Original Article

Study of FGF21 Levels in Transgender People and its Association with Metabolic Parameters

Lohit Kumbar, Baratam Hari Kiran, Mala Dharmalingam, Pramila Kalra

Department of Endocrinology, M. S. Ramaiah Medical College, Bengaluru, Karnataka, India

Abstract

Background: Fibroblast growth factor (FGF21) is a metabolic regulator whose role in humans is unidentified. FGF21 has generated a lot of potential of becoming a therapeutic agent for the management of type 2 diabetes mellitus and dyslipidaemia. The role of FGF21 in gender dysphoria individuals has not been studied. **Objective:** Primary objective was to assess FGF21 levels in transgender individuals and compare with controls and secondary objective was to compare FGF21 levels with lipid and glucose parameters in transgender people. **Results:** Twenty-three transfemales and 21 transmales were included in the study and compared with 44 controls. Height and fasting blood glucose of transfemales was statistically greater than transmales, with no other differences in baseline characteristics. Although FGF21 levels were numerically greater in transfemales (183.50 ± 97.39), it was not statistically significant. FGF21 levels did not vary statistically when compared to controls although it was numerically higher. Univariate analysis was done in transgender patients and FGF21 levels were positively correlated with serum total cholesterol and serum LDL cholesterol in transfemales but not in transmales. Multivariate analysis was also done taking 50th centile and 75th centile of FGF21 levels of controls and was found that only serum total cholesterol and serum LDL positively correlated with FGF21 levels in transfemales with 75th centile as cutoff. **Conclusion:** FGF21 levels correlated positively with serum triglycerides and serum LDL cholesterol in transfemales but not in transmales. Hence, FGF21 levels can be used as a marker for the development of metabolic syndrome in transfemales.

Keywords: FGF21, glucose, lipid, metabolic syndrome, transgender

Introduction

Fibroblast growth factor (FGF21) is a member of the FGF family, which is preferentially expressed in the liver. FGF21 is a metabolic regulator whose role in humans is unidentified.[1]

The FGF21 is encoded by chromosome 19. This factor is produced in the liver, skeletal muscle, white adipose tissue and pancreas. The regulation of metabolism of glucose and lipids may depend on FGF21.[2]

Transgender individuals are characterized by incongruence between gender identity and assigned gender. The etiological reason for this phenomenon is yet to be identified but psychological and biological factors have been implicated. To mitigate the feeling of gender dysphoria, interventions such as gender-affirming hormonal therapy (GAHT) and gender-affirming surgery are done during the medical care of transgender persons.[3,4]

The regulation of glucose and lipid metabolism may depend on FGF21.[2] Studies have also shown that feeding and fasting may regulate FGF21 expression.[5] FGF21 may be a risk factor for some diseases like insulin resistance, type 2 diabetes mellitus and metabolic syndrome (MS).[6]

Gender-affirming therapy with hormones in transgender persons affects many components of MS. Testosterone therapy in transgender males causes more atherogenic lipid profile with lower high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol (LDL-C) values. But insulin sensitivity studies have shown mixed results. Oestrogen therapy in transgender females causes increased triglyceride levels but no increase in the risk of diabetes mellitus.[7,8] The primary mechanism of FGF21 is

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Address for correspondence: Dr. Pramila Kalra, Department of Endocrinology, M. S. Ramaiah Medical College, Mathikere, New BEL Road, Bengaluru - 560 009, Karnataka, India.
E-mail: kalrapramila@gmail.com

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maintaining energy balance through central nervous system control of food intake adaptation of liver, adipose tissue and pancreatic metabolism in fasting and feeding periods. FGF21 induces hepatic gluconeogenesis in the fasting state to secure energy supply to the tissues. In the liver, FGF21 activates the master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which negatively regulates FGF21 expression. On the contrary, pharmacological FGF21 treatment decreases plasma glucose levels, with the mechanism being not well understood. FGF21 has an impact on pancreatic β- and α-cell function. FGF21 treatment in rodent models increases islet insulin content and glucose-induced insulin secretion and inhibits glucagon secretion.[9] Studies on obesity/diabetes rodent models have reversed hepatic steatosis and obesity with FGF21 treatment. FGF21 has generated much potential of becoming a therapeutic agent for the management of type 2 diabetes mellitus and dyslipidaemia.[10]

The role of FGF21 in gender dysphoria individuals has not been studied. Hence, we intend to study the FGF21 levels in transgender individuals.

