Observational Study

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Serum levels of insulin-like growth factor 1 are negatively associated with log transformation of thyroid-stimulating hormone in Graves' disease patients with hyperthyroidism or subjects with euthyroidism

A prospective observational study

Fen-Yu Tseng, MD, PhD[a,*], Yen-Ting Chen, MSc[b], Yu-Chiao Chi, MSc[b], Pei-Lung Chen, MD, PhD[a,c,d], Wei-Shiung Yang, MD, PhD[a,b]

Abstract

Insulin-like growth factor 1 (IGF-1) has a molecular structure similar to that of insulin. As an essential mediator of growth hormone, IGF-1 plays a vital role in growth of children and anabolic effects of adults. We evaluated the serum levels of IGF-1 in patients with hyperthyroidism or euthyroidism.

In this study, 30 patients each of Graves' disease with hyperthyroidism (HY group) and euthyroid individuals (EU group) were recruited. The HY patients were treated with antithyroid regimens as clinically indicated. No medications were given to EU patients. The demographic characteristics and anthropometric and laboratory data of both groups at baseline and 6 months were compared. Associations between levels of IGF-1 and free thyroxine (fT4), thyroid-stimulating hormone (TSH), or log transformation of TSH (logTSH) were analyzed.

At baseline, the HY patients had significantly higher serum IGF-1 levels than EU patients (median [Q1, Q3]: 305.4 [257.4, 368.1] vs. 236.7 [184.6, 318.8] ng/mL, $P = .007$). At 6 months, the HY patients still had higher serum levels of IGF-1 than EU patients (299.5 [249.9, 397.9] vs 222.1 [190.2, 305.4] ng/mL, $P = .003$). At baseline, the serum levels of IGF-1 in the HY and EU patients were positively associated with fT4 ($\beta = 29.02$, $P = .002$) and negatively associated with TSH ($\beta = -31.46$, $P = .042$) and logTSH ($\beta = -29.04$, $P = .007$). The associations between serum levels of IGF-1 with fT4 or TSH became insignificant at 6 months. However, the serum IGF-1 levels had persistent negative associations with logTSH at 6 months ($\beta = -26.65$, $P = .021$). The negative associations between IGF-1 and logTSH at baseline and 6 months remained significant even after adjustment with sex and age ($\beta = -20.22$, $P = .023$ and $\beta = -20.51$, $P = .024$, respectively).

The HY patients had higher serum IGF-1 levels than EU patients. The serum IGF-1 concentrations were negatively associated with logTSH in patients with hyperthyroidism or euthyroidism.

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, BH = body height, BMI = body mass index, BW = body weight, FPG = fasting plasma glucose, fT3 = free triiodothyronine, fT4 = free thyroxine, GD = Graves' disease, HDL-C = high density lipoprotein-cholesterol, IGF-1 = insulin like growth factor 1, LDL-C = low density lipoprotein-cholesterol, logTSH = log transformation of thyroid-stimulating hormone, LT4 = levothyroxine, T2DM = type 2 diabetes mellitus, T-C = total cholesterol, TG = triglycerides, TRAb = TSH receptor autoantibody, TSH = thyroid-stimulating hormone.

Keywords: euthyroidism, free thyroxine, hyperthyroidism, IGF-1, logTSH, thyroid-stimulating hormone

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[a] Department of Internal Medicine, National Taiwan University Hospital, [b] Graduate Institute of Clinical Medicine, College of Medicine, [c] Department of Medical Genetics, National Taiwan University Hospital, [d] Graduate Institute of Medical Genomics and Proteomics, College of Medicine, National Taiwan University, Taipei, Taiwan.

[*] Correspondence: Fen-Yu Tseng, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan 100 (e-mail: fytseng@ntu.edu.tw).

