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Association between Levels of Serum Midkine with Insulin Resistance as New Potential Diagnostic Marker for Thyroid Cancer in its Early Stages

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Abstract

Background and aim: Thyroid cancer is the most frequent endocrine cancer on the world. This malignancy accounts for 1.3 percent of all cancers and accounts for roughly 0.5 percent of cancer-related deaths worldwide each year. Midkine are implicated in the spread of cancer and orchestrate development, cell survival, neural expansion, and inflammation. Its expression is confined to the kidney, lung, thyroid, and small intestine in healthy adult tissue. In this study, we aimed to evaluate the Serum Midkine in patients with newly diagnosed thyroid cancer, and to identify any correlation with biochemical parameters studied.

Materials and methods: A case-control study design involved 120 Iraqi subjects, 60 of whom had thyroid cancer (48 females and 12 males) to compare the results with 60 healthy adults (50 females and 10 males) whose ages were close to the group of patients ranging from (27-60) years. All subjects' serum levels of Midkine, as well as metabolic indices such as BMI, WHR, (TT3, TT4, TSH), FSG, HOMA-IR, Insulin, QUICKI, C, TG, HDL-C, VLDL-C, LDL-C, and zinc, were measured. The findings were subjected to statistical analysis in order to analyze the differences between the gr5oups tested and to determine the relationship between parameters studied.

Results: According to the statistical analysis, there was no significant difference in mean age between the patients and the control groups. Serum MDK was significantly elevated in thyroid cancer group compared to healthy control groups (202.1 ± 47.4 versus 149.6 ± 41.0 ng/mL, P=0.003), respectively. Serum BMI, TSH, FSG, insulin, HOMA-IR, TC and TG level for thyroid cancer group was significantly higher than healthy control group. However, as compared to the control group, the mean levels of HDL-C, Zinc and QUICKI shown a significant decreased in thyroid cancer group.

No significant association was found between Midkine and either biochemical parameters studied, except BMI, TSH, insulin and HOMA-IR have a significant positive correlation with Midkine level.

Conclusion: The current investigation found that thyroid cancer patients had considerably higher levels of Midkine than the control group. These results suggest that Midkine may act as a biochemical marker for the early detection and diagnosis of the thyroid cancer.

Keywords: Lipid profile • Midkine • Thyroid cancer • HOMA-IR • QUICKI • Zinc

Introduction

Thyroid cancer is the most frequent endocrine cancer on the planet. This malignancy accounts for 1.3 percent of all cancers and accounts for roughly 0.5 percent of cancer-related deaths worldwide each year. Although differentiated thyroid carcinoma has a low mortality rate, it has a high rate of relapse or persistence, which leads to higher morbidity [1].

Thyroid cancer incidence has increased dramatically worldwide in recent decades [2]. It's unclear if the rise in thyroid cancer is due to greater use of thyroid sonography and sono-guided fine needle aspiration cytology examinations, or if it's due to an actual increase in thyroid cancer caused by an unknown cause. Large tumors have also become more common. Furthermore, despite earlier detection and better treatment, thyroid cancer-related mortality has increased [3]. As a result, variables other than early diagnosis may play a role. Past childhood radiation to the head and neck, family history of thyroid cancer, ionizing radiation exposure [4], and inadequate or excessive iodine consumption are all risk factors for thyroid cancer, which are well-known, but none of them can account for an increase in thyroid cancer cases [5]. Other variables, such as diabetes, obesity, and metabolic syndrome, have been identified [6,7], thyroid cancer has been linked to insulin resistance, chemical toxins and dietary variables [8-12].

Tumor cells, in particular, require a high fatty acid turnover rate to meet the tumor's energetic and synthetic needs [13]. Obesity, as a result, insulin resistance has increased in recent decades, in a similar trend to thyroid cancer [14]. Thyroid hormones affect trace element metabolism, particularly zinc metabolism [15]. In addition, abnormalities in these elements have been linked to goiter and other thyroid diseases, including cancer [16].

The thyroid gland has a higher concentration of trace elements than other tissues, and it has been demonstrated that thyroid hormones influence the metabolism of these elements changes in these components have also been linked to the development of goiter and other thyroid diseases, such as cancer [17]. After removal of the malignant thyroid tissue, Zn serum levels increased dramatically (when compared to pre-operative levels) (p 0.001) [18]. The activity of the enzyme superoxide dismutase (SOD) was dependent on Zn. Changes in this enzyme's activity correspond to changes in Zn serum levels [19].

