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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
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Detection of Subclinical Cardiomyopathy in Patients with Hashimoto Thyroiditis

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

By

Mohamed Sayed Hassan Ali
M.B., B.Ch.; Ain Shams University (2015)

Under supervision of

Prof. Heba Hassan Elsedfy
Professor of Pediatrics
Faculty of Medicine, Ain Shams University

Dr. Rana Abd Elhakim Ahmed Mahmoud
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Dr. Marwa Magdy Hassan Nawar
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Dr. Nora Hussein Mahmoud El-Samman
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Contents

Title	Page No.
List of Abbreviations	i
List of Tables	iv
List of Figures	v
Introduction	1
Aim of the Work	2
Review of Literature	
Epidemiology	3
Thyroid Hormones and Cardiovascular Function and Diseases	15
Patients and Methodology	26
Results	32
Discussion	50
Summary	56
Conclusion	58
Recommendations	59
References	60
Arabic Summary	–

List of Abbreviations

Abb.	Full term
2D	Two Dimensional
2D-STE	2 Dimensional speckle tracking echocardiography
3D	Three Dimensional
AB	Antibody
AITD	Autoimmune thyroid disorder
AMI	Acute myocardial infarction
BMI	Body mass index
BSA	Body surface area
Ca2+	Calcium
CIMT	Cardiac intimal media thickness
cm	Centimeter
CS	Circumferential strain
CV	Cardiovascular
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EF	Ejection fraction.
FS	Fraction shortening
fT3	Free triiodothyronine
fT4	Free thyroxine
GLS	Global longitudinal strain
HDL	High-density lipoprotein
HF	Heart failure
HLA	Human Leukocyte Antigen
HR	Heart rate
HT	Hashimoto thyroiditis
IG4-RD	Immunoglobulin G4-related disease
IVST	Inter ventricular septum thickness

List of Abbreviations Cont...

Abb.	Full term
K+	Potassium
Kg	Kilogram
LDL	Low-density lipoproteins
LS	Longitudinal strain
LV	Left ventricular
LVED	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
LVESd	Left ventricular end-systolic diameter
LVGLS	LV global longitudinal strain
LVPWT	Left ventricular posterior wall thickness
MHCs	Myosin heavy chains
Na+	Sodium
NIS	Sodium iodide symporter
PLB	Phospholamban
RNA	Ribonucleic acid
RS	Radial strain
SBP	Systolic blood pressure
SCH	Subclinical hypothyroidism
SDS	Standard deviation score
SERCA2	Sarcoplasmic reticulum calcium adenosine triphosphatase
SNPs	Single nucleotide polymorphisms
STE	Speckle-tracking echocardiography
SVR	Systemic vascular resistance
T3	Triiodothronine
T4	Thyroxin
TDI	Tissue Doppler imaging
TG	Triglycerides

List of Abbreviations Cont...

Abb.	Full term
TH	Thyroid hormones
TH1	T helper 1
TH2	T helper 2
TPO	Thyroperoxidase
TRH	Thyrotropin-releasing hormone
TRs	Thyroid hormone receptors
TS	Torsional strains
TSH	Thyroid-stimulating hormone
TSI	Thyroid-stimulating immunoglobulin
WT	Weight

List of Tables

Table No.	Title	Page No.
Table (1):	Comparison between control group and patient group regarding demographic data.	32
Table (2):	Comparison between control group and patients group regarding anthropometric measures	33
Table (3):	Comparison between control group and patients group regarding vital data	35
Table (4):	Comparison between control group and patients group regarding lipid profile	36
Table (5):	Comparison between control group and patients group regarding thyroid profile, antithyroglobulin antibody and anti-microsomal antibody	38..
Table (6):	Comparison between control group and patients group regarding echocardiography M-mode parameters, LVGLS (left ventricle global longitudinal strain) and CIMT (carotid intima media thickness).	40
Table (7):	Correlation of CIMT with anthropometry, lipid profile, level of thyroid antibodies	42
Table (8):	Comparison between patients regarding CIMT.	43
Table (9):	Comparison between newly diagnosed patients and known patients regarding M-mode parameters, LVGLS (left ventricle global longitudinal strain) and CIMT (carotid intima media thickness).	45
Table (10):	Correlation between echocardiography parameters CIMT, with duration of disease and antibodies levels.	47
Table (11):	Correlation between initial thyroid profile and echocardiography parameters	49

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Comparison between control group and patients group regarding height SDS	34
Figure (2):	Comparison between case group and control group regarding lipid profile.	37
Figure (3):	Comparison between patient group and control group regarding antithyroglobulin antibodies	39
Figure (4):	Comparison between patient group and control group regarding anti microsomal antibodies	39
Figure (5):	Comparison between patient group and control group regarding LVGLS z-score	41
Figure (6):	Comparison between duration of the disease and CIMT z-score.	44
Figure (7):	Comparison between not newly diagnosed and newly diagnosed regarding LVGLS.	46
Figure (8):	Correlation between duration of the disease and LVGLS.	48