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1. Introduction

Insulin-like growth factor 1 (IGF-1) is a protein majorly generated from the liver. With response to growth hormone (GH) and effects like insulin, IGF-1 may influence energy metabolism.[1,2] Thyroid hormones could also affect energy pathways.[3] In a literature review, studies concerning the associations between GH/IGF-1 axis and thyroid function statuses revealed controversial results.[4–10] In hyperthyroid cats, serum IGF-1 concentrations increased significantly after antithyroid treatment.[4] The IGF-1 levels were negatively associated with levels of free thyroxine (fT4) both at diagnosis and after treatment.[4] A population-based study revealed that high serum IGF-1 levels were related to decreased serum thyroid-stimulating hormone (TSH) levels in women.[5] Eke Koyuncu et al[6] reported that patients with hypothyroidism had lower serum IGF-1 levels than hyperthyroid patients or euthyroid controls. Besides this, they also reported a significant correlation between IGF-1 and TSH in patients with overt hypothyroidism.[6] In another study

by Akin et al,[7] patients with subclinical hypothyroidism had lower IGF-1 concentrations and with subclinical hyperthyroidism had similar IGF-1 levels when compared to the healthy control group. For subclinical hypothyroid patients, levothyroxine (LT4) replacement could prevent abnormalities related to GH/IGF-1 axis.[7] Iglesias et al reported that the IGF-1 levels in patients with hyperthyroidism were similar to those in healthy controls. The IGF-1 levels in those patients reduced significantly after antithyroid treatment.[8] On the contrary, patients with hypothyroidism had significantly lower serum IGF-1 levels than healthy volunteers. However, LT4 replacement therapy in those hypothyroid patients did not induce significant changes in IGF-1 levels.[8] Martin et al reported that nearly one-fifth of newly diagnosed Graves disease (GD) patients had IGF-1 deficiency. In addition, IGF-1 deficiency was associated with more severe free triiodothyronine (fT3) hyperthyroidism.[9] It was said that GH and IGF-1 might affect the severity of GD.[10] In summary, previous studies could not reach consistent conclusions about associations between serum levels of IGF-1 and fT4 or TSH. The present study was designed to compare the IGF-1 levels in patients with different thyroid function statuses. We also evaluated the associations between serum levels of IGF-1 with fT4, TSH, or log transformation of TSH (logTSH).

2. Subjects and methods

This study was approved by the research ethics committee of the National Taiwan University Hospital (NTUH) in accordance with the Declaration of Helsinki. From the year 2010 to 2011, 82 first-visit patients with thyroid disorders were identified through Endocrinology clinics. Among them, 20 subjects who had medical history of thyroid disorders, other comorbidities, or under medications were excluded. We provided full explanations of the purpose, nature, and procedures of the study and got consent from each of the 62 enrolled patients (Fig. 1)

Demographic and anthropometric data of recruited subjects were recorded. Body mass index (BMI) was calculated as body weight (BW) in kilograms divided by body height (BH) in meter squared (m^2). Levels of fasting plasma glucose (FPG), aspartate transaminase (AST), and alanine transaminase (ALT) were measured by using the Olympus AU series 680 (Beckman Coulter, Nyon, Switzerland) with hexokinase method, colorimetric method, and colorimetric method, respectively. Serum total cholesterol (T-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured by using the Olympus AU series 5800 (Beckman Coulter, Nyon, Switzerland) with the cholesterol oxidase phenol 4-aminoantipyrine peroxidase method, glycerophosphate oxidase-phenol aminophenazone method, accelerator selective detergent, and liquid selective detergent, respectively. TSH and fT4 levels were measured by using Siemens DPC Immulite 2000 (Siemens, Erlangen, Germany). The reference levels of fT4 and TSH used in our hospital were 0.6 to 1.75 ng/dL and 0.1 to 4.5 μIU/mL, respectively. Values outside the laboratory measurement range (fT4 level > 5.4 ng/dL or TSH level < 0.004 μIU/mL) were recorded as an fT4 level of 5.4 ng/dL or a TSH level of 0.004 μIU/mL, respectively. Serum IGF-1 concentrations were determined by enzyme-linked immunosorbent assay (Mediagnost, Reutlingen, Germany). TSH-receptor antibody (TRAb) levels were determined by using the radioimmunoassay method (TSH receptor autoantibody coated tube kit, RSR, Cardiff, UK). The results were recorded as negative, borderline positive, or positive if the percentage inhibition of TSH binding was < 10%, 10–15%, or > 15%, respectively. All assays were performed following the manufacturers' instructions.

We performed thyroid ultrasonographic examination for all of the enrolled subjects at baseline. The sonographic examinations were performed by endocrine specialists by using the Toshiba Aplio Ultrasound System (SSA-790) with a PLT-805AT probe. Aspiration cytological examination was performed as clinically indicated. None of the patients had malignant lesions.

