



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY

**Study of The Relation between 8_Hydroxy-2'-
deoxyguanosin (8_OHDG) and Suspicious
Thyroid nodule in a Patients with
Multinodular Goiter**

Thesis

Submitted for partial fulfillment of Master Degree in
Endocrinology and Metabolism

Faculty of Medicine, Ain Shams University

Presented by

Ruwida Fouli Farag Mohamed Eljazwi

(M.B., B.Ch, Libyn International Medical University)

Supervised by

Prof. Dr./ Nermin Ahmed Sheriba

*Professor of Internal Medicine and Endocrinology
Faculty of Medicine, Ain Shams University*

Prof. Dr./ Maram Mohamed Maher Mahdy

*Professor of Internal Medicine and Endocrinology
Faculty of Medicine, Ain Shams University*

Dr./ Dina Ahmed Marawan

*Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine, Ain Shams University*

**Faculty of Medicine
Ain Shams University**

2021

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبِّحْكَ لَا إِلَهَ إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgement

*First and foremost thanks to **ALLAH**, the Most Merciful.*

*I wish to express my deep appreciation and sincere gratitude to **Prof. Dr. Nermin Ahmed Sheriba**, Professor of Internal Medicine and Endocrinology, Ain Shams University, for her close supervision, valuable instructions, continuous help, patience, advices and guidance. She has generously devoted much of her time and effort for planning and supervision of this study. It was a great honor to me to work under her direct supervision.*

*I wish to express my great thanks and gratitude to **Prof. Maram Mohamed Maher Mahdy**, Assistant professor of Internal Medicine and Endocrinology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

*I wish to express my great thanks and gratitude to **Dr. Dina Ahmed Marawan**, Lecturer of Internal Medicine and Endocrinology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

*Last and not least, I want to thank all my **family**, my colleagues,, for their valuable help and support.*

Finally I would present all my appreciations to my patients without them, this work could not have been completed.

 **Ruwaida Fouli Farag Mohamed Eljazwi**

List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables	iii
List of Figures.....	iv
Introduction.....	1
Aim of the Work.....	4
Review of Literature	
Multinodular Goiter.....	5
8-hydroxy-2'-deoxyguanosine (8_OHdG) Marker and its association with Cancer.....	52
8_OHdG marker in patients with Multinodular Goiter	67
Subjects and Methods	82
Results.....	91
Discussion	111
Summary.....	125
Conclusions	127
Recommendations	128
References.....	129
Arabic Summary	—

List of Abbreviations

Abbr.	Full-term
AFTNs	: Autonomously functioning thyroid nodules
ATA	: American Thyroid Association
cAMP	: cyclic adenosine monophosphate
CT	: Computed tomography
EGF	: Epidermal growth factor
ETA	: European thyroid association
FNA	: Fine needle aspiration
FNAB	: Fine needle aspiration biopsy
GCMS	: Gas chromatography with mass spectrometry
GC-MS	: Gas-chromatography-massspectrometry
GPXs	: Glutathione peroxidases
H&E	: Hematoxylin and eosin
H₂O₂	: Hydrogen peroxide
hOGG1	: 8-oxoguanine DNA glycosylase
HPLC	: High-performance liquid chromatography
IGF-I	: Insulin-like growth factor-1
MNG	: Multinodular goiters
MRI	: Magnetic resonance imaging
mRNA	: Messenger ribonucleic acid
MTC	: Medullary thyroid carcinoma
MTNS	: McGill Thyroid Nodule Score
NIS	: Na ⁺ /I ⁻ symporter
PET	: Positron emission tomography

PTC	: Papillary thyroid carcinoma
ROS	: Reactive oxygen species
SD	: Standard deviation
SOD	: Superoxide dismutase
Tg	: Thyroglobulin
TGF-β1	: Transforming growth factor
TIRADS	: Thyroid Imaging Reporting and Data System
TPO	: Thyroid peroxidase
TSH	: Thyroid stimulating hormone
8-OHDG	: 8_Hydroxy-2'-deoxyguanosin
8-OHGua	: C8-hydroxyguanine

List of Tables

Table No.	Title	Page No.
Table (1):	The various types of thyroid nodules	9
Table (2):	ACR/EU - TIRADS differences in terms of classification of nodules.....	35
Table (3):	ACR/EU - TIRADS differences in terms of management of nodules by risk category.....	35
Table (4):	Management of Nodules.....	48
Table (5):	Application of 8_hydroxydeoxyguanosine as potential biomarker for various clinical diseases	60
Table (6):	Demographic and laboratory data of Group 1 (MNG patients).....	92
Table (7):	Demographic and laboratory data of Group 2 (Healthy control)	94
Table (8):	Comparison between Group 1 (MNG patients) and Group 2 (Healthy control) as regards age.....	95
Table (9):	Comparison between Group 1 (MNG patients) and Group 2 (Healthy control) as regards Sex	96
Table (10):	Comparison between Group 1 (MNG patients) and Group 2 (Healthy control) as regards Thyroid profile (TSH, fT3 and fT4)	97

