Impact of Endothelin-1 Cyclooxygenase -2(Cox-2) And Thyroid Hormones in Papillary Thyroid Carcinoma

ManarAbedelameer[1], Jwan Oday Abdulsattar[2], Zaizafoon Nabeel Nasif, [3]
[1, 2, 3]Chemistry Department, College of Science, Mustansiriyah University/Iraq
Email: manarabedelameer@gmail.com

Abstract
The most frequent endocrine cancer is thyroid cancer, ladies are 2-3 times as likely than males to have thyroid cancer. The purpose of this study is to investigate the impact of Cyclooxygenase-2 (COX-2) and Endothelin-1(ET-1) in sera of papillary thyroid cancer (PTC) patients. ET-1was analyzed utilizing ELISA (Enzyme-Linked Immunosorbent Assay) kitand spectrophotometric assays were used to determine the other biochemical parameters, thirty healthy individuals served as the study's control group, along with sixty PTC patients. The patients were split into patient groups made up of 20% men and 80% women, and a control group made up of 24% men and 76% women. Comparable (P>0.01) ET-1 levels between PTC patients and controls were found in the study's findings. In the serum of PTC patients compared to controls, COX-2 levels were substantially greater (P0.01). Additionally, the coefficients of variation percent results for patients are more accurate than in the control group for each parameter. Receiver Operator characteristics (ROC) and Area Under the Curve (AUC) were measured to evaluate sensitivity and specificity, the higher the sensitivity, the more likely the carriers of the disease will be classified correctly, while specificity cares about healthy people. PTC patients have exhibited significant (P<0.01) higher TSH, T3, and T4 levels than control.

1. Introduction

The thyroid gland is the body's largest endocrine gland. Between the C5 and T1 vertebrae, the thyroid gland is a highly vascularized organ located anteriorly in the neck, in the platysma deep, prevalent endocrine tumor. Thyroid cancer can develop from follicular or non-follicular thyroid cells Eighty percent of thyroid cancer patients are papillary thyroid carcinoma (PTC), follicular thyroid cancer (FTC) which accounts for up to 11% of cases, Hürthle cell cancer (HCC) which accounts for 3% of cases, and anaplastic thyroid carcinoma (which accounts for 3 percent of cases) are all follicular malignancies ((ATC) 2 %). Differentiated thyroid cancer refers to the combination of PTC and FTC, which accounts for the great majority of malignancies (DTC). The rise in new thyroid cancer diagnoses can be attributed to PTC. The cause of the rise in the incident and prevalent instances is unknown, but many feel it is related to the increased use of radiological techniques that discover tiny nonpalpable thyroid tumors during routine medical exams[1]. Thyroid carcinomas in middle-aged adults havean average 10-year survival rate of between 80% and 95%. Local or regional tumor recurrences happen in 5–20% of people with papillary thyroid carcinoma (PTC). Inadequate initial therapy or the presence of a tumor with an aggressive component can both lead to recurrences[2]. Thyroid hormones (THS) are key regulatory chemicals that play important functions in vertebrate physiology and development, including fetal and post-natal nervous system development as well as adult brain function maintenance [7,8]. The thyroid gland produces both T3 and T4; T3 and T4 production, however, do not occur in equal amounts. Unlike T3, which is only 20% directly produced by the thyroid gland, T4 is totally produced by the thyroid gland. 80 percent of the remaining T3 is created by extrathyroidal deiodination of T4. The primary organs involved in extrathyroidal deiodination are the liver and/or kidneys [5].

The anterior pituitary secretes and synthesizes thyroid-stimulating hormone (TSH, thyrotropin), a glycoprotein, in response to thyrotropin-releasing hormone (TRH), a tripeptide derived from the hypothalamic median eminence. As a result, iodide transport, hormone production, T3, T4, and thyroglobulin release are all boosted [6].