INTRODUCTION

Hashimoto thyroiditis (HT) is the most common cause of thyroid diseases in children and adolescents and it is also the most common cause of acquired hypothyroidism in iodine-sufficient areas ***(Slatosky et al., 2000).***

HT is an autoimmune disease caused by destruction of thyroid cells by cell and antibody-mediated immune processes. This disease is also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis. HT is characterized by increased thyroid volume, lymphocyte infiltration of parenchyma, and the presence of antibodies specific to thyroid antigens. HT with Graves' disease called autoimmune thyroid disorder (AITD) had increased in frequency during the recent years ***(Mcleod and Cooper, 2012).***

Thyroid hormone levels affect many biological functions including the cardiovascular system; however, it is unclear if the effect is a result of affection of myocardial contractility or loading condition or both ***(Razvi et al., 2018).***

Patients with HT are more likely to develop cardiovascular diseases ***(Chen et al., 2015)*** and malignant neoplasm ***(Chen et al., 2013).***

Left and right ventricular myocardial dysfunction associated with euthyroid HT has been suggested to be related to the abnormal inflammatory state associated with autoimmunity as well as to endocrine effect ***(McLeod, 2013).***

AIM OF THE WORK

1. To evaluate the value of using speckle tracking echo-cardiography and estimation of carotid intima-media thickness (cIMT) in early detection of myocardial dysfunction in children with Hashimoto thyroiditis.

2. To study the frequency of subclinical cardiomyopathy associated with Hashimoto thyroiditis.

Chapter 1

EPIDEMIOLOGY

HT is the most common cause of acquired hypothyroidism in childhood, with a prevalence of 1 to 3%, peaking during adolescence ***(Crisafulli et al., 2018)*** with a female-to-male ratio of 4–8:1 ***(Segni, 2000).***

At the time of diagnosis, thyroid function in children may be variable ranging from euthyroidism (52.1%), to overt (22.2%) or subclinical hypothyroidism (SCH) (19.2%) or, more rarely to either subclinical or overt hyperthyroidism (6.5%) ***(Wasniewska et al., 2012).***

Autoimmune thyroidtis has shown increased incidence in monozygotic twins compared to dizygotic twins as Danish studies demonstrated rate of 55% in monozygogtic twins as compared to 3 % in dizygotic twins ***(Brix et al., 2011).***

Associations:

Autoimmune thyroiditis is commonly associated with chromosomal abnormalities such as Down syndrome ***(Karlsson et al., 1998),*** turner syndromes ***(Elsheikh et al., 2001)*** Klinefelter syndrome and Noonan syndrome. HT also could be associated with chronic urticarial ***(Verneuil et al., 2004)*** and rarely to immune-complex glomerulonephritis ***(Gurkan et al., 2009).***

Molecular and cellular mechanisms of thyroid hormones action

Thyroid function is regulated by the hypothalamic-pituitary-thyroid axis via a classic endocrine feedback loop mechanism. Thyrotropin-releasing hormone (TRH) is secreted at the level of the hypothalamus and stimulates the anterior pituitary to produce thyroid-stimulating hormone (TSH), which in turn, drives the thyroid gland to release thyroid hormones (TH).TH levels regulate TRH and TSH production and release ***(Larsen, 1982).***

TSH has a log-linear relationship with thyroxine (T4) levels; therefore, mild changes in TH concentrations lead to large changes in TSH. Thus, serum TSH is a robust marker of systemic TH status. The 2 main iodinated THs are T4 and triiodothyro-nine (T3). Both have biological effects; how-ever, T3 is considered the active and more potent hormone. The normal negative feed-back regulation of thyroid function is disrupted by illness, including conditions such as acute myocardial infarction (AMI) or heart failure (HF), and is characterized by a reduction in serum TH without a concomitant rise in circulating TSH level. With the recognition that TSH is extremely sensitive to subtle changes in circulating TH concentrations and with the advent of high-sensitivity TSH assays, clinicians are able to detect subtle changes in thyroid function, leading to the concept of subclinical thyroid disease ***(Ravzi et al., 2018).***

Etiology (Pathophysiology)

Although that there is no definite etiology for HT, pathogenesis though to be related to genetic factors, environmental triggers and epigenetic effect ***(Hasham and Tomer, 2012).***

1- Genetic susceptibility:

A genetic susceptibility to HT disease has been shown in epidemiological studies that focused on familial predisposition. ***Brix et al***. showed in Danish twins that monozygotic twins exhibited a concordance rate of more than 50%, while dizygotic twins showed absence of any concordance. Moreover, data from the same study regarding thyroid autoantibodies showed a high concordance rate for monozygotic twins that was nearly 80%, when compared to dizygotic ones (40%) ***(Brix et al., 2011).***

Several genes have been shown to be involved in HT pathogenesis, including genes of immune response and thyroid function. Among the genes that control the immune response, a relevant role is played by those coded in the Human Leukocyte Antigen (HLA) complex; thus, it has been showed that the HLAeB* 46:01 gene is associated with the development of HT, as demonstrated in Chinese children is a case-control and family-based study. In another study of 444 Japanese patients with HT, some genes (HLA-A* 02:07 and HLA-DRB4) were