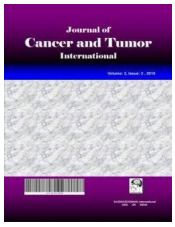

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Role of Midkine in Predicting Malignancy in Patient with Solitary Thyroid Nodule

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Authors' contributions

This work was carried out in collaboration between both authors. Author NAI designed the study, wrote the protocol, wrote the first draft of the manuscript and managed the literature searches. Author AMH performed the statistical analysis and managed the analyses of the study. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Solitary thyroid nodules are a common clinical problem. None of sonographic features is sufficient to discard or detect malignancy efficiently. Midkine is a novel heparin-binding growth factor, plays critical roles in carcinogenesis. In this study, we aimed to evaluate serum midkine levels in patients with solitary thyroid nodules to predict malignancy.
Methods: A total of 100 patients who had solitary thyroid nodules were enrolled in the study. Serum midkine levels were measured. Fine needle aspiration cytology was done to all nodules (25 suspicious/ malignant and 75 benign).
Results: Serum midkine levels were significantly higher in patients who had nodules with the following sonographic features; hypoechoic nodules compared to isoechoic and hyperechoic nodules (P=0.024), nodules with microcalcification compared to nodules with macrocalcification or without calcification (P = 0.011), nodules with irregular borders compared to nodules with regular borders (P = 0.014) and nodules more than 2 cm in length than shorter ones (P = 0.011). Serum

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midkine levels were also higher in nodules with absent halo compared to those with clear halo but with no significant difference (P = 0.660). Also, levels of serum medikine were significantly higher in suspicious/ malignant nodules than in benign nodules (P < 0.001).
Conclusion: Serum midkine can predict malignancy in solitary thyroid nodule and also well correlated with sonographic features of thyroid nodules. We suggest that midkine levels may serve as a novel biochemarker in association with sonographic features in evaluation of solitary thyroid nodules.

Keywords: Midkine; thyroid nodule.

1. INTRODUCTION

Thyroid nodules are a common clinical problem, the prevalence of malignancy in thyroid nodules is about 5–15% [1]. 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 [1–4].

Growth factors and cytokines play fundamental roles in various pathological processes. Midkine, a 13-kDa, heparin-binding growth factor involved in cellular differentiation, proliferation, survival, and migration [5]. Midkine are strongly expressed during embryonic periods, and are crucial in embryonic development, yet its expression in adult tissues is generally very weak. However, midkine plays important roles in various pathogenesis, in particular malignant diseases [6,7].

Increased midkine expression has been reported in many types of malignancies, including oral and esophageal squamous cell carcinomas [8], gastrointestinal cancer [9], pancreatic cancer [10], prostate cancer [11], breast cancer [12], and Wilms tumor [13]. Moreover, a high level of midkine expression has been associated with advanced tumor stage and a poor prognosis [14]. In general, midkine is thought to contribute to tumor development and progression by enhancing the growth, survival, migration, epithelial-mesenchymal transition (EMT), and angiogenic activity of tumors [15]. Because of such a wide range of cancer-related biologic activities and the antitumor effect after midkine inhibition, midkine has been suggested to be a good molecular target for the treatment of certain malignancies [16].

The aim of the current study was to evaluate serum midkine levels in patients with solitary thyroid nodules to predict malignancy.

2. PATIENTS AND METHODS

***Patients*:** This prospective study included 100 subjects, with solitary thyroid nodule attending to the outpatient clinic of endocrinology department of Ain Shams University Hospital and Maadi Military Hospital. All patients were naïve, have no past history of thyroid disease, no other co-morbidities, and none of them was receiving thyroid medications. This study was approved by the local Institutional Review Board and written informed consent was obtained from every patient included in the study.

***Blood Samples*:** Venous blood samples were taken in the morning after 8 hours fasting for thyroid stimulating hormone (TSH) which was measured by direct chemiluminescence method. Normal limits were TSH: 0.4 to 4 μIU/mL.

