Alteration in Thyroid Functions in Female Patients with Breast Cancer Receiving Adjuvant Chemotherapy

Thesis

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By

Walid Mohamed Mahmoud
M.B.B.Ch, Ain Shams University
Resident of Internal Medicine - Ain Shams University

Under Supervision of

Prof. Dr. / Mohamed Saad Hamed
Professor of Internal Medicine & Endocrinology
Faculty of Medicine - Ain Shams University

Dr. / Laila Mahmoud Ali Hendawy
Assistant Professor of Internal Medicine & Endocrinology
Faculty of Medicine - Ain Shams University

Dr. / Hany Khairy Mansour
Lecturer of Internal Medicine & Endocrinology
Faculty of Medicine - Ain Shams University

Faculty of Medicine – Ain Shams University
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List of Abbreviations

Abb.	Full term
5-FU	*5-fluorouracil*
ACTH	*Adrenocorticotropic hormone*
ATC	*Anaplastic thyroid cancer*
CEA	*Carcinoembryonic antigen*
DHFU	*Dihydrofluorouracil*
DIT	*Diiodotyrosine*
DPD	*Dihydropyrimidine dehydrogenase*
dTMP	*Deox-ythymidine monophosphate*
dUMP	*Deoxyuridine monophosphate*
ELISA	*Enzyme-Linked Immunosorbent Assay*
ER	*Endoplasmic reticulum*
FDG-PET	*F-fluorodeoxyglucose–positron emission tomography*
FdUMP	*Fluorodeoxyuridine monophosphate*
FNA	*Fine-needle aspiration*
FSH	*Follicle-stimulating hormone*
FTC	*Follicular thyroid cancer*
FUTP	*Fluorouridine triphosphate*
GIST	*Gastrointestinal stromal tumors*
hCG	*Human chorionic gonadotropin*
LH	*Luteinizing hormone*
MCT	*Monocarboxylate transporter*
MEN	*Multiple Endocrine Neoplasia*
MIT	*Monoiodotyrosine*
MTC	*medullary thyroid cancer*
NACB	*National Academy of Clinical Biochemistry*
NTI	*Non thyroidal illness*
pCR	*Pathological complete response*

List of Abbreviations cont...

Abb.	Full term
PTC	*Papillary thyroid cancer*
RT_3	*Elevated reverse T_3*
SUV	*Standardized uptake values*
T_3	*Triiodothyronine*
T_4	*Thyroxine*
Tg	*Thyroglobulin*
TKIs	*Targeted tyrosine kinase inhibitors*
TPO	*Thyroid peroxidase*
TR	*T3 receptors*
TRAb	*TSHR autoantibodies*
TREs	*Thyroid hormone response elements*
TRH	*Thyrotropin-releasing hormone*
TS	*Thymidylate synthase*
TSH	*Thyroid-stimulating hormone*
TSHr	*Stimulating hormone receptor*
TSHR	*Thyrotropin receptors*
TSHr	*TSH receptors*
TSI	*Thyroid stimulating immunoglobulin*
UDG	*Uracil-DNA-glycosylase*
β	*beta*

INTRODUCTION

Endocrine disorders are among the most commonly reported long-term complications of cancer treatment by adult survivors of childhood cancers ***(Stava et al., 2007).***

In adults, cytotoxic drugs are infrequently associated to overt endocrine toxicity. However, excluding gonadotoxic consequence ***(Torino et al., 2009)***, only few studies thoroughly evaluated the endocrine dysfunction induced by cytotoxic anticancer therapy in this population ***(Yeung et al., 2012).***

These disorders encompass a broad variety of pathophysiological mechanisms, may be subtle in presentation, sometimes difficult to be identified, and even more difficult to relate to a particular chemotherapeutic regimen due to the lack of specific wide clinical trials ***(Yeung et al., 2012).***

The alteration of thyroid hormone metabolism, more commonly known as "euthyroid sick syndrome", may occur in patients with advanced cancers. Thyroid dysfunction, such as the altered synthesis or clearance of thyroid hormone-binding proteins are observed in certain malignancies, or may be caused by treatments that modify total but not free concentration of thyroid hormones. However, the clinical influence of this abnormality is marginal, if any ***(Stava et al., 2007).***

Incontrast to Cytotoxics and hormonal therapies, several novel antineoplastic agents, including targeted therapies and

immunotherapies, are unexpectedly associated with thyroid dysfunction and thyroid disease, despite their high selectivity of action ***(Torino et al., 2009).***

AIM OF THE WORK

The aim of the study is to determine the influence of adjuvant chemotherapy on thyroid functions in female patients with breast cancer after radical mastectomy.