Midkine (MDK), also known as neurite growth-promoting factor 2 (NEGF2), is a basic heparin-binding growth factor of low molecular weight 13-kDa. MDK was first identified as the Midkine gene product, whose expression increases at early stages of the retinoic acid–induced differentiation of murine to carcinoma stem cells and also in the mid-gestation period of mouse embryogenesis, especially within the kidneys, as a result, the denotation (midgestation, kidney) [20]. It is a highly conserved protein that shares 87 percent of its sequence with mouse Midkine and comprises a family of heparin-binding growth factors with pleiotrophin [21]. Expression of the MDK gene in human adult tissues is extremely low and restricted. Mounting evidence has indicated that MDK plays a significant role in carcinogenesis related activities, such as proliferation, migration, antiapoptosis, mitogenesis, transformation, and angiogenesis, in

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many types of solid tumors [21,22].

Also it was implicated in the spread of cancer and orchestrates development, cell survival, neural expansion, and inflammation. Its expression is confined to the kidney, lung, thyroid, and small intestine in healthy adult tissue [23]. However, the diagnostic value of serum MDK for thyroid cancer, particularly for those at the early stage, has not yet been investigated in Iraq.

In this study we aimed to evaluate the Serum Midkine in patients with newly diagnosed thyroid cancer.

Materials and Methods

Subjects and study design

All studies were conducted with approvals from the regional ethical committee of University of Kufa, Faculty of Science. Informed consent forms were obtained from each participant before beginning the research. This study was designed as a case control study as two different groups included 120 subjects, 60 thyroid cancer patients (48 females and 12 males), ranging in age from 20 to 60 years. Patients were registered in "Diwaniya Teaching Hospital" in Al-Qadisiyah, Iraq, throughout the period from January 2020 to September 2021. To compare the results, 60 healthy adults were included as a control group. Their ages ranged from 20 to 60 years, similar to the patients' (50 females and 10 males).

Exclusion criteria

Subjects suffered from chronic diseases like diabetes mellitus, cardiovascular diseases, systemic sickness, chronic kidney disease, and smokers were excluded in this study.

Collection of samples

Five milliliters of venous blood were taken from cancer thyroid patients and a healthy group between 8:30 AM and 10:00 AM using antecubital venipuncture using G 23 needles after an 8-12 hour fast. At room temperature, 5 ml of blood was allowed to coagulate in a test tube. After centrifugation at (3000 × g) for 15 minutes, the serum was divided into four tubes and kept at -20°C until analysis.

Anthropometric evaluation

The Body Mass Index was assessment by dividing weight in kilograms by length of individual in square meter: BMI=(weight in kg)/ (height in meters).

Biochemical evaluation

Serum Thyroid-Stimulating Hormone (TSH), Total Triiodothyronine (TT3), and Total Thyroxine (TT4) levels were measured by using ELISA micro plate washer and reader, which is a compact immunoassay system based on the Enzyme Linked Immunosorbent Assay (ELISA) principles, and a commercial kit from CORTEZ (USA). The concentrations of fasting serum glucose, total cholesterol, High Density Lipoprotein Cholesterol (HDL-C), and triglyceride were measured by colorimetric method for quantitative in vitro diagnostic measurement using a commercial kit from LiNEAR (SPAIN). Low Density Lipoprotein Cholesterol (LDL-C) levels were calculated by Fried Ewald's formula [24]. Serum zinc concentration was measured by using Spectrophotometer advice at (578 nm) using a commercial kit from LTA (Italia). Fasting insulin levels were measured by immunoenzymometric assay (TYPE 3) with a commercial kit from Monobind Inc. (USA). Enzyme-linked immunosorbent assay kits (MELSIN, China) measured Serum Midkine, Insulin resistance was calculated by using homeostasis model assessment (HOMA-IR) score that employs the formula: fasting insulin concentration (μIU/L) glucose (mmoL/L)/22.5. Individuals with HOMA-IR>2.7 were accepted as insulin resistant. QUICKI values (quantitative insulin sensitivity check index) was estimated by equation: QUICKI=1/ log(I0)+log(G0), where I0 is the fasting insulin (μIU/ml), and G0 is the fasting glucose (mg/dL) [25,26].

Bio-statistical analysis

Microsoft Excel 2010 and SPSS-24 (Statistical Package For Social Science-Version 24) software were used to conduct the statistical analysis. The data were subjected to statistical analysis, with the t-test being used to examine the differences between the analyzed groups. Pearson's correlation coefficient was employed to assess the correlation between parameters.