***Imaging*:** Thyroid ultrasounds of patients enrolled in the study were performed by using a high-resolution ultrasound device with 7.5 MHz probe, prior to FNAB. Sonographic features of thyroidal nodules were evaluated and recorded: width and height of the nodule, nodular structure (pure solid, cystic, and mixed), echogenicity (hypoechoic, isoechoic, and hyperechoic), nodular border (smooth, irregular), presence of peripheral halo, and presence and type of calcification (microcalcification, macrocalcification).

Fine Needle Aspiration Biopsy: FNAB was performed with ultrasound-guided FNAB using a 22-gauge needle and 10cc syringe. Two samples were obtained from each nodule.

Serum Midkine: To obtain the sera of patients, venous blood samples were centrifuged for 5 minutes at 5000 rpm. Midkine level (ng/mL) in serum was studied by using commercially

available OmniKine Human Midkine ELISA Kits (Assay Biotechnology Company, CA, USA).

***Cytopathology*:** The results of FNAC were divided into two groups as benign and suspicious/malignant.

***Statistical Analysis*:** Statistical evaluation was carried out by using SPSS program version 21.0 (SPSS Inc., Chicago, IL, USA). The normality of distribution of quantitative variables was analyzed with Shapiro-Wilk test. Descriptive statistics for numeric variables were defined as mean ± standard deviation and median (interquartile range) and as numeric and percentage for the categorical data. Quantitative variables were compared in the two groups via the Mann-Whitney U test (Z), while Kruskal-Wallis Test (X^2) was used for comparison of the three groups. ROC curve was used to determine best cutoff and sensitivity and specificity of serum midkine in predicting suspicious/malignant thyroid nodules. Results were evaluated in 95%confidence interval and P value < 0.05 was considered statistically significant.

3. RESULTS

A total of 100 cases with solitary thyroid nodule were enrolled in this study, their mean age was 38.38 ± 10.45 years, 68 of cases (68%) were women. Median TSH and median serum midkine were 2.50 (3.3) μIU/mL and 0.38 (0.57) ng/mL, respectively. There were statistical significant difference regarding serum midkine based on gender (Z=3.442, P=0.001) and age (X^2=6.056, P=0.014). However, no statistically significant difference based on TSH levels as well as thyroid status (P > 0.05) (Table 1).

Serum midkine level was found to be significantly higher in the patients with hypoechoic nodules than in patients with isoechoic and hyperechoic nodules (P= 0.024). While there was no significant difference on comparing hyperechoic to isoechoic nodules (P= 0.087) (Table 2).

Serum midkine level was found to be significantly higher in nodules with microcalcification compared to nodules with macrocalcification or without calcification (P = 0.011). There was no significant difference between serum medicine level for patients with nodules containing macrocalcification and no calcification (P = 0.071) (Table 2).

Serum midkine level was found to be higher in nodules with irregular borders compared to nodules with regular borders with statistical significant difference (P = 0.014); in nodules with absent halo compared to clear halo but with no statistical significant difference (P = 0.660). Also serum midkine was higher in tallest nodules with statistical significant difference (P = 0.011), and was higher in nodules with TIRADS 5 (P = 0.041) (Table 2).

According to cytopathology, 75 (75%) cases were with benign cytology and 25 (25%) cases with malignant/suspicious cytology. Serum midkine level was higher in malignant/suspicious nodules than in benign nodules with high statistical significant difference (P < 0.001) (Table 3) (Fig. 1).

Area under curve (AUC) in ROC curve was (AUC = 0.875, P < 0.001) on analysis of serum midkine in solitary thyroid nodules. A serum midkine cut-off value 0.68 ng/mL was found to have sensitivity 76% and specificity 86% in detecting malignant/suspicious nodules (Table 4) (Fig. 2).

