < 0.01$) among patients in the malignant nodule hyperthyroidism group compared to controls.

**Table 2.** Serum Levels of TSH and Anti-TPO.

| Parameters | Control | Malignant nodule Hyperthyroidism | P value |
|---|---|---|---|
| TSH (mIU/L) | 2.9±0.33 | 0.08±0.01 | <0.01 |
| Anti-TPO (IU/ml) | 9.21±2.13 | 36.24±6.34 | <0.01 |

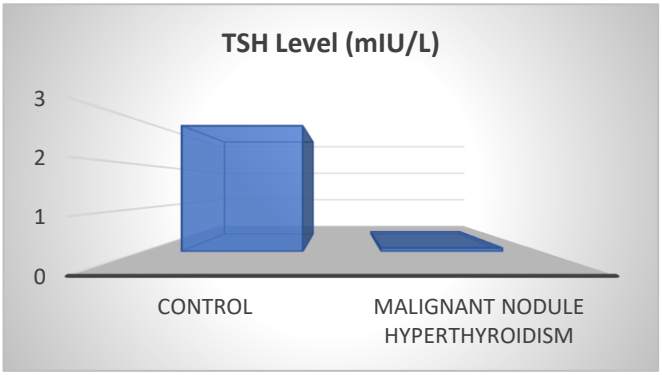


**Figure 1.** Serum Level of TSH (mIU/L).

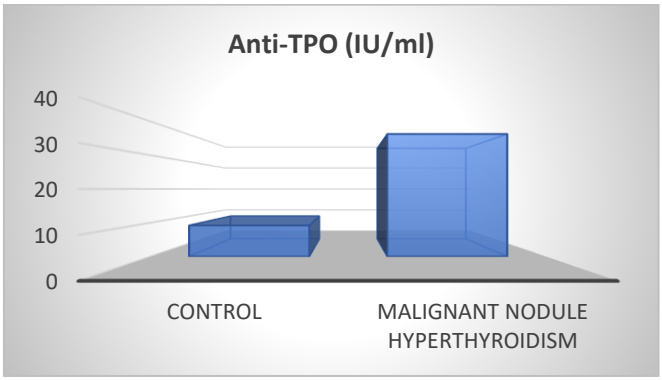


**Figure 2.** Serum Level of Anti-TPO (IU/ml).

Previous studies have reported a significant relationship between preoperative serum TSH levels and the presence of thyroid cancer. Specifically, elevated TSH levels have been associated with an increase in aggressive tumor types, suggesting that the preoperative value of TSH can serve as a means to identify nodules that need surgical intervention or other treatments, such as more prolonged watchful waiting. The presence of TSH receptors on well-differentiated thyroid cancers provides additional support for the notion that TSH is a factor that promotes both thyroid growth and tumor proliferation [18, 19]. As TSH plays a role in thyroid carcinoma via several oncogenes and growth factors, TSH is thought to play an integral role in the development and progression of thyroid cancer. This concept is reinforced by clinical evidence demonstrating increased survival in patients receiving TSH-suppressive levothyroxine medication, as well as documented cases of tumor enlargement following T4 withdrawal or administration of recombinant TSH [20].Thyroid autoantibodies were reported to be associated with malignant thyroid nodules [21,22].

Thyroid peroxidase (TPO) is a protein abundantly expressed in thyroid tissue. TPO gene is found in chromosome 2, and it is approximately 150 kb, which is made up of 16 introns and 17 exons. Besides being important for creating thyroid hormone as well as how the thyroid works overall; TPO is also relevant for diagnosis and treatment of various thyroid disorders. Research shows that TPO is expressed at relatively higher levels in normal thyroids compared to benign nodules, while having significantly lower levels (or complete lack thereof) in cases of papillary thyroid cancer. For this reason, TPO expression is widely used as a clinical marker to distinguish benign from malignant thyroid lesions [23,24].

### B. ACE activity and Gene Expression

The (mean ± SD) of serum ACE activity (IU/L) and fold-change (FC) gene expression for the malignant nodule hyperthyroidism patients and control group are reported in Table (3) and Figures (3) and (4). Analysis demonstrated a significant elevation in ACE activity ($P < 0.01$) and an increase in FC gene expression ($P < 0.05$) in patients group compared with the control.

