Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 13s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Association Of Fgf21 Gene Polymorphism And Serum Fgf21 Levels In Type 2 Diabetes Mellitus Susceptibility

Shashank Kambali M[1], Rajesh Paluru[2], R Anusha[3], Kayalvizhi E[4], Ramnath V[5]*

.[1]PhD Scholar, Faculty of Medicine, Meenakshi Academy of Higher Education and Research, Chennai, Tamilnadu, 600078.

[2]Professor, Department of Physiology, Viswabharathi Medical College & General Hospital, Kurnool, Andhra Pradesh, 518467.

[3]III Year MDS, MeenakshiAmmal Dental College and Hospital, Chennai, Tamilnadu, 600095.

[4]Professor, Department of Physiology, Meenakshi Medical College Hospital and Research Institute, Kanchipuram, Tamil Nadu, 631552.

[5*]Professor, Faculty of Allied Health Sciences, Meenakshi Academy of Higher Education and Research, Kanchipuram, Tamil Nadu, 631552.

[2]Department of Pharmacology, Nitte College of Pharmaceutical Sciences Bangalore 560064.

[*3]Department of Pharmaceutical Analysis, Seven Hills college of Pharmacy, Tirupati, Andhra Pradesh 517561.

[4]Department of Chemistry, Institute of pharmaceutical Education and Research, Ale, Tal. junnar, Pune. Maharashtra, India Pin- 412411.

[5]Department of Pharmaceutics, Bengal college of Pharmaceutical Technology, Dubrajpur, Birbhum,731123.

[*]**Corresponding author:**

Dr.Ramnath V

Professor, Faculty of Allied Health Sciences, Meenakshi Academy of Higher Education and Research (MAHER), Kanchipuram, Tamil Nadu, 631552.

.Cite this paper as: Shashank Kambali M, Rajesh Paluru, R Anusha, Kayalvizhi E, Ramnath V, (2025) Association Of Fgf21 Gene Polymorphism And Serum Fgf21 Levels In Type 2 Diabetes Mellitus Susceptibility *Journal of Neonatal Surgery*, 14 (13s), 1289-1298.

ABSTRACT

Background: Fibroblast growth factor 21 is a key endocrine regulating protein factor involved in ontogenesis and metabolism, produced primarily in the liver, expressed in adipose tissue, skeletal muscle, pancreas, heart, and other organs. It increases insulin sensitivity, stimulates lipolysis, and suppresses lipogenesis in-turn affects glucose and lipid metabolism. The present study was aimed to screen for rs1800629 and rs1799964 polymorphisms in type 2 diabetic patients.

Methods:A total of 100 samples comprising of 60 cases and 40 controls were enrolled. Patients were selected based on American Diabetes Association Criteria 2007, non-diabetic age matched healthy individuals were selected as controls. Following extraction of DNA, genotyping for rs838133 and rs499765 was performed by allele specific PCR. Appropriate statistical toolswere used to analyse the results.

Results: The serum FGF21 levels was elevated in cases compared to controls ($p<0.05$). The distribution of genotypes for rs838133 varied significantly between the groups ($p =0.02$), however it was not for rs499765. The CC genotype of rs838133 demonstrated a four fold risk towards disease susceptibility while the A allele and C allele showed an OR of 0.44 and 2.25 respectively. Further categorization of cases into subgroups viz., cases who exercise and cases who do not exercise, did not significant results with respect to genotypes, however there was an allelic association. The A allele and allele C demonstrated an OR value of 0.33 and 3.0 respectively. For rs499765, the C allele and G allele revealed an OR value of 0.51 and 1.93 conferring its protective and predisposing role among cases who exercise and who do not exercise.

Conclusion: FGF21 polymorphism appeared to be a potential molecular marker for diabetes risk in our population. This is the first report from South India; however, replicative studies considering other probable causative factors for T2DM risk are warranted.

1. INTRODUCTION

Diabetes mellitus (DM) is the most prevalent metabolic disorder affecting populations worldwide [1]. It is a chronic disease caused by either insulin deficiency or insulin resistance, leading to elevated blood glucose levels. Diabetes is a significant cause of morbidity and mortality, primarily due to its long-term complications rather than its immediate effects. Among these complications, individuals with diabetes face a heightened risk of cardiovascular disease (CVD) compared to those with normal glucose tolerance.