Cyclooxygenases (COX) are enzymes in the arachidonate-prostaglandin cascade that catalyze the initial catalytic step in the formation of prostaglandin and thromboxane from arachidonic acid, a 20-carbon unsaturated fatty acid produced by the phospholipase A2 enzyme. The two forms of cyclooxygenases are both cyclooxygenase 1 (COX-1), which is continuously expressed, and cyclooxygenase 2 (COX-2), which is the product of an early gene and is responsive to a variety of stimuli. Numerous physiological and pathological conditions have been linked to COX-2.

processes, among them renal damage, tumor development, and inflammation. Prostaglandin-endoperoxide synthase-2 (PTGS-2) or COX-2 is an enzyme that has been linked to inflammatory and cancer-causing activities [11,12]. Prostaglandin-endoperoxide synthase-2 (PTGS-2) is another name for the (Cyclooxygenase-2) enzyme, which has been connected to inflammatory and malignant processes

doi.org/10.31838/hiv22.02.531 Received: 20.06.22, Revised: 02.08.22, Accepted: 24.08.22

[13,14]. Evidence suggests that COX-2 expression is greater in the tumor tissues of elderly PTC patients, which may help to explain why PTC behaves more aggressively in this age range. COX-2 expression is also associated with a poor prognosis in a number of malignancies, and COX-2 inhibition specifically slows tumor growth [15,16].

Endothelins (EDNs) are a family of peptides that induce DNA replication and cellular growth in a variety of tissues, with the primary function of altering vascular tone, angiogenesis, and mitosis. Furthermore, EDNs have been linked to cancer progression [13]. The gif image peptides endothelin-1 (ET-1), which is produced by the endothelium, was initially discovered to be a potent and long-acting vasoconstrictor. It belongs to a class of peptides with several functions (ET-1, -2, and -3) that acts on two G protein-coupled receptors, ET A (ET A R) and The ET B (ET B R) (ET B R). ET A R has a higher binding affinity for ET-1 and ET-2 over ET-3, but ET B R has a similar affinity for all three peptides. ET-1 has been linked to the pathogenesis of a variety of cardiac illnesses, including arterial and pulmonary hypertension due due to the ability of vascular smooth muscle cells to become mitogenic thanks to its vasoactive effects [14]. ET-1 has recently been found to have a significant role in a number of carcinogenesis-related processes, including regulation of cell proliferation, vasculature, and bone metastasis. Particularly ET-1 has been shown to play a key impact in the development and spread of ovarian and prostate cancers by activating ET A R. Because of this, ET A R antagonists have demonstrated anti-tumor properties in a number of cancers [15]. In this study, the effect of T3, T4, TSH, endothelin 1, and cyclooxygenase-2 and their relationship with each other on patients with papillary thyroid cancer are proven.

2. Experimental part

2.1. Collection of Blood Sample

Serums of 30 patients with thyroid cancer, whose ages ranged (from 30-49) years, Additionally, 30 healthy individuals between the ages of 30-49 were recruited from Al-Amal Hospital for Tumors in Baghdad between the hours of 9:00 a.m. and 12:00 a.m. between January and May 2021. Venous blood measuring five milliliters was taken from the front

2.2 Kits

Endothelin-1elisa kit Was supplied by (Shanghai YL Biont /CHINA). It has been worked out according to the methods attached to. For measuring the level of hormones (T3, T4, TSH) used elisa kits from (Trust well).

2.3 Estimation of COX-2 Activity in PTC patients

A colorimetric assay for the peroxidase activity in the serum of PTC patients is used to determine the COX-2 enzyme's activity [16]. This approach relies on monitoring the enzyme-catalyzed hydrogen peroxide oxidation of tetramethyl-P-phenylenediamine (TMPD). At 610 nm, the blue response was observed. The quantity of enzyme needed to change 1 mol of hydrogen peroxide into the product under test conditions is referred to as one unit of activity.

4 Statistical Analysis

SPSS-V28 was used to process the results' statistics. Each parameter underwent descriptive analysis, and the findings were presented as a mean standard deviation (SD). To compare the means of the control and patient groups, an independent-sample t-test was utilized. The associations between all study variables in this paper were also examined using Spearman's rank correlation coefficient analysis.

3. Result and Discussion

The most prevalent type of well-differentiated thyroid cancer is called papillary carcinoma (PTC), and it manifests as an irregular firm or cystic mass or nodule in healthy thyroid parenchyma [17]. This study's objective was to assess the diagnostic efficacy of biochemical parameters in thyroid cancer patients from Iraq. Investigating serum levels of Et-1, COX-2, T3, T4, and TSH for potential utility in the timely identification, monitoring, diagnosis, and follow-up of PTC patients is of special interest in the present work. The respondents were split between males (20%) and females (80%) in the patient group of the study, which included 60 PTC patients and 30 healthy people as controls figure (1), males (24%) and female (76%) in control group figure (2) with thyroid cancer (PTC, stage: 1). Figure 3 reported that the mean age of the sufferers and healthy control was between 30 and 49 years, and there were notable disparities in every attribute between the two groups.

