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The effect of Thyroidectomy on Deiodinase Activity in Patients with Euthyroid Goiter in Iraqi Population

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Abstract

Background: Goiter is an enlargement in the thyroid gland usually twice its normal volume or more than 40 grams by weight. Goiter with normal TSH, tri-iodothyronine (T_3) and thyroxine (T_4) is called euthyroid goiter and it may be colloid or nodular in nature. Furthermore, these nodules could be benign or malignant.

Deiodinase type 2 (DIO2) play a major role in conversion of T_4 to biologically active T_3 and in clearance of reverse T_3 (rT_3). The deiodinase activity may play a role in compensating the thyroid function post-thyroidectomy by increasing the rate of conversion of T_4 to biologically active T_3.

Aims: study the effects of thyroidectomy on deiodinase activity. Also evaluate whether the type of goiter influence the possible effect of thyroidectomy on deiodinase activity.

Methods: The subjects enrolled in the study were 150, these subjects categorized into two groups as following: Patient group, which involves (75) of patients diagnosed with thyroid cancers and euothyroid goiter and prepared for surgery as a definite treatment, of each patient, three samples were drown pre and post-thyroidectomy.

Control group, includes 75 subjects comprised of healthy volunteers and subjects who found to be normal. Serum level of Free Thyroxine (fT_4) and serum level of Free Triiodothyronine (fT_3) were measured by Enzyme Linked Immunosorbent assay.

Sum activity of peripheral deiodinases was calculated by using Equilibrium levels of fT4, fT3 and estimated constant parameters for plasma protein binding, distribution and elimination

Results: The sum activity of deiodinases was significantly increased two weeks post-thyroidectomy compared to its level pre-thyroidectomy and this increase was still noticed one month post-thyroidectomy.

Conclusion: The increase in activity of deiodinases is one of the earlier mechanisms to compensate the rapid decline in the thyroid drive such as post-thyroidectomy. Goiter type does not affect these changes.

Key words: Goiter, Thyroidectomy, Deiodinase activity.

INTRODUCTION

The thyroid gland is positioned directly below the larynx in the anterior portion of the neck. This butterfly-shaped organ is fixed to both the larynx and the trachea via fibrous tissue. It extends from oblique line on thyroid cartilage down to 4th or 5th tracheal ring, attached to cricoid cartilage via suspensory ligament (1). Thyroid gland weighs about 30-40 gram in normal adult and is slightly heavier in female. Microscopically, the thyroid is composed of several follicles containing colloid surrounded by a single layer of thyroid epithelium and the follicular cells synthesize thyroglobulin, which is then stored as colloid (2).

Production of the two thyroid hormones is regulated via a classic endocrine feedback loop; low levels of T_3 and T_4 stimulate the release of thyrotropin- releasing hormone (TRH) in the hypothalamus. TRH, in turn, stimulates production of thyroid stimulating hormone (TSH) in the pituitary gland which regulates the thyroid hormone production; TSH which is released rapidly with increased TRH determines the normal physiologic set point for thyroid hormone levels (3).

Thyroid hormone plays an essential physiologic role in the development and metabolism (4).

Thyroxine (T4) is the major secretory product of the thyroid gland and a precursor of the active form of the hormone, triiodothyronine (T3), which is mainly produced in peripheral tissues by deiodination of T4 (5).

In peripheral tissues T4 is converted to T3 by selenium dependent iodothyronine deiodinase enzymes (6). In plasma, more than 99% of T4 and T3 is bound to transport proteins. The protein bound hormones are in equilibrium with the free forms (i.e. fT_4 and fT_3) that are available for the tissues. Iodothyronine deiodinase represent a family of selenoproteins involved in local and peripheral homeostasis of thyroid hormones (7).