4. DISCUSSION

Diagnosis of thyroid nodules has been facilitated by popularization of high-resolution US and whenever thyroid nodules are discovered clinically or incidentally, exclusion of malignancy gains importance. Fine needle aspiration cytology is still the most reliable and the most accurate and cost-effective method for preoperative evaluations [1,2]. However, its predictive value is still limited. Because it is invasive, the detection of malignancy depends in part on operator experience and may vary with respect to technical performance, nondiagnostic cytology rate is high, and also malignancy cannot be excluded in about 25% of thyroid nodules, possibly leading to unnecessary thyroid surgery [2,3] Due to this limitation, researches have focused on genetic (BRAF, RAS, and RET/PTC) and biological (galactine-3, HBME-1, and cytokeratin 19)markers that may aid in diagnosis and follow up [1,4,17].

Midkine is a heparin-binding growth factor that plays roles in growth, survival, inflammation/immunity, blood pressure, cellular proliferation, migration of cellular functions, angiogenesis, fibrinolysis, host defense and tissue protection, neurogenesis, and carcinogenesis [18-23]. It may enhance tumor invasion and therefore influence rates of survival [24-26].

Table 1. Demographic and clinical characteristics in relation to serum midkine concentrations

Demographic and clinical characteristics	Serum midkine	Z/X^2	P
Gender			
Female	0.32(0.37)	3.442[1]	0.001**
Male	0.72(1.02)		
Age (Years)			
<30	0.32(0.18)	6.056[2]	0.014*
30-45	0.44(0.57)		
>45	0.50(0.93)		
TSH (μIU/mL)			
< 0.4	0.32(0.26)	2.897[2]	0.235
0.4-4	0.39(0.41)		
> 4	0.55(1.05)		
Thyroid status			
Hypo-thyroidism (Manifest/Subclinical)	0.55(1.05)	2.897[2]	0.235
Eu-thyroidism	0.39(0.41)		
Hyper-thyroidism (Manifest/Subclinical)	0.32(0.26)		

*[1]; Mann-Whitney Test (Z), [2]; Kruskal-Wallis Test (X^2), **; High statistical significant*
**; Statistical significant*

Table 2. Sonographic features in relation to serum midkine concentrations

Sonographic features	Serum Midkine	Z/X^2	P
Nodular echogenicity			
Hypo-echoic	0.70(1.10)	5.089[2]	0.024
Hyper-echoic	0.36(0.67)		
Iso-echoic	0.34(0.29)[3]		
Calcifications			
Micro-calcification	0.59 (0.98)	8.943[2]	0.011*
Macro-calcification	0.44 (0.56)		
No Calcification	0.30 (0.37)[4]		
Border			
Regular	0.33 (0.37)	-2.451[1]	0.014*
Irregular	0.55 (0.85)		
Halo			
Present	0.36 (0.43)	-0.440[1]	0.660
Absent	0.41 (1.08)		
Width			
< 1cm	0.40 (0.40)	2.050[2]	0.359
1-2 cm	0.34 (0.77)		
> 2 cm	0.40 (0.86)		
Length			
< 1cm	0.32 (0.33)	8.943[2]	0.011*
1-2 cm	0.44 (0.87)		
> 2 cm	0.99 (1.24)		
TIRADS			
TIRADS 2	0.24 (0.45)	8.252[2]	0.041*
TIRADS 3	0.28 (0.15)		
TIRADS 4	0.34 (0.43)		
TIRADS 5	0.50 (0.79)		

[1]; Mann-Whitney Test (Z), [2]; Kruskal-Wallis Test (X^2), [3]; Statistical significant on comparing to hypoechoic nodules (Z=2.254, P=0.024), [4]; High Statistical significant on comparing to microcalcification (Z=2.885, P=0.004)
**; Statistical significant*
TIRADS; Thyroid Imaging Reporting and Data System