Results

Table 1 show the mean of age has no significant difference between patients group compared with control group. Nevertheless, found the mean of BMI, TSH, FSG, and insulin, HOMA-IR, TC, TG and Midkine levels a significant increase in thyroid cancer group when compared with control group. While, means of serum Zinc, QUICKI, and HDL-C levels in patients group have a significant decrease compared with control group.

Table 1. Demographic and clinical characteristics for thyroid cancer patients and control groups.

Parameters	Groups		P Value
	Control	Thyroid cancer	
	Mean ± SD	Mean ± SD	
	(n=30)	(n=60)	
Age (year)	42.03 ± 7.17	43.0 ± 7.20	0.148
SBP (Hmmg)	120.12 ± 9.05	130.13 ± 12.05	0.01
DBP (Hmmg)	76.01 ± 0.38	78.70 ± 2.38	0.054
BMI (Kg/m2)	24.3 ± 2.0	28.2 ± 3.8	0
W/H	0.82 ± 0.19	0.88 ± 0.22	0.054
TT3 (ng/mL)	1.92 ± 0.33	2.14 ± 0.93	0.53
TT4 (ng/mL)	73.3 ± 12.5	88.0 ± 36.2	0.108
TSH (μIU/mL)	2.30 ± 0.81	5.56 ± 1.73	0.022
FSG (mg/dL)	82.5 ± 6.38	104.3 ± 28.2	0.05
Insulin (μU/mL)	3.92 ± 1.34	12.1 ± 3.46	0
HOMA-IR	0.80 ± 0.28	3.22 ± 1.54	0
QUICKI	0.47 ± 0.04	0.30 ± 0.01	0
T-CHO (mg/dL)	112.0 ± 12.3	133.6 ± 17.5	0.011
TG (mg/dL)	94.1 ± 10.7	102.5 ± 9.8	0.049
HDL-C (mg/dL)	43.9 ± 8.92	30.9 ± 10.8	0.022

VLDL-C (mg/dL)	20.4 ± 7.94	24.5 ± 9.32	0.253
LDL-C (mg/dL)	59.2 ± 18.5	64.3 ± 30.8	0.052
Zinc (µg/dL)	115.4 ± 8.55	90.5 ± 10.0	0.01
Midkine (ng/mL)	149.6 ± 51.0	202.1 ± 47.4	0.003

Significance: A p-value of ≤ .05 was considered significant, Data represented as Mean ± SD, SD: Stander Deviation, n: Number of subjects, BMI: Body Mass Index, W/H: Waist to Hip Ratio, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, TT3: Total Thyroxine, TT3: Total Triiodothyronine, TSH: Thyroid-Stimulating Hormone, FSG: Fasting Serum Glucose, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, T-CHO: Total Cholesterol, TG: Triglyceride, HDL-C: High Density Lipoprotein-Cholesterol, LDL-C: Low Density Lipoprotein-Cholesterol, VLDL-C: Very Low Density Lipoprotein-Cholesterol.

The linear regression analysis shown in Table 2, the correlation between Serum Midkine and other biochemical studied in patients with thyroid cancer. No significant correlation was noticed between MDK and either biochemical parameters studied, except BMI, TSH, insulin and HOMA-IR have a significant positive correlation with Midkine level shown in Figure 1.

Table 2. Correlation between levels of serum midkine and others biochemical studied in thyroid cancer patients group.

Parameters	Midkine (ng/mL)	
Age (year)	r	-0.110
	P-value	0.56
BMI (kg/m2)	r	0.001
	P-value	0.99
W/H	r	0.078
	P-value	0.68
TT3 (ng/mL)	r	0.072
	P-value	0.70
TT4 (ng/mL)	r	0.123
	P-value	0.51
TSH (µIU/mL)	r	0.004
	P-value	0.984
FSG (mg/dL)	r	0.239
	P-value	0.36
Insulin (µU/mL)	r	0.028
	P-value	0.88
HOMA-IR	r	0. 05
	P-value	0.050
QUICKI	r	-0.127
	P-value	0.50
TC (mg/dL)	r	0.113
	P-value	0.55
TG (mg/dL)	r	0.207
	P-value	0.47
HDL-C (mg/dL)	r	-0.072
	P-value	0.70
VLDL-C (mg/dL)	r	0.090
	P-value	0.63
LDL-C(mg/dL)	r	0.129
	P-value	0.49
Zinc (µg/dL)	r	-0.162
	P-value	0.39

Significance: P-value of ≤ .05 was considered significant, r: Person's correlation, BMI: Body Mass Index, W/H: Waist to Hip Ratio, TT3: Total Thyroxine, TT3: Total Triiodothyronine, TSH: Thyroid-Stimulating Hormone. FSG: Fasting Serum Glucose, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, TC: Total Cholesterol, TG: Triglyceride, HDL-C: High-Density Lipoprotein-Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, VLDL.C: Very Low Density Lipoprotein-Cholesterol.