**Table 3.** Serum Level of ACE activity (IU/L) and FC.

| Groups | mean ± SD ACE activity | mean ± SD FC | P value |
|---|---|---|---|
| Control | 2.37±0.99 | 0.91±0.27 | P <0.01 |
| Malignant nodule Hyperthyroidism | 3.32±0.44 | 1.283±0.31 | P <0.05 |

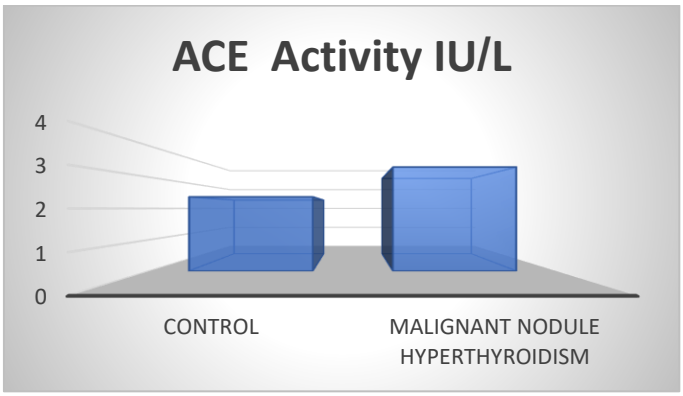


**Figure 3.** Serum Level of ACE activity (IU/L).

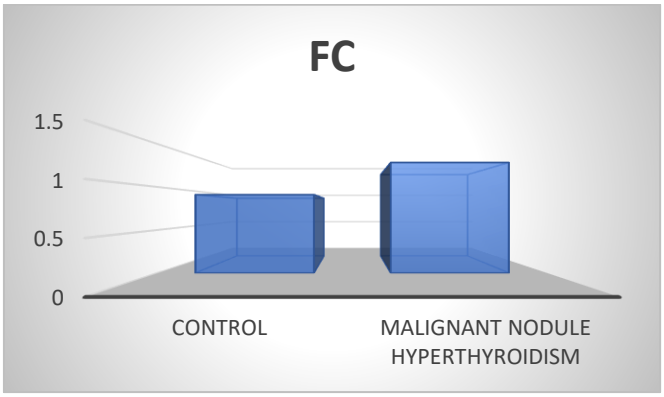


**Figure 4.** Serum Level of FC.

The renin angiotensin system (RAS) is made up of the enzymes and peptide hormones involved in a variety of functions which include regulating cell growth, vascularization of tissues through angiogenesis, the production of fibrous scar tissue, and controlling blood pressure (via AT1R). The major peptide cleaving enzyme of the RAS is ACE, but it has also been shown to cleave other peptides like bradykinin and substance P. There is increasing evidence linking ACE to cancer development mechanisms. Even though its contribution to angiogenesis through AT1R has been well characterized, its more global effects on the tumor microenvironment are not well characterized. Within the localized inflammatory and angiogenic response, cancer cells and stromal components, including fibroblasts and macrophages, can also stimulate ACE in thyroid tumors [25]. Thyroid hormones (T3 and T4) can directly affect the ACE gene expression resulting in elevation of the enzyme production [26].

**C. Progranulin**

Table (4) and Figure (5) show the (mean ± SD) serum Progranulin (pg/ml) levels of the patients and controls. A very high significant increase (P< 0.001) in Progranulin levels was observed in the malignant nodule hyperthyroidism group compared with the control group.

**Table 4.** Serum Progranulin (PGRN) Levels pg/ml.

| Groups | mean ± SD | P value |
|---|---|---|
| Control | 10.20±2.33 | |
| Malignant nodule Hyperthyroidism | 33.7±5.1 | P<0.001 |

