Association of insulin-like growth factor-1 with thyroid nodules

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Abstract. The aim of the present study was to investigate the relationship between insulin-like growth factor-1 (IGF-1) and thyroid nodules. A total of 56 patients with thyroid nodules confirmed by physical examination and ultrasound screening were randomly selected. The patients were divided into three groups by radionuclide scan: the hot nodule group (group 1, n=18); the cold and solid nodule group (group 2, n=18); and the cold and cystic nodule group (group 3, n=20). Cystic fluid samples from patients with cystic cold thyroid nodules were defined as group 4. A control group of 18 healthy adults matched for age, gender and body mass index (group 0) was also included. For all participants, levels of the thyroid hormones, TT3, TT4, TSH and IGF-1, were determined by radioimmunoassay. The measurement data were expressed as the mean ± standard deviation (SD). The analysis of variance was performed by the t-test and the correlation analysis was performed by linear regression. The serum levels of IGF-1 in the solid cold nodule group were significantly higher than those in the hot nodule group (P<0.05). Serum levels of IGF-1 in the cystic cold nodule group were significantly lower than those in the control group (P<0.05). The serum IGF-1 levels in the cystic fluid were significantly lower than those in the cystic cold nodule (P<0.05) and the control groups (P<0.05). Additionally, the mean serum IGF-1 level in patients with thyroid adenoma was significantly higher than that in the control group (P<0.05). The serum IGF-1 level may not be involved in the pathogenesis of hot thyroid nodules and cold and cystic thyroid nodules; however, it may play a significant role in the pathogenesis of certain solid cold thyroid nodules.

Introduction

The thyroid gland is an endocrine organ situated at the front and sides of the neck, anterior to the trachea, just inferior to the larynx, and behind the sternohyoid and thyrohyoid muscles.

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Weighing approximately 20 g (15-25 g) and measuring 2x3 cm in adult humans, it consists of two lobes connected by an isthmus. It is a highly vascular organ, deriving its blood from the superior and inferior thyroid arteries. Microscopically, it is made up of spherical vesicles separated by connective tissue (1). The thyroid produces hormones that regulate the metabolism and are essential to the proper development and differentiation of the cells in the body. The use of imaging technology in the investigation of disorders of the head and neck has increased awareness of nodular thyroid disease in all areas of medicine. During inspection, nodules may manifest themselves as a swelling at localizations corresponding to the thyroid gland, whereas other nodules are found during palpation (2). Thyroid nodules are a common endocrine problem in the clinic, and present as various conditions, including thyroid cysts, thyroid adenomas and thyroid cancers (3). A nodule is a lump consisting of an abnormal growth of thyroid tissue within an otherwise normal thyroid gland, ranging in size from a few millimeters to a few centimeters. Nodules are believed to be a result of excessive distention of certain follicles that have undergone involution and of an increase in the regions of epithelial hyperplasia (2). Tumors derived from thyroid epithelial cells are among the most common clinically recognized neoplasms. The neoplasms include benign follicular adenomas, well-differentiated papillary or follicular carcinomas, poorly differentiated 'insular' carcinomas, and dedifferentiated or anaplastic carcinomas (4). However, the potential causes for thyroid nodules remain unidentified at present.

Insulin-like growth factor-1 (IGF-1, known as somatomedin C) is a small peptide hormone (molecular weight 7.647 kDa) (5). Circulating IGF-1 is bound to a family of insulin-like growth factor-binding proteins (IGFBPs). Most IGF-1 is carried by IGFBP-3 (6). In contrast to the pulsatile secretion of the growth hormone (GH), serum IGF-1 levels are relatively stable, with modest diurnal variation (7). Measurements of the serum levels of IGF-1 have become essential laboratory tools in the management of somatotropic axis disorders in adolescents and adults. Previous studies investigated the potential role of IGF-1 in various diseases, including cardiovascular disease (8), cancer (9) and osteoporosis (10). Increases in systemically circulating IGF-1 levels were associated with an increased risk of numerous cancer types and more rapid disease progression (11). Epidemiological studies indicated that high circulating levels of IGF-1 were associated with an increased risk of second primary tumors (SPTs) of the head and neck (12), breast (13),

Table I. Age, gender and body mass index distribution in each group (mean ± SD).

Group	No.	Age (years)	Gender (male/female)	BMI (kg/m^2)
0	18	43.33±12.96	6/12	21.2±3.6
1	18	42.17±12.24	5/13	22.5±2.2
2	18	42.67±15.28	6/12	21.8±3.3
3	20	49.60±11.81	8/14	22.6±2.7
4	17	49.65±12.30	6/11	22.3±3.5

Group 0, control group; group 1, patients with hot thyroid nodules; group 2, patients with solid cold thyroid nodules; group 3, patients with cystic cold thyroid nodules; group 4, cystic fluid samples from patients with cystic cold thyroid nodules; BMI, body mass index.

prostate (14) and lung (15). Experimental evidence suggested that IGF-1 plays a significant role in the growth of thyroid cells, and is possibly involved in the pathogenesis of thyroid-related diseases. One study found that IGF-1 stimulated protein and DNA synthesis and promoted the proliferation and differentiation of thyroid cells (16).

