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Possibility of measuring serum taurine level as an early marker in the prognosis of thyroid disorders, especially thyroid cancer

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Abstract

People's awareness of thyroid diseases has gradually grown along with the gradual rise in thyroid cancer incidence. Thyroid dysfunction imposes a significant psychological burden on those who are diagnosed, as it affects most physiological processes. At the moment, ultrasonography and fine needle aspiration cytology are the primary methods used to diagnose thyroid cancer. There are still certain thyroid nodules that cannot be accurately and adequately classified as benign or malignant prior to surgery. Consequentially, we suggested using a more sensitive biomarker to diagnose thyroid cancer. Taurine is measured in the plasma of 60 patients from the National Cancer Institute and 10 healthy volunteers. After a full clinical examination, 20 patients were diagnosed with goitres, 20 with benign tumours, and 20 with malignant tumours. The results showed non-significant ($P > 0.05$) changes in the levels of TSH in all patients except in the goitre group ($P < 0.001$). Serum taurine levels exhibited values that significantly differed from normal ($P< 0.05$) for goitre and benign tumours and ($P < 0.001$) for malignant tumours. In conclusion, it would appear that taurine can be used as a sensitive biomarker in the early prognosis of thyroid cancer.

Keywords: Thyroid Cancer; Goiter; Taurine; FSH; Oxidative Stress

1. Introduction

Among the endocrine system's malignancies, thyroid cancer is the most common. Currently, the number of cases is continually increasing [1,2]. The epithelial thyroid cancers that arise from thyroid follicular cells can be categorised pathologically into three main types: papillary thyroid carcinoma (PTC), which is the most frequent one, with a percentage of 85–90% [3], follicular thyroid carcinoma (FTC) (5–10%), and anaplastic thyroid carcinoma (ATC), which accounts for less than 2% of all thyroid cancer cases. In addition to the medullary thyroid carcinoma (MTC) (3-4 %) that originates from parafollicular (C) cells with a different mechanism of carcinogenesis, PTC and FTC are considered differentiated thyroid cancer (DTC) because of their well-defined differentiation and indolent tumour growth [3,4]. In Egypt, thyroid cancer represents around 1.5% of all cancers and constitutes about 30% of endocrine malignancies. The incidence rate among Egyptian females is 0.0027%, which is much higher than that among males [3,5]. In Egypt, according to the national cancer registry programme, TC is the fifth most frequent cancer in females [6]. An increased risk of thyroid cancer has been reported in patients with thyroid nodules [7]. However, there are other risk factors, including a history of radiation, a family history, a history of goitre, sex, a deficiency in iodine, obesity, smoking, and alcohol consumption [3, 5, 6].

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Certain laboratory tests, such as thyroid-stimulating hormone (TSH), also known as thyrotropin, which is a sensitive and specific marker of systemic thyroid status, are used to confirm the diagnosis of thyroid dysfunction. Also, it aids in the diagnosis of a few thyroid conditions. The normal range of TSH can be altered by a number of factors, including age, gender, and other medical disorders. In addition, we can assess levels of thyroglobulin, triiodothyronine, and other autoantibodies. To understand the significance of these tests, it is crucial to examine the patient's overall condition [8].

Thyroid ultrasound use as initial imaging to diagnose TC increased. However, some studies found that the use of thyroid ultrasound was associated with thyroid cancer incidence [9]. The ultrasound is confirmed by a fine-needle aspiration biopsy (FNAB). Unfortunately, 20–30% of patients who undergo FNAB have indeterminate results, which leads the physician to unnecessarily deal surgically with 80% of patients with benign nodules. Early prognosis and determining the type and stage of the tumour are crucial for diagnosis and treatment decisions [10]. Consequently, there is a serious demand to recognise new biomarkers to identify thyroid cancer [8, 10].