Thirty patients with fT4 levels > 1.75 ng/dL and TSH levels < 0.1 μIU/mL at baseline were diagnosed as with hyperthyroidism (HY group). All of the HY patients had positive examination results for TRAb. Their thyroid ultrasound examination revealed characteristics compatible with autoimmune thyroiditis. The HY patients received antithyroid regimens initially with carbimazole 10 mg or propylthiouracil 100 mg 3 times daily. The doses of the

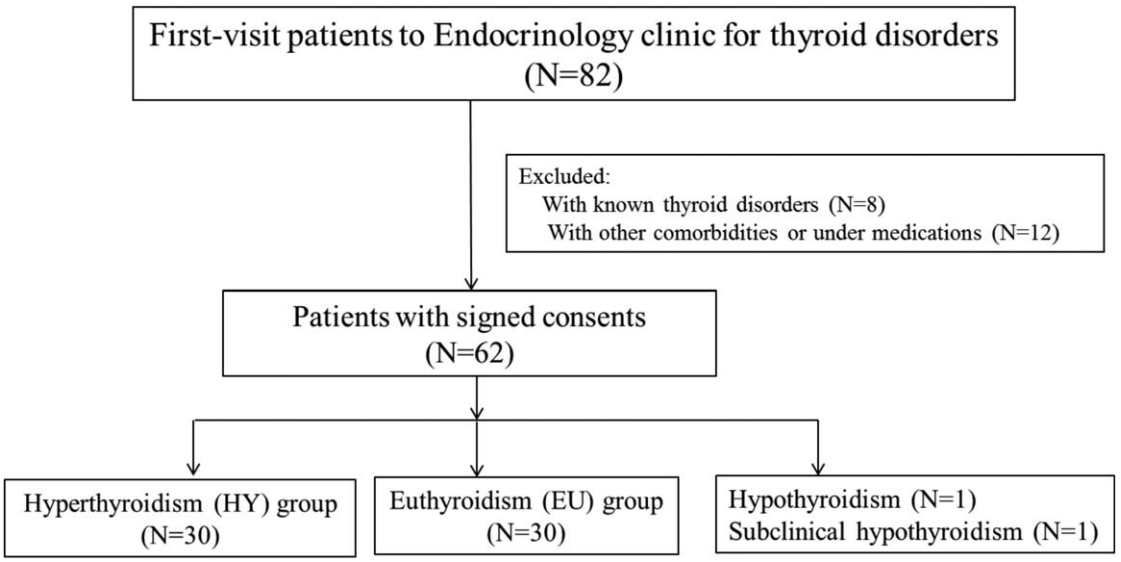

Figure 1. Flow diagram showing the enrollment of the study subjects.

antithyroid drugs were titrated according to their improvement in thyroid function. Follow-up laboratory data were obtained at 6 months.

Thirty patients with both fT4 and TSH levels within reference ranges were defined as in euthyroid status (EU group). None of them had positive TRAb examination results. The EU patients were kept on follow-up without medications. Follow-up laboratory data were obtained at 6 months.

There were only 2 patients with overt or subclinical hypothyroidism (fT4 0.28 ng/dL, TSH 55.3 μIU/mL and fT4 0.72 ng/dL, TSH 34.5 μIU/mL, respectively). They were treated with LT4 to attain euthyroidism. Follow-up laboratory data were obtained at 6 months. Owing to the low number of hypothyroid patients, the data pertaining to these 2 patients were described but not included in the statistical analysis.

We used nonparametric method in the statistical analysis. The data for the numerical variables were presented as median values (Q1, Q3). Categorical data were expressed as percentages. The Mann–Whitney *U* test was used for comparisons of numerical variables between the HY and EU patients, both at baseline and at 6 months. Proportions and categorical variables were tested by using the Fisher exact test.

We intended to elucidate the associations between serum levels of IGF-1 and fT4, TSH, or logTSH in all thyroid function spectrum. However, we had only 2 patients with overt/subclinical hypothyroidism. To analyze the possible associations between serum IGF-1 levels and other variables, data of the HY patients and EU patients at baseline were pooled together. The predictive effects of demographic, anthropometric, or laboratory parameters for IGF-1 concentrations at baseline were evaluated by performing a linear regression analysis. Significant correlations in univariate linear regression analysis were further tested for adjustment with sex and age. Data of the HY patients and EU patients at 6 months were pooled together. We validated the analysis for the associations between laboratory parameters and serum IGF-1 levels by using the follow-up data at 6 months. All of the analyses were performed by using the SAS version 9.1 statistical package for Windows (SAS, Cary, NC). A $P < .05$ was considered statistically significant.