The aetiology is not yet clear however genetic, biochemical, immunological and environmental factors are implicated in the aetiopathogenesis of this multifactorial condition [2]. Several candidate genes have been proposed as important contributors to diabetes mellitus but none have yet achieved acceptance as major cause [3].

Fibroblast growth factor 21 (FGF-21) is a protein that in mammals is encoded by the FGF21gene.FGF21 gene codes for a member of the fibroblast growth factor group. It is located on chromosome 19q13.33, consists of four exons and a size of 2,810 bases [4]. It is a hormone generated mostly by the liver and plays an essential role in ontogenesis, metabolism and signalling to the hypothalamus paraventricular nucleus to limit alcohol and sugarconsumption, increasing glucose absorption by adipocytes, and working as an insulin sensitivity enhancer [5,6].In adipose tissue, the encoded protein increases glucose absorption. Epperlein et al., (2021) suggested Fibroblast growth factor 21 (FGF21) as a regulator of addictive behaviour like eating, food and drug cravings [7].

Functional single nucleotide polymorphism (SNP) at flanking region (rs499765) and exon 1 (rs838133) of human FGF21 gene have been shown to be linked with altered promoter activity and alteredgene expression, resulting in translational dynamics or abnormal splicing of FGF21[8].In view of the above, the present study was aimed to screen for rs499765 and rs838133 polymorphisms in South Indian population.

MATERIALS AND METHODS

Study population

The study was carried out in 100 cases comprising of 60 type 2 diabetes patients and 40 normal healthy age matched Controls. Samples were obtained from Aayan Hospital, Hyderabad, India. Patients were selected based on American Diabetes Association Criteria 2007. Informed consent was taken from subjects prior to sample collection. Ethical clearance was obtained from institutional ethics committee. Detailed information regarding the symptoms of type 2 diabetes, its duration, complications and information on personal history like dietary habits, smoking, exercise was collected through proforma.

Molecular analysis

Five millilitres of blood sample were collected from all the participants using EDTA as anticoagulant. Genomic DNA was extracted by standard protocol routinely used in our laboratory. For each subject, the FGF21 genotyping was performed by allele specific polymerase chain reaction using one common forward and two reverse primers (specific for wild allele and variant allele). The primers were designed using the online software Primer 3 (https://primer3.ut.ee) and the primer sequences are illustrated in Tables 1. PCR amplification was carried out in a total volume of 10 µl containing 50 ng template DNA, 0.15 µl of each primer (Bioserve, India) 5.00 µlmaster mix (Emrald GT,).

PCR was performed in a thermocycler (Biorad) with following conditions for rs499765: an initial denaturation step for 5 min at 95 °C, then 30 cycles consisting of 30 s of denaturation at 94 °C, 45 s of annealing at 59 °C and a final extension for 5 min at 72°C. The PCR was carried out in a 10 µ l volume with an initial denaturation at (94°C for 5 min), denaturation on (94°C for 30 s), annealing at (56°C for 30 s), extension on (72°C for 60 s) for 30 cycles, and a final extension at (72°C for 5min) for rs838133. The amplicons obtained were run on 2% agarose gel along with 100 bp ladder and analysed in gel documentation system (Biorad) for genotyping.The product size of rs499765 and rs838133 SNPs are 122 bp and 196 bp respectively (Figure 1).

Table 1: The allele specific primer sequence of rs838133 and rs499765

rs838133 (A>C)	5'-3'	Product Size
Common Forward	CTGGAGCTTCTGCATCTATC	242 bp
A specific Primer	CAGCACAGAAACCCACAAT	
C specific Primer	CAGCACAGAAACCCACAAG	

rs499765 (C>G)	5'-3'	Product Size
Common Forward	ACAGAACCCACACTGAGAAG	196 bp
C specific primer	GTTTGCAAAGGATTTGGGACG	
G specific primers	GTTTGCAAAGGATTTGGGACC	

Statistical Analysis

All the statistical analysis was performed with the help of SPSS statistical software (IBM SPSS). Allele and genotype frequencies were determined from observed genotype counts. Genotypic, allelic frequencies and Hardy-Weinberg equilibrium were calculated using chi-square analysis. The association between genotypes and diabetes mellitus risk was evaluated by calculating the odds ratios (OR) at 95 % confidence interval. A two tailed p-value of <0.05 was considered to be statistically significant.

