Original Article

Serum Fibroblast Growth Factor 21 Levels in Patients with Hyperthyroidism and its Association with Body Fat Percentage

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Abstract

Background: Most of the actions of thyroid hormone (TH) on body metabolisms like maintenance of basal metabolic rate (BMR) and body fat are similar to that of fibroblast growth factor 21 (FGF21). We hypothesized that in patients with hyperthyroidism, the pathological changes in the BMR, body fat are mediated by TH through FGF21. **Objectives:** To study the association of serum FGF21 levels with hyperthyroidism and correlate body fat percentage with serum FGF21 levels in hyperthyroid patients. **Study Design:** Case-control prospective follow-up study. **Methodology:** A total of 68 hyperthyroid patients and age, sex-matched healthy controls who fulfilled the inclusion and exclusion criteria were studied. Among them, 45 cases were followed up at 3 to 6 months after the achievement of euthyroidism. Body fat percentage was calculated from Jackson and Pollock 3 site equation and Siri equation. BMR percentage was calculated by the Gale formula. **Results:** The mean age in years in the cases was similar to that of controls (36.14 ± 10.01 vs. 36.57 ± 10.53, $P = 0.81$).The serum FGF21 levels at baseline were significantly elevated in patients with hyperthyroidism compared to controls [median 406.6 pg/ml (interquartile range, 262.9–655.6) vs. 252.3 (125.1–341) $P < 0.001$] and declined dramatically following treatment with anti-thyroid drugs [405 (275.5–680.4) vs. 203.6 (154.6–230.6) $P < 0.001$]. Serum FGF21 levels negatively correlated with body fat percentage ($r = –0.268$, $P = 0.002$). After adjusting to various confounding factors, serum FGF21 was independently associated with hyperthyroidism and was significant. (OR [95%CI] 3.78 (1.046–13.666) $P = 0.043$). **Conclusion:** Serum FGF21 levels were elevated in hyperthyroid patients and decreased following treatment with anti-thyroid drugs. It was independently associated with hyperthyroidism. There may be a future therapeutic role of FGF21 inhibition in the reversal of these changes in addition to anti-thyroid drugs in patients with hyperthyroidism.

Keywords: Basal metabolic rate, body fat percentage, FGF21, hyperthyroidism

Introduction

The thyroid gland produces thyroid hormone (TH), which is vital for growth, development, and metabolic homeostasis.[1] It is responsible for the maintenance of basal metabolic rate (BMR), adaptive thermogenesis, and also body weight by modulating energy intake and expenditure.[1]

Hyperthyroidism is a condition in which excess TH produced by the thyroid gland, leads to an increase in the metabolic rate with negative energy balance causing weight loss, increased energy expenditure, and associated with accelerated lipolysis and gluconeogenesis.

The fibroblast growth factor 21 (FGF21) belongs to the FGF family functioning as an endocrine hormone. FGF21 gene encodes a 209-amino-acid protein which is converted into an active polypeptide of 181-amino acids and is synthesized in the liver.[2]

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FGF21 acts as a hormone in regulating glucose and lipid metabolism and energy expenditure.[3] FGF21 facilitates fatty acid oxidation, increases peripheral tissues glucose uptake, and stimulates thermogenesis by inducing brown adipose tissue.[4]

The active form of TH is triiodothyronine (T3), which markedly increases hepatic FGF21 mRNA expression, which is dependent on the stimulation of following receptors, i.e., TH receptor, peroxisome proliferator-activated receptor, and retinoid X receptor.[5]

Numerous studies on serum FGF21 levels in patients with thyroid dysfunction have shown variable results. A study

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conducted by Fangsen Xiao *et al*. showed that serum FGF21 levels were elevated in patients with hyperthyroidism and declined after thionamide treatment, and serum FGF21 level was independently associated with hyperthyroidism.[6] A study conducted by Yenna Lee *et al*. showed that plasma FGF21 levels were significantly increased in patients with hypothyroidism independently of BMI or lipid or glucose metabolism.[7] In the present study, serum FGF 21 levels were measured in hyperthyroid patients and its association with body fat percentage.

