Observational Study

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Evaluation of serum insulin-like growth factor 1 and its significance in thyroid cancer

An observational study

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Abstract

Serum insulin-like growth factor 1 (IGF-1) is elevated in different cancers. However, relationships between serum IGF-1 and thyroid cancer (TC) are scarce. The present study aimed to investigate the clinical significance of serum IGF-1 in TC.

Serum was collected from 124 TC patients, 50 patients with benign nodules, and 50 healthy controls. Serum IGF-1 levels were measured and compared. Relationships were investigated between IGF-1 and clinical characteristics. A receiver operating characteristic (ROC) curve was plotted to explore the diagnostic value of IGF-1 in TC.

Serum IGF-1 levels were significantly higher in TC than that of healthy controls and benign nodules ($P = .003$; $P < .001$). Serum IGF-1 levels were higher in TC patients with advanced stage than early stage ($P = .029$). Higher serum IGF-1 levels were found in patients with lymph node metastasis present and (tumor size >1 cm) than that of patients without lymph node metastasis ($P = .018$) and (tumor size ≤ 1 cm) ($P = .031$). Serum IGF-1 levels were higher in patients with a solitary nodule than multinodular nodules ($P = .043$). The serum IGF-1 cutoff value for a TC diagnosis was 216 ng/mL with a sensitivity of 53.2%, a specificity of 74.0%, a positive predictive value (PPV) of 83.5%, and an area under the curve was of 0.71.

Serum IGF-1 was significantly correlated with tumor stage, size, and lymph node metastasis. Serum IGF-1 shows great potential as a laboratory marker for TC.

Abbreviations: AUC = the area under the curve, FNA = fine-needle aspiration, IGF-1 = insulin-like growth factor 1, NPV = the negative predictive value, PPV = the positive predictive value, ROC = receiver operating characteristic, TC = thyroid cancer.

Keywords: clinical significance, insulin-like growth factor-1, thyroid cancer

1. Introduction

Thyroid cancer (TC) is the most common endocrine tumor with the fastest increasing incidence.[1] Both insulin resistance and environmental changes have increased TC greatly.[2,3] Histologically, papillary thyroid cancer (PTC) is the most common TC, accounting for about 85% of all TC diagnoses.[4]

Ultrasound examinations are widely used to identify TC nodules in the neck, but it is heavily dependent on the technique and clinical experience of the operator.[5] Subsequent to a suspicious ultrasound, fine-needle aspiration (FNA) followed by cytological examination is the gold standard for identifying the nodule type (benign, malignant).[6] However, 15% to 30% of thyroid nodules evaluated using FNA are not clearly benign or malignant.[7] In addition, a negative predictive value and high cost are the main weaknesses of FNA.[8] Although biomarkers for TC have been investigated for >50 years,[9] serum biomarkers for TC diagnosis are still lacked.[10] Therefore, the search for non-invasive biomarkers for TC is urgently needed.

Insulin-like growth factor-1 (IGF-1) is a polypeptide that induces mitosis, prevents apoptosis, and increases cell migration in cancer.[11,12] Serum IGF-1 levels are significantly elevated in certain cancers, such as breast, lung, and colorectal.[13–15] IGF-1 plays a critical role in TC development.[16] However, the relationship between serum IGF-1 and TC has not been reported yet. The present study aimed to investigate the clinical significance of serum IGF-1 in TC.

2. Materials and methods

2.1. Subjects

One-hundred and twenty-four patients with untreated TC (40 men, 84 women; age 42 ± 12 years) were identified by the Department of Endocrine and Breast Surgery at the First Affiliated Hospital of Chongqing Medical University, China. Serum was collected from the TC patients, 50 patients (17 men, 33 women; age 48 ± 13 years) with benign thyroid nodules, and

Editor: Parag Parekh.

This study was supported by a grant from the National Nature Science Foundation of China (No. 81972011), the Chongqing Health Commission (No. 2021MSXM095, 2020MSXM009).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Hou YL, Chen JJ, Zhang X, Chen H. Evaluation of serum insulin-like growth factor 1 and its significance in thyroid cancer: an observational study. Medicine 2021;100:21(e26165).