Table 3. Cytological features in relation to serum midkine concentrations

Cytopathology	Serum Midkine	Z	P
Benign Cytology	0.32 (0.28)	-5.596[1]	<0.001**
malignant/suspicious cytology	1.25 (0.98)		

*[1]; Mann-Whitney Test (Z), **; High statistical significant*

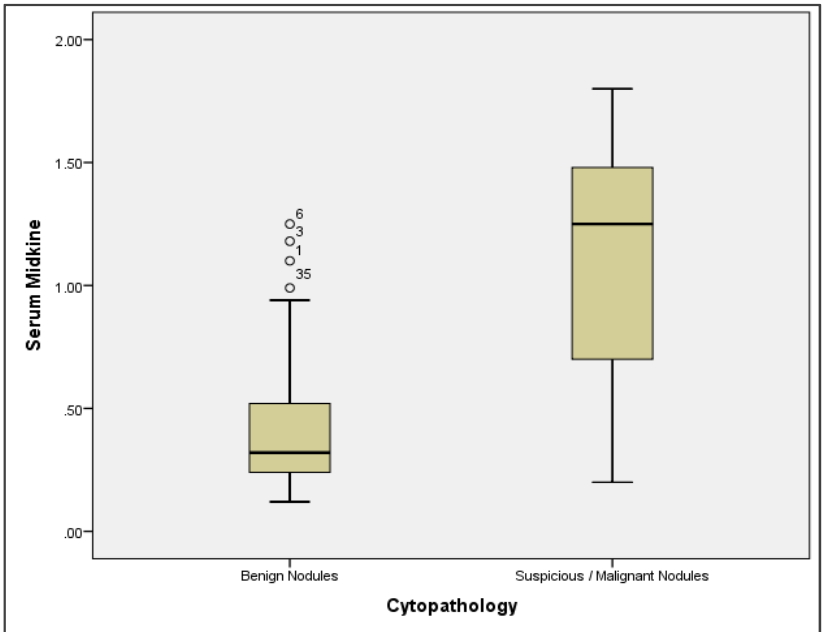

Fig. 1. Levels of serum midkine in benign and suspicious/malignant

Table 4. Area under Curve (AUC) and best cutoff value of Midkine to predict suspicious/ malignant thyroid nodules

AUC	Cut-off	Sensitivity	Specificity	95% CI	
				Lower bound	Upper bound
0.875	0.68 ng/mL	76%	86%	0.786	0.963

A limited number of previous studies indicated that midkine expression did not occur in normal thyroid tissue, but midkine expression is mainly derived from the tumor tissue of PTC patients [4,27]. In two different publications, midkine expression was found to be correlated with aggressive clinicopathological features of papillary thyroid carcinoma (PTC). They suggested that midkine could be a reliable biomarker for diagnosis and prognosis of PTC [4,25].

Midkine is frequently up-regulated in many types of cancer, including gastrointestinal, pancreatic, breast, and lung cancers, and melanoma [15]. In endocrine malignancies, increased midkine expression in the serum and cancer tissues of patients with PTC ranged from 70% to 90% of cases [4,24,25].

The aim of the current study was the evaluation of serum midkine levels in patients with thyroid nodules for a probable association of midkine levels and sonographic and histopathological features of thyroid nodules.

We found that serum midkine levels were significantly higher in patients who had nodules with the following sonographic features; hypoechoic nodules compared to isoechoic and hyperechoic nodules (P=0.024), nodules with microcalcification compared to nodules with macrocalcification or without calcification (P = 0.011), nodules with irregular borders compared to nodules with regular borders (P = 0.014) and nodules more than 2 cm in length than shorter ones (P = 0.011). Also, levels of serum medikine were significantly higher in suspicious/ malignant nodules than in benign nodules (P < 0.001).