This study therefore aimed to investigate the possible association between IGF-1 and the pathogenesis of thyroid nodules by determining serum IGF-1 levels in patients with thyroid nodules.

Patients and methods

Patients. A total of 56 patients with thyroid nodules were admitted to our hospital between March and July 2007 were randomly selected. The diagnosis of thyroid nodules in these patients was established by physical examination and ultrasound screening (ultrasound examinations were performed using Toshiba Nemio 17 equipment and a linear 7.5 MHz probe). After undergoing a radionuclide scan, the patients with thyroid nodules were divided into three groups: the 18 patients with hot thyroid nodules formed group 1; the 18 patients with solid cold thyroid nodules formed group 2; and the 20 patients with cystic cold thyroid nodules formed group 3. A control group of 18 healthy adults matched for age, gender and body mass index (group 0) was also included in the study (Table I). A physical examination, ultrasound and assays on the serum levels of thyroid-stimulating hormone (TSH), total triiodothyronine (TT3) and total thyroxine (TT4) were also performed on the individuals in the control group to exclude those with asymptomatic thyroid nodules. After an overnight fast of at least 8 h, anthropometric measurements and blood samples were collected from each participant in the hospital by a team of trained research nurses and assistants. Blood samples were maintained in ice prior to transportation back to our laboratory for further processing. Complete blood images, renal and liver function tests, as well as lipid and glucose were assayed within 6 h of collection.

The exclusion criteria were: patients with diffuse goiter and iodine deficiency or hypothyroidism; patients who had been taking glucocorticoid medication within 1 week prior to the study (glucocorticoids are known to affect serum IGF-1 levels); patients who had been taking methotrexate; patients with hemolysis, jaundice or hyperlipidemia (all are known

to affect serum IGF-1 levels); and diabetic patients with thyroid nodules (diabetic patients often have abnormal serum IGF-1 levels).

The study was approved by the Research Ethics Committee of the College of Medicine, Xi'an Jiaotong University. Informed consent was obtained from the patients and control subjects.

Ultrasound-guided fine-needle aspiration was performed on patients with cold thyroid nodules, using 21-gauge needles and 20-ml syringes. Patients were subject to follow-up following the aspiration. Subsequently, cystic fluid samples were prepared from patients with cystic cold thyroid nodules, and defined as group 4. Hyper-viscous cystic fluids in 3 patients were excluded (thus, cystic fluids from 17 patients were included in group 4).

Measurement of serum IGF-I levels. Fasting venous blood (2 ml) was collected and maintained at room temperature for 5 h. Subsequently, the blood samples were centrifuged for 5 min to harvest the supernatant, which was stored at -20℃ for later analysis. For each participant, the levels of the thyroid hormones, TT3, TT4 and TSH, were determined by radioimmunoassay. Free IGF-1 was determined using the Active non-extraction IGF-I immunoradiometric assay (IRMA) kit (DSL-2800, Inc., Webster, TX, USA), as previously described (17,18). Briefly, this assay was a non-competitive assay in which the sample was sandwiched between two antibodies. It is a direct assay of the dissociable fraction of IGF-1. In the present study, the sensitivity was 0.03 ng/ml and inter- and intra- assay coefficients of variation were 9.9 and 10.1% (at 6.9 and 4.3 ng/ml), respectively.

Statistical analysis. The measurement data were expressed as the mean ± standard deviation (SD). The analysis of variance was performed by the t-test, and the correlation analysis by linear regression. Statistical analysis was performed using SPSS 11.5 software. P<0.05 was considered to be statistically significant.

Results

The results of fine-needle aspiration biopsy in the 18 cases of solid cold thyroid nodules revealed that there were 10 patients with thyroid adenoma, 6 patients with thyroid goiter and

Table II. IGF-1 levels in each group based on the result of fine-needle aspiration biopsy (mean ± SD).

Group	No.	IGF-1 level (ng/ml)
0	18	200.33±126.51
P	2	308.75±55.96
A	13	264.03±118.97
G	6	109.09±50.57

Group 0, control group; group P, patients with papillary carcinoma; group A, patients with thyroid adenoma; group G, patients with thyroid goiter; IGF-1, insulin-like growth factor-1.

Table III. IGF-1 levels in each group (mean ± SD).

