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The relationship between β-catenin and thyroid function after total thyroidectomy

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Abstract

Decreased T3, T4 are one of the major complications following total thyroidectomy that can range in severity from asymptomatic to an acute life-threatening condition. This decrease was accompanied by an increase in the hormone TSH and the study showed a decrease in protein β-catenin after total thyroidectomy. The current study aims to evaluate the changes that occur in T3, T4, TSH and β-catenin in total thyroidectomy patients, with regard to the periods after the operation.Materials and methods included the presence of three groups of patients with different characteristics in terms of times after the total removal of the thyroid gland, and a fourth group is the healthy group, and each group consisted of 30 samples. Patients with cancer, diabetes, blood pressure, and pregnant women were excluded from the study. Results of this study have shown, decreased T3, T4 and β-catenin was different from one group to another, but all three groups were low than the control group, where the first group was lowest, and then the second and third groups. At the same time, the TSH showed opposite results to the thyroid hormones, as it was noted that the first group was higher than the other groups, and the groups after extraction were larger than the control. The study showed a decrease in the function of the thyroid gland after thyroidectomy, and this was accompanied by an increase in thyroid-stimulating hormone and a decrease in β-catenin in the studied groups after thyroidectomy.

Keywords: β-catenin and thyroid hormones, Hypothyroidism.

العلاقة بين بيتا– كتنيين ووظيفة الغدة الدرقية بعد استئصال الغدة الدرقية الكلي

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الخلاصة

يعتبر انخفاض ثلاثي يودوثيرونين والثيروكسين أحد المضاعفات الرئيسية بعد استئصال الغدة الدرقية الكلي والتي يمكن أن تتراوح في شدتها من حالة غير مصحوبة بأعراض إلى حالة خطيرة تهدد الحياة. رافق هذا الانخفاض زيادة في الهرمون المحفز للغدة الدرقية وأظهرت الدراسة انخفاضًا في البروتين بيتا –كتنيين بعد استئصال الغدة الدرقية بالكامل. الهدف: تهدف الدراسة الحالية إلى تقييم التغيرات التي تحدث في ثلاثي يودوثيرونين والثيروكسين والهرمون المحفز للغدة الدرقية والبيتا كتنيين في استئصال الغدة الدرقية الكلي للمرضى بالنسبة لفترات ما بعد العملية. المواد والطرق: اشتمل على وجود ثلاث مجموعات من المرضى بخصائص مختلفة من حيث المرات بعد الاستئصال الكلي للغدة الدرقية، والمجموعة الرابعة هي المجموعة الصحية، وتتكون كل مجموعة من 30 عينة. تم استبعاد مرضى السرطان والسكري وضغط الدم والنساء الحوامل من الدراسة. نتائج هذه الدراسة: أوضحت أن انخفاض كل من ثلاثي يودوثيرونين والبيتا كتنيين كان مختلفًا من مجموعة إلى أخرى، لكن المجموعات الثلاث جميعها كانت منخفضة عن المجموعة الضابطة، حيث كانت المجموعة الأولى هي الأقل، ثم المجموعة الثانية والثالثة. في الوقت نفسه أظهر الهرمون المحفز للغدة الدرقية نتائج معاكسة لهرمونات الغدة الدرقية، حيث لوحظ أن المجموعة الأولى كانت أعلى من المجموعات الأخرى، والمجموعات بعد الاستخراج كانت أكبر من المجموعة الضابطة. الخلاصة: أظهرت الدراسة انخفاضًا في وظيفة الغدة الدرقية بعد استئصال الغدة الدرقية، وكان ذلك مصحوبًا بزيادة في هرمون المحفز للغدة الدرقية وانخفاض في البيتا كتنيين في المجموعات المدروسة بعد استئصال الغدة الدرقية.

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1. Introduction

The glands and tissues that make up the endocrine system are in charge of creating and releasing hormones that are vital for controlling a variety of vital body processes, including growth, development, metabolism, sexual function, reproduction, sleep, and mood[1-3]. This complex system consists of specialised endocrine glands including the thyroid, parathyroid, and adrenal glands as well as tissues like fat (adipose tissue), which also has a secondary endocrine role, and bone, which also secretes a wide variety of hormones. Furthermore, it has been suggested that the microbial biome, a group of microbes that live inside of humans, functions as a "virtual endocrine organ," generating chemical signals that further affect human physiology [3,4]. The thyroid gland is a crucial component of the endocrine system and is essential for maintaining a normal metabolism. It releases thyroxine (T4) and triiodothyronine (T3) under the control of thyroid-stimulating hormone (TSH) produced by the pituitary gland. The production of thyroid hormones requires iodine [4, 5].