3. Results

During their first visit, the HY patients had higher fT4, FPG, AST, and ALT, but lower TSH, BMI, T-C, and LDL-C than EU patients. The HY patients apparently had higher serum levels of IGF-1 than EU patients (median [Q1, Q3]: 305.4 [257.4, 368.1] ng/mL vs 236.7 [184.6, 318.8] ng/mL, $P = .007$) (Table 1, a vs. c).

Among the 30 HY patients, 10 (33.3%) attained euthyroid status, 15 (50%) had a subclinical hyperthyroid status, 4 (13.3%) remained in hyperthyroid status, and 1 (3.3%) shifted to a hypothyroid status (fT4 level 0.43 ng/dL, TSH 59 mIU/mL) at 6 months. All of euthyroid patients remained in euthyroid status at 6 months. The HY patients still had higher levels of ALT and fT4 than EU patients at 6 months (Table 1, b vs d). The serum IGF-1 levels of the HY patients were persistently higher than those of EU patients at 6 months (299.5 [249.9, 397.9] ng/mL vs 222.1 [190.2, 305.4] ng/mL, $P = .003$) (Table 1, b vs d).

During the study period, only 2 patients were presented with overt/subclinical hypothyroidism. These 2 patients had baseline serum IGF-1 levels of 320.9 and 150.1 ng/mL, respectively. At 6 months, their serum IGF-1 levels were 205.2 and 233.4 ng/mL, respectively.

The linear regression analysis performed by pooling data pertaining to HY or EU patients revealed that baseline levels of IGF-1 were negatively associated with age, baseline BMI, TSH, logTSH, T-C, and LDL-C ($\beta = -5.42$, $P < .001$; $\beta = -10.56$, $P = .012$; $\beta = -31.46$, $P = .042$; $\beta = -29.04$, $P = .007$; $\beta = -0.92$, $P < .001$; and $\beta = -1.10$, $P = .002$, respectively) (Table 2). The baseline serum levels of IGF-1 were positively associated with BH, baseline fT4, and TRAb ($\beta = 4.64$, $P = .005$; $\beta = 29.02$, $P = .002$; $\beta = 1.18$, $P = .004$, respectively) (Table 2). The associations between IGF-1 levels and BMI, fT4, logTSH, or TRAb at

Table 1

Characteristics of subjects with hyperthyroidism or euthyroidism.

	Hyperthyroidism (HY group) (N = 30)		Euthyroidism (EU group) (N = 30)		*P**	
	Initial[a]	The sixth month [b]	Initial[c]	The sixth month[d]	a vs c	b vs d
Male: female	9: 21		4: 26		0.209	
Age, y	37 (29, 43)		43 (32, 52)		0.110	
BH, cm	161 (158, 170)		160 (157, 165)		0.268	
BW, kg	56.6 (49.8, 61.0)	57.5 (54.0, 67.1)	60.5 (55.0, 67.0)	60.0 (55.0, 67.0)	0.150	0.567
BMI	21.7 (19.5, 23.2)	22.7 (20.3, 23.9)	23.1 (21.2, 26.0)	23.0 (21.8, 26.0)	0.024†	0.099
AST, U/L	26.5 (22.0, 32.0)	21.5 (17.0, 24.0)	18.5 (17.0, 22.0)	19.0 (16.0, 22.0)	<0.001†	0.107
ALT, U/L	35.5 (28.0, 49.0)	23.5 (18.0, 27.0)	14.5 (12.0, 18.0)	15.0 (13.0, 20.0)	<0.001†	0.003†
fT4, ng/dL	3.19 (2.22, 3.92)	1.14 (0.89, 1.58)	0.99 (0.87, 1.06)	0.96 (0.86, 1.06)	<0.001†	0.024†
TSH, μIU/mL	0.004 (0.004, 0.006)	0.006 (0.004, 1.450)	1.105 (0.651, 1.370)	0.904 (0.490, 1.420)	<0.001†	0.111
FPG, mg/dL	88.5 (82, 93)	88 (79, 95)	86 (79, 89)	84.5 (79, 89)	0.047†	0.269
T-C, mg/dL	146.5 (121, 171)	181.5 (158, 207)	194 (182, 228)	191 (178, 227)	<0.001†	0.139
TG, mg/dL	80 (60, 100)	86.5 (69, 103)	79.5 (61, 125)	92 (69, 154)	0.617	0.456
HDL-C, mg/dL	49 (40, 58)	53 (47, 63)	56 (47, 65)	51 (43, 69)	0.053	0.994
LDL-C, mg/dL	82.8 (66, 99.8)	110.2 (88.0, 130.0)	129 (105.4, 140.6)	107.4 (89.0, 136.4)	<0.001†	0.621
TRAb, %	60.2 (44.2, 72.3)		3.5 (2.5, 6.2)		<0.001	
IGF-1, ng/mL	305.4 (257.4, 368.1)	299.5 (249.9, 397.9)	236.7 (184.6, 318.8)	222.1 (190.2, 305.4)	0.007†	0.003†

