Assessment of Serum Midkine Level in benign and Malignant Thyroid Nodules: Can Midkine be a marker of thyroid malignancy?

Thesis

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By

Maha Mohamed Mostafa EL-Nabarawy

M.B, B.CH

Under supervision of

Prof Dr./ Nermin Ahmed Sheriba

Professor of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine – Ain Shams University

Dr./ Maram Mohamed Maher Mahdy

Assistant Professor of Internal Medicine,
Diabetes and Endocrinology
Faculty of Medicine – Ain Shams University

Dr./ Rana Hashem Ibrahim EL Attary

Lecturer of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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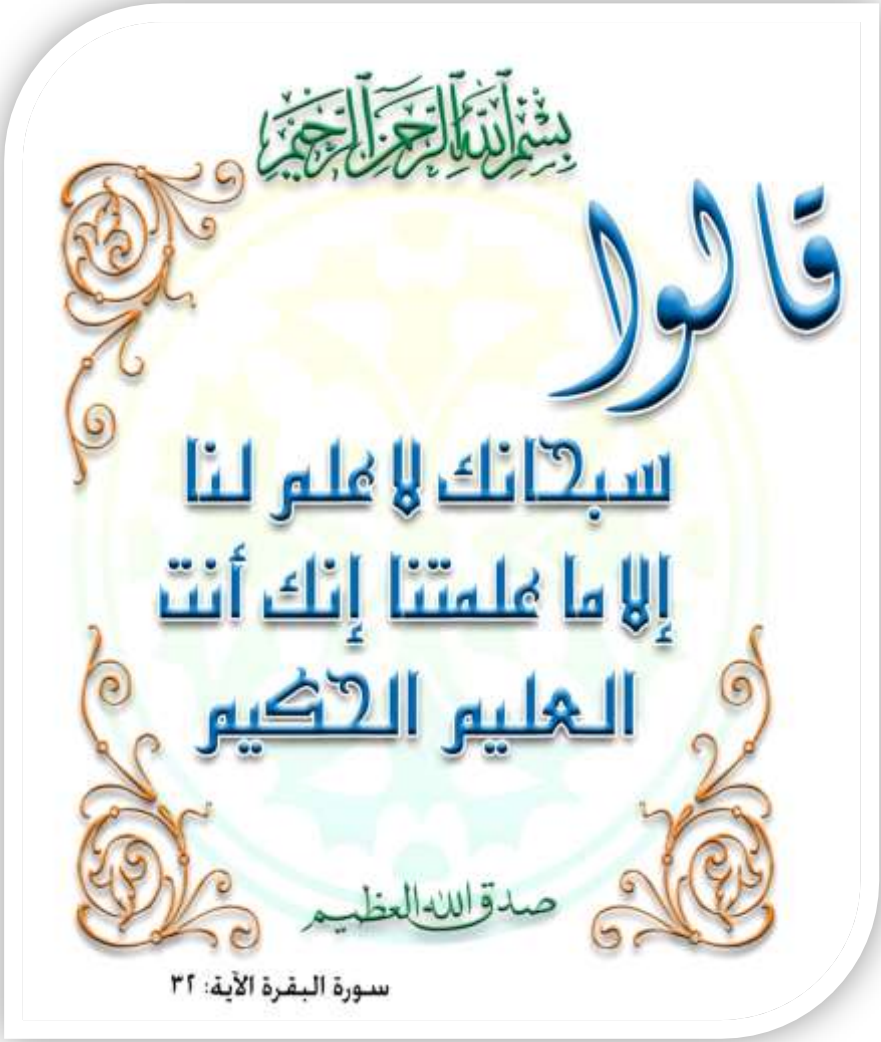
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✍ *Maha Mohamed Mostafa EL-Nabarawy*