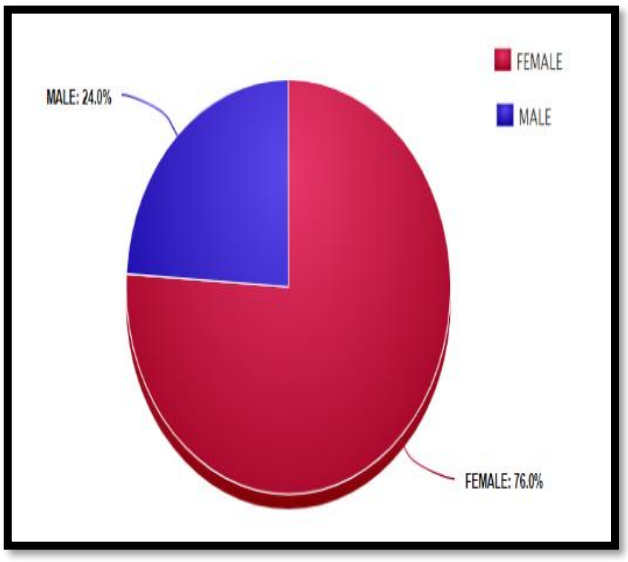

Figure 1. The anthropological characteristics of control groups

The diagram shows the distribution of the studied subjects according to gender for control group.

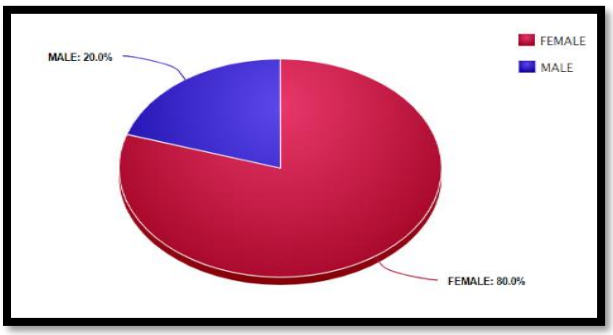

Figure 2. The anthrobiological characteristics of patients with papillary thyroid cancer.

The diagram shows the distribution of the studied subjects according to gender for the patient group.

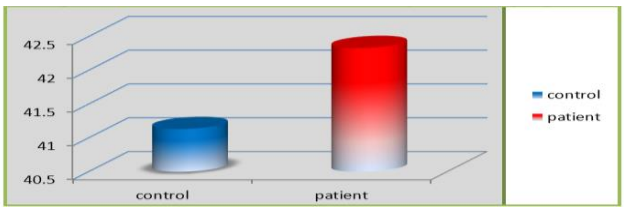

Figure 3: the mean age for a patient with PTC and the control group.

60 patients had their thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxin (T4), Et-1 levels checked prior to surgery in the treatment period of (PTC) serum. The parameter levels were established using the average scores for each serum factor investigated, and they are shown in Table 1.

Table 1: Age, TSH, T4, T3, ET, and COX levels in control and PTC groups

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P- value
Age	C	60	41.1333	5.72081	.73855	.173 NS
	P	60	42.3333	4.74312	.61233	
TSH	C	60	1.0500	.45752	.05907	.001*
	P	60	1.3171	.30179	.16806	
T4	C	60	7.0333	1.88632	.24352	.014*
	P	60	12.0357	3.19121	.41198	
T3	C	60	.2737	.09657	.01247	.001*
	P	60	2.3843	1.04985	.13554	
ET	C	60	25.5136	4.75339	.61366	.001*
	P	60	33.7492	13.24588	1.71004	
Cox	C	60	2.6563	.96965	.12518	.003*
	P	60	1.6932	.61558	.07947	

* Significant at p <0.01,
NS: Non-Significant.
C: control. P: patient.