Materials and Methods

Study period

The duration of the study will be for a period of 6 months from August 2019 to January 2020.

Methods

Transgender patients attending endocrinology OPD were taken for the study. Serum samples for FGF21, fasting blood glucose, glycosylated haemoglobin (HbA1c), serum cholesterol, serum HDL, serum LDL and serum triglyceride were collected. In addition, other investigations as per routine standard of care were done. Patients were categorized into three groups. The first group was transfemales who were on hormonal therapy. The second group was transmales who were on hormonal therapy. The third group included age and BMI-matched control. FGF21 levels were compared among the three groups. FGF21 levels were correlated with lipid parameters like serum cholesterol, serum triglyceride, serum HDL, serum LDL and glucose parameters like FBS and HbA1c. The average dose of oestrogen received by the transfemales was 4–6 mg/day, and the average dose of testosterone received by the transmales was 200 mg/month.

Individuals with gender dysphoria aged more than 18 years who were on gender-affirming therapy for at least 6 months at the time of recruitment and were diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) or who had undergone transgender surgery and who were willing to give their consent were included in the study. Age- and BMI-matched controls were included in the study. Individuals with chronic diseases like chronic kidney disease, diabetes mellitus, chronic steroid therapy, chronic liver disease, thyroid illness and so on were excluded from the study.

The primary objective was to assess FGF21 levels in transgender individuals and compare them with controls. The secondary objective was to compare FGF21 levels with lipid and glucose parameters in transgender people.

Statistical methods

Statistical analysis of data: All the continuous variables such as androgen levels and FGF21 were expressed as mean and SD. In the case of non-normality, values were expressed as median with interquartile range. The difference in the mean/median values was tested for statistical significance by analysis of variance or Kruskal–Wallis test, categorical variables were expressed as percentages and associations were tested for statistical significance by Chi-square or Fischer's exact test.

Ethical Clearance Statement

Ethics committee- M S Ramaiah Medical College and hospital, Bangalore (DRP/IFP/406/2019/DATED 13-8-2019). Our study procedure follows the guidelines laid down in declaration of Helsinki.

Results

Baseline characteristics of transgender patients are summarized in Table 1. Height and fasting blood glucose of transfemales was statistically significant than the transmales, with no other differences in baseline characteristics. Although FGF21 levels were numerically greater in transfemales, it was not statistically significant. Although serum TSH was statistically higher in transmales, it was in the normal range in both groups. Height and weight were significantly higher statistically in transfemales when compared to transmales and controls. Other baseline characteristics comparing transgender with controls are summarized in Table 2. Although it was numerically higher, FGF21 levels did not vary statistically compared to controls.

Univariate analysis was done in transgender patients, and FGF21 levels were positively correlated with serum total

Table 1: Baseline characteristics of transgender patients

	Transfemales *n*=23	Transmales *n*=21	*P*
Age (years)	27.37±4.27	27.67±6.09	0.862
Height (cm)	170.34±7.43	157.66±5.67	**<0.001**
Weight (kg)	65.37±12.59	60.5±16.28	0.270
BMI (kg/m^2)	22.52±4.26	24.24±6.02	0.278
Hip circumference (cm)	88.96±10.53	90.71±11.38	0.598
Waist circumference (cm)	80.26±10.27	80.33±12.37	0.983
Fasting blood sugar (mg/dl)	91.87±8.56	86.14±5.77	**0.014**
HbA1c (%)	5.63±0.40	5.58±0.33	0.691
Serum TSH (mIU/l)	1.75±0.90	2.73±1.16	**0.003**
Serum total cholesterol (mg/dl)	196.96±3.43	183±32.10	0.146
Serum triglyceride (mg/dl)	184.74±292.84	117.95±44.95	0.308
Serum HDL (mg/dl)	47.52±12.04	45.14±12.74	0.528
Serum LDL (mg/dl)	121.81±26.97	120.17±30.90	0.724
Serum FGF21 (ng/l)	183.50±97.39	136.95±90.47	0.116