2-Aminoethane-1-sulfonic acid $C_2H_7NO_3S$, or taurine (Tau), is a free β-amino acid that exists in high concentrations in several cell types, such as the heart, brain, retina, and skeletal and cardiac muscles. Tau is considered a conditionally essential amino acid. Humans primarily depend on Tau biosynthesis in the liver and partially on diet, such as meat, seafood, and human milk [11, 13]. It exhibits many physiological functions such as osmoregulation, membrane stabilisation, antioxidant and anti-inflammatory activities, glucose regulation, bile acid conjugation, detoxification, blood pressure regulation, neurotransmission, reproduction, immunity, and modulation of mitochondrial function. Tau plays an important role in modulating glutamate and gamma-aminobutyric (GABA) neurotransmission and prevents excitotoxicity in vitro primarily through modulation of intracellular calcium homeostasis [12, 13]. In taurine-fed mice, studies observed that it affects neuronal function directly through activation of $GABA_A$ and glycine receptors and indirectly through biochemical modifications and the alteration of endocrine function [13]. In a recent study on rats, they found that taurine pre-administration produced anti-depressant-like activity and prevented the dysregulation of hormones and neurotransmitters while inhibiting the up-regulation of neurotrophic factors [14].

Recent studies have proposed that changes in systemic Tau levels can be used to predict the formation and malignant transformation of certain tumours. For example, the serum level of Tau was found to be significantly lower in patients with breast cancer than in patients in the high-risk breast cancer group or the healthy control group. Thus, Tau is considered a novel biomarker for the early diagnosis of breast cancer [15]. It was also demonstrated that Tau could induce apoptosis and suppress proliferation in colorectal and breast cancer cells [16, 17]. Other studies reported that Tau exerted a protective effect against chemical-induced tumorigenesis of liver cancer in male F344 rats [15].

In this study, we investigate the possibility of using taurine as a marker in the prognosis of thyroid cancer.

2. Patients and method

Four groups of a total of 70 candidates were studied in this work. Three groups consisting of 60 patients at the National Cancer Institute (NCI) at Cairo University were diagnosed with a thyroid tumour and underwent surgery after a full clinical examination, ultrasonography, hormonal assay, and ultrasound fine needle aspiration (FNA) biopsy. In addition, 10 normal volunteers of comparable age and sex served as controls in the first group. In the second group, 20 patients had goitre (an enlarged thyroid gland). The third group consists of 20 cases with benign thyroid tumours. The last group is made up of twenty patients who were diagnosed with different types of thyroid cancer. A preoperative blood sample was taken from each patient to measure the serum levels of TSH, FT3, FT4, and taurine. A sample of fresh tumours and their corresponding safety margins were obtained from the second, third, and fourth groups for histopathological examination.

Sample extraction was done by placing 250 µl of patient plasma into a glass tube. 750 µl of methanol was then added. Tubes were mixed by vortex for 1 min and centrifuged at 10,000×g at 4 °C for 10 min. The supernatant was transferred to HPLC autosampler vials, and 5 µl was injected onto the LC-MS system.

The LC-MS-MS system consisted of an Agilent 1200 HPLC system (Agilent Technologies, CA, USA) coupled to an ABSCIEX Q TRAP 3200 mass spectrometer (ABSCIEX, Germany) equipped with an electrospray ionisation (ESI) interface. Data acquisition was performed with Analyst 4.0 software (ABSCIEX). The separation was performed using an Atlantis T3 (3 µm, 150 × 3 mm) reversed-phase analytical column (Waters, Ireland). The mobile phase pumped at a flow rate of 250 µl/ min consisted of 0.2% formic acid in both methanol and water (2:98, v/v). Overall run time was 5 min; the method was modified from a previous study [18]. Quantification was performed with multiple reaction monitoring (MRM) by using curtain gas collision-induced dissociation and the following ion transitions: m/z 123.8:79.9 for taurine.

Serial dilutions of standards were prepared at concentrations ranging from 0.68–11 ug/ml for taurine in drug-free media and extracted as mentioned in sample preparation to make a calibration curve (Figure (1).