Table (11):	Comparison between Group 1 (MNG patients) and Group 2 (Healthy control) as regards 8_OHDG	98
Table (12):	Comparison between (Group IA) patients with MNG without malignancy after FNA and (Group IB) patients with malignancy As regards diagnostic and libratory data.....	99
Table (13):	Comparison between sex and TIRADS score in patients group as regards 8_OHDG.	103
Table (14):	Correlation between 8_OHDG and all variables (Age, TSH, fT3, fT4 and size of nodules) in all patients groups.	107
Table (15):	The ROC curve between patients and controls as regard 8_OHDG	110

List of Figures

Figure No.	Title	Page No.
Figure (1):	Anatomy of thyroid gland.....	5
Figure (2):	Thyroid Gland. The thyroid gland is located in the neck where it wraps around the trachea..	7
Figure (3):	Hypothesis for thyroid nodular transformation. The starting point for the development of MNG is hyperplasia induced by goitrogenic stimuli (e.g., iodine deficiency)..	14
Figure (4):	ACR TI-RADS criteria, levels and recommendations	30
Figure (5):	The 2017 ACR-TIRADS system.....	32
Figure (6):	EU-TIRADS algorithm for classification of nodules and FNA decision-making	34
Figure (7):	Technetium-99m (99mTc) thyroid scan of a large, nontoxic multinodular goiter. Multiple cold and hot nodules are observed in the enlarged thyroid gland..	37
Figure (8):	Histologic pattern of a mildly differentiated follicular thyroid carcinoma (250 X).....	40
Figure (9):	Diagnostic sequence and therapeutic decisions in managing a patient with an apparent single nodule of the thyroid.....	46
Figure (10):	Formation of 8_OHDG	53
Figure (11):	Toxins mediated alterations in DNA structure and the mechanis of DNA damage.	57

Figure (12):	The classification of thyroid nodules on the basis of results from clonality studies.	70
Figure (13):	The two concepts of thyroid nodular transformation	73
Figure (14):	Factors that might contribute to the development of thyroid tumors.....	77
Figure (15):	The figure shows the key molecules involved in those parts of thyroid hormone synthesis which—in conditions of iodine and most probably also selenium deficiency—lead to oxidative stress, DNA damage and possibly mutagenesis.	79
Figure (16):	Comparison between Group 1 (MNG patients) and Group 2 (Healthy control) as regarding 8_OHDG level	98
Figure (17):	Comparing the two studied groups as regarding 8OHDG level	101
Figure (18):	Show Thyroid nodule size showing high significant difference of thyroid nodule size between Group 1B (MNG with malignancy)	102
Figure (19):	Shows that there is no statistically significant difference between studied subgroups regarding TIRADS classification	102
Figure (20):	Correlation between 8_OHDG and size of nodules in all patients group	109
Figure (21):	The Cutpoint and Sensitivity and Specificity.....	110

Introduction

Thyroid nodules are a common clinical problem affecting numerous individuals worldwide. The prevalence of palpable thyroid nodules is approximately 5% among women and 1% among men living in iodine-sufficient parts of the world (**Haugen et al., 2016**).

High-resolution ultrasound can detect thyroid nodules in 19%–68% of randomly selected individuals, with higher frequencies in women and the elderly (**Tan and Gharib. 1997**).

Although the majority of thyroid nodules are benign, certain risk factors, such as a solid nodule, age over 70 years or below 20 years, a history of previous head and neck irradiation, male sex, and a history of familial thyroid cancer or multiple endocrine neoplasia syndrome, may increase the risk of developing cancerous thyroid nodules (**Arora et al., 2008**).

Multinodular goiters (MNG) defined as an enlarged thyroid gland with multiple nodules, have historically been thought of as a benign condition with a low risk of associated malignancy, and may be present in up to 4% of the population in iodine sufficient countries. However, recent studies have suggested that the incidence of malignancy in patients with MNG approaches that of patients with a solitary thyroid nodule (**Gandolfi et al., 2004**).

Pre-operative diagnosis of thyroid cancer is commonly done through fine-needle aspiration (FNA) While it remains one of the best pre-operative methods of determining nodule malignancy, large studies have found FNAs to be non-diagnostic in up to 25% of the cases **(Rago et al., 2010)**. Furthermore, the presence of multiple nodules can present difficulties in adequately evaluating the entire thyroid because sampling every nodule is not practical **(Ríos et al., 2004)**. The presence of multiple nodules also creates challenges in following individual nodules for growth overtime, which is an additional factor that is used to increase the suspicion for malignancy.

Early molecular conditions for nodular and tumor transformation in the thyroid gland consist of a sequence of molecular events that include oxidative stress and DNA damage as the trigger for somatic mutations. The oxidative burden is already detectable in the normal thyroid gland and is likely to be linked to hormone synthesis and H₂O₂ production **(Guth et al., 2009)**. It has been suggested that oxidative stress can cause DNA damage followed by an increase in the spontaneous mutation rate, which is a platform for tumor genesis **(Levine and Sistrunk. 2018)**.