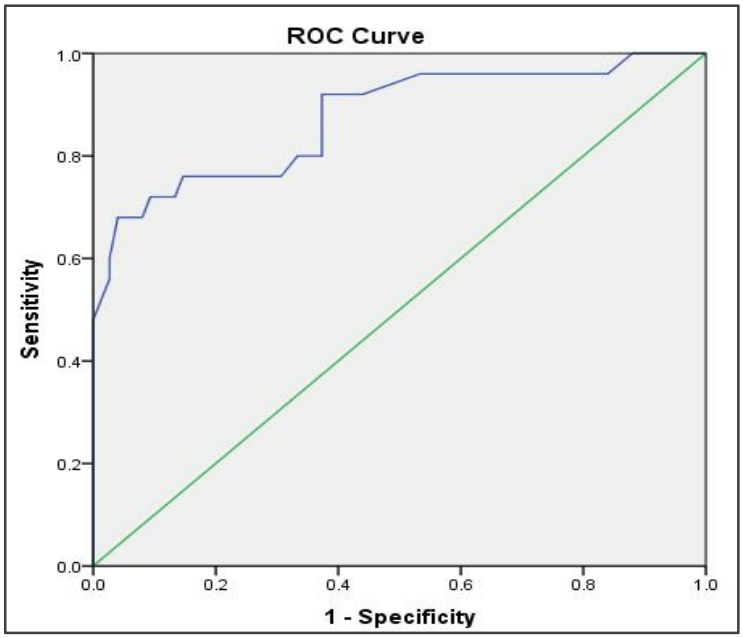

Fig. 2. ROC curve to determine sensitivity and specificity of serum midkine in predicting suspicious/malignant thyroid nodules

Our results were in agree with those of Kuzu et al. [28] who found that both serum midkine (SMK) and nodular midkine (NMK) levels were higher in malignancy/suspicious nodules compared with benign nodules. And, they found that SMK and NMK levels were higher among patients with suspicious ultrasound features for malignancy such as presence of microcalcification, irregular border, hypoechoic, hypoactive, and heterogeneous components, and absence of halo.

Also, Jee et al. [29] found that higher midkine concentrations in FNAB materials were obtained from PTC than the midkine concentrations found in patients with benign thyroid disease. And, Ikematsu et al. [24] have showed that SMK in patients with cancer was significantly higher than controls. They also found no difference between gender and age groups as well as any tumors stage and size and also demonstrated a decrease in SMK levels after surgery [4,24].

Moreover, another study showed that midkine immunohistochemistry could be adopted for differential diagnosis between PTC and multi nodular goiter, and for prediction of synchronous metastases [30]. Encouraged by the immunohistochemistry results, Jia et al. [31] performed a serum MK study, evaluating its role as a diagnostic and prognostic biomarker for differentiated thyroid cancer (DTC) [26]. They found better diagnostic capability of midkine than Tg to differentiate DTC from benign thyroid nodules before surgery. And, they demonstrate that midkine can potentially be used as a surrogate biomarker for the prediction of DTC metastases when Tg is not suitable to monitor the disease due to TgAb positivity.

Shao et al. [4] reported that strong midkine positivity and high expression scores were associated with clinicopathological features of PTC, e.g. extrathyroidal invasion, lymph node metastasis and tumor stages III/IV.

Similarly, Jee et al. [29] reported that metastatic PTC had more midkine concentrations than those without metastasis and argued that midkine may be beneficial both in the diagnosis and in the prognosis of malignant thyroid disease. No lymph node metastasis has been determined in our patients who had undergone surgery. Accordingly, we are not capable of commenting on the effect of midkine concentration on invasion and prognosis of malignant thyroid disease. Angiogenic and fibrinolytic activities of midkine may help to enhance the spread of cancer by creating an appropriate microenvironment [18,19]. Hence, midkine may yield a target molecule for antitumor drugs. Indeed, an oligonucleotide that blocks

midkine suppressed tumor formation in mice with rectal carcinoma and inhibited the angiogenesis in tumoral tissue [18]. Several studies have demonstrated that interference with midkine activity yields promising experimental results in chemotherapy for various cancers [19,27,32,33].