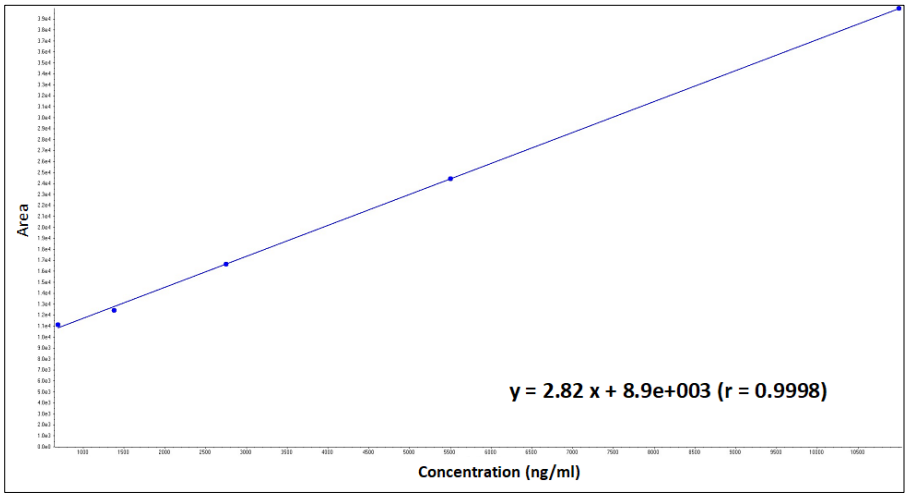

Figure 1 Calibration curve for Tau on concentration range (0.68-11 ug/ml)

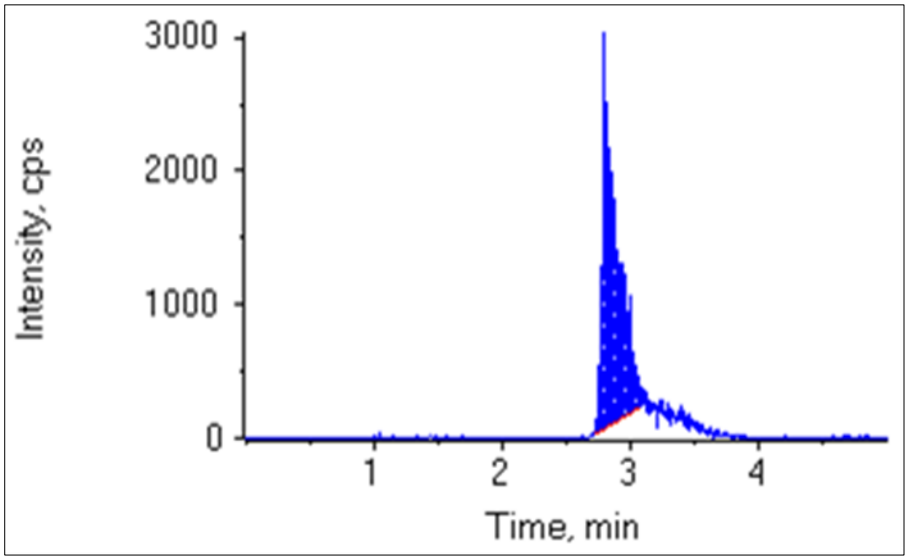

Figure 2 Chromatograms for detection of Tau with concentration 1000 ng/ml at retention time 2.81 min.

2.1. Statistical analyses

All the data were analysed by IBM SPSS 28.0 software for Windows (IBM Corp.). The differences among treatments in each group were determined by one-way analysis of variance (ANOVA). The significance of mean differences between groups was tested by Dunnett's T3 test. The means with P-values ≤0.05 were considered significantly different. The data were expressed as mean ± SD.

3. Results

One way analysis of variance (Anova test) is used to compare means of serum taurine and thyroid functions in different pathological conditions as shown in table 1.