Objectives

Primary objective

To study the association of serum FGF21 levels with hyperthyroidism.

Secondary objective

To correlate body fat percentage with serum FGF21 levels in hyperthyroid patients.

Materials and Methods

Source of data

The data were collected from patients attending the outpatient department of Endocrinology at M.S. Ramaiah Hospitals after taking informed consent. The data for the study were collected from January 2017 to December 2018. It was a case-control prospective follow-up study.

Method of collection of data

Procedure

Newly diagnosed hyperthyroid patients from typical clinical presentation, elevated TH levels (Total T3 and/or Total T4), and suppressed TSH who were drug naivewere included in the study (as per American Thyroid Association 2016 guidelines[8]). Patients with endogenous hyperthyroidism in the form of Graves' disease and toxic nodular goiter (multinodular goiter) were included. Age and sex-matched healthy controls were included in the study.

Inclusion criteria

Male and female patients aged above 18 years of age with the diagnosis of hyperthyroidism who were not planned for radioactive ablation or thyroid surgery within next 3 months and who were initiated on antithyroid drugs (methimazole, carbimazole, and propylthiouracil) were included.

Exclusion criteria

Diabetes mellitus, cancer, pregnancy and lactation, subacute thyroiditis, hypothyroidism, hepatitis, renal failure, and infectious diseases

Ethical clearance

Prior to the commencement, ethical clearance was obtained for the study from the Institutional Human Ethics Committee, Ramaiah Medical College, Bangalore.

Anthropometric measurements

The waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Weight was measured by electronic balance. Height was measured by Harpenden's stadiometer.

BMR, muscle strength, and body fat percentage were calculated in both groups at baseline and in cases at follow-up. BMR was estimated by Gale's formula (pulse pressure difference + pulse rate –111).[9]

Body fat percentage calculation

Body fat percentage and body density (BD) were calculated from the Siri equation and Jackson and Pollock 3- site skinfold equation, respectively. Skinfold thickness was measured using skinfold Vernier caliper. Skinfold thickness in female patients was measured in the presence of a female nurse.

Body density: BD was calculated as mentioned below by Jackson and Pollock 3-site skinfold equation.[10,11]

For Men:

$$BD = 1.10938 - 0.0008267(Y) + 0.0000016(Y2) - 0.0002574(Age)$$

Where Y = sum of Chest, Abdominal, and Thigh skinfolds in mm

For Women

$$BD = 1.0994291 - 0.0009929(Z) + 0.0000023(Z2) - 0.0001392(Age)$$

Where Z = sum of Triceps, Thigh, and Supra iliac skinfolds in mm.

Body fat percentage

Body fat percentage was calculated by Siri equation[12] shown below

$$\text{Body fat percentage} = [(4.95/BD) - 4.5] \times 100$$

Blood investigations

T3, T4, TSH, AST, ALT, complete blood count, and serum creatinine were done as a part of the study protocol at baseline in both cases and controls and at follow-up in cases. Hba1c was done in both cases and controls at baseline.

TSH, T3, and T4 were estimated by electrochemiluminescent immunoassay method. HbA1c was estimated by high performance liquid chromatography.

Technetium 99 pertechnetate (Tc99) scan was done at baseline for all patients with hyperthyroidism for confirmation of diagnosis.

FGF 21 measurement

Serum FGF21 concentrations were measured using ELISA kit (E-EL-H0074; Elab Science) according to the manufacturer's

Table 1: Baseline characteristics of cases and controls

Parameter	Cases ($n=68$)	Controls ($n=63$)	*P*
AGE, year	36.14±10.01	36.57±10.53	0.81
BMI, kg/m^2	20.44±2.13	23.64±1.81	<0.001
Hb, g/dl	13.15±1.31	13.63±1.59	0.22
TSH, mIU/ml	0.02±0.01	2.57±1.0	<0.001
T4(nmol/l)	227.13±43.42	100.63±14.04	<0.001
T3(nmol/l)	5.47±1.28	1.77±0.27	<0.001
HBA1C %	5.4±0.28	5.6±0.36	0.34
PULSE RATE (per min)	110±8	80±4	<0.001
SBP, mm hg	119±8	116±6	0.19
DBP, mm hg	77±6	78±6	0.73
BMR%	42.17±11.3	8.07±3.88	<0.001
Waist circumference, cm	72.6±3.7	79.8±4.5	0.01
AST, U/L	22.4±8.9	19.2±6.6	0.18
ALT, U/L	22.8±9.3	18.5±7.9	0.21
BODY FAT %	22.11±2.93	26.68±3.29	<0.001
FGF21 (pg/ml)	406.6 (262.9-655.6)	252.3 (125.1-341)	<0.001