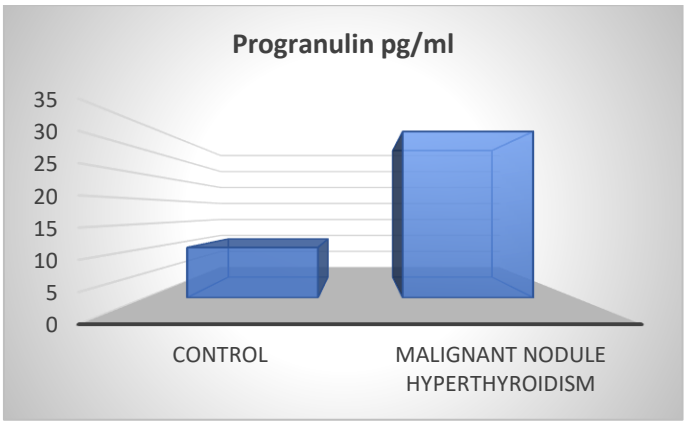


**Figure 5.** Serum PGRN Levels pg/ml.

Elevated serum PGRN levels are being linked to various human cancers, although evidence regarding its role in hematological malignancies remains limited. PGRN functions as a potent growth-related molecule with diverse effects on tumor biology. It promotes angiogenesis (new blood vessels), invasion of surrounding tissue, migration to new sites, proliferation (growth), transformation into cancerous cells, resistance to anticancer therapies, and mechanisms to evade the immune system.[27] In the extracellular matrix of cells, PGRN binds to multiple cell surface receptors, triggering either intracellular signals or internalization of the receptor complex. Multiple studies have revealed its ability to bind Sortilin, a mechanism that improves tumor cell proliferation, migration, survival, and contributes to medication resistance. PGRN exerts its effects through activation of key signaling pathways, particularly the p44/42 MAPK and PI3K pathways. It may also encourage the development of stromal cells in the tumor microenvironment. Other molecules, such as tumor necrosis factor and ephrin type-A receptor 2, have also been proposed as mediators of PGRN-related action [28,29,30]. Progranulin overexpression has been observed in various cancers, including breast, ovarian, and cholangiocarcinoma tissues [31,32,33,34,35,36,37]. Progranulin overexpression stimulates angiogenesis, invasion and migration, proliferation, malignant transformation, and immune evasion, all of which can result in the development of cancer [33].

**D. Sphingosine**

Table (5) and Figure (6) show the mean (± S. D.) Sphingosine serum levels (pg/ml) for both study population and the control population. Sphingomyelin, found in malignant nodules, was significantly higher in subjects with hyperthyroid malignant nodules than in the control group (P < 0.001).

**Table 5.** Serum Sphingosine Levels pg/ml.

| Groups | mean ± SD | P value |
|---|---|---|

| | | |
|---|---|---|
| Control | 3.66±0.53 | |
| Malignant nodule Hyperthyroidism | 6.92±1.51 | P<0.001 |

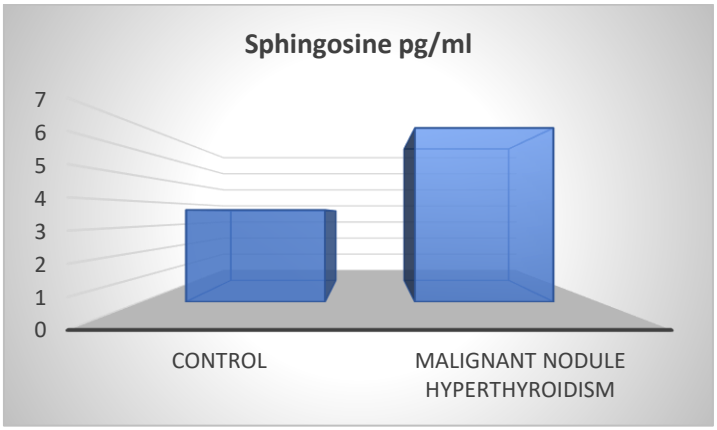


**Figure 6.** Serum Sphingosine Levels pg/ml.

Many studies highlight a major role that the bioactive lipid sphingosine-1-phosphate (S1P) plays in cancer. S1P is generated and broken down by multiple enzymes such as sphingosine kinases, S1P lyases, and S1P phosphatases. S1P signals through its 5 G-protein-coupled receptors (S1P1-5) at the cell surface; however, S1P can also act directly on cellular targets such as histone deacetylase (HDAC) 1 and 2, mediating epigenetic regulation. S1P plays a role in cancer development by promoting cancerous transformation, cell survival and apoptosis, cell movement and metastasis, and tumor microenvironment neovascularisation [38,39].

**Conclusion**

The analysis revealed that current study biomarkers were significantly higher in thyroid cancer patients than in the control group with TSH and Anti-TPO levels showing a significant increase implying the presence of thyroid malfunction and autoimmune reactions. ACE activity may be associated with tumor-related inflammation, fibrosis or angiogenesis. The levels of progranulin may indicate that it is a biomarker of aggressive thyroid cancer. These results demonstrate the impaired endocrine and inflammatory processes in thyroid cancer, and ACE and progranulin are becoming potential factors of malignancy. Their diagnostic as well as prognostic value in the management of thyroid cancer requires further studies to confirm their usefulness.

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