Table 1 Means of serum taurine and thyroid functions in different pathological conditions

		Sum of Squares	Df	Mean Square	F	P value
Tau µmol/l	Between Groups	106354.980	3	35451.660	73.904	<.001
	Within Groups	31660.244	66	479.701		
	Total	138015.224	69			
TSH µ IU/ml	Between Groups	37.281	3	12.427	9.817	<.001
	Within Groups	83.544	66	1.266		
	Total	120.825	69			
F T3 pg/ ml	Between Groups	8.560	3	2.853	8.540	<.001
	Within Groups	22.051	66	.334		
	Total	30.611	69			
F T4 ng/ dl	Between Groups	.473	3	.158	1.200	.317
	Within Groups	8.668	66	.131		
	Total	9.141	69			

Serum Tau level, TSH, FT3, FT4 are measured in the four groups as shown in table 2

Table 2 Measurements serum Tau level, TSH, FT3, FT4

Condition	Serum level of			
	Tau µmol/l	TSH µ IU/ml	F T3 pg/ ml	F T4 ng/ dl
Control (n=10)	178.67±12.06 (d)	2.61±0.32 (e)	3.65±0.12 (g)	1.39±0.08 (i)
Goiter (n=20)	218.64±4.91 (c)	0.63±0.08 (f)	2.96±0.16 (h)	1.21±0.10 (i)
Benign (n=20)	112.50±3.76 (b)	2.21±1.59 (e)	2.56±0.12 (h)	1.12±0.06 (i)
Malignant (n=20)	58.89±3.25 (a)	1.42±0.75 (e)	2.71±0.12 (h)	1.20±0.09 (i)

Means in the same column with no common letters differ significantly ($P < 0.05$).

The concentration of Tau decreases as the severity of the disease increases. Tau levels in goitre and benign thyroid tumour patients differed significantly ($P < 0.05$) (121.64±21.98 and 112.5±16.89 respectively), while they were remarkably lower in thyroid cancer patients ($P < 0.001$) (58.89±14.54). Taurine levels in the third and fourth groups were significantly lower than those in the control healthy group (178.67±38.15), while the goitre patients recorded higher values because of inflammatory conditions. TSH levels showed no significant difference ($P > 0.05$) between benign and malignant tumours (2.06±1.23 and 1.29±1.45 respectively), but they were higher than those in the goitre group (0.63±0.37) which also differed from the normal group (2.61±1.02). The levels of f T3 in all patients are insignificantly different ($P > 0.05$), but they have a significant difference from those in the control group (3.65±0.38). In the four groups, f T4 showed no significant difference ($P > 0.05$).

4. Discussion

The thyroid gland is a vital endocrine organ as it is involved in many physiological functions, metabolic activities, development, and growth. Year by year, the incidence of thyroid disorders is increasing [19, 20], and researchers have found that it is complicated to know the mechanisms of their occurrence. Since the thyroid gland is crucial to maintaining human homeostasis, thyroid abnormalities can seriously impair the normal functioning of numerous organ systems. Although they can usually be easily identified and treated, if left neglected, they can have disastrous global health and economic effects [19].

However, many studies have been trying to find sensitive and specific biomarkers for the diagnosis of thyroid diseases, especially thyroid cancer, in the early stages to avoid inaccurate diagnosis and unnecessary surgeries that may lead to

other risks [20]. In our study, we observed significantly variable measurements of the highly sensitive amino acid taurine in different thyroid diseases.

Some researchers proposed measuring related hormones such as TSH, T3, and T4, which are considered the cornerstones along with ultrasound imaging in the initial diagnosis of thyroid disorders. A study found that there is an association between thyroid stimulating hormone (TSH) levels and thyroid diseases, which means that there is a risk of cancer in patients with elevated or suppressed levels of TSH [21]. Thyrotropin (TSH) is a pituitary hormone that is secreted from the anterior pituitary by activation of TRH receptors. TSH is considered the main growth factor of the thyroid and a regulator of thyroid functions as well [20]. Consequently, its deviations from the reference range can affect the progression or onset of thyroid cancer, and it acts as a predictor of thyroid cancer risk [21]. Unfortunately, the reference range of TSH is a matter for debate as it is influenced by many limitations such as age, gender, ethnicity, medications and supplements, interference with immunoassays, individual set points, diurnal and circannual variations, pregnancy, obesity, smoking, environmental factors, and pollutants, as well as its low specificity [22,23]. For instance, Huang et al. suggested that TSH levels showed opposite effects in different genders and were also affected by various pathological subtypes of thyroid cancer [24]. So, we cannot depend on variations of TSH alone to diagnose thyroid disorders [20, 23, 24]. Although some researchers found a significant relationship between TSH and thyroid cancer, we didn't find a significant difference between the control group and the cancerous groups. Yet we found suppressed levels of TSH in the patients with goitre.