Data are expressed as mean±SD or median (interquartile range). BMI: Body mass index, Hb: Hemoglobin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMR: Basal metabolic rate, AST: Aspartate transaminase, ALT: Alanine transaminase

Table 2: Comparison of characteristics in cases before and after treatment

Parameter	Cases ($n=45$)	Follow-up ($n=45$)	*P*
BMI, kg/m^2	20.62±2.48	21.83±2.72	<0.001
PULSE RATE, (per min)	110±8	81±3	<0.001
BMR%	42.2±11.7	8.6±3.8	<0.001
SBP, mm hg	120±8.6	115±5.8	0.004
DBP, mm hg	77±6.8	77±6.6	0.83
Waist circumference, cm	72.4±3.8	74.6±3.5	<0.001
TSH, mIU/ml	0.02±0.01	1.18±0.8	<0.001
T4(nmol/l)	227.98±46.74	81.02±19.49	<0.001
T3(nmol/l)	5.5±1.47	1.38±0.30	<0.001
BODY FAT%	22.41±2.91	25.12±3.15	<0.001
FGF21 (pg/ml)	405 (275.5-680.4)	203.6 (154.6-230.6)	<0.001

Data are expressed as mean±SD or median (interquartile range). BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMR: Basal metabolic rate, AST: Aspartate transaminase, ALT: Alanine transaminase

instructions. Serum FGF 21 levels were measured in both cases and controls. Blood samples were collected from 8 to 9 AM after a 12-h overnight fast, and serum separated and stored at –80°C for FGF21 and biochemical assays. Serum FGF21 levels were repeated in those patients in whom euthyroidism was achieved at 3 to 6 months follow-up. This assay was verified to be highly specific to human FGF21 and not cross-reacted with other members of the FGF family. The detectable range of the assay was 31.25 to 2000 pg/ml. The intra and inter assay coefficients of variation were 6.4% and 6.7%, respectively.

Table 3: Correlation of various parameters with FGF21 in all study subjects

Parameter	Correlation coefficient (*r*)	*P*
T4	0.346	<0.001
T3	0.335	<0.001
TSH	-0.389	<0.001
BMR %	0.383	<0.001
BODY FAT%	-0.268	0.002
BMI	-0.201	0.021
AGE	0.135	0.124
SBP	0.287	0.001
DBP	0.051	0.559
WC	-0.191	0.029
PR	0.342	<0.001

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMR: Basal metabolic rate, W.C: Waist circumference, PR: Pulse rate

Table 4: Odds ratios (OR) for association between various parameters and hyperthyroidism with use of multivariate logistic regression

Variable	Odds ratio OR (95%CI)	*P*
MODEL 1		
FGF21	4.143 (1.942-8.837)	<0.001
MODEL 2		
FGF21	4.143 (1.942-8.837)	<0.001
MODEL 3		
FGF21	3.780 (1.046-13.666)	0.043

Model 1=no adjustment for any confounding factor. Model 2=adjustment for age and gender. Model 3=adjustment for age, gender. BMI, body fat percentage, and waist circumference. The multivariate logistic regression analysis showed that after adjusting for age, gender, BMI, body fat percentage and waist circumference, and serum FGF21 levels were significantly associated with hyperthyroidism (OR [95%CI] 3.780 (1.046-13.666) *P*=0.043)

Sample size calculation

The sample size is 63 i.e., 63 cases and 63 controls. The sample size was calculated by N master software developed by the department of biostatistics, CMC, Vellore. A study conducted by Fangsen Xiao *et al*. revealed that FGF 21 (pg/ml) to be 228.10(169.85–320.10) and 290.67(156.60–502.33) among controls and hyperthyroidism patients, respectively.[6] On the basis of findings from the above study, it was estimated that 63 subjects in each group need to be recruited with an alpha level of 5% and keeping the power of study at 80%.

