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Serum levels of fetuin-A are negatively associated with log transformation levels of thyroid-stimulating hormone in patients with hyperthyroidism or euthyroidism

An observational study at a medical center in Taiwan

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Abstract

Fetuin-A is a protein with various biological functions. It plays a role in insulin resistance and arterial calcium deposition. Thyroid dysfunction may affect energy expenditure, glucose metabolism, and the risk of cardiovascular diseases. In the present study, we compared the serum fetuin-A concentrations in hyperthyroid patients with those in euthyroid patients.

We recruited 30 newly-diagnosed hyperthyroid patients (the HY group) and treated them with anti-thyroid regimens as clinically indicated. We recruited 30 euthyroid individuals (the EU group) as controls. We compared laboratory parameters at the baseline and at 6 months. We then determined the associations between the levels of fetuin-A and free thyroxine (fT4), thyroid-stimulating hormone (TSH), or log transformation of TSH (logTSH).

At the baseline, the HY patients had significantly higher serum fetuin-A levels than the EU patients (median [Q1, Q3]: 735.4 [537.9, 843.4] ng/mL vs 561.1[449.2, 670.5] ng/mL, $P = .010$). At 6 months, the serum fetuin-A levels of the HY patients decreased but were still higher than those of the EU patients (698.4 [627.6, 924.3] ng/mL vs 616.5 [498.2, 727.7] ng/mL, $P = .002$). At baseline, the serum levels of fetuin-A were negatively associated with logTSH ($\beta = -53.79$, $P = .010$). At 6 months, the levels of fetuin-A were positively associated with fT4 ($\beta = 86.91$, $P = .039$), and negatively associated with logTSH ($\beta = -104.28$, $P < .001$). Changes to the levels of fetuin-A within 6 months were negatively associated with changes to logTSH ($\beta = -57.80$, $P = .019$). The negative associations between fetuin-A levels and logTSH at baseline and at 6 months, and the changes during the 6 months remained significant after adjustment for sex and age ($\beta = -51.72$, $P = .016$; $\beta = -103.11$, $P < .001$; and $\beta = -59.36$, $P = .020$, respectively).

The patients with hyperthyroidism had higher serum fetuin-A levels than the patients with euthyroidism. In patients with hyperthyroidism, the serum fetuin-A concentrations decreased after the anti-thyroid treatment. In the present study, serum fetuin-A concentrations were negatively associated with logTSH.

Abbreviations: Δfetuin-A = changes of fetuin-A during the follow-up period, ΔlogTSH = changes of logTSH during the follow-up period, 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 thyroid-stimulating hormone, T-C = total cholesterol, TG = triglycerides, TRAb = TSH receptor autoantibody, TSH = thyroid-stimulating hormone.

Keywords: euthyroidism, fetuin-A, free thyroxine, hyperthyroidism, logTSH, thyroid stimulating hormone

1. Introduction

Fetuin-A, which is also known as alpha 2-Heremans-Schmid glycoprotein (AHSG), is a multifunctional protein.[1] In the fetus, fetuin-A is synthesized by multiple tissues.[1] In adults, >95% of fetuin-A is secreted by the liver.[1,2] Fetuin-A inhibits insulin receptor tyrosine kinase[3,4] and regulates bone remodeling and ectopic mineralization.[5–7] Increased levels of fetuin-A have been linked to obesity and metabolic syndrome,[8–10] chronic hyperglycemia and type 2 diabetes mellitus,[11–14] non-alcoholic fatty liver disease,[15–17] and the risk of albuminuria.[18] Fetuin-A is one of the hepatokines linked to obesity and cardiovascular diseases.[19] The association between serum levels of fetuin-A and the risk of cardiovascular disease has been discussed in the literature.[20–23] High serum fetuin-A levels are associated with increased risks for myocardial infarction and ischemic stroke,[20] carotid artery stiffness,[21] and the severity of coronary artery disease.[22,23] In contrast, low fetuin-A levels had been linked to an increased risks of coronary artery calcification and associated diseases.[24,25]

Editor: Daryle Wane.