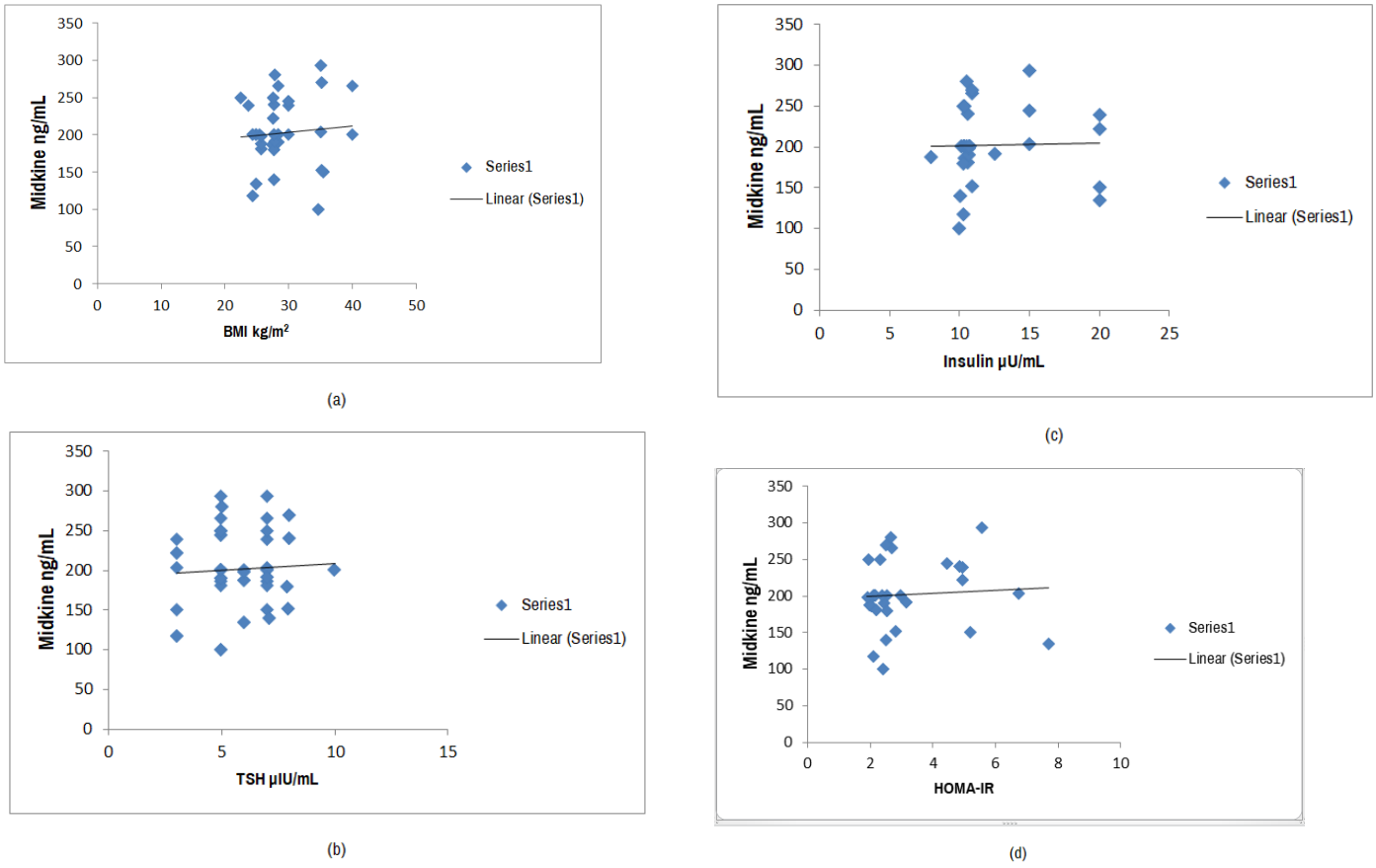

Figure 1. Correlation between Serum Midkine and (a) BMI, (b) TSH, (c) Insulin and (d) HOMA-IR in thyroid cancer patients group.