Chapter (1)

THYROID GLAND & GOITRE

Anatomy & structure of thyroid gland:

The thyroid gland is a butterfly-shaped organ that sits at the front of the neck. It is composed of two lobes, left and right, connected by a narrow isthmus. Nearly 50% of thyroid glands exhibit a pyramidal lobe arising from the center of the isthmus. The normal adult thyroid gland weighs 10-25 g. Each lobe being about 5 cm long, 3 cm wide and 2 cm thick, and the isthmus about 1.25 cm in height and width. The isthmus extends from the second to third tracheal rings, with the uppermost part of the lobes extending to the thyroid cartilage, and the lowermost around the fourth to sixth tracheal rings ***(Kim et al., 2013).***

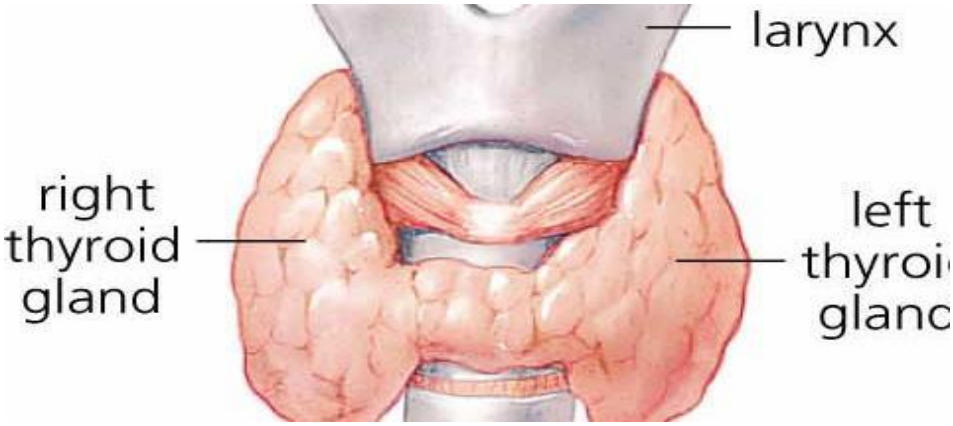

Figure 1: Thyroid gland

The thyroid gland is covered by a thin fibrous capsule, which has an inner and an outer layer. The outer layer is continuous with the pretracheal fascia, attaching the gland to the cricoid and thyroid cartilages, via a thickening of the fascia to form the posterior suspensory ligament of thyroid gland also known as Berry's ligament. This causes the thyroid to move up and down with swallowing. The inner layer extrudes into the gland and forms the septae that divides the thyroid tissue into microscopic lobules ***(Szinnai, 2014).***

Relations:

Typically four parathyroid glands, two on each side, lie on each side between the two layers of the capsule, posterior to the thyroid lobes. The infrahyoid muscles lie in front of the gland and the sternocleidomastoid muscle to the side. Behind the outer wings of the thyroid lie the two carotid arteries. The trachea, larynx, lower pharynx and esophagus all lie behind the thyroid. In this region, the recurrent laryngeal nerve and the inferior thyroid artery pass next to or in the ligament, as shown in figures (2) & (3) ***(Babademez et al., 2010).***