The authors have nothing to disclose.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:46(e13254)

Received: 16 August 2018 / Accepted: 22 October 2018

http://dx.doi.org/10.1097/MD.0000000000013254

Thyroid hormones are important regulators of energy expenditure,[26] body weight,[27] insulin resistance,[28,29] lipid metabolism,[30,31] and cardiac function.[32–34] Thyroid dysfunction may affect the endocrine products of adipose tissue.[31] Patients with hyperthyroidism have higher levels of adipocyte fatty acid-binding protein[35] or follistatin[36] than patients with euthyroidism. Thyroid dysfunction may also affect hepatokine levels.[37] Previous studies have suggested that thyroid function have an impact on serum levels of fetuin-A.[38–41] However, the correlations between serum free thyroxine (fT4) or thyroid-stimulating hormone (TSH) levels and fetuin-A levels in different thyroid function scenarios were not consistent throughout those reports.[38–41] Serum levels of fetuin-A in patients with hyperthyroidism[38] or subclinical hyperthyroidism[39] decreased after treatment. Compared with the controls, plasma fetuin-A levels were reported to be reduced in female patients with hypothyroidism.[40] However, fetuin-A levels were higher in patients with subclinical hypothyroidism than in healthy individuals.[41] To the best of our knowledge, to date there has been no investigation of the associations between fetuin-A levels and fT4 or TSH across the entire spectrum of thyroid function. In their study, Pamuk et al[38] enrolled hyperthyroid patients but no euthyroid controls. In the present study, we compared fetuin-A serum levels of hyperthyroid patients with those of euthyroid patients. We investigated the associations between fetuin-A levels and thyroid function parameters by pooling the data from hyperthyroid patients and euthyroid patients.

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, first-visit patients with thyroid disorders were identified through Endocrinology clinics. 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 enrolled patient.

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) were measured with the hexokinase method by using the Olympus AU series 680 (Beckman Coulter, Nyon, Switzerland). Aspartate transaminase (AST) and alanine transaminase (ALT) were measured with the colorimetric method also by using the Olympus AU series 680. 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 fetuin-A concentrations were determined by enzyme-linked immunosorbent assay (BioVendor, Brno, Czech Republic). TSH-receptor antibody (TRAb) levels were determined by using the radioimmunoassay method (TSH receptor autoantibody coated tube kit, RSR, Cardiff, United Kingdom). The results were recorded as negative, borderline positive, or positive if the percentage inhibition of TSH binding was <10%, 10% to 15%, or >15%, respectively. All the 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 group patients had positive examination results for TRAb. Their thyroid ultrasound exam revealed characteristics compatible with autoimmune thyroiditis. The HY group patients received anti-thyroid regimens initially with carbimazole 10 mg or propylthiouracil 100 mg 3 times daily. The doses of the anti-thyroid drugs were titrated according to their improvement in thyroid function. Follow-up laboratory data were obtained at the 6th month.

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 group patients were kept on follow-up without medications. Follow-up laboratory data were obtained at the 6th month.

Two patients were diagnosed to have overt/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 levo-thyroxine to attain euthyroidism. Due to the small patient number, the data of these 2 patients were described but not included in the analysis.

Because of the small sample size, we used non-parametric method of 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 group and EU group, both at baseline and at the 6th month. Proportions and categorical variables were tested by using the Fisher exact test. Changes of the data at the 6th month and baseline were calculated. The significance of the differences of variables during the period was calculated by Wilcoxon signed rank sum test. To analyze the possible associations between serum fetuin-A levels and other variables, data of the HY group and the EU group at baseline or at the 6th month were pooled together, respectively. The predictive effects of demographic, anthropometric, or laboratory parameters for fetuin-A concentrations were evaluated by performing a linear regression analysis. Log transformation of TSH level was calculated as logTSH. The predictive effect of logTSH for fetuin-A concentration was also calculated. All of the analyses were performed by using the SAS version 9.1 statistical package for Windows (SAS, Cary, NC). A $P < 0.05$ was considered as statistically significant.

3. Results

At the first visit, the HY group had higher fT4, FPG, AST, and ALT, but lower TSH, BMI, T-C, and LDL-C than the EU group. The hyperthyroid patients apparently had higher fetuin-A than the euthyroid patients (median [Q1, Q3]: 735.4 [537.9, 843.4] ng/mL vs 561.1 [449.2, 670.5] ng/mL, $P = .010$) (Table 1, a vs c).

Table 1

Characteristics of subjects with hyperthyroidism or euthyroidism.