Numerical data were presented as median (Q1, Q3).

ALT = alanine transaminase, AST = aspartate transaminase, BH = body height, BMI = body mass index, BW = body weight, FPG = fasting plasma glucose, fT4 = free thyroxine, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, T-C = total cholesterol, TG = triglyceride, TRAb = TSH-receptor antibody; IGF-1 = insulin-like growth factor 1, TSH = thyroid-stimulating hormone.

a: Hyperthyroid patients, initial data. b: Hyperthyroid patients, data at the sixth month. c: Euthyroid patients, initial data. d: Euthyroid patients, data at the sixth month.

* Fisher exact test for comparisons of categorical variables between hyperthyroid and euthyroid patients. Mann–Whitney *U* tests for comparisons of numerical variables between hyperthyroid and euthyroid patients. (a vs c and b vs d).

† $P < .05$.

Table 2

Univariate regression model with concentrations of IGF-1 as dependent variables, and demographic, anthropometric, and laboratory parameters as independent variables in hyperthyroid or euthyroid patients (N = 60).

	IGF-1 (0)		IGF-1 (6)	
Independent variable	**β(95% CI)**	***P***	**β(95% CI)**	***P***
Sex	−40.90 (−102.01, 20.22)	.186	−23.06 (−86.80, 40.68)	.472
Age	−5.42 (−7.26, −3.59)	<.001*	−5.50 (−7.41, −3.58)	<.001*
BH	4.64 (1.45, 7.83)	.005*	3.52 (0.12, 6.91)	.043*
BW	−0.53 (−3.25, 2.20)	.701	0.18 (−2.77, 3.12)	.904
BMI	−10.56 (−18.68, −2.44)	.012*	−8.11 (−17.51, 1.29)	.089
FT4	29.02 (10.88, 47.16)	.002*	16.15 (−21.01, 53.32)	.388
TSH	−31.46 (−61.70, −1.21)	.042*	1.06 (−2.44, 4.56)	.547
LogTSH	−29.04 (−49.73, −8.35)	.007*	−26.65 (−47.20, −4.09)	.021*
FPG	−0.20 (−3.09, 2.70)	.892	0.26 (−1.67, 2.18)	.789
AST	1.08 (−2.40, 4.55)	.537	0.66 (−3.70, 5.03)	.761
ALT	0.70 (−0.81, 2.21)	.356	0.69 (−1.49, 2.87)	.530
T-C	−0.92 (−1.43, −0.40)	<.001*	−0.87 (−1.55, −0.20)	.013*
TG	−0.25 (−0.73, 0.22)	.292	−0.11 (−0.58, 0.36)	.649
HDL-C	−1.54 (−3.20, 0.13)	.069	−1.20 (−2.30, −0.10)	.033*
LDL-C	−1.10 (−1.78, −0.41)	.002*	−0.65 (−1.47, 0.17)	.118
TRAb	1.18 (0.39, 1.96)	.004*		

IGF-1 (0): levels of IGF-1 at baseline. IGF-1 (6): levels of IGF-1 at the sixth month. For IGF-1 (0): sex, age, and anthropometric and laboratory data at baseline were used as independent variables. For IGF-1 (6): sex, age, and anthropometric and laboratory data at the 6th month were used as independent variables.