Statistical Methods

All the statistical analyses were performed using Statistical Package for Social Sciences version 18.0 (SPSS, Inc). Normally, distributed data were presented as mean ± SD. Non-parametric data were log arithmically transformed. Chi-square test and Student's unpaired t test were used for comparison of categorical and continuous variables, respectively. In case of non-normality, Mann-Whitney U test was used. The Student's paired t test was used for comparison

of the data before and after anti-thyroid treatment. Pearson's correlation analyses were used to examine the relationship between serum FGF21 levels and other parameters. Multivariable logistic regression was used to calculate the adjusted odds ratio ORs and 95% CIs. $P < 0.05$ was considered statistically significant.

Results

A total of 68 patients with hyperthyroidism and 63 age, sex, BMI matched healthy controls attending outpatient of Endocrinology department from January 2017 to December 2018 were studied. Among 68 patients with hyperthyroidism (sixty-six were Graves disease and two were toxic multinodular goiter), 45 patients achieved euthyroidism at 3 to 6 months after starting anti-thyroid drugs and were studied. Seven patients were lost to follow-up including 2 cases of toxic multinodular goiter, 6 patients underwent radio ablation, and 10 patients did not achieve euthyroidism at 3 to 6 months of treatment owing to poor compliance and non-adherence to therapy. The mean duration of follow-up was 4.6 ± 1.06 months. The male to female ratio in cases was 0.74(29/39) and in controls was 0.70 (26/37) *P* value = 0.87 [Table 1]. All hyperthyroid patients showed diffuse increased uptake on tc99 m scan suggestive of grave's disease.

Discussion

To our knowledge, this is the first study on serum FGF21 levels in patients with hyperthyroidism from India.

In our study, we found that the mean age in years was greater in hyperthyroid patients than the study done by Fansen Xiao *et al*.[6] (36.14 ± 10.01 vs. 33.7 ± 10.1). This is in concordance with the study done by Reddy SV *et al*. in north India in which the median age at onset in hyperthyroid patients was 36 years.[13] Male to female ratio in the cases was higher in our study than the study done by Fansen Xiao *et al*.[6] (29/39 vs. 31/88). The male to female ratio in a study done by Reddy SV *et al*. was lower than our study (74/161). The male to female ratio is higher in our study because in our country women come less frequently to the hospital because of socioeconomic reasons. A study done by Dutta *P et al*. showed that the mean BMI in kg/m^2 in hyperthyroid patients in Indian population was 20.5 ± 0.7 which was similar to our study in which mean BMI was 20.44 ± 2.13. They also showed that the mean waist circumference in cm in hyperthyroid patients in Indian population was 73.4 ± 2.3, whereas mean waist circumference in our study was 72.6 ± 3.7.[14]

In our study, the mean pulse rate and BMR percentage were higher in cases than the controls and was significant which is in concordance with the study done by Fansen Xiao *et al*.[6] BMR percentage was calculated from pulse rate and pulse pressure using Gale formula[9] in both the studies as it is widely used method. TH stimulates BMR by increasing ATP production for metabolic processes and by generating and maintaining ion gradients.[15] TH directly stimulates the Na+ K+ ATPase, but this effect has more impact on BMR in hyperthyroidism than in euthyroid or hypothyroid individuals.[15]

In our study, the serum total T4 and total T3 were higher, and TSH was lower in cases than the controls which are similar to study done by Fangsen Xiao *et al*. and was significant. However, in the study done by Fangsen Xiao *et al*., free T4 and free T3 levels were done instead of total T4 and T3. According to ATA 2016 guidelines, measurement of total T3 is preferred over free T3 because the assays for estimating free T3 are less widely validated and less robust than for free T4.[8] Although guidelines recommend measurement of free T4 over total T4, a study done by Li H *et al*. in south Asians showed that TSH and FT4 are the most valuable indicators in assessing thyroid function in a healthy population, and TSH and TT4 are the most meaningful in hyperthyroidism and hypothyroidism.[16]