	Hyperthyroidism (HY group) (N = 30)		Euthyroidism (EU group) (N = 30)		P#			
	Initial[a]	The 6th month [b]	Initial[c]	The 6th month[d]	a vs c	b vs d	a vs b	c vs d
Male: Female	9: 21		4: 26		.209			
Age, y	37 (29, 43)		43 (32, 52)		.110			
BH, cm	161 (158, 170)		160 (157, 165)		.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)	.150	.567	.104	.159
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)	.024*	.099	.131	.136
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)	<.001*	.107	.006*	.835
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)	<.001*	.003*	<.001*	.794
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)	<.001*	.024*	<.001*	.126
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)	<.001*	.111	.002*	.608
FPG, mg/dL	88.5 (82, 93)	88 (79, 95)	86 (79, 89)	84.5 (79, 89)	.047*	.269	.496	.673
T-C, mg/dL	146.5 (121, 171)	181.5 (158, 207)	194 (182, 228)	191 (178, 227)	<.001*	.139	<.001*	.422
TG, mg/dL	80 (60, 100)	86.5 (69, 103)	79.5 (61, 125)	92 (69, 154)	.617	.456	.350	.048*
HDL-C, mg/dL	49 (40, 58)	53 (47, 63)	56 (47, 65)	51 (43, 69)	.053	.994	.047*	.758
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)	<.001*	.621	<.001*	.071
Fetuin-A, ng/mL	735.4 (537.9, 843.4)	698.4 (627.6, 924.3)	561.1 (449.2, 670.5)	616.5 (498.2, 727.7)	.010*	.002*	.056	.211

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, TSH = thyroid stimulating hormone.

a: Hyperthyroid patients, initial data.

b: Hyperthyroid patients, data at the 6th month.

c: Euthyroid patients, initial data.

d: Euthyroid patients, data at the 6th 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). Wilcoxon signed rank sum test for comparisons of initial data and data at the 6th month within HY group (a vs b) or within the EU group (c vs d).

* $P < .05$.

Compared with the baseline data, the HY patients experienced a significant decrease in AST, ALT, and fT4, and a significant increase of TSH, T-C, HDL-C, or LDL-C at 6 months (Table 1, a vs b). The HY patients still had higher fT4 and ALT than the EU patients at 6 months (Table 1, b vs d). With the anti-thyroid regimens, the fetuin-A serum levels of the HY group decreased with borderline significance ($P = .056$) (Table 1, a vs b). At 6 months, the HY patients still had higher levels of fetuin-A than the EU patients (698.4 [627.6, 924.3] ng/mL vs 616.5 [498.2, 727.7] ng/mL, $P = .002$) (Table 1, b vs d).

At baseline, univariate linear regression analysis revealed that the levels of fetuin-A had no associations with fT4 or TSH (Table 2). The serum levels of fetuin-A were positively associated with ALT ($\beta = 3.81$, $P = .008$) and negatively associated with logTSH ($\beta = -53.79$, $P = .010$) (Table 2). The associations between fetuin-A levels and ALT or logTSH at baseline remained

Table 2

Univariate regression model with concentrations of fetuin-A as dependent variables, and demographic, anthropometric, and laboratory parameters as independent variables in all subjects (N = 60).

	Fetuin-A(0)		Fetuin-A(6)		Δfetuin-A	
Independent variable	β(95% CI)	P	β(95% CI)	P	β(95% CI)	P
Sex	−50.34(−169.68, 69.01)	.402	−22.90 (−169.03, 123.24)	.755		
Age	−1.54 (−6.03, 2.94)	.494	−3.46 (−8.87, 1.94)	.205		
BH	1.80 (−4.78, 8.39)	.586	1.00 (−7.04, 9.04)	.804		
BW	−0.12 (−5.40, 5.16)	.964	0.92 (−5.87, 7.71)	.786	−15.61 (−31.82, 0.61)	.059
BMI	−4.78 (−21.34, 11.78)	.566	−1.42 (−23.67, 20.83)	.899	−41.29 (−84.16, 1.57)	.059
FT4	32.44 (−4.66, 69.54)	.085	86.91 (4.57, 169.24)	.039*	21.02 (−22.74, 64.77)	.340
TSH	−49.12 (−108.41, 10.17)	.103	−1.50 (−9.52, 6.51)	.709	−6.51 (−13.64, 0.62)	.073
LogTSH	−53.79 (−94.04, −13.53)	.010*	−104.28 (−147.99, −60.57)	<.001*	−57.80 (−105.65, −9.96)	.019*
FPG	1.18 (−4.41, 6.77)	.675	1.99 (−2.37, 6.36)	.364	−1.35 (−6.37, 3.67)	.592
AST	5.29 (−1.31, 11.89)	.114	−3.98 (−13.90, 5.93)	.425	−1.81 (−8.54, 4.92)	.593
ALT	3.81 (1.05, 6.57)	.008*	1.32 (−3.67, 6.30)	.599	1.24 (−2.32, 4.80)	.488
T–C	−0.11 (−1.21, 0.99)	.846	−0.59 (−2.22, 1.04)	.471	−0.93 (−2.38, 0.51)	.200
TG	0.26 (−0.67, 1.19)	.577	−0.46 (−1.53, 0.61)	.391	−1.44 (−3.03, 0.16)	.076
HDL−C	−1.28 (−4.57, 2.01)	.439	−1.08 (−3.69, 1.54)	.412	−0.54 (−3.31, 2.23)	.699
LDL−C	0.10 (−1.35, 1.54)	.894	0.01 (−1.92, 1.93)	.995	−0.49(−2.24, 1.26)	.578