ß = parameter estimate, 95% CI = 95% confidence interval.

Sex: female vs male. ALT = alanine transaminase, AST = aspartate transaminase, BH = body height, BMI = body mass index, BW = body weight, FPG = fasting plasma glucose, fT4 = free thyroxine, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, LogTSH = log transformation of TSH levels, T-C = total cholesterol, TG = triglyceride, TRAb = TSH-receptor antibody, TSH = thyroid-stimulating hormone.

* Linear regression, $P < .05$.

baseline remained significant after adjustment with sex and age (β = −9.28, $P = .006$; β = 19.25, $P = .015$; β = −20.22, $P = .023$; and β = 0.73, $P = .034$, respectively) (Table 3).

At 6 months, the serum levels of IGF-1 were positively associated with BH (β = 3.52, $P = .043$) but negatively associated with age, logTSH, T-C, and HDL-C (β = −5.50, $P < .001$; β = −26.65, $P = .021$; β = −0.87, $P = .013$; and β = −1.20, $P = .033$, respectively) (Table 2). After adjustment with sex and age, only the associations between serum IGF-1 levels and logTSH remained significant (β = −20.51, $P = .024$) at 6 months (Table 3).

4. Discussions

With effects on energy metabolism, thyroid function statuses could affect adipokines or hepatokines.[11,12] IGF-1, which is released from the liver, is shown to be associated with

Table 3

Linear regression model using serum IGF-1 levels as dependent variable, and demographic, anthropometric and laboratory parameters as independent variables in hyperthyroid or euthyroid patients (N = 60), adjusted with sex and age.

	IGF-1 (0)		IGF-1 (6)	
Independent variable	**β(95% CI)**	***P***	**β(95% CI)**	***P***
BH	1.95 (−3.65, 7.54)	.489	0.23 (−5.64, 6.11)	.937
BW				
BMI	−9.28 (−15.76, −2.80)	.006*		
FT4	19.25 (3.83, 34.68)	.015*		
TSH	−20.71 (−45.69, 4.28)	.102		
LogTSH	−20.22 (−37.49, −2.96)	.023*	−20.51 (−38.23, −2.79)	.024*
FPG				
Cre				
AST				
ALT				
T-C	−0.34 (−0.87, 0.18)	.196	−0.31 (−0.96, 0.33)	.336
TG				
HDL-C			−0.78 (−1.72, 0.16)	.104
LDL-C	−0.46 (−1.10, 0.19)	.163		
TRAb	0.73 (0.06, 1.40)	.034*		

IGF-1 (0): levels of IGF-1 at baseline. IGF-1 (6): levels of IGF-1 at the sixth month. For IGF-1 (0): sex, age, and anthropometric and laboratory data at baseline were used as independent variables. For IGF-1 (6): sex, age, and anthropometric, and laboratory data at the 6th month were used as independent variables.

ß = parameter estimate, 95% CI = 95% confidence interval.

Sex: female versus male. ALT = alanine transaminase, AST = aspartate transaminase, BH = body height, BMI = body mass index, BW = body weight, FPG = fasting plasma glucose, fT4 = free thyroxine, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, LogTSH = log transformation of TSH levels, T-C = total cholesterol, TG = triglyceride, TRAb = TSH-receptor antibody, TSH = thyroid-stimulating hormone.

* Linear regression, $P < .05$.

energy metabolism.[1,2] Previous studies concerning IGF-1 levels in different thyroid function statuses showed disputable results.[4–10] In the present study, HY patients had higher IGF-1 levels than the EU patients, both at baseline and at 6 months. In patients with hyperthyroidism or euthyroidism, the serum IGF-1 levels showed a negative association with logTSH, both at baseline and 6 months even after adjustment for sex and age.

With an association between TSH and IGF-1 receptors, GH/IGF-1 axis has been reported to play a role in Graves' orbitopathy.[13–16] Martin et al[9] reported that IGF-1 status in newly diagnosed GD patients was not altered by gender or TRAb. In the present study, all the HY patients showed positive results for TRAb and thyroid ultrasound compatible with GD. Our analysis revealed that IGF-1 levels had a negative association with age, but was not altered by gender. At baseline, the IGF-1 levels were positively correlated with TRAb. Since TRAbs were measured only during patient enrollment, we cannot report on the levels at 6 months.