In our study, we have excluded most conditions that can alter serum FGF21 levels like diabetes, renal failure, acute hepatitis, cancer, and any acute or chronic infections. We found that serum FGF21 levels were markedly elevated in patients with hyperthyroidism compared to healthy age and sex-matched healthy controls which is in concordance with study done by Fangsen Xiao *et al*., but the serum FGF21 levels in patients with hyperthyroidism were relatively higher in our study than their study (median 406.6 pg/ml [interquartile range 262.9–655.6] vs. 290.67 pg/ml [156.6–502.33]).[6] In contrast, a study done by Bonde *et al*. showed that in humans, FGF21 serum levels were unaltered in hyperthyroidism, but that study was limited by small sample size and lack of normal controls.[17] A study conducted by Guang Wang *et al*. showed that the patients with overt hypothyroidism had significantly lower FGF21 levels. Levothyroxine replacement treatment significantly increased the plasma FGF21 levels in the patients with overt hypothyroidism.[18] The serum FGF21 levels were higher in our study probably because of a higher level of insulin resistance in the Indian population.[19,20] The other possible explanations for higher levels of FGF21 levels in Indians are probably because of the presence of increased body fat especially visceral fat and increased levels of triglycerides in our population.[21-24] In our study, among 68 cases, 45 (66.1%) were followed up at 3 to 6 months after achieved euthyroidism following treatment with anti-thyroid drugs, whereas in the study done by Fangsen Xiao *et al*. among 119 cases, only 41 (34.4%) were followed up at 3 months after achieving euthyroidism. A study conducted by Chng CL *et al*. showed that the average duration of treatment that was required to reach euthyroidism in Asians was 38 ± 16.3 weeks.[25]

In our study, the weight gain observed in cases following treatment with anti-thyroid drugs was around 3.2 kg and was significant but was less compared to weight gain observed in the study done by Fangsen Xiao *et al*., which was around 5.7 kg. A study done by Dutta *P et al*. showed that in Indians the weight gain observed in hyperthyroid patients following treatment with anti-thyroid drugs for 3 months was 3.9 kg.[14] The mean BMI and waist circumference increased in cases

following treatment with anti-thyroid drugs and was significant [Table 2], which is similar to studies done by Fangsen Xiao *et al*. and Dutta *P et al*.[6,14] The mean BMR percent reduced in cases following treatment and was significant, which is in concordance with the study done by Fangsen Xiao *et al*.[6]

In our study, the serum FGF21 levels significantly declined in cases following treatment with anti-thyroid drugs and were statistically significant, which is similar to the study done by Fangsen Xiao *et al*.[6] The change in serum FGF21 levels in cases following treatment was higher in our study than their study.(ΔFGF21, 201.4 pg/ml vs. 147.8 pg/ml)

In our study, the mean body fat percentage was lower in cases than in controls and was significant. [22.11 ± 2.93% vs. 26.68 ± 3.29% *P* value < 0.001] The mean body fat percentage increased in cases following treatment with anti-thyroid drugs and was significant. [22.41 ± 2.91% vs. 25.12 ± 3.15% *P* value < 0.001]. This is line with few studies which showed treatment of hyperthyroidism results in an increase in the lean mass, fat mass, or both of them as the major component of weight gain. With the achievement of euthyroid status, the energy intake and resting energy expenditure is significantly decreased. This resulted in a significant increase in body weight, fat mass, and percentage body fat, without any significant change in fat-free mass in the initial 1 month after euthyroid status is established.[25-27] In our study, we used Jackson and Pollock 3 site equation for calculation of BD and Siri equation for calculation of body fat percentage which is a well-validated equation used in many studies.[28,29] The mean percentage of body fat obtained from the three equations of Jackson and Pollock (3-site, 4-site, and 7-site) was very close to that of body fat obtained from DEXA but suggest using Jackson-Pollock 3-site equation as it is simpler and faster than other methods.[30]

In our study, we found that serum FGF21 levels were positively correlated with serum T4, T3, pulse rate, and BMR% in all the subjects and were significant [Table 3], which is in concordance with study done by Fangsen Xiao *et al*. Serum FGF21 levels negatively correlated with serum TSH, waist circumference, and percentage of body fat in all subjects and were significant. There was no statistically significant correlation of serum FGF21 levels with age and BMI in all subjects. There was also no statistically significant correlation of serum FGF21 levels with the above parameters when cases and controls were evaluated separately probably because of the small sample size.