Fetuin-A(0): levels of fetuin-A at baseline. Fetuin-A(6): levels of fetuin-A at the 6th month. For fetuin-A(0): sex, age, and anthropometric and laboratory data at baseline were used as independent variables. For fetuin-A(6): sex, age, and anthropometric and laboratory data at the 6th month were used as independent variables. Δfetuin-A: difference of fetuin-A between basline and at the 6th month. For Δfetuin-A: changes of BW, BMI, and laboratory data between baseline and at the 6th month were used as independent variables.

β = parameter estimate, 95% CI = 95% confidence interval, 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, Sex = female vs male, T-C = total cholesterol, TG = triglyceride, TSH = thyroid stimulating hormone.

* Linear regression, $P < .05$.

significant after adjustment for sex and age (β=3.69, P=.011; and β=–51.72, P=.016, respectively).

At 6 months, the serum levels of fetuin-A were positively associated with the levels of fT4 (β=86.91, P=.039) and negatively associated with logTSH (β=–104.28, P<.001) (Table 2). After adjustment for sex and age, the associations between serum fetuin-A levels and fT4 or logTSH at 6 months remained significant (β=86.16, P=.044, and β=–103.11, P<.001, respectively).

Changes of fetuin-A between baseline levels and at 6 months (Δfetuin-A) were negatively associated with changes in logTSH between baseline levels and at 6 months (ΔlogTSH) (β=–57.80, P=.019) (Table 2). The negative association between Δfetuin-A and ΔlogTSH persisted after adjustment for sex and age (β= –59.36, P=.020).

4. Discussion

Fetuin-A has a complex structure with 3 major domains that acts as calcium-binding sites, glycosylation sites, and phosphorylation sites.[1] Fetuin-A levels are highest during infancy and subsequently decline gradually.[1] In adults, levels of fetuin-A may be affected by lifestyle, weight, and disease status.[1] Overfeeding may increase,[42] and calorie restriction may reduce[43] fetuin-A levels. Previous studies have suggested an increase in fetuin-A levels in obese patients,[44] and a decrease in fetuin-A levels in morbidly obese patients after dramatic BW loss.[45] Patients with hyperthyroidism commonly experience weight loss and usually regain weight after anti-thyroid regimens. In the present study, there was no difference in BW between the HY group and the EU group, both at baseline and at 6 months. The HY patients initially had higher serum fetuin-A levels than the EU patients. At 6 months, the HY patients still had higher fT4 and higher fetuin-A levels than the EU patients. The changes in fetuin-A levels cannot be explained by the BW change in the HY group. Linear regression analysis also revealed no associations between serum fetuin-A levels and BW or BMI, either initially and at 6 months.

Thyroid hormones are important regulators of glucose metabolism. Shoumer et al[29] reported that the fasting glucose levels were significantly higher in hyperthyroid patients than in control individuals. Compared with the healthy population, patients with type 2 diabetes are more likely to have subclinical hypothyroidism which may be associated with increased diabetic complications.[46] Increased fetuin-A levels have been linked to hyperglycemia and diabetes.[11–14] In the present study, the HY patients had higher baseline levels of FPG than the EU patients. At 6 months, the difference of FPGs in the HY and the EU patients were not significant. Compared with the EU group, the elevated fetuin-A levels in the HY group could not be linked to FPG levels. Linear regression analysis also revealed no associations between fetuin-A levels and FPGs, both at baseline and at 6 months.