Decreased hepatic responsiveness to GH resulted in low IGF-1 levels in chronic liver disease.[17,18] Lowered serum level of IGF-1 has been noted as a typical indicator of decreased hepatic reserve in nonalcoholic fatty liver disease,[19,20] liver cirrhosis,[21] and hepatocellular carcinoma.[22] The direction of the causal relationship between decreased IGF system components and the chronic damage of liver parenchyma needs to be investigated.[19] Keeping this in mind, we excluded patients with chronic liver disease from our study. Our analysis revealed no association between serum levels of IGF-1 and AST or ALT.

With significant structural homology to insulin, IGF-1 and its binding proteins play a vital role in glucose homeostasis and type 2 diabetes (T2DM).[1,2] Earlier studies suggested that low serum levels of IGF-1 were associated with obesity,[23] impaired glucose tolerance,[24] insulin resistance,[25] diabetes,[26] low HDL-C,[27–29] and metabolic syndrome.[30,31] Sotak et al[32] reported a significantly higher prevalence of thyroid diseases in patients with T2DM when compared to control gup. The FPG levels were higher in patients with hyperthyroidism or autoimmune thyroid diseases than those in control group.[32] In consistent with this, our study also showed higher FPG levels in the HY group compared to the EU group. Our analysis revealed no associations between serum IGF-1 levels and FPG. In this study, we did not measure the level of IGF-1-binding proteins, IGF-1 receptors, insulin, or C peptide. We therefore cannot comment on those glucose homeostasis-related parameters in HY or EU patients. At baseline, the serum IGF-1 levels were positively associated with BH and negatively associated with BMI, T-C, and LDL-C. The negative association between serum IGF-1 levels and BMI remained the same even after adjustment with sex and age. However, the association between serum IGF-1 levels and T-C or LDL-C became insignificant after adjustment with sex and age. At 6 months, serum IGF-1 levels were positively associated with BH and negatively associated with T-C or HDL-C. These associations became insignificant after adjustment with sex and age.

The interactions between serum levels of IGF-1 and thyroid function statuses have been discussed bidirectionally. Thyroid hormones affect the secretion and effects of GH, and thus may mediate synthesis and secretion of IGF-1.[33] The GH/IGF axis can affect growth, function of the thyroid, and metabolism of thyroid hormones.[34,35] To the best of our knowledge, serum IGF-1 levels had been reported to be high,[36,37] normal,[8] or low[4] in hyperthyroidism. In the present study, the HY patients had higher IGF-1 levels than EU patients. The literature review suggested that treatment for hyperthyroidism could result in increased[4] or decreased[8,37] serum IGF-1 levels. In the present study, not all of the HY patients retained euthyroidism at 6 months and they still had higher fT4 and IGF- l levels than EU patients. Compared to euthyroid controls, the serum IGF-1 levels had been reported to be lower in overt[6,8] or subclinical[7] hypothyroidism. For hypothyroid patients, serum IGF-1 levels increased[7,38] or remained unchanged[8] after LT4 replacement. We had only 2 patients with overt/subclinical hypothyroidism. Under LT4 replacement, they retained euthyroid status at 6 months. Compared to the baseline data, these 2 patients had decreased or increased serum IGF-1 levels at 6 months. Due to the low number of patients, we cannot infer changes in serum IGF-1 in hypothyroidism. Studies correlating the serum levels of IGF-1 and thyroid function parameters revealed debatable results.[4,5] The IGF-1 levels had been reported to be negatively correlated with fT4 in hyperthyroid cats,[4] negatively associated with TSH in women,[5] or positively correlated with TSH in hypothyroid patients.[6] With pooling data of HY and EU patients, our analysis revealed positive associations between serum levels of IGF-1 and fT4 and negative associations between serum levels of IGF-1 and TSH at baseline. However, those associations were not significant at 6 months. Our analysis revealed negative correlations between serum IGF-1 levels and logTSH, both at baseline and at 6 months, and it remained the same even after adjustment with sex and age. Moreover, our data suggested that logTSH might be a better indicator of serum IGF-1 levels than fT4 or TSH in patients with hyperthyroidism or euthyroidism.