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List of Abbreviations

Abbr.	Full-term
ACR	**:** American College of Radiology
AFP	**:** α-fetoprotein
ALK	**:** Anaplastic lymphoma kinase
ALK	**:** Anaplastic lymphomakinase
AUS	**:** Atypia Undetermined Significance
BIRADS	**:** Breast image reporting and data system
CA	**:** Carbohydrate antigen
CEA	**:** Carcinoembryonic antigen
CT	**:** Computed tomography
DTC	**:** Differentiated thyroid cancer
EAE	**:** Experimental autoimmune encephalitis
EIA	**:** Enzyme-linked immunoassay
ELISA	**:** enzyme-linked immunosorbent assay
ERK	**:** Extracellular signal-regulated kinase
ESCC	**:** Esophageal squamous cell carcinoma
FNA	**:** Fine needle aspiration
FNAB	**:** Fine needle aspiration biopsy
H&E	**:** Hematoxylin and eosin
HCC	**:** Hepatocellular carcinoma
HIF1α	**:** Hypoxia-inducible factor 1α
LDL	**:** Low-density lipoprotein

LRP : LDL receptor-related protein
MCP : Monocyte chemoattractant protein
MFP : Medial floor plate
MK : Midkine
mRNA : Messenger ribonucleic acid
MTNS : McGill Thyroid Nodule Score
NF : Nuclear factor
ODNs : Oligodesoxy-ribonucleotides
OSCC : Oral squamous cell carcinoma
PA : Plasminogen activator
PCR : Polymerase chain reaction
PTC : Papillary thyroid cancer
PTN : Pleotropin
RT : Real-time
SD : Standard deviation
siRNA : Small interfering RNA
SPSS : Statistical package for social science
Tg : Thyroglobulin
TIRADS : Thyroid image reporting and data system
TPO : Thyroid peroxidase
TSH : Serum thyrotropin
WT : Wilms' tumor
ζ (PTPζ : Protein tyrosine phosphatase

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Abstract

Background: Thyroid nodules are a common clinical problem. The prevalence of malignancy in thyroid nodules is currently about 5–15%. Optimal prediction of malignancy in nodular thyroid disease is needed to achieve the best medical and surgical intervention. Midkine (MK), a novel heparin-binding growth factor, plays critical roles in a variety of biological phenomena such as carcinogenesis, inflammation/immunity, blood pressure, cellular proliferation, survival, migration of cellular functions, angiogenesis, fibrinolysis, and host defense and tissue protection. **Aim of the Work:** The aim of this study is to evaluate the value of serum Midkine as a marker of Malignancy in Patients with Nodular Thyroid Disease. **Patients and Methods:** This comparative study was conducted on 75 subjects with age ranging from 25-80 years selected from outpatient clinic of Internal Medicine and Endocrinology of Ain Shams University Hospital. **Results:** Serum Midkine level showed a significant increase in cases with malignant thyroid nodules having irregular borders and microcalcifications than in cases with benign thyroid nodules. **Conclusion:** Serum Midkine might be the indicator of malignant thyroid cytopathology, suggesting that midkine might serve as a novel biomarker in assessment of thyroid nodules. The present study explored the usefulness of midkine as a biomarker in the differentiation between benign and malignant thyroid nodules in samples from serum.

Key words: Serum Midkine, benign/malignant thyroid nodules, thyroid malignancy

Introduction

Thyroid nodule is typically asymptomatic, and 33% to 68% of adults have thyroid nodules when evaluated by ultrasound. Most thyroid nodules are benign, but about 7% to 15% of individuals with thyroid nodules harbor thyroid cancer. Thyroid nodules may also cause morbidity due to hyperthyroidism or local compression. Population-based studies suggest a doubling in thyroid cancer incidence in recent decades, but nearly all of this increase is attributable to clinically occult cancers detected incidentally on imaging or pathology **(Ronald and Andrew, 2017).**

Optimal prediction of malignancy in nodular thyroid disease is needed to achieve the best medical and surgical intervention. Fine needle aspiration biopsy (FNAB) is widely used and has improved preoperative prediction of malignancy but still has disadvantages including operator variability and nondiagnostic reports. Therefore researchers have focused on identifying novel biologic markers that might be associated with malignancy in thyroid nodules **(Jin and McHenry, 2012).**