Three deiodinases have been described. Deiodinase type 1 (DIO 1) and DIO 2 play a major role in conversion of T_4 to biologically active T_3 and in clearance of reverse T3 (rT_3). Although both deiodinases are determinants of peripheral thyroid hormone levels, DIO 2 is particularly renowned for its role in local T3 production. DIO 2 is also an important source of plasma T3, i.e. plasma T3 largely originates from the thyroid gland as T4, to be converted to T_3 by DIO 2 in peripheral tissues (8).

Type 2 deiodinase (encoded by DIO2) converts T4 into T3 by outer ring 5´- deiodination whereas type 3 deiodinase (encoded by DIO3) depletes T4 and T3 by inner ring 5´ deiodination, producing reverse T3 (rT3) and 3,3´-diiodothyronine (T2), respectively (9).

The study was aimed to evaluate the deiodinase activity in response to abrupt decline in thyroid function (thyroidectomy), and whether the type of goiter mat influence the potential change of deiodinase activity.

SUBJECTS AND METHODS

The study was designed as a case control study that was carried out in the Department of Biochemistry at the Faculty of Medicine, University of Babylon in conjunction with the Babel Private Hospital.

The subjects enrolled in the study were 150, these subjects categorized into two groups as following:

- Patient group, which involves (75) of patients diagnosed with thyroid cancers and euothyroid goiter and prepared for surgery as a definite treatment according to the surgical team decision, with an age range of 20-65 years composed from 12 males with an age range of 22-62 years and a mean of 42.2 ± 11.2 years and 63 females with an age range of 20-65 years and a mean of 41.6 ± 9.4 years. Of each patient, three samples were drown as follows:
- A_1 pre-thyroidectomy, samples from the patients were taken within 2 hours before surgery
- A_2: samples from the patients were taken two week Post-thyroidectomy.
- A_3: samples from the patients were taken one month Post-thyroidectomy.
- Control group, includes 75 subjects comprised of healthy volunteers and subjects who found to be normal as suggested by senior consultant during their attendance to medical Consultation Unit, with an age range of 21-65 years composed from 14 males with an age range of 25-62 years and a mean of 38.2 ± 7.5 years and 61 females with an age range of 21-65 years and a mean of 40.1 ± 9.1 years.

Body mass index (BMI)

Body mass index (BMI) which is ratio of a person weight to height was used in the current study to evaluate the effect of weight of individuals on other parameters. BMI calculated as follow:

BMI (kg/m^2) = weight (kg) / (height)^2 (m^2)

There are four BMI categories (10).

Exclusion criteria

Include hypertension, diabetes mellitus, renal, hepatic disorders, pregnancy, patients receiving drugs that could interfere with thyroid function (Amiodarone, Iodine, Lithium and antidiabetic drugs) and patients affected by malabsorption-related conditions.

Inclusion criteria

Patients with euothyroid goiter (benign and malignant nodules) with treatment decision of thyroidectomy.

Ethical Approval

The protocol was approved by the Institutional Review Board. After explaining the objectives of the study and obtaining written informed consent from all patients prior to the collection of samples, baseline characteristics, and clinical data of participants were collected by interviewing and recorded using the study questionnaire.

Collection of the blood samples

Five ml of blood were obtained from each subject by vein puncture, and pushed slowly into disposable tubes containing separating gel and allowed to clot at room temperature for 30 minutes and then centrifuged at 2000 ×g for approximately 15 minutes then the sera were obtained and stored at -20˚C until analysis.

Determination of serum concentrations of fT3 and fT4

It is based on solid phase competitive ELISA as prescribed earlier (11, 12). A standard curves were prepared relating color intensity to the concentration of each of fT_3 and fT_4 to obtain the concentration of samples of the study individuals.

Sum activity of peripheral deiodinases (GD)

Equilibrium levels of fT_4, fT_3 and estimated constant parameters for plasma protein binding, distribution and eliminaion are used as measures of conversion efficiency, as previously described (13).

$$\hat{G}_D = \frac{\beta_{31}(K_{M1} + (\mathrm{FT}_4))(1 + K_{30}(\mathrm{TBG}))(\mathrm{FT}_3)}{\alpha_{31}(\mathrm{FT}_4)} \text{nmol/s}$$

Although the two measures are closely related in the linear part of the substrate relationship defined by Michaelis-Menten kinetics, only the more complex formula (GD) accounts for the saturation kinetics of the enzyme.