High levels of reactive oxygen species (ROS) are known as oxidative stress, which is induced by radiation, long-term stress, intense physical exercise, some medications, an unbalanced diet [25, 26], and insufficient antioxidants that reduce ROS production, neutralise them, or even interfere with their action [27, 28].

Oxidative stress causes chemical modification and damage to macromolecules in the body such as protein, carbohydrates, lipids, and DNA that leads to acute or chronic diseases of the nervous, respiratory, cardiovascular, and immune systems and induces ageing and cancer as well [29].

Studies found that the biomarkers of oxidative stress have elevated levels in thyroid disorders such as hypothyroidism, hyperthyroidism, goitre, thyroiditis, autoimmune thyroid diseases, and thyroid cancer through the activation of many signalling mechanisms. Patients with different types of thyroid cancer have suppressed levels of antioxidants [30, 31].

In healthy conditions, the thyroid gland uses ROS in the biosynthesis of T3 and T4, and the thyroid cells are well adapted to endogenously produced ROS in basal and goitre conditions as long as antioxidant defence systems such as superoxidase dismutase (SOD), glutathione peroxidase (GPx), vitamin C, and E can regulate the production and scavenging of ROS [30]. However, lacking in cellular homeostasis of ROS due to a deficiency of antioxidants can disturb thyroid functions and lead to carcinogenesis [27, 30, 31]. Consequently, measuring the activity of antioxidants lets us evaluate the conditions of the antioxidant defence system, as suppressed levels may be a sign of insufficient defence against free radicals and would be helpful in the prognosis of some diseases.

In thyroid disease research, many biomarkers of oxidative stress are investigated. For instance, levels of GPx and malondialdehyde (MDA) were significantly different between the control and TC groups after thyroidectomy, favouring antioxidants [31–34]. In this investigation, it was evident that patients with TC had lower serum taurine levels than those in the control group. Ultrasound imaging and a fine-needle aspiration cytology helped confirm the diagnosis.

Tau has limited direct antioxidant effects, but it has crucial indirect antioxidant effects via maintaining redox balance and modulating some transcription factors (e.g., Nrf2 and NF-B). It has membrane-stabilising effects and inhibiting effects on ROS-producing enzymes [35].

The high Tau levels in phagocytes and inflammatory lesions suggest its role in innate immunity [36], which we investigated in patients with goitre, and since Tau is present in high concentrations in leukocytes, one may hypothesise that Tau deficiency will affect the functions of immune cells. In fact, prolonged Tau deficiency in cats leads to profound abnormalities in the immune system, including significant leukopenia and a decrease in the number of white blood cells [36]. According to research, taurine's major function is to protect cells from acute and long-term inflammatory and oxidative stress and to maintain their homeostasis. As when there is infection, acute or chronic inflammation, cancer, or ageing, oxidative stress is a primary contributor to tissue damage. In tissues exposed to high amounts of oxidants, taurine is discovered in particularly high concentrations, pointing to its potential function in reducing oxidative stress [28].

Tau has been shown in numerous studies to have anti-inflammatory, antioxidant, and hypoglycemic properties. Tau has recently been demonstrated to have anticancer characteristics as it suppresses the initiation and progression of cancer and promotes apoptosis in some malignancies by variably regulating proapoptotic and antiapoptotic proteins [37]. Tau also lessens the negative effects of chemotherapy [37, 38]. Some research teams discovered that when Tau and cyclophosphamide (CTX) were administered to tumour-bearing mice, Tau improved the adverse effects of CTX and the antitumor effect by decreasing immune system and bone marrow proliferation, indicating that taurine had synergistic and attenuating effects on CTX [37]. According to a study, Tau and cisplatin together dramatically boosted the apoptosis of cervical cancer cells more than taurine or cisplatin alone [36, 37, 42]. Prior to cisplatin (CDDP) injection, taurine administration was able to prevent kidney function deterioration, stop the decline of antioxidants, and reduce DNA damage. Tau also reduced CDDP-induced pathological changes and prevented p53 activation. In the kidneys of rats that had received CDDP injections, this study shows the protective effects of taurine in reducing the expression of pro-inflammatory mediators and enhancing antioxidant capacity. In order to reduce CDDP-induced nephrotoxicity in vivo. Tau may therefore be an advantageous dietary supplement [37].