Group	No.	IGF-1 level (ng/ml)
0	18	200.33±126.51
1	18	139.95± 90.27
2	18	220.87±131.66
3	20	158.79± 61.37
4	17	83.39± 67.85

Group 0, control group; group 1, patients with hot thyroid nodules; group 2, patients with solid cold thyroid nodules; group 3, patients with cystic cold thyroid nodules; group 4, cystic fluid samples from patients with cystic cold thyroid nodules; IGF-1, insulin-like growth factor-1.

2 patients with papillary carcinoma. The serum IGF-1 levels progressively increased in the patients with thyroid goiter, thyroid adenoma and papillary carcinoma. Of the 20 patients with cystic cold thyroid nodules, there were 16 cases of a simple thyroid cyst, 3 cases of a thyroid cyst combined with thyroid adenoma and 1 case of a thyroid cyst combined with chronic lymphatic thyroiditis. The mean IGF-1 level in patients with thyroid cysts combined with thyroid adenoma was higher than that in cases with a thyroid cyst alone. The mean IGF-1 level in patients with thyroid adenoma was significantly higher than that in the control group ($P<0.05$) (Table II).

As shown in Table I, no significant difference in the age distribution was noted among the different groups ($P<0.05$). The IGF-1 levels revealed a gradual decreasing trend from group 2, through groups 0, 3 and 1, to group 4 (Table III). The mean IGF-1 level in patients with solid cold thyroid nodules was significantly higher than that in patients with hot thyroid nodules ($P<0.05$), whereas the mean circulating IGF-1 level in patients with cystic cold thyroid nodules was significantly lower than that in the control group ($P<0.05$). The mean IGF-1 level in cystic fluids was significantly lower than that in the control group ($P<0.05$), and also lower than the mean circulating IGF-1 level in group 3 ($P<0.05$). In addition, the linear regression analysis suggested that IGF-1 had no significant correlation with the levels of TT3, TT4 and TSH.

Discussion

The incidence of thyroid nodules is approximately 4-7% in adults. Currently, ultrasound is the main technique available for thyroid nodule screening. A high-resolution ultrasound scan is capable of identifying thyroid nodules in approximately 40-50% of the general population (19), and with widespread use of the high-frequency ultrasound scan, the detection rate of thyroid nodules is increasing (20). Most sonographically-detected thyroid nodules are benign (21), and less than 7% of nodules reveal malignancy (22). Furthermore, fine-needle aspiration cytology, providing a highly reliable means of differentiating between benign and malignant thyroid nodules, has been widely used in the clinical diagnosis of thyroid nodules due to its high accuracy and low cost (2). Thyroid radionuclide scanning is also a useful tool in the diagnosis and identification of thyroid nodules. Radioisotope imaging used to be the routine practice until the introduction

and widespread acceptance of fine-needle aspiration cytology (23). The majority of autonomous functioning thyroid adenomas are benign, and usually present as hot nodules on a radionuclide scan. Conversely, there is a chance of malignant lesions when radionuclide scanning reveals a cold nodule. However, finding a cold nodule on the radionuclide scan may also result from cystic thyroid conditions, bleeding or calcification. However, the mechanism for the development of the thyroid nodule has yet to be fully clarified.

IGF-1, a potent mitogen for numerous cell types, promotes the progression of mitosis via the promotion of DNA synthesis, and has long-term effects on cell proliferation, differentiation and apoptosis (6). It also plays a role in the transformation, infiltrative growth and metastasis of tumor cells (24). Shevah et al carried out a study on the relationship between malignant tumors and IGF-1 in 222 patients with congenital IGF-1 deficiencies (including Laron syndrome, GH gene deletion, GHRH receptor defects and IGF-1 resistance), and in 338 of their first-degree and second-degree relatives. The result revealed that none of the IGF-1-deficient patients developed cancer, whereas 9-24% of the family members had a history of malignancy, suggesting that congenital IGF-1 deficiency played a significant role in preventing the onset of the cancer (25). By contrast, Tita et al observed a relatively high incidence of thyroid cancer in acromegaly patients (26), indicating that high levels of serum IGF-1 play a part in the occurrence of thyroid neoplasm. Eszlinger et al observed lower concentrations of IGF-1 in cold nodules compared to surrounding normal tissues (27). These authors concluded that IGF-1 played a more prominent role during early clonal expansion and that aberrant intrinsic signaling through a somatic mutation conferred the predominant selective growth advantage in later stages of hot or cold nodules. High serum IGF-1 levels were correlated to thyroid nodules in males (28). In a further study (29), the expression level of IGF-1 in thyroid carcinoma tissues was found to be significantly higher than that of the control group. This increased expression level demonstrated that in the course of thyroid cancer progression, overexpressed IGF-1 stimulated the upregulation of IGF-1 receptors, leading to the association of excess IGF-1 with its receptor, which in turn resulted in an abnormal proliferation, differentiation and apoptosis of thyroid cells, and ultimately led to the development of thyroid cancer.