Statistical analysis

All statistical analyses were performed using statistical package for social sciences (SPSS), version 17. Data were expressed as mean ± SD. The normality of the distribution of all variables were assessed by the analysis of variance (ANOVA) test and Pearson correlation tests that have been used to determine the significant difference between the studied groups. Categorical values were assessed using Chi-square ($\chi 2$) test. P values less than 0.05 were considered significant and less than 0.01 were considered highly significant (14).

RESULTS

The analysis of study subjects' demographic features showed that there was no significant differences between patients' group and control group regarding gender distribution, age and BMI as shown in table 1.

Sum activity of deiodinases (nmol/s)

The sum activity of deiodinases was significantly increased two weeks post-thyroidectomy ($P<0.01$) compared to its level pre-thyroidectomy and this increase was still noticed one month post-thyroidectomy. However, the sum activity of deiodinases in patient groups was lower than that of control group, as shown in table 2.

Effect of gender, age and BMI on study parameters

There was neither gender nor weight related variation in sum activity of deiodinases, while the sum activity of deiodinases was significantly higher ($P<0.01$) in patients younger than 35 years compared to other age groups in patients with euthyroid goiter prior to thyroidectomy and two weeks post-thyroidectomy, as shown in table 3.

Histopathological classification of the goiter

There was no significant difference among types of goiter when distributed according to gender, age and body mass index, as shown in table 4.

The sum activity of deiodinases in patients with thyroid carcinoma was significantly higher ($P < 0.05$) than those with other types of goiter, as shown in table 5.

Table (1) Demographic features of the study groups

Demographic feature	Study Group				P value
	A_1	A_2	A_3	control	
Men **Women**	12 (16 %) 63 (84 %)	12 (16 %) 63 (84 %)	12 (16 %) 63 (84 %)	14 (18 %) 61 (82 %)	0.96
Age (years)	41.9 ± 10.3	41.9 ± 10.3	41.9 ± 10.3	39.15 ± 8.3	0.15
BMI (kg/m^2)	26.8 ± 3.6	26.8 ± 3.6	26.8 ± 3.6	25.1 ± 3.2	0.5

A_1: Pre-thyroidectomy, A_2: two weeks post-thyroidectomy, A_3: one month post-thyroidectomy, BMI: body mass index.

Table (2) the mean ±SD in sum activity of peripheral deiodinases (nmol/s) in patient and control groups

Group	N	Mean ± SD	95% CI
A_1 group	75	14.7 ± 2.5 [a**, b**, c**]	14.1 – 15.3
A_2 group	75	19.2 ± 2.2 [a**]	18.5 – 20.8
A_3 group	75	17.8 ± 1.8 [a**]	17.2 – 18.3
Control group	75	26.4 ± 8.5	26.5 – 38.6

SD: standard deviation, CI: confidence interval, A_1: Pre-thyroidectomy, A_2: two weeks post-thyroidectomy, A_3: one month post-thyroidectomy.
[a]: ANOVA test between A_1, A_2 and A_3 versus control group; ** $P < 0.01$.
[b]: ANOVA test between A_1, A_2 versus A_3; ** $P < 0.01$.
[c]: ANOVA test between A_1 versus A_2; ** $P < 0.01$.