Received: 28 November 2020 / Received in final form: 21 February 2021 / Accepted: 10 May 2021

http://dx.doi.org/10.1097/MD.0000000000026165

50 controls (20 men, 30 women; age 45 ± 11 years). The TC diagnosis was confirmed by histopathologic examination of the surgically resected tissue. The identified patients and controls provided written consent to participate in the study and the protocol was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Tumor staging was evaluated according to the 6th edition of the International Union Against Cancer: Tumor–Node–Metastasis Classification for Malignant Tumors.[17]

2.2. Sample collection

Venous blood (2.0 mL) was collected from each subject into tubes without anticoagulant. The serum was separated by centrifugation at 2000 × *g* for 10 minutes, and samples were stored at −80° C until use.

2.3. Serum IGF-1 measurement

Serum IGF-1 levels were measured using chemiluminescence immunoassay (Immulite 1000, Siemens Healthcare Diagnostics Inc., Germany). The intermediate precision for the IGF-1 assay was 2.0%, and the measuring range was from 20 to 100,000 ng/mL.

2.4. Statistical analysis

The normality of data was checked by the Kolmogorov–Smirnov test and the data were not normally distributed. Serum IGF-1 levels were summarized as the median (interquartile range). Results were compared between groups using the Mann–Whitney *U* test. A receiver operating characteristic (ROC) curve was plotted to determine the area under the curve (AUC), sensitivity, and specificity of serum IGF-1 for TC. Statistical analysis was performed using SPSS 13.0 software (SPSS, Inc.; Chicago, IL), and $P < .05$ represented a statistically significant result.

3. Results

3.1. Patient characteristics

The clinical characteristics of TC patients are summarized in Table 1. Forty patients were men (32.3%) and 84 were women (67.7%). According to the TNM clinical stage, 87 patients (72.5%) were in early stage (I, II) and 33 patients (27.5%) were in advanced stage (III, IV). There were 30 patients who had lymph node metastasis (39.5%) and 46 were without metastasis (60.5%).

3.2. Serum IGF-1 levels in TC

Serum IGF-1 levels in TC patients, healthy controls, and benign thyroid disease were 228 (180, 305), 185 (150, 212), and 154 (128, 195) ng/mL, respectively. Further analysis indicated that serum IGF-1 levels were higher in TC than that of healthy controls ($Z = -2.984$, $P = .003$) and benign thyroid disease ($Z = -3.637$, $P < .001$). However, no significance in serum IGF-1 levels was found between benign thyroid disease and healthy controls ($P > .05$), as shown in Fig. 1.

3.3. Relationship between serum IGF-1 and TC clinical characteristics

Serum IGF-1 levels in patients with advanced stage (III, IV) and patients with early stage (I, II) were 279 (185, 413) and 224 (178, 265) ng/mL, respectively. Further analysis showed that serum IGF-1 levels were higher in advanced stages than early stages ($Z = -2.186$, $P = .029$) (Fig. 2A). Serum IGF-1 levels in patients with lymph node metastasis and patients without lymph node metastasis were 263 (199, 327) and 208 (126, 264) ng/mL, respectively. Interestingly, patients with lymph node metastasis had elevated serum IGF-1 compared with patients without lymph node metastasis ($Z = -2.356$, $P = .018$) (Fig. 2B). Serum IGF-1 levels in patients with tumors >1 cm and <1 cm were 235 (194, 324) and 192 (170, 242) ng/mL, respectively. Further analysis indicated that patients with a tumor size >1 cm had higher serum IGF-1 than patients with a smaller tumor size ($Z = -2.160$, $P = .031$) (Fig. 2C). Serum IGF-1 levels in patients with a solitary nodule and multinodular nodules were 235 (181, 319) and 210 (155, 243) ng/mL, respectively. Interestingly, serum IGF-1 in patients with a solitary nodule was higher than in patients with multinodular nodules ($Z = -2.024$, $P = .043$) (Fig. 2D).

Table 1

Clinical characteristics of TC patients.

	n (%)
Sex	
Male	40 (32.3)
Female	84 (67.7)
Tumor size, cm*	
>1	68 (68.8)
≤1	34 (31.2)
Lymph node metastasis*	
Absent	46 (60.5)
Present	30 (39.5)
Tumor stages*	
Early stage (I+II)	87 (72.5)
Advanced stages (III+IV)	33 (27.5)
Multifocal tumor*	
No	88 (75.9)
Yes	28 (24.1)

TC = thyroid cancer.
* Some data missed.