The average scores of ET-1, T3, T4, and TSH action in patients increased significantly (p> 0.05), except COX-2 when compared with control group. T3, T4 hormones typically circulate in the blood and are bound to the plasma protein thyroxine binding globulin (TBG). Although T3 hormone concentration is much lower than T4 (T3 makes up about 20% of thyroid hormones, while T4 makes up the other 80%), T3 has four times the effect on physiological processes as T4. T3 determination is crucial in the early detection of thyroid illness. T3 and T4 concentrations in the human blood rise, preventing the pituitary gland from producing TSH. TSH synthesis in the pituitary gland also increases as T3 and T4 hormone concentrations have similar results reported by Cooper et al, and Fiore et al. [22,23]. Various tumor cells have been demonstrated to multiply in preliminary experiments in reaction to physiological T4 levels. Acid tetraiodothyroacetic (tetrac), a T4 derivative, inhibits T4's activities on tumor cells. According to preliminary clinical evidence, euthyroid hypothyroxinemia, which lowers systemic T4 levels while preserving a normal metabolic state with T3, slows the growth of a number of solid tumors. endorsed the study released by Davis et al [20]. Fiore et al. established that PTC patients have considerably higher serum TSH levels than those with benign thyroid diseases and that the frequency of PTC increases with serum TSH, peaking in those with serum TSH levels that are above the normal range [21]. Cooper et al. demonstrated higher serum TSH is linked to an increased risk of cancer in a thyroid nodule [18]. According to the National Health and Nutrition Examination Survey, the age-specific pattern of TSH reported in people residing in iodine-sufficient locations in the study was similar to the TSH background levels in PTC patients. by Vitti et al [19]. Greater incidences of malignancy are associated with higher blood TSH concentrations, indicating that TSH has a tropic effect on thyroid tissue, encouraging neoplasia and carcinogenesis. Iodine shortage results in a decrease in circulating thyroid hormones, which is followed by an increase in serum TSH agreed to Boelaert [22]. Through a negative feedback loop in the pituitary gland, thyroid hormones (T3) and its propeptide thyroxine (T4) in the blood inversely regulate TSH release. In a mouse model, high TSH levels were linked to PTC pathogenesis. Thyroid hormones have also been linked to the promotion of tumor growth in agreement with Huang et al research paper [23]. Only a higher risk of PTC in women was associated with TSH levels above the normal range. Inverse PTC and TSH levels in both men and women were within the normal range in agreement with A. E. M [22]. Melching-Kollmuss and colleagues showed When individuals have glands that exhibit metabolic abnormalities, mutations, or have thyrotoxicosis, complicated combinations of genetic and hormonal

variables can cause thyroid tumors to develop instead of just being caused by the hyperplastic stimulus of TSH alone[24]. Iodine may contribute to the onset and progression of thyroid autoimmunity. Antithyroid antibody stimulation may potentially raise the likelihood of thyroid damage and future cancer (such as PTC) [25].

The expression of the enzyme COX-2 at inflammatory areas and in a variety of carcinoma types may contribute to the aggressiveness of these tumors. Even so, the underpinning mechanistic role and possibilities association are that the presence of COX-2 may be a key diagnostic indicator of microcarcinoma, as its increased expression demonstrated an affiliation with lymph node metastasis. COX-2 is also expressed in benign and malignant thyroid tumors, particularly in papillary carcinoma. Similar results have been observed, with coexpression of COX-2 being connected to a particular histological subtype of PTC by Seiwerth et al [26].