Bold letters indicate statistical significance $P<0.05$

Table 2: Baseline comparison between transgender patients and controls

	Transfemales $n=23$	Transmales $n=21$	Controls $n=43$	*P*
Age (years)	27.37±4.27	27.67±6.09	26.39±5.61	0.607
Height (cm)	170.34±7.43	157.66±5.67	156.19±4.54	**<0.001**
Weight (kg)	65.37±12.59	60.50±16.28	55.90±8.05	0.007
BMI (kg/m^2)	22.52±4.26	24.24±6.02	22.95±3.39	0.390
Hip circumference (cm)	88.96±10.53	90.71±11.38	82.89±7.11	**0.002**
Waist circumference (cm)	80.26±10.27	80.33±12.37	76.74±7.03	0.203
FGF21 (ng/l)	183.50±97.39	136.95±90.47	157.51±138.99	0.428

Bold letters indicate statistical significance $P<0.05$. BMI: Body mass index, FGF: Fibroblast growth factor

cholesterol and serum LDL cholesterol in transfemales but not in transmales. Other parameters did not correlate with FGF21 levels which are summarized in Table 3.

Multivariate analysis was also done taking 50th centile and 75th centile of FGF21 levels of controls. It was found that only total serum cholesterol and serum LDL were positively correlated with FGF21 levels in transfemales with 75th centile as the cut-off [Table 4].

Discussion

Our study demonstrated that FGF21 levels were similar in the transmales and transfemales and did not differ when compared with the age- and BMI-matched controls. In a study done by Auer *et al*.,[3] FGF21 serum concentration decreased in transwomen ($P = 0.010$). Nevertheless, it remained unchanged in the transmen after a follow-up period of 12 months. In a healthy individual, there is an increase in serum FGF21 levels with ageing independent of body composition, highlighting the effect of age on metabolic demand.[11]

In a study by Zhang *et al*.,[2] serum FGF21 levels in overweight/obese subjects were significantly higher than in lean individuals, whereas in our study FGF21 levels did not correlate with weight or BMI.

In a study by Kralisch *et al*.,[1] done in diabetics and non-diabetics, FGF21 levels positively correlated with age, blood pressure, weight, BMI, waist circumference, hip circumference, fasting glucose, fasting insulin, total cholesterol, LDL cholesterol and triglyceride. Multivariate regression analysis from the same study showed that gender, systolic blood pressure, triglyceride, gamma-glutamyl transferase and IGF1 remained independently associated with circulating FGF21 levels after adjustment for age, WHR, Stumvoll index, HDL cholesterol, GFR and $P < 0.05$.[1] Triglyceride and serum LDL levels were positively correlated with FGF21 levels in transfemales, whereas no such association was seen with transmales in our study, whereas in a study by Auer *et al*.,[3] in transwomen, a reduction in triglycerides was associated with a decrease in fat mass and an increase in FGF 21 levels ($P < 0.001$). Interestingly in transmen, no significant changes were seen in TGs during the observation period; however, FGF21 had a positive association. Furthermore, in transmales, an increase in LDL-C was predicted by a decrease in FGF 21.[3] In a study by Ruo-Yao Gao *et al*.,[12] it was shown that hypertension, BMI, WC, body fat mass, SBP, DBP and metabolic parameters like logarithmically transformed TG (log-TG), LDL-C level, log-glucose, log-insulin and

Table 3: Univariate analysis of lipid and glucose parameters among transgender

Univariate analysis	Transfemales		Transmales	
	R	*P*	*R*	*P*
Fasting blood glucose	0.136	0.535	−0.067	0.774
Glycosylated haemoglobin	0.369	0.083	−0.198	0.390
TSH	0.278	0.199	0.072	0.758
Total cholesterol	0.694	**<0.001**	0.278	0.222
Serum triglyceride	0.168	0.443	0.282	0.215
Serum HDL	0.095	0.668	0.002	0.995
Serum LDL	0.687	**<0.001**	0.210	0.361