2. RESULTS

BiochemicalAnalysis

The FGF21 levels differed significantly among the cases and control group ($p<0.05$) and their subgroups ($p<0.05$) The FGF21 levels in overall study group, CWE and CWDE is given in Table 2.

Table 2: Mean FGF21 levels among cases, controls and subgroups.

Groups	FGF21 Levels	t-statistic	p-value
Cases (60)	382.83 ± 159.71	8.5580	**0.0001***
Controls (40)	156.59 ± 59.66		
CWE (30)	331.72 ± 151.25	2.5966	**0.01***
CWDE (30)	433.94 ± 153.67		

CWE: Cases who exercise; CWDE: Cases who do not exercise

MolecularAnalysis

Genotype Frequencies (Total cases vs. total controls)

Table 3 describes the percentage distribution of rs838133 polymorphisms among cases and control groups. The overall genotype frequencies of AA, AC and CC of rs838133 were 18.3%, 38.3% and 43.4% in patients, while they were 30%, 55 % and 15% in controls respectively. The frequency of A and C alleles were 0.38 and 0.62 in cases while it was 0.58 and 0.42 in controls correspondingly. The genotype ($\chi2 = 7.26$; $p = 0.02$*) and allele frequencies ($\chi2 = 7.23$; $p = 0.007$*) differed significantly between the groups.

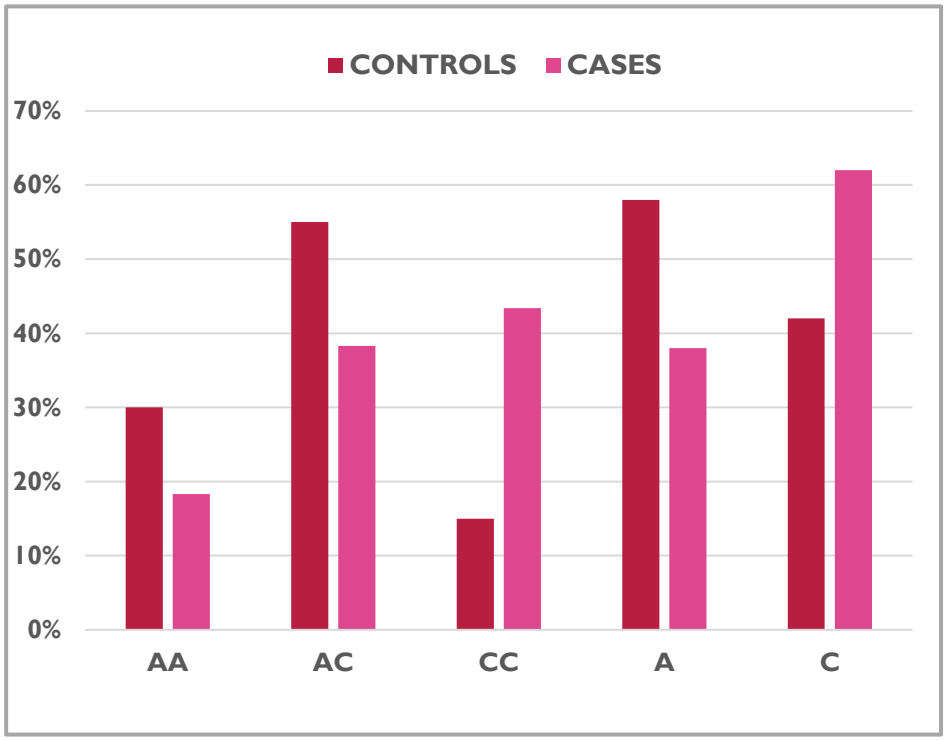
The genotype frequencies of CC, CG and GG of rs499765 polymorphism were 13.3%, 45% and 41.7% in patients, while they were 20%, 55% and 25% in controls, respectively. The frequency of C and G alleles were 0.36 and 0.64 in cases while it was 0.48 and 0.52 in controls correspondingly. The genotype ($\chi2 = 2.08$; $p = 0.35$) and allele frequencies ($\chi2 = 2.48$; $p = 0.11$) did not differ between the groups. [Table 4]