Table (3) the effect of gender, age and BMI on sum activity of deiodinases in patient and control groups

Anthropometric measures		Study group			
		A_1	A_2	A_3	Control
Gender	Men	14.6 ± 2.3	18.4 ± 2.2	17.3 ± 1.3	34.4 ± 8.1
	Women	14.8 ± 2.7	20 ± 2.2	18.3 ± 2.3	32.1 ± 8.9
P value		0.24	0.25	0.50	0.77
Age (years)	20 – 35	20.7 ± 6.6*	17.4 ± 8.1	13.6 ± 1.9	33.2 ± 7.9
	36 – 50	17.6 ± 6.5	15.9 ± 7.9	15.6 ± 2.7	32.5 ± 8.9
	51 – 65	14.4 ± 5.9	13.9 ± 2.7	15.2 ± 2.3	29.1 ± 8.7
P value		0.01	0.04	0.09	0.95
BMI	Underweight	14.8 ± 8.5	13.7 ± 2.9	15.7 ± 2.1	26.3 ± 8.2
	Normal weight	19.9 ± 8.1	15.8 ± 4.9	14.2 ± 1.7	37.1 ± 8.4
	Overweight	16.9 ± 8.9	16.4 ± 8.2	14.9 ± 2.7	28.9 ± 8.9
P value		0.17	0.85	0.43	0.35

SD: standard deviation, A_1: Pre-thyroidectomy, A_2: two weeks post-thyroidectomy, A_3: one month post-thyroidectomy; * T test statistical significance.

Table (4) distribution types of goiter according to gender, age and body mass index

Anthropometric measures		Multi-nodular goiter	Colloid goiter	Thyroiditis	Thyroid cancer	P value
Gender	Men	8 (18%)	1 (11%)	1 (10%)	2 (17%)	0.7
	Women	36 (82%)	8 (89%)	9 (90%)	10 (83%)	
Age (years)	20 – 35	10 (23%)	3 (33%)	2 (20%)	7 (58%)	0.24
	36 – 50	24 (54%)	4 (44%)	4 (40%)	3 (25%)	
	51 – 65	10 (23%)	2 (22%)	4 (40%)	2 (17%)	
BMI	Underweight	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0.41
	Normal weight	14 (61%)	3 (13%)	2 (9%)	4 (17%)	
	Overweight	28 (56%)	6 (12%)	8 (16%)	8 (16%)	

A_1: Pre-thyroidectomy, A_2: two weeks post-thyroidectomy, A_3: one month post-thyroidectomy, BMI: body mass index.

Table (5) Mean ± SD of sum activity of deiodinases in different types of goiter of patient group

Parameter	Group	Mean ± SD				P value
		Multinodular goiter	Colloid goiter	Thyroiditis	Thyroid cancer	
Sum activity of deiodinases (nmol/s)	A_1 group	17.1 ± 7	16.4 ± 6.4	16 ± 6.7	22.3 ± 4.1	0.04
	A_2 group	16.9 ± 8.7	14.9 ± 2.9	15.6 ± 4.6	14.5 ± 4.5	0.69
	A_3 group	14.7 ± 2.6	14.5 ± 1.8	14.5 ± 2.8	14.9 ± 2.2	0.98

SD: standard deviation, A_1: Pre-thyroidectomy, A_2: two weeks post-thyroidectomy, A_3: one month post-thyroidectomy; * ANOVA test statistical significance.

DISCUSSION

Thyroid goiter is about four times more common in women than men and their frequency increases with advancing age and iodine deficiency (15). Causes for the higher incidence of thyroid goiter in women are unclear. Both estrogen and progesterone may contribute to the strong female preponderance in thyroid nodular disease. Kung et al. reported that pregnancy was associated with new thyroid nodule formation and an increase in size of preexisting thyroid nodules (16). Results of the present study showed that female gender is an independent risk factor not only for goiter but also for thyroid nodules, although some authors could not confirm any gender-related associations (17).

The T_4-T_3 conversion was estimated by calculating the sum activity of peripheral deiodinases. The measure is similar to the fT_3–fT_4 ratio, albeit more precise wherein it accounts for non-linear enzyme saturation kinetics.