In the current study, the concentration of serum IGF-1 in patients with hot nodules or cold nodules was not significantly different from that in the control group, which was consistent with the result of Hsiao *et al* (30). However, it was noted that no comparison based on further grouping of thyroid nodules was made in the study by Hsiao *et al*. In the further grouping analysis, the serum IGF-1 level in the hot nodule group was significantly lower than that in the solid cold nodule group and the control group, suggesting that circulating IGF-1 does not play any role in the pathogenesis of thyroid hot nodules. The IGF-1 level in cystic fluid from patients with cystic thyroid nodules was determined in the present study, and the results revealed that it was significantly lower than that in the control group, and also lower than the circulating IGF-1 level in these patients. Moreover, the circulating IGF-1 level in patients with cystic cold nodules was also significantly lower than that in the control group, suggesting that IGF-1 is not involved in the development of cystic thyroid nodules. However, no significant difference in IGF-1 levels was observed between the solid cold nodule group and the control group. In the further grouping analysis based on fine-needle aspiration cytology, the serum IGF-1 levels progressively increased in the patients with thyroid goiter, thyroid adenoma and papillary carcinoma. The mean IGF-1 levels in patients with thyroid adenoma were significantly higher than those in the control group. Thus, IGF-1 may play a significant role in the pathogenesis of certain solid cold thyroid nodules. Further studies are required to investigate the association between IGF-1 and solid cold thyroid nodules.

Few studies have addressed the fluctuation of IGF-1 levels in the various stages of human development thus far. Animal studies revealed that the circulating IGF-1 level was low in prenatal mice. After birth, IGF-1 produced by the liver becomes the major source of circulating IGF-1, and the level of circulating IGF-1 increases markedly in adolescence and adulthood (29). A previous study demonstrated that the IGF-1 level decreased with age in healthy males from early adulthood to old age (29). This indicated that tumor cell growth was probably growth factor-dependent in the early stages of cancer development, but became growth factor-independent in the later stages. In addition, IGF-1 and estrogen may play synergistic roles through the IGF-1 signaling cascade (31), which is consistent with the fact that thyroid nodules occur more frequently in females between 40 and 60 years old. Therefore, larger scale trials are required to further investigate the association between IGF-1 and thyroid nodules.

Although the exact site where IGF-1 exerts its effects remains unidentified, the experiments *in vitro* demonstrate that IGF-1 is capable of stimulating DNA synthesis, upregulating the expression of cyclin D1 and facilitating the transition from the G1 to the S phase. Furthermore, IGF-1 suppresses apoptosis and induces cell proliferation via modulation of the Bcl and Bax proteins (32). The protein-tyrosine kinase (PTK)-dependent signaling pathway, regulated by IGF-1, has also been proven to be capable of inducing thyroid proliferation (33). The binding of IGF-1 to the IGF-1 receptor initiates conformational changes in this tetrameric transmembrane receptor tyrosine kinase that initiates autophosphorylation and subsequent activation of Ras/Raf-mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt) signaling cascades (34).

Serum IGF-1 is mainly produced by the liver and is regulated by age, gender, pubertal stage, nutritional status, the immune system, social factors, liver and renal functions, ethnicity, gene polymorphisms, GH and other hormones including thyroxine, cortisol, sex steroids and insulin (35,36). Numerous factors are currently known to affect the level of circulating IGF-1, including age, diabetes (37), inflammatory bowel disease (38), hepatic disease (39), acromegaly (26), rheumatoid arthritis (40) and other carcinomas and conditions. Moreover, the administration of glucocorticoid agents also affect the circulating IGF-1 level (41). In this study, we have attempted to exclude any possible interfering factors, e.g., hemolysis, jaundice, hyperlipidemia, and the use of DNA synthesis-inhibiting drugs (e.g., methotrexate), by examining medical histories and conducting physical examinations.

Currently, there is a paucity of studies addressing the correlation of IGF-1 with thyroid nodules. Consequently, IGF-1 may exert its effect through autocrine and paracrine pathways; therefore, the use of circulating IGF-1 levels in predicting and diagnosing thyroid nodules is not advisable.

In conclusion, circulating IGF-1 may not be involved in the development of hot thyroid nodules and cystic cold nodules. It may play a significant role in the pathogenesis of certain solid cold thyroid nodules. Large scale trials and further studies are required to strengthen the relationship between IGF-1 and solid cold thyroid nodules, which may provide new insights into the pathogenesis of this condition, and reveal new means for the diagnosis and treatment of thyroid nodules in the future.

Acknowledgements

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