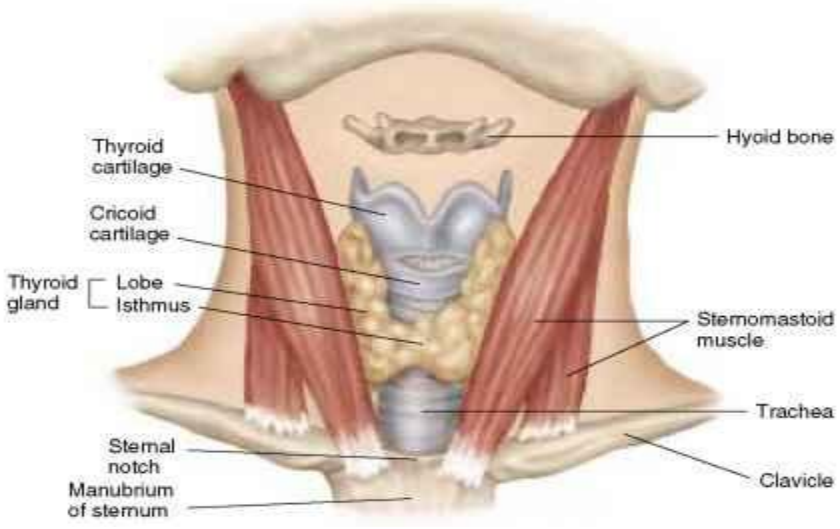

Figure 2: Relations of thyroid gland.

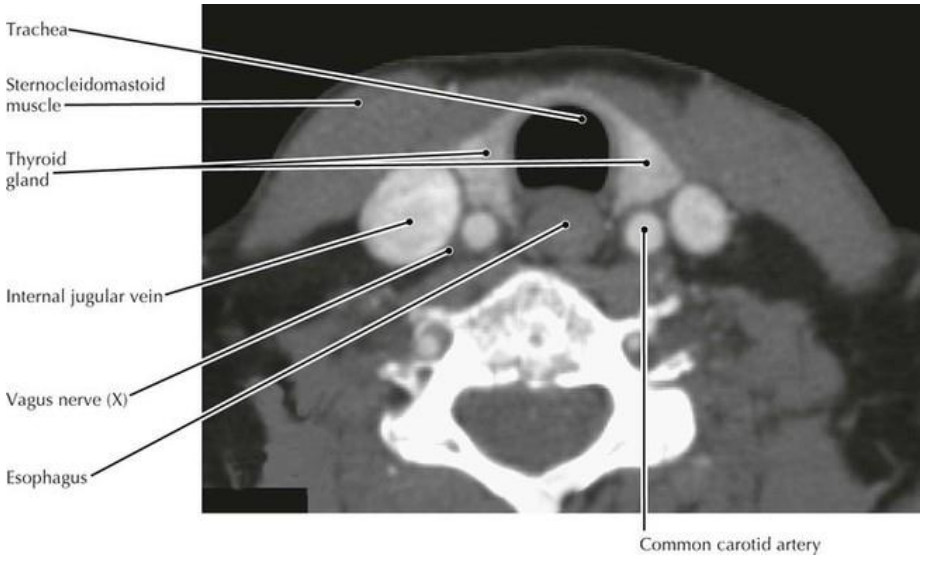

Figure 3: Anterior & posterior relations of thyroid gland by CT scan.

Thyroid hormones:

Edward Calvin Kendall was responsible for the isolation of thyroxine in 1915. The thyroid hormones, triiodothyronine (T_3)

and its prohormone, thyroxine (T_4), are tyrosine-based hormones and partially composed of iodine, produced by the thyroid gland, that are primarily responsible for regulation of metabolism. The major form of thyroid hormone in the blood is thyroxine (T_4), which has a longer half-life than T_3. In humans, the ratio of T_4 to T_3 released into the blood is between 14:1 to 20:1 ***(Bianco et al., 2012).***

Thyroxine is produced by attaching iodine atoms to the ring structures of this protein's tyrosine residues; thyroxine (T_4) contains four iodine atoms, while triiodothyronine (T_3), otherwise identical to T_4, has one less iodine atom per molecule. Thyroxine T4 (3,5,3',5'-tetraiodothyronine) is converted to the active T_3 within cells by deiodinases (5'-iodinase). The effects of T_4 in vivo are mediated via T_3 (T_4 is converted to T_3 in target tissues). T_3 is 3- to 5- fold more active than T_4 ***(Friesema et al., 2008).***

Synthesis of thyroid hormones:

Central

Thyroid hormones (T_4 and T_3) are produced by the follicular cells of the thyroid gland and are regulated by TSH made by the thyrotropes of the anterior pituitary gland, as shown in figure (4). Thyroglobulin (Tg) is a 660 kDa, dimeric protein produced by the follicular cells of the thyroid and used entirely within the thyroid gland. The thyroglobulin protein