The association between serum fetuin-A levels and metabolic syndrome has been demonstrated in previous studies.[8,10,15,47] Ix et al[8] reported that higher fetuin-A levels were strongly associated with metabolic syndrome, and with higher LDL-C, TG, and lower HDL-C concentrations. Thyroid function status may affect the lipid profile.[30] In the present study, the HY patients initially had lower T-C and LDL-C than the EU patients. The differences in the lipid profiles between the HY and EU groups disappeared at 6 months. Linear regression analysis revealed no significant correlations between lipid profiles and serum fetuin-A levels, both initially and at 6 months.

Reported associations between thyroid function and serum fetuin-A levels were inconsistent in previous studies.[38–41] Pamuk et al[38] reported that fetuin-A levels in patients with hyperthyroidism decreased after achieving euthyroidism. The basal fetuin-A levels were positively associated with basal fT4 and negatively correlated with basal TSH.[38] Without recruiting euthyroid controls, there were no comparisons between fetuin-A levels in hyperthyroid or euthyroid patients in that study.[38] The correlations between fetuin-A and fT4 or TSH after treatment were also not evaluated.[38] In a study that included female hypothyroid patients and controls, Bakiner et al[40] reported a negative correlation between plasma TSH and fetuin-A levels. Patients with Hashimoto thyroiditis and subclinical hypothyroidism had lower fetuin-A levels than those found in the control group.[48] In contrast, Bilgir et al[41] reported that fetuin-A levels were higher in patients with subclinical hypothyroidism than in the control group. In middle-aged and elderly Chinese, serum fetuin-A levels were positively associated with log (free triiodothyronine) and inversely associated with log (thyroid peroxidase antibody).[49] Gagnon et al[50] reported that recombinant human TSH stimulation for surveillance of thyroid cancer recurrence had no effect on serum levels of fetuin-A. The present study revealed that the HY patients had significantly higher serum fetuin-A levels than the EU patients. The fetuin-A levels of the HY patients decreased after administration of the anti-thyroid regimens. During the study period, only 2 patients presented with overt/subclinical hypothyroidism. These 2 patients had baseline serum fetuin-A levels of 753.2 and 445.2 ng/mL, respectively. At 6 months, their serum fetuin-A levels were 496.7 and 587.9 ng/mL, respectively. Changes in fetuin-A levels following levo-thyroxine treatment to induce euthyroidism were not consistent in these 2 patients. Owing to the low number of patients, we did not include the data pertaining to these 2 patients in the linear regression analysis. Huang et al[17] reported that serum fetuin-A concentrations were significantly associated with AST and ALT. In the present study, basal fetuin-A levels were positively associated with basal ALT. At 6 months, the fetuin-A levels were positively associated with fT4. However, those associations were not consistent for the baseline or 6 month results, or for changes within the follow-up period. Our analysis demonstrated that baseline levels of fetuin-A were negatively associated with baseline levels of logTSH. The association between logTSH and fetuin-A levels was further validated by the follow-up data obtained at 6 months. Furthermore, changes in fetuin-A levels during 6 months were negatively associated with changes in logTSH. These observations revealed persistent negative correlations between logTSH and serum fetuin-A levels in patients with hyperthyroidism or euthyroidism.

The present study had several limitations. First, we enrolled 30 patients with hyperthyroidism and 30 patients with euthyroidism. The sample size was small. Second, we did not include data pertaining to 2 patients with overt/subclinical hypothyroidism in the linear regression analysis. The question of whether the negative associations between logTSH and fetuin-A levels exist in the whole thyroid function spectrum requires further investigation. 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 fetuin-A levels were therefore biased. Fourth, the HY patients were treated with carbimazole or propylthiouracil. The effects of different medications on fetuin-A levels were not evaluated. Fifth, the correlations between thyroid autoantibodies and the levels of fetuin-A were not investigated in

the present study. Sixth, the responses to the anti-thyroid regimens varied in the HY patients. Serial changes in fetuin-A levels over periods shorter than 6 months were not evaluated in the present study. Seventh, the study was performed at a medical center in Taiwan, and may therefore have limited relevance to the general situation. Eighth, our study revealed a negative correlation between the fetuin-A level and logTSH. The true interactions between fetuin-A and thyroid hormones require further investigation.

In conclusion, the HY patients had higher serum fetuin-A levels than the EU patients. The serum fetuin-A levels of the HY patients declined following the administration of anti-thyroid regimens. Serum levels of fetuin-A were negatively associated with logTSH. The associations between levels of fetuin-A and logTSH throughout the entire spectrum of thyroid function merits further investigation.

Author contributions

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