The majority of the time, peripheral tissues convert T4 to T3. Thyroid hormones support growth and development, but their main function is to regulate basal metabolic rate. All bodily tissues may be negatively impacted by a hormone deficit or overproduction, resulting in hypothermia or hyperthermia, respectively. Mental retardation may be the outcome of developmental deficiencies [3, 6]. Because TSH continuously stimulates the thyroid, inadequate iodine intake might result in goitre. Enzymatic deiodination transforms T4 into T3, the thyroid hormone's active form, in the majority of target cells. The failure of the thyroid gland to produce enough thyroid hormone to fulfil the body's needs is referred to as hypothyroidism (HPT) in medicine. There are two categories: overt HPT and subclinical HPT. Subclinical HPT develops when the thyroid gland produces appropriate levels of T4 in response to the same stimulus as overproduction of TSH, while overproduction of TSH causes overt HPT to develop [7,8].

The armadillo protein family includes the 781 amino acid protein β-catenin. It was first discovered to be an E-cadherin-associated protein in the late 1980s and was characterised while Drosophila embryonic development genes were being screened[9,10]. Twelve Armadillo (ARM) repetitions make up the core region of β -catenin, which is flanked by the well-characterised amino terminus domain (NTD) and carboxyl terminus domain (CTD). The final ARM repeat and the flexible portion of the CTD must be separated by a certain conserved helix for β -catenin to function as a signalling protein. Each ARM repeat has three triangular helices and is made up of a repeating 42 amino acid motif. Together, the ARM repetitions form a superhelix with a lengthy, positively charged groove. With its core ARM domain structure, the central region of β -catenin serves as a scaffold and an interaction platform for binding partners [10-13].

The Wnt/ β-CATENIN signalling pathway is essential for maintaining dynamic body homeostasis and for embryonic development. A crucial Wnt pathway-signalling molecule called β-CATENIN also functions as a cytoskeletal linker protein, controlling morphogenesis, cell migration, and tissue boundaries. Disease may result from an imbalance between adherens junctions and Wnt signalling. It has been thoroughly investigated and discussed how β-CATENIN mediates the interplay and balance of these two functions or preserves their independence [13]. For a number of thyroid conditions, total thyroidectomy is advised, especially when the pathologic process requires surgery on both thyroid lobes and when the risk of recurrence is high, as in the case of benign multinodular goitre, Graves' disease, and cancer. In the past, complete thyroidectomy was avoided by surgeons due to worries about the

hazards of lengthy operation and the side effects of hormone replacement. However, as we go into the twenty-first century, thyroid hormone replacement and monitoring are both easily accessible and precise, and the technological parts of a safe complete thyroidectomy have been established. Total thyroidectomy is thus anticipated to rise in popularity for both benign and malignant thyroid diseases [14–16] .This study was conducted to determine the changes that occur in the function of thyroid hormone and β-CATENIN protein after total thyroidectomy.

2. Patients and Methods

This study has been conducted at Nasiriyah Teaching Hospital in Thi-Qar, The Endocrine Glands Center in Thi Qar governorate, Biochemistry Laboratory, at the period between 1/4/2022 to 1/4/2023. It included (90) patients, control (30) and patients. (90). Divided into three groups, each group containing 30 patients:
There were (120) women subjects, control and patients with euthyroid goiter aged (25-45) years were included in this study. They divided into four groups as the following: -

Group A (control): - included thirty (30) healthy subjects aged (25-45).
Group B (patients, after thyroidectomy): - included patients from one day to one month after thyroidectomy.
Group C (patients, after thyroidectomy): included patients from one month and one day to one year after thyroidectomy
Group D (patients, after thyroidectomy): included patients from one year, one day and more after thyroidectomy. Medical tests were performed on the patients' serum, including (T3, T4, TSH and β-catenin, (SIGMA-ALDRICH, America)), using the ELISA device
Ethical approval: The samples were taken from Al-Nasiriyah Teaching Hospital after obtaining official approvals from the Dhi Qar Health Department and after studying the research project no.(204/2022) .I obtained approval to complete the research in the institutions of the Dhi Qar Health Department according to the decision No(Dhi Qar/2022204 in 7/8/2022).