Discussion

The present study showed increased level of the novel adipocytokines (Midkine) in thyroid cancer group. Diagnosis of thyroid cancer has been facilitated by popularization of high-resolution US and whenever thyroid nodules are discovered clinically or incidentally, exclusion of malignancy gains importance [27]. 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, non-diagnostic cytology rate is high, and also malignancy cannot be excluded in about 25% of thyroid nodules, possibly leading to unnecessary thyroid surgery [28]. Due to this limitation, researches have focused on genetic and markers that may aid in diagnosis and follow up [29].

The ratio of patients with increased Serum MK levels to total cancer patients examined agreed with that of patients with increased MK expression in tumor tissues reported previously [30,31]. Thus, MK expressed in carcinomatous tissues is probably secreted into the bloodstream, leading to an increase in serum MK level in cancer patients. It is notable that the increased expression of MK in carcinomatous tissues and the elevated serum MK levels in cancer patients did not show specification for a particular tissue. This is reminiscent of the case of p53 mutations in human carcinomas, suggesting the biological importance of MK in carcinogenesis. The role of MK in carcinogenesis and/or tumor progression, as indicated by its transforming activities is consistent with this assumption [32,33]. 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 .It may enhance tumor invasion and therefore influence rates of survival [34].

The results of present study are close to those reported and the study involved three independent cohorts with a total of 933 participants including 388 HCC cases and 545 different controls enrolled from different medical centers [35]. Results showed that MDK levels were significantly elevated in HCC tissues as well as serum samples; serum MDK at the cutoff value of 0.654 ng/mL for HCC diagnosis showed an obviously higher sensitivity compared with AFP (86.9% versus 51.9%) with similar specificities (83.9% versus 86.3%); even in very early-stage HCC, the sensitivity of MDK was significant higher than AFP (80% versus 40%); in those AFP-negative HCC cases, the sensitivity could reach as high as 89.2%; and serum MDK level was significantly decreased in HCC patients after curative resection and elevated when tumor relapsed.

Midkine is frequently up-regulated in many types of cancer, including gastrointestinal, pancreatic, breast, and lung cancers, and melanoma [36]. MDK has been shown to have anti-apoptotic activity to embryonic and to Wilms' tumor cells also promotes migration of various cells such as embryonic neurons neutrophils and macrophages [37]. These two activities of MK might be helpful in survival and invasion of tumor cells.

The results of present study were in agree with those of Kuzu, who found that both Serum Midkine (SMK) and Nodular Midkine (NMK) levels were higher in malignancy/suspicious nodules compared with benign nodules. They found that SMDK and NMDK levels were higher among patients with suspicious ultrasound features for malignancy [38].

According to another study, there was a significant difference in MDK levels, with thyroid nodule contour being higher in thyroid nodules with irregular contour than thyroid nodules with regular contour (P=0.001) and calcification being higher in microcalcification than macrocalcification (P=0.006) [39]. Between papillary cancer and follicular carcinoma, there was a statistically significant difference in MK levels (P=0.001).

Similarly, the Serum Midkine levels were considerably higher in patients with nodules that showed the following sonographic characteristics: In addition, Serum Medikine levels in suspicious/malignant nodules were substantially greater than in benign nodules (P 0.001) [40].

Infiltrating macrophages were the predominant source of Midkine in the

neointima of atherosclerotic arteries, and those Midkine directly stimulates smooth muscle cell migration from the media to the intima, using an in-stent restenosis model of hypercholesterolemic rabbits. This highlights the functional link between Midkine knockdown and reduced inflammatory cell recruitment, particularly of innate immune cells. In the process of (neo) angiogenesis, monocytes are known to operate as permissive cells with the formation of collateral arteries and capillary sprouting. When monocytes are activated, they emit angiogenic cytokines and growth factors, such as MCP-1, TNF-, bFGF, and MMPs, to mention a few [41].

Conclusion

The current investigation found that thyroid cancer patients have considerably higher levels of Midkine than the control group. These results suggest that Midkine levels in thyroid cancer patients may be as a predictor marker against thyroid cancer complications. Further studies with larger population are needed to justify its performance in clinical search.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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