Haglund et al demonstrated COX-2 is overexpressed in a number of human malignancies, it is expressed in human thyrocytes in vitro, and pro-inflammatory cytokines increase COX-2 expression in human thyroid epithelial cells, the study findings are consistent with prior in vivo investigations that found COX-2 expression in thyroid cancer and thyroiditis, but the minimal expression in non-neoplastic thyroid tissue in tumor sample [27]. In some human neoplasms, the relationship between COX-2 activity and carcinogenesis is investigated. The PTC group had considerably increased COX-2 activity in agreement with Lewiski et al [28]. One of the major drivers in cancer irritation is the COX-2 pathway. Although COX-2 activity in healthy tissue is generally undetectable, it is abundantly expressed in a number of human cancers. COX-2 can support carcinogenesis through a number of mechanisms, including the inhibition of apoptosis, enhanced cell proliferation, stimulation of angiogenesis, and the development of an inflammatory environment that favors tumor growth. Additionally, research has been done on COX-2 expression in distinct thyroid cancer histotypes, the bulk of which was targeted at determining its prognostic significance by comparing expression levels with clinic pathological aspects of patients. Other studies have attempted to quantify COX-2 expression's predictive significance in thyroid carcinoma agreeing with Al-Kuraya et al [11]. Endothelin-1 (ET-1) has been identified as a significant endothelial-derived vasodilator, with the former promoting vasoconstriction. They may also be implicated in numerous mechanisms impacting carcinogenesis, furthermore to their function in controlling vascular tone In PTC, overexpression of the ET-1 axis, such as the ET-1 precursor, and its mitogenic components may have a detrimental effect by promoting tumor cell survival and proliferation as well as vasculature and bone metastases. according to Van Beneden et al [15]. Although different cancer cell types respond differently to ET1 activation, autocrine ET1 signaling is important for tumor development and survival agree to Bagnato et al [29]. ET-1 appears to have a role in tumor invasion and metastasis, according to a recent study, ET-1 can suppress tissue inhibitors of matrix metalloproteinases (TIMP) 1 and 2 in human ovarian cancer cell lines. ET-1 can control the expression of MMPs such as MMP-2 and MMP-9, as well as tissue inhibitors of matrix metalloproteinases (TIMP) 1 and 2. ET-1 can reduce the progression of bone metastases in prostate cancer. When human prostate cancer cells come into contact with bone, their production of ET-1 increases, preventing osteoclastic bone resorption agreed to by the research by Taylor et al [30].

By observing the results of the (ROC), we have found that all the tests gave results of high sensitivity, except for TSH. The results were excellent as the T3 (1.000), ET-1(0.723), T4 (0.910) and COX-2 (0.807) as shown in Table 2 and Figure (4). The Pearson's correlation coefficient between T3 and T4, COX-2 and TSH, COX-2, and ET is shown in Table 3.

Table2: Area Under the Curve (AUC) for all parameters.

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
TSH	.465	.061	.512	.345	.585
T4	.910	.027	.000	.857	.963
T3	1.000	.000	.000	1.000	1.000
ET	.723	.046	.000	.633	.813
Cox	.807	.042	.000	.725	.888
The test result variable(s): TSH, T4, ET, and cox has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					

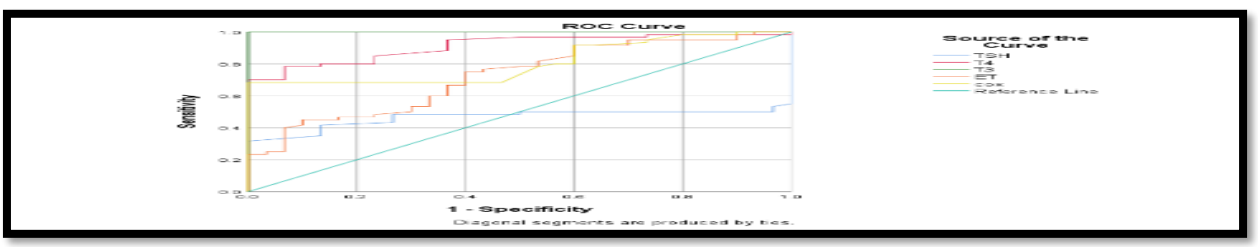

Figure4: RecevierOperatic caracteristis (ROC) curve.

Table3: Pearson's correlations between variables in P TC in the patient's group.						
	Age	TSH	T4	T3	ET	Cox
Age	1	.032	.009	.047	-.123	.029
TSH	.032	1	-.233	-.150	.238	.932**
T4	.009	-.233	1	.272*	-.153	-.216
T3	.047	-.150	.272*	1	-.084	-.174
ET	-.123	.238	-.153	-.084	1	.263*
cox	.029	.932**	-.216	-.174	.263*	1
*. Correlation is significant at the 0.05 level **. Correlation is significant at the 0.01 level						

4. Conclusion

ET-1 and COX-2 showed a significant increase in PTC patients compared to control, indicating over-release prostanoids, Patients with papillary thyroid cancer also experience pain and high levels of TSH, T3, and T4 in their blood. Future research will still be needed to determine the best early detection method for this aggressive thyroid carcinoma malignancy.

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