3.4. Diagnostic efficacy of serum IGF-1 for TC

The ROC curve for serum IGF-1 in TC had an AUC of 0.71 (95% CI: 0.62–0.79). Youden index was calculated to set an optimum

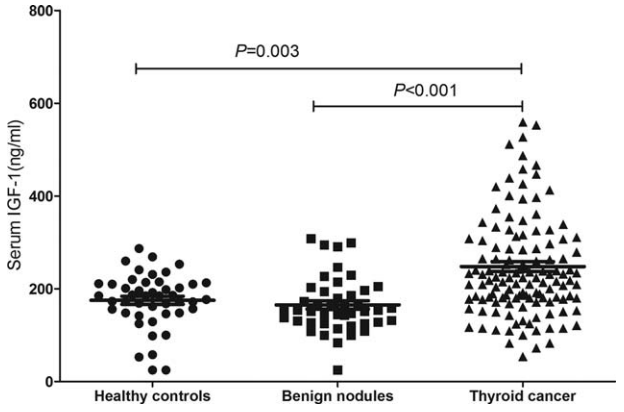

Figure 1. Serum IGF-1 among different groups. IGF-1 = insulin-like growth factor 1.

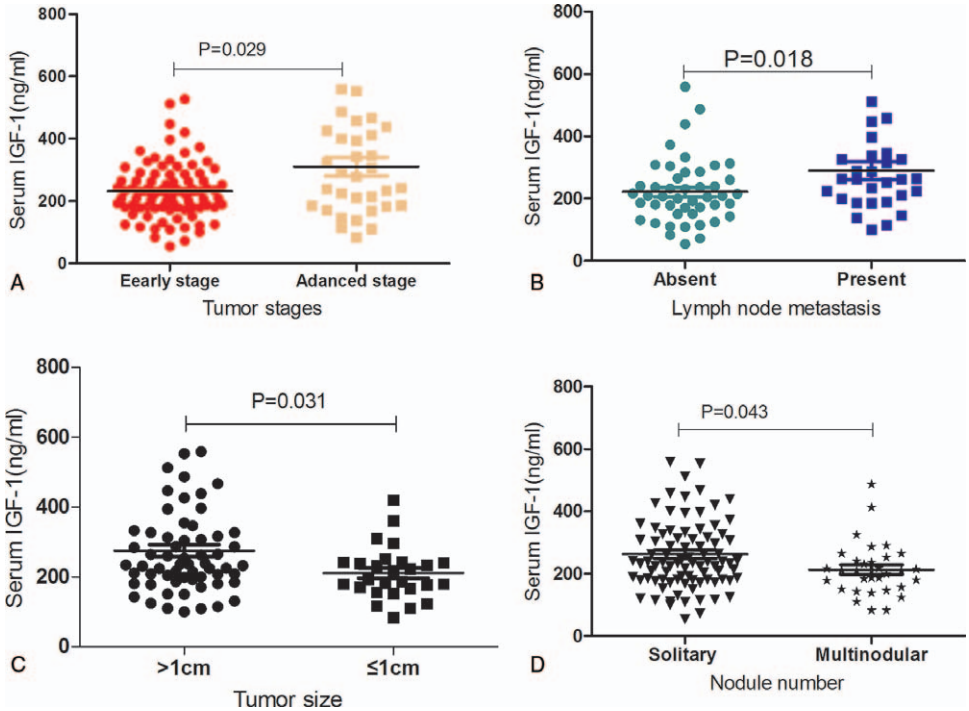

Figure 2. Relationships between serum IGF-1 and TC clinical characteristics. IGF-1 = insulin-like growth factor 1, TC = thyroid cancer.

cutoff value of 216 ng/mL with a sensitivity of 53.2%, a specificity of 74.0%, and a PPV of 83.5%. In addition, the diagnostic properties of serum IGF-1 and the FNA test or ultrasound for TC were also summarized and compared. The results indicated that FNA test had better diagnostic efficacy than serum IGF-1 ($P < .001$), no significance in PPV and NPV was found between serum IGF-1 and ultrasound examinations for TC diagnosis ($P > .05$). It was shown in Table 2.