In our study, univariate logistic regression analysis showed that serum FGF21 levels were significantly associated with hyperthyroidism (OR [95% CI], 4.143 [1.942–8.837]; *P* < 0.001) [Table 4]. In the study done by Fangsen Xiao *et al*., univariate logistic regression analysis showed the OR for the association of serum FGF21 with hyperthyroidism was 1.734 [1.285–2.340] *P* value <0.001.

The multivariate logistic regression analysis showed that after adjusting to age, gender, BMI, body fat percentage and waist circumference, and serum FGF21 levels were significantly associated with hyperthyroidism (OR [95% CI] 3.780 (1.046–13.666) *P* value = 0.043). In the study done by Fangsen Xiao *et al*., multivariate logistic regression analysis showed that after adjusting to age, gender, and family history, the OR for FGF21 was 1.734 [1.281–2.348] *P* value <0.001. However, the OR was 3.123[1.306–7.467] *P* value = 0.01, when adjusted for various other confounding factors.

Several animal studies have confirmed the effect of TH on the expression of FGF21. A study done by Adams *et al*. showed that in mice acute treatment with T3 increases the level of circulating FGF21 levels by activating TH receptor β and crosstalk with PPARα, which mediates the action of T3 in the liver.[5] In a later study, they showed that chronic treatment with T3 also improved circulating FGF21 levels, but the systemic injection of FGF21 decreased serum TH level, indicating that FGF21 and thyroid hormone showed a mutual regulation in the mice.[31] Most actions of FGF21 are similar to that of the TH. It also modulates thermogenesis. FGF21 also converts white adipose tissue to beige adipose tissue and activates uncoupling protein 1- driven thermogenesis and energy expenditure.[32] In hyperthyroid patients, elevated serum FGF21 levels may mediate TH action on energy homeostasis.

Few other studies were done to study the association of serum FGF21 levels with thyroid disorders. A study conducted by Tianxu Fu *et al*. showed that FGF21 might participate in maintaining metabolic balance in humans through a mechanism different from TSH. Among metabolic syndrome free patients, FGF21 has no significant relationship with the TSH level and may be unrelated to thyroid autoimmunity.[33] A study conducted by Yenna Lee *et al*. showed that plasma FGF21 levels were significantly increased in patients with hypothyroidism independently of BMI, or lipid or glucose metabolism.

Limitations of the study

One of the limitation of our study was all the study subjects were recruited from a single hospital only, which makes it difficult to extrapolate these results to the general population. BMR is not an accurate measure to evaluate energy expenditure. BD and body fat percentage were calculated by Jackson and Pollock 3 site equation and Siri equation, respectively. Although they are validated methods, there are several new accurate methods for the calculation of body fat percentage. HOMA-IR and lipid profiles were not done in our study that would help in studying the association of insulin resistance and hyper triglyceridemia with serum FGF21 in our population.

Conclusions

Serum FGF21 levels are elevated in hyperthyroid patients in Indian population and show an independent association with hyperthyroidism. The levels declined significantly following treatment with anti-thyroid drugs once euthyroidism is achieved. They show an inverse correlation with body fat percentage and positive correlation with BMR.

These findings provide us therapeutic insight into the role of FGF21 inhibition in patients with hyperthyroidism for reversal of thyrotoxic symptoms. This could be particularly important in patients with thyrotoxic crisis where FGF21 inhibition can help in rapid reversal of life-threatening symptoms.

Our study has provided insight into all these mechanisms, and further studies are needed to establish the therapeutic use.

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Conflicts of interest

There are no conflicts of interest.

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