Midkine is a multifunctional cytokine predominantly expressed during embryogenesis, while in adult organisms, its expression is resumed during inflammation, tissue repair, and carcinogenesis. Midkine displays a number of activities that might be relevant for cancer development, e.g., it has

been demonstrated to act as a mitogen, an antiapoptotic, and angiogenic factor, a chemoattractant and haptotactic factor, an immunomodulator, and an inductor of synthesis of several cytokines and growth factors, such as IL-8, TGF-β, MIP-2, and MCP-1 **(Muramatsu, 2010).**

There is release of Midkine from cancer tissue into the blood. Serum midkine is found in 87% percent of various cancers. High serum and tissue Midkine levels have been proposed as indicative of malignancy in numerous tumors and to be a prognostic marker of their behavior **(Kadomatsu et al., 2013).**

In thyroid cancer, tissue Midkine overexpression has been reported to be in correlation with clinicopathological features of the tumor, hypothesizing that Midkine might play a role as a biomarker for diagnosis and more aggressive behavior of thyroid cancer such as lymph node metastasis and extrathyroidal invasion. Also they found that benign adenomatoid nodules showed less Midkine overexpression than the malignant nodules **(Kato et al., 2000).**

The studies for Serum Midkine in differentiated thyroid cancer were very rare but it was found higher in differentiated thyroid cancer than benign thyroid lesions **(Meng et al., 2015).**

Aim of the work

The aim of this study is to evaluate the value of serum Midkine as a marker of Malignancy in Patients with Nodular Thyroid Disease.

Approach to Thyroid Nodules

Introduction

The thyroid gland is a highly vascular, brownish-red gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic. The gland varies from an H to a U shape and is formed by 2 elongated lateral lobes with superior and inferior poles connected by a median isthmus, with an average height of 12-15 mm, overlying the second to fourth tracheal rings **(Sakr, 2016).**

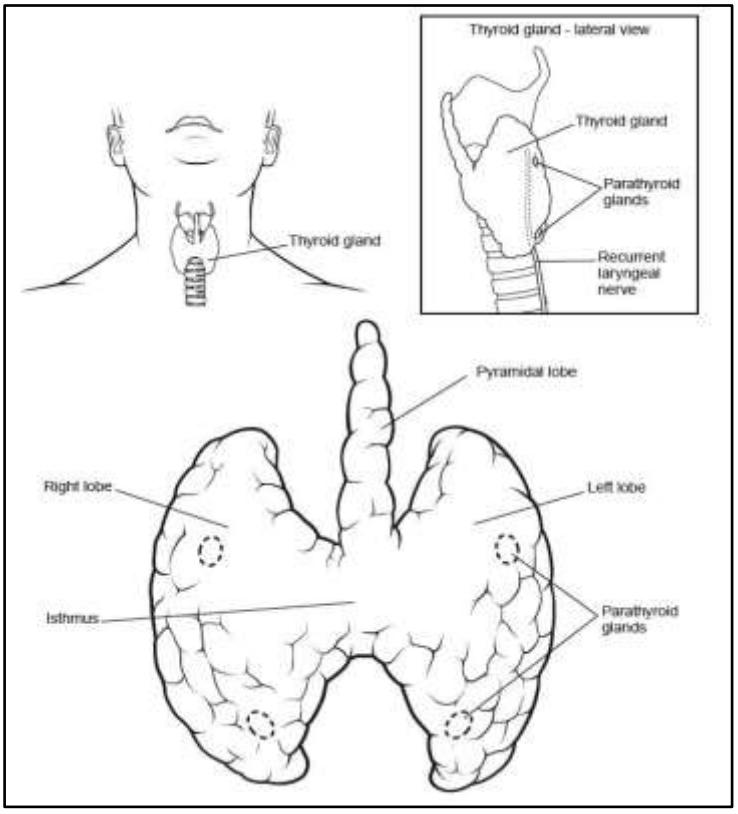

Figure (1): Anatomy of thyroid gland **(Dorion, 2015).**