IGF-1 can promote the progression of mitosis and influence cell proliferation, differentiation, and apoptosis.[39] Völzke et al[5] reported that high serum IGF-1 levels are associated with goiter and thyroid nodules in men. Liu et al[40] reported that the protein and mRNA levels of IGF-1 and IGF-1R were significantly higher in paraffin-embedded thyroid tissues from patients with follicular adenomas, nodular goiters, and papillary thyroid cancer when compared to controls. Of note, they concluded that IGF-1 might play an important role in the genesis and development of certain solid cold thyroid nodules.[40] Recent studies suggested no associations between GD with incidental thyroid carcinoma[41] and hyperthyroidism with benign prostatic hypertrophy.[42] Our analysis revealed that HY patients had higher IGF-1 levels than EU patients. Even with possible roles in cell proliferation, durations of IGF-1 elevation in hyperthyroidism or GD may affect their contributions to the development of goiter or thyroid neoplasms. This study recruited first-visit patients with newly diagnosed thyroid disorders. None of the study subjects had malignant lesions. Hence, we have no sufficient data to infer the associations between elevations of IGF-1 in hyperthyroidism with the development of goiter or thyroid neoplasm.

The present study had several limitations. First, the sample size was small. In the present analysis, the estimated statistical power for higher IGF-1 levels in HY patients than in EU patients was 0.85, and for negative association between IGF-1 and logTSH at baseline and 6 months were 0.80 and 0.66, respectively. Second, data pertaining to only HY and EU patients were used in the statistical analysis, excluding the data from patients with overt/subclinical hypothyroidism. Therefore, the question of whether the negative associations between logTSH and IGF-1 levels exist in the whole thyroid function spectrum remains to be investigated. Third, fT4 levels >5.4 ng/dL were recorded as 5.4 ng/dL, and TSH levels < 0.004 μIU/mL were recorded as 0.004 μIU/mL. The true effects of advanced thyrotoxicosis with fT4 or TSH outside the reference ranges on IGF-1 levels were

therefore biased. Fourth, the HY patients were treated with carbimazole or propylthiouracil. The effects of different medications on IGF-1 levels were not evaluated. Fifth, the responses to the antithyroid regimens varied in the HY patients. Serial changes in IGF-1 levels over periods shorter than 6 months were not evaluated in the present study. Sixth, our analysis revealed positive correlations between serum IGF-1 levels and TRAb at baseline. However, we had no TRAb follow-up data to validate the correlations between TRAb and the levels of IGF-1 at 6 months. Seventh, the association between serum levels of IGF-1 and goiter as reported in the literature[5,43,44] was not analyzed in the current study. Eighth, the study was performed at a medical center in Taiwan, and may therefore have limited relevance to the general situation. Ninth, associations between GH, IGF-1-binding proteins, or IGF-1 receptors with thyroid function have been discussed in the literature.[8,10,36–38,45–48] We had no data of GH, IGF-binding proteins, or IGF-1 receptors in the present study. Our analysis revealed a negative correlation between the IGF-1 levels and logTSH. The true interactions between IGF-1 and thyroid function statuses require further investigation.

In conclusion, HY patients had higher serum IGF-1 levels than EU patients. Serum levels of IGF-1 were negatively associated with logTSH. Whether the associations between the levels of IGF-1 and logTSH persist in the whole thyroid function spectrum deserves further investigation.

Author contributions

Conceptualization: Fen-Yu Tseng, Yen-Ting Chen, Wei-Shiung Yang.
Data curation: Fen-Yu Tseng, Yen-Ting Chen, Yu-Chiao Chi.
Formal analysis: Fen-Yu Tseng.
Investigation: Fen-Yu Tseng, Yu-Chiao Chi, Pei-Lung Chen, Wei-Shiung Yang.
Methodology: Fen-Yu Tseng, Yen-Ting Chen, Yu-Chiao Chi.
Project administration: Fen-Yu Tseng, Pei-Lung Chen.
Resources: Pei-Lung Chen, Wei-Shiung Yang.
Supervision: Wei-Shiung Yang.
Validation: Fen-Yu Tseng, Wei-Shiung Yang.
Writing – original draft: Fen-Yu Tseng.
Writing – review & editing: Fen-Yu Tseng.

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