2.1 Collection of blood sample

About (6mL) of blood samples from patients (after thyroidectomy) and controls were taken and allowed to clot at room temperature in empty disposable tubes centrifuge to separate it in the centrifuge at 3000 rotors per minute (rpm)for 10min, the serum samples were separated and stored at (-20ºC) for later measurement of biochemical parameters, unless used immediately.

2.2 Statistical analysis

The statistical analysis proceeded in all groups of study, descriptive statistics analyzed by using Microsoft Excel 2010 and one way ANOVA(analysis of variations) test with LSD (least significant difference) were performed using mean and standard deviation (SD) for continuous variables. All analyses were performed with statistical Package for the social sciences SPSS for Windows (version 23.0 SPSS Inc, Chicago, 111).

3. **Results**

The mean age of the patients who were involved in our study was 25-45 years, all patients were females, they do not have malignant diseases, diabetes, or blood pressure, in addition,

they are not pregnant, the main surgical procedure was total thyroidectomy, and the main cause for surgery was a goiter benign or non-toxic. The results in table (1) showed that there were no significant differences in T3 of the studied groups when compared with each other after the total thyroidectomy in different times, but these three groups showed significant differences when compared with the control group **(**D) (P≤0.05). A slight decrease in group (A) when compared with groups (B and C) accompanied this. While the results showed a decrease T_3 after the total, thyroidectomy compared with the control group **(**D). The results showed that there were significant differences in T4 for group (A) when compared with groups (B, C) of patients (P≤0.05) and the control group **(**D), while groups (B and C) did not show significant differences when compared with each other, as well as with the control group **(**D) (P≤0.05). A slight decrease in-group (A) when compared with groups (B, C) accompanied this. While the results showed a decrease T_4 after the total, thyroidectomy compared with the control group **(**D). However, the mentioned table showed increase in level of thyroid-stimulating hormone (TSH) in postoperative groups compared with preoperative group control group **(**D). While there were significant differences in the serum concentration of TSH in preoperative control and postoperative groups (P≤0.05). Where the first group (A) had the total increase, then the second and third group (B, C) and all the totals were higher than the control group (D).For β-catenin, levels there were significant differences (P≤0.05), among all studied groups as shown in Table (1) . However, the mentioned table showed a significant decrease in level β-catenin after total thyroidectomy, was different from one group to another (P≤0.05), but all three groups (A, B and C) were lower than the control group (D), where the first group (A) was more low, then the second and third groups (B and C), which were higher than the first groups (A), and lower than the control group (D) (P≤0.05).

Table 1- Results of the parameters involved in our study

Parameter Groups	T3 ng/mL	T4 n.mol/L	TSH µIU/mL	β-catenin ng/mL
Group1	0.47 ± 0.01^{b}	88.11 ± 6.73^{b}	8.27 ± 1.03^{a}	0.17 ± 0.08^{b}
Group2	0.60 ± 0.02^{b}	109.72 ± 8.11^{a}	8.10 ± 1.44^{a}	0.19 ± 0.05^{b}
Group3	0.64 ± 0.01^{b}	110.86 ± 7.29^{a}	5.82 ± 0.42^{ab}	0.23 ± 0.02^{b}
Control	1.23 ± 0.08^{a}	115.69 ± 5.75^{a}	2.84 ± 0.02^{b}	0.34 ± 0.09^{a}
L.S.D	0.19	17.40	3.35	0.10

4. Discussion

The control of body weight is greatly influenced by thyroid hormones. TSH levels were elevated, but there were no significant differences in age, sex, preoperative thyroid function

tests, or postoperative thyroid status, according to the researchers [17]. Thyroid hormones are reduced after complete thyroidectomy and levothyroxine (T4) [18–19] administration is commonly utilized in thyroid hormone replacement treatment to raise unacceptably low levels of natural thyroid hormones. Finding the right T4 dosage regimen is essential, particularly for patients who have had thyroidectomies since some of them continue to suffer hypothyroidism for a long time. Different thyroid illnesses, including hypothyroidism, partial thyroidectomy, and complete thyroidectomy, are treated with thyroid hormone replacement therapy (THRT). The main goal of hormone replacement therapy is to make sure that the hormone that is deficient is sufficiently given, leading to physiological consequences. Although whole thyroidectomy is now more preferred [20-21].