In human nasopharyngeal cancer cells in vitro, colon cancer and hepatocellular carcinoma, Tau has an apoptosis-inducing impact [37, 40]. Tau could counteract the reduction in tumour cell apoptosis brought on by MST1 knockout in lung, prostate, hepatocellular and colorectal carcinoma. In addition, Tau also prevents the metastasis of prostate cancer cells by controlling the expression of PSA, MMP-9, TIMP-1, and TIMP-2 under dihydrotestosterone (DHT)-stimulated conditions [38 - 41].

The primary method of combating cancer is immune surveillance, which enables immune cells to identify and eradicate tumour cells. According to a study, Tau has the ability to counteract the lymphopenia brought on by the administration of interleukin-2 and can inhibit T-cell apoptosis by lowering the expression of fatty acid synthase (FAS), as researchers investigated in mice's spleen tumour cells [36, 41].

In contrast to individuals with benign breast lesions and high-risk breast cancer, breast cancer patients had significantly lower serum Tau levels, according to Agouza's study. Additionally, the study supported the notion that measuring the serum Tau level in high-risk patients is significant for aiding in the early detection of breast and bladder cancers [38, 42, 43]. In a study of 50 patients with irregular uterine bleeding, serum taurine levels were significantly lower in patients with endometrial cancer than those of healthy individuals. This finding raises the possibility that detecting serum Tau levels in patients with irregular uterine bleeding could aid in the early diagnosis of endometrial cancer [37]. As a result, the discovery of metabolomic biomarkers and early disease diagnosis and treatment depend greatly on the identification of differentially expressed metabolites between non-cancer and cancer patients [36].

It is noteworthy that in some prior investigations, Tau reduced the oxidative stress caused by the co-toxicity of chlorpyrifos (CP) and Pb. It has been established that taurine supplementation increases the activity of serum paraoxonase and arylesterase to protect against the increased oxidative stress caused by hypothyroidism. It is feasible that taurine's bioprotective and antioxidant qualities improved thyroid function and thyroid gland histoarchitecture in a study on male Wistar rats [44]. Qiu S. et al. demonstrated that liver function was restored by nanotaurine by lowering Aspartate aminotransferase (AST) and Alanine Aminotransferase (ALT) levels and minimising histology damage. In addition, nano-taurine reduced inflammatory cytokines, including interleukin (IL)-6, tumour necrosis factor (TNF)-α, intercellular adhesion molecule (ICAM)-1, NLR pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein containing CARD (ASC), and oxidants including superoxide dismutase (SOD), malondialdehyde (MDA), glutathione (GSH), catalase (CAT), and ROS, showing anti-inflammatory and antioxidant properties [45]. Mizota T. et al. observed that the hypotaurine-taurine system has energy-saving antioxidative hepatoprotective action in acute liver failure patients [46].

Recently, the serum taurine level was used as a novel early biomarker in hepatocellular carcinoma and breast cancer. Antioxidant depletion now causes angiogenesis to increase and tumour growth to be stimulated [43, 35, 37].

In the current investigation, serum Tau levels were shown to be elevated in individuals with goitre, reduced in those with benign tumours, and significantly lower than normal in those with malignant tumours. However, two past studies found elevated Tau in papillary thyroid microcarcinoma (PTMC) [47]. O'Connell TM et al. observed that Tau had an earlier, more sensitive response to the inflammatory reactions than that of the inflammatory marker GlycA in mice with cancer cachexia [48].

Conclusion: The encouraging findings of this study suggest that low serum Tau levels in patients with thyroid nodules can be used as an early indicator for the presence of TC and may be a promising screening marker for TC. To ensure the

specificity of taurine as a screening marker in TC, more studies on a larger sample of patients are required to correlate the various clinical phases of TC with the percent drop in serum Tau level.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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