Bold letters indicate statistical significance $P<0.05$. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormone

Table 4: Multivariate analysis of lipid and glucose parameters among transgender with 50th and 75th centile FGF21 levels of controls

	With 75th centile of FGF21 as cut-off		With 50th centile of FGF21 as cut-off	
	B	*P*	*B*	*P*
Age	0.072	0.788	0.215	0.643
Gender	0.177	0.674	0.343	0.558
Weight	4.312	**0.038**	1.181	0.277
Height	1.120	0.290	0.964	0.326
Hip circumference	1.452	0.228	0.373	0.541
Waist circumference	2.645	0.104	0.275	0.600
BMI	2.686	0.101	0.386	0.534
Fasting blood glucose	1.194	0.274	0.026	0.873
HbA1c	0.987	0.321	0.095	0.758
TSH	1.184	0.277	0.019	0.890
Total cholesterol	6.345	**0.012**	3.538	0.060
Serum triglyceride	0.602	0.438	0.338	0.561
Serum HDL	0.678	0.410	1.197	0.274
Serum LDL	5.589	**0.018**	1.574	0.210

Bold letters indicate statistical significance $P<0.05$. BMI: Body mass index, FGF: Fibroblast growth factor, HDL: High-density lipoprotein, HbA1c: Glycosylated haemoglobin, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormone

log-HOMA-IR positively correlated with FGF21. The other parameters like log-creatinine and log-UACR also correlated positively, whereas HDL-C and eGFR negatively correlated with serum FGF21 levels in T2DM patients.

In a study by Claver *et al*.,[4] transwomen tended to increase more in HOMA-IR after adding estradiol than ciswomen, resulting in a higher HOMA-IR value at 22 years. Possibly, this increase is due to the significant increase in body fat in transwomen. In our study, HOMA-IR was not done, but FGF21 levels did not correlate with fasting blood glucose or HbA1c.

In a study by Kralish *et al*.,[1] done in diabetic patients, there was a significant increase in serum FGF21 levels in type 2 diabetic patients compared with non-diabetic controls after adjustment for gender and age ($P < 0.001$). However, our study was a cross-sectional study; hence, hormonal therapy before and after treatment on FGF21 levels could not be assessed.

A study by Zhang *et al*.,[2] which studied the association of FGF21 levels with obesity, suggested that the paradoxical rise in FGF21 levels in obesity may be a protective response by the human body to overcome the metabolic stress imposed by obesity. On the contrary, obesity may result in resistance to FGF21 actions, leading to its compensatory increase in FGF21. There are no studies to our knowledge to compare FGF21 levels before and after sex reversal surgery. A study by Crujeiras *et al*.[13] showed no differences in FGF21 levels between various energy-restricted dietary treatments. However, the study showed a significant increase in FGF21 levels in morbidly obese patients after bariatric surgery, especially after 1 month (148.8 pg/ml higher than baseline).

Several studies in the Chinese population have revealed that higher serum FGF21 is an independent predictor of the MS in Asians, and FGF21 levels are significantly elevated among prediabetic and diabetic patients and can predict the development of diabetes.[2,14] The discovery of FGF21 as a potent agent for treating obesity and type 2 diabetes mellitus in animals has inspired the development of engineered FGF21 analogues and mimetics with improved potency and pharmacokinetic profiles. Several FGF21 analogues and mimetics have progressed to early clinical trials in patients with obesity, type 2 diabetes mellitus and NASH. In these trials, the primary endpoints of glycaemic control have not been met, whereas substantial improvements were observed in dyslipidaemia, hepatic fat fractions and serum markers of liver fibrosis in patients with NASH.[6]

The limitation of the study was that only female controls were taken for comparison. Previous studies have demonstrated no possible sexual differences in FGF21-concentrations in either adults or children except for one study where FGF21 levels were significantly higher in girls compared with boys, which was partly attributed to the higher triglyceride levels in girls.[15] Pre- and post-GAHT and sex reassignment surgery levels of FGF21 levels were not studied as the sample size was less and the study was not powered for this.