4. Discussion

The present study indicated that serum IGF-1 levels were higher in TC patients than patients with benign nodules or healthy controls. Previous studies reported that higher serum IGF-1 is related to future risk of cancer.[18] Tang et al[19] reported that IGF-1 expression was positive in lung cancer tissues. Shen et al[20] found serum IGF-1 levels to be higher in gastric cancer patients than controls, and serum IGF-1 might be a biomarker for gastric cancer. Dzierska et al[21] also reported higher serum IGF-1 levels in gastric cancer patients than controls. Although Starzyńska et al[22] reported that IGF from bone marrow-derived stem/progenitor cells were not elevated in patients with pancreatic cancer, serum IGF-1 was significantly higher in pancreatic cancer than chronic pancreatitis.[23] Zheng et al,[24] also reported that IGF-1 promotes metastasis of pancreatic cancer. IGF-1 also plays a critical role in TC development.[25] Liu et al[26] reported overexpression of IGF-1 in TC tissue compared with normal thyroid tissue. Pazaitou-Panayiotou et al[27] found that serum IGF-1 was higher in female TC patients than controls. These results are similar to ours. Thus, IGF-1 might play a critical role in TC development.

An ideal biomarker is expected to correlate with clinical characteristics. Our study indicated that serum IGF-1 correlated closely with TC tumor stage, lymph node metastasis, tumor size, and nodule number. Previous studies reported that serum IGF-1 correlated closely with clinical characteristics of colorectal cancer, including tumor size, metastasis, and tumor stage.[28] In addition, IGF-1 expression correlated closely with clinical stage, tumor grade, and disease recurrence in bladder cancer.[29] Pazaitou-Panayiotou et al[27] reported a trend in that intra-thyroidal invasion appeared in TC patients with higher IGF-1 levels. The results of our study were in accordance with the literature and showed IGF-1 to be associated with clinical tumor characteristics. It is generally believed that multinodular nodules

Table 2

Diagnostic properties of FNA test and serum IGF-1 for TC.

Diagnostic property	FNA test	Ultrasound	Serum IGF-1	P1	P2
Sensitivity	96.1% (120/124)	70.2% (87/124)	53.2% (66/124)	<0.001	0.009
Specificity	100% (50/50)	36.0% (18/50)	74.0% (37/50)	<0.001	<0.001
PPV	100% (120/120)	73.1% (87/119)	83.5% (66/79)	<0.001	0.123
NPV	92.5% (50/50+4)	32.7% (18/55)	38.9% (37/95)	<0.001	0.558

FNA = fine-needle aspiration, NPV = the negative predictive value, P1 = diagnostic properties compared between serum IGF-1 and FNA test, P2 = diagnostic properties compared between serum IGF-1 and Ultrasound, PPV = the positive predictive value.

are associated with a lower risk of malignancy than solitary nodules.[30] The present study indicated that serum IGF-1 levels were significantly higher in patients with a solitary nodule than patients with multinodular nodules. These results indicate that serum IGF-1 and nodule number could be combined for TC diagnosis.

By plotting ROC, we found the optimum cutoff value of 216 ng/mL with a sensitivity of 53.5% and a specificity of 74.5%. Although the presented diagnostic value of IGF-1 for thyroid cancer detection displayed low sensitivity and acceptable specificity, serum IGF-1 might be a complementary marker in combination with ultrasound examinations or FNA for TC diagnosis. Thus, serum IGF-1 might be a potential complementary biomarker for TC, especially for patients with ultrasound examinations or FNA.

Our study had some limitations: TC consists primarily of papillary, follicular, medullary, and anaplastic cancer.[31] However, we investigated only the clinical significance of serum IGF-1 in PTC. In future studies, we will enroll more patients with other types to provide enough data to confirm the findings of the present study.

5. Conclusion

In conclusion, serum IGF-1 levels in TC were significantly higher than controls and correlated closely with tumor stage, lymph node metastasis, tumor size, and nodule number. ROC analysis indicated that serum IGF-1 might be a potential biomarker for TC. The present study indicated that serum IGF-1 displays great potential as a laboratory marker for TC.

Author contributions

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