Partial thyroidectomy has been much more often replaced in recent years with total or total thyroidectomy for treating benign thyroid disorders. Following surgery, research showed that hypothyroidism following thyroid removal lingered for up to 15 years. In comparison to 100% of patients who received near-total thyroidectomy and 87% of patients who got partial thyroidectomy, 28% of patients who underwent hemithyroidectomy developed persistent hypothyroidism. In addition, 46% of patients who had a hemithyroidectomy developed transient hypothyroidism, compared to 100% of patients who had a near-total thyroidectomy and 93% of those who had a partial thyroidectomy [22]. The most frequent long-term side effect of a complete thyroidectomy is hypothyroidism, which is increasingly important in the treatment of thyroid disorders. The utility of complete thyroidectomy to treat benign illnesses is still up for dispute, however. For individuals with Multinodular Goitre (MNG), a total thyroidectomy is recommended when there is severe nodular disease affecting both lobes. The justification for removing the gland entirely is less compelling when one lobe is generally normal. In the long run, 10% of patients with unilateral illness may have recurrence, although only 50% of them will need surgical intervention. For such individuals, a first hemithyroidectomy is probably sufficient [23,25].

There are no comparable or closely related studies that can be used to interpret the laboratory data from this investigation. Previous research that might be interpreted mostly focused on genetic and animal studies. However, Graves' disease, an autoimmune condition marked by elevated thyroid hormone production that may affect multiple organ systems in the body, including the skeletal system, has been linked to the thyroid gland and β-catenin. Due to the shortened bone remodelling cycle, it may result in a decrease in bone density [26]. In order to maintain bone mass, the Wnt cascade-signaling pathway, which includes β-catenin as a component of the canonical Wnt pathway, is also important. While the Wnt pathway may be stimulated to promote bone mass, it can also be inhibited to induce bone loss. Thyroid hormones may impact the quantities of β-catenin in the cell cytoplasm, which in turn can change how effective they are Thyroid hormones work via altering deiodinase and thyroid hormone receptors. This shows that variations in bone density may be influenced by β-catenin levels and thyroid hormones, including hyperthyroidism. The three cell types seen in the adult skeleton, osteoblasts, osteoclasts, and osteocytes, which together contribute to the control of bone remodelling, depend on the Wnt/β-catenin pathway. Bone density falls when the Wnt pathway is inhibited, but bone mass rises when it is activated [26–28].

Additionally, the Wnt signalling pathway is crucial for adult stem cell maintenance and differentiation in addition to embryonic development. Particularly, Wnt signalling has been recognised as a crucial regulatory route in mesenchymal stem cells' osteogenic development. The Wnt signalling pathway is induced to promote bone production, while the pathway is

inactivated to cause conditions of decreased bone density [29].Many studies have shown that β-catenin is a 92-kDa multifunctional protein that, in its membrane location, links the intracellular part of the E-cadherin complex to actin cytoskeleton, which is a critical step in morphogenesis and maintenance of tissue integrity. Alternatively, through Wnt signaling-mediated stabilization, β-catenin may act as a down-stream transcriptional trans-activator of several target genes. Alterations in β-catenin protein expression levels and genetic rearrangement located in β-catenin exon3 have been shown to contribute to the malignant character of various carcinomas and are likely to affect both intercellular adhesion and signal transduction, which are believed to be two independent functions of β-catenin protein. There are no studies similar to our study, but some studies related to (B-Cat) that were conducted on patients with types of cancerous tumors can be reviewed. A relationship has been indicated between B-Cat expression and the cancer stage in patients with colorectal, lung, urinary tract carcinomas or glioma. An interesting report concerns one of the studies carried out in a Polish center. It has been shown that high level of nuclear B-Cat before the treatment is an unfavorable independent prognostic factor in patients with colorectal cancer. Median survival time in this group was twice lower with elevated level of nuclear B-Cat than in patients with normal concentration. Different results were obtained in a study that determined B-Cat in prostate cancer cells [30,31].

5. Conclusion

Total thyroidectomy affects the functions of the thyroid gland by affecting the concentration of hormones (T3,T4,TSH), Therefore, patients often have symptoms of hypothyroidism and it affects the body's functions. At the same time, changes were observed in the concentration of beta-catenin, and this in itself affects the body's functions. The study showed that there are relationships between the process of total thyroidectomy and protein.

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