Conclusion

FGF21 levels correlated positively with serum triglycerides and LDL cholesterol in transfemales but not in transmales. Thus, FGF21 can also be a useful marker for the prediction of the development of MS in transfemales.

Key message

Transgender people receiving hormonal therapy are increasing and hence metabolic syndrome. Thus, it is necessary to identify people at risk for metabolic syndrome prior to its development as well as during the course of the treatment using parameters like FGF21.

Informed Consent

Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kralisch S, Tönjes A, Krause K, Richter J, Lossner U, Kovacs P, *et al*. Fibroblast growth factor-21 serum concentrations are associated with metabolic and hepatic markers in humans. J Endocrinol 2013;216:135-43.
2. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, *et al*. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 2008;57:1246-53. Erratum in: Diabetes 2019;68:235.
3. Auer MK, Ebert T, Pietzner M, Defreyne J, Fuss J, Stalla GK, *et al*. Effects of sex hormone treatment on the metabolic syndrome in transgender individuals: Focus on metabolic cytokines. J Clin Endocrinol Metab 2018;103:790-802.
4. Klaver M, de Mutsert R, van der Loos MATC, Wiepjes CM, Twisk JWR, den Heijer M, *et al*. Hormonal treatment and cardiovascular risk profile in transgender adolescents. Pediatrics 2020;145:e20190741.
5. Klaver M, de Mutsert R, Wiepjes CM, Twisk JWR, den Heijer M, Rotteveel J, *et al*. Early hormonal treatment affects body composition and body shape in young transgender adolescents. J Sex Med 2018;15:251-60.
6. Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: From bench to clinic. Nat Rev Endocrinol 2020;16:654-67.
7. Matikainen N, Söderlund S. Fibroblast Growth Factor 21 as a Regulator of Energy Metabolism in the Liver and Adipose Tissue. Nutrition in the Prevention and Treatment of Abdominal Obesity. 2019. p. 131-52.
8. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2017;102:3869-903.
9. Van Velzen D, Wiepjes C, Nota N, van Raalte D, de Mutsert R, Simsek S, *et al*. Incident diabetes risk is not increased in transgender individuals using hormone therapy. J Clin Endocrinol Metab 2022;107:e2000-7.
10. Kleinert M, Müller TD. A new FGF21 analog for the treatment of fatty liver disease. Diabetes 2020;69:1605-7.
11. Hanks LJ, Gutiérrez OM, Bamman MM, Ashraf A, McCormick KL, Casazza K. Circulating levels of fibroblast growth factor-21 increase with age independently of body composition indices among healthy individuals. J Clin Transl Endocrinol 2015;2:77-82.

12. Gao RY, Hsu BG, Wu DA, Hou JS, Chen MC. Serum fibroblast growth factor 21 levels are positively associated with metabolic syndrome in patients with type 2 diabetes. Int J Endocrinol 2019;2019:5163245. doi: 10.1155/2019/5163245.
13. Crujeiras A, Gomez-Arbelaez D, Zulet M, Carreira MC, Sajoux I, de Luis D, *et al.* Plasma FGF21 levels in obese patients undergoing energy-restricted diets or bariatric surgery: A marker of metabolic stress? Int J Obes 2017;41:1570-8.
14. Chen C, Cheung BMY, Tso AWK, Wang Y, Law LS, Ong KL, *et al*. High plasma level of fibroblast growth factor 21 is an independent predictor of type 2 diabetes: A 5.4-year population-based prospective study in Chinese subjects. Diabetes Care 2011;34:2113-5.
15. Bisgaard A, Sørensen K, Johannsen TH, Helge JW, Andersson AM, Juul A. Significant gender difference in serum levels of fibroblast growth factor 21 in Danish children and adolescents. Int J Pediatr Endocrinol 2014;2014:7. doi: 10.1186/1687-9856-2014-7.