Midkine expression is regulated by retinoic acid in the gestational period, whereas its expression in malignancies is regulated by hypoxia, cortisol, growth factors, and cytokines [15]. Zhang et al. [30] suggested that midkine expression was associated with nuclear factor-kappa B (NF-κB).

Recently, midkine expression has been identified more frequently in PTCs with BRAFV600E mutation than in PTCs with the BRAF wild type [24]. Also, Choi et al. found that a BRAFV600E mutation induced up-regulation of midkine expression in isolated primary thyrocytes, which was diminished by the BRAF-specific inhibitor PLX4032.

These data clearly suggest that BRAF activation can induce midkine expression in thyrocytes and that the up-regulation of midkine expression in PTCs might be due to activation of the BRAF oncogene [34].

In many types of malignancies, midkine expression increases with advancing tumor stage and is strongly correlated with a poor prognosis [11,14]. Increased midkine expression has been associated with extrathyroidal extension, tumor stage, and lymph node metastases [24]. Metastasis is a multistep process that includes tumor cell invasion, migration, survival in a foreign environment, and colonization at a distant site. Although the function of midkine, particularly in the metastasis of PTCs, has not yet been fully elucidated, this cytokine may be involved in these multistep by enhancing the migration and survival of PTC cells through autocrine and paracrine signaling. The cell migration–promoting activity of midkine has been demonstrated in several types of cells, such as neutrophils, neural cells, macrophages, smooth muscle cells, and osteoblasts [15].

In some precancerous lesions, SMK levels have been found to be increased [27]. Overall, midkine expression is closely related with progression of tumor stage and poor prognosis such as neuroblastomas, glioblastomas, and bladder carcinomas [25]. If tumor tissues increase secretion of midkine, it becomes evident in serum. Some publications suggest that SMK levels have been increased in some precancerous lesion [27]. The expression of midkine gene in human tumor cells may reflect tumor formation and give clues to the biological behavior of neoplasms. Hence, the expression of midkine may serve as a tumor marker for diagnosis and follow-up. From another point of view, blockade or knockdown of midkine can constitute an effective option for cancer therapy [27].

In addition to DTC, studies indicate that midkine can outperform several currently used blood tumor specific biomarkers, such as alpha fetoprotein (AFP) for hepatocellular carcinoma (HC) [35,36], carcinoembryonic antigen for colorectal cancer [37], carcinoembryonic antigen and cytokeratin 19 fragments for esophageal squamous cell carcinoma [38].

As pointed out by Jones [6], there are several barriers to overcome before midkine can be approved in standard clinical practice. First, larger prospective clinical studies to measure patient outcomes are required to confirm the value of midkine, which will allow clinicians to make a better clinical decision leading to a meaningful outcome. Second, elevation of serum midkine is not specific to a particular oncology type. We believe the strategy to overcome this limitation is to measure midkine in conjunction with other known and specific biomarkers. Finally, another important limitation of the study is that midkine have been analyzed in patients with PTC after thyroidectomy just before ablation therapy, that is, when they were in a hypothyroid condition. It is unknown about the effect of thyroid hormone on midkine levels. It is also unknown how midkine performs as a tumor marker in PTC patients when they are treated with thyroid hormone or in patients with follicular thyroid cancer. All these issues will be taken into consideration in our future researching agenda.

5. CONCLUSION

Serum midkine can predict malignancy in solitary thyroid nodule and also well correlated with sonographic features of thyroid nodules. We suggest that midkine levels may serve as a novel biochemarker in association with sonographic features in evaluation of solitary thyroid nodules. To guide clinical practice, further prospective trials with larger numbers of patients and long term follow-up are warranted to evaluate the actual diagnostic, prognostic, and therapeutic potentials of midkine.

CONSENT AND ETHICAL APPROVAL

This study was approved by the local Institutional Review Board and written informed consent was obtained from every patient included in the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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