In athyreotic patients in therapy with LT_4 substitution, both circulating and intracellular T_3 levels strictly depend on the deiodinase-mediated T_4 to T_3 conversion. However, in approximately 20% of athyreotic patients, LT_4 did not ensure physiological T_3 levels unless suppressing TSH (18), although other studies were controversial on this aspect (19,20).

Deiodinase activity increases in the face of falling T_4, the net effect is homeostatic, promoting maintenance of normal T_3 levels. Second, DIO-2 is expressed in the endoplasmic reticulum, and DIO-2-generated T_3 can accumulate in the nucleus of specific tissues while plasma thyroid hormone levels remain unchanged; i.e. DIO-2 allows for local control of thyroid hormone signaling. For example, sympathetic stimulation of brown adipose tissue leads to cAMP generation, which in turn induces DIO-2 and fills up the tissue with T_3, a crucial mechanism for adaptive thermogenesis (21).

A high L-T_4 dose may not invariably remedy T_3 deficiency owing to T_4-induced conversion inefficiency but could actually hinder its attainment through the inhibitory actions of the substrate itself and/or reverse T_3 (rT_3) on deiodinase type 2 activity (22). A study by Cettour-Rose et al. (23) confirmed that rT3, when infused into rats, inhibited deiodinase type 2 activity in the pituitary, cerebral cortex and brown adipose tissue, but interestingly, this did not have much impact on circulating T4, T3 and TSH concentrations in the animals. However, in this model the rT3 effect was studied under rather artificial conditions in the absence of an abundant T4 supply with elevated FT4 levels that characterizes the treatment situation.

In contrast, another experimental study has shown that escalating only the L-T4 dose fails to normalize serum T3 in the rat, and as a result, irrespective of local variations by type of deiodinase, all organs examined such as the brain, liver and skeletal muscle were hypothyroid at the tissue level in the presence of a normal serum TSH (24).

The lack of TSH stimulation and absence or functional deficiency of the thyroid gland may also impair T_4–T_3 conversion (25). Another important consideration is that, just as fT_4 and fT_3 dissociate under L-T4 therapy, so do TSH and FT_3. While a high proportion of patients was able to achieve a target of a suppressed TSH below the lower reference limits or a TSH value < 1 mU/l in autoimmune thyroiditis, their FT3 levels at the same time frequently remained below the median FT3 level found in normal subjects. The situation differs from conditions in which L-T4 absorption may be impaired and, as a consequence, elevated TSH levels persist. Thus, not even an L-T4 dose in which TSH is fully suppressed and FT4 by far exceeds its upper reference limit can guarantee above average FT3 levels in these patients, indicating an FT3–TSH disjoint (26).

As a consequence, although dose escalation may help some patients who maintained a sufficiently efficient thyroid hormone conversion to raise their FT_3 for euthyroidism and well-being, the strategy may not be invariably successful in all patients. In a study, 15% of athyreotic patients could not even raise their FT_3 above the lower reference limit on L-T_4 (27). Another controlled follow-up study after hemithyroidectomy for benign euthyroid goitre suggests that this deficiency may have unwanted clinical consequences. In this study, weight gain after 2 years in association with a lowered thyroid function within the laboratory reference range was interpreted as a clinical manifestation of a permanently decreased metabolic rate (28).

L-T4 dose requirements have been well studied and various regimes based on weight, BMI or more refined algorithms have been proposed to put patients on a presumed adequate dose from the very beginning (29,30). As useful as these algorithms may be for average predictions and initial guidance in the general population, they do not take into account individual variations in the response to L-T4, such as conversion efficiency. Dosing strategies solely based on a TSH definition of euthyroidism neglect the important role of fT_3, which has emerged as an equally significant parameter in defining thyroid physiology (31). Central and peripheral regulatory mechanisms do not constitute divided levels of control, as has previously been assumed. Rather they are integrated via feed-forward control of deiodinase activity by TSH and operate jointly to maintain T3 homeostasis as an overarching goal (25).To more entails can be study by molecular levels to give more suggestion.(32,33).

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