Table 3: Genotype and allelic frequency distribution of FGF21 rs838133 A>Cpolymorphisms among patients and controls

rs838133 A>C	AA N (%)	AC N (%)	CC N (%)	A	C
Controls(40)	12(30)	22(55)	6(15)	0.58	0.42
Patients(60)	11(18.3)	23(38.3)	26(43.4)	0.38	0.62
	χ^2=7.26; p=0.02*			**χ^2=7.23;p=0.007***	

HWE	Controls	χ^2= 0.628; p = 0.428
	Patients	χ^2= 1.99; p = 0.15

HWE – Hardy Weinberg Equilibrium

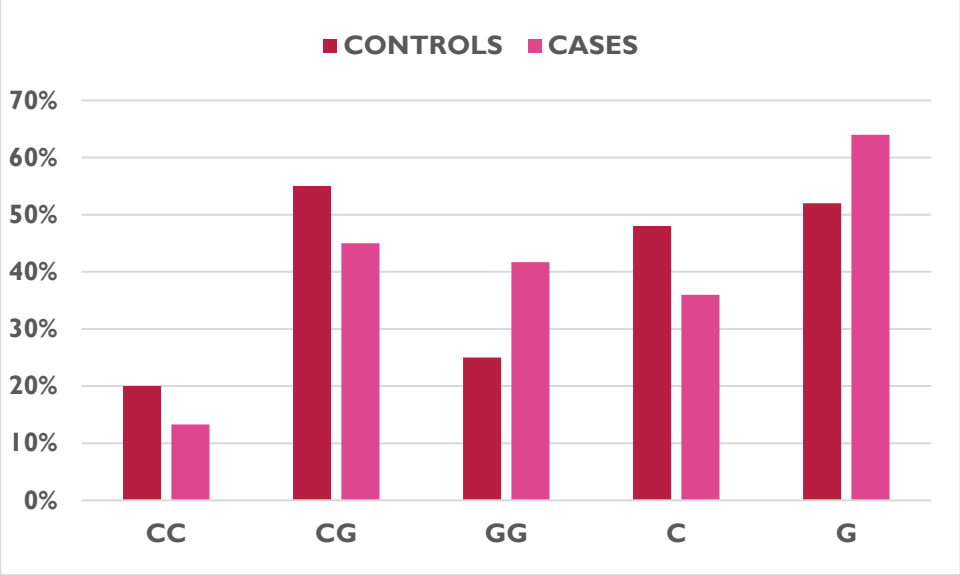


Graph 1: Genotype and allelic frequency distribution of FGF21 rs838133 A>Cpolymorphisms among patients and controls

Table 4: Genotype and allelic frequency distribution of FGF21rs499765 A>Cpolymorphisms among patients and controls

rs499765 C>G	**CC N (%)**	**CG N (%)**	**GG N (%)**	**C**	**G**
Controls (40)	8 (20)	22 (55)	10 (25)	0.48	0.52
Patients (60)	8 (13.3)	27 (45)	25 (41.7)	0.36	0.64
	χ^2= 2.08; p = 0.35			χ^2=2.48;p=0.11	
HWE	Controls	χ^2= 0.422; p = 0.515			
	Patients	χ^2= 0.027; p = 0.86			

HWE – Hardy Weinberg Equilibrium



Graph 2: Genotype and allelic frequency distribution of FGF21 rs499765 polymorphisms among patients and controls

Risk Analysis (Total cases vs. total controls)

The C allele and CC genotype predominated in the casesand revealed an OR value of 2.25 and 4.33 respectively (p=0.007*) while the A allele was showing an OR value of 0.44 (p=0.005*) conferring its protective and predisposing role towards disease susceptibility. The genotypic distributions of the two polymorphisms were in accordance with Hardy Weinberg equilibrium in both patients and controls (p > 0.05).[Table 5]

Table 5:Risk analysis of FGF21 rs838133 and rs499765 polymorphisms among patients and controls

Comparison of groups	**OR**	**95% CI**	**p-value**
AA vs. AC+CC	0.52	0.20 – 1.34	0.22
AC vs. AA + CC	0.50	0.22 – 1.14	0.51
CC vs. AA + CC	4.33	1.58 – 11.8	**0.005***
A vs. C	0.44	0.25 – 3.96	**0.007***
C vs. A	2.25	1.27 – 3.96	**0.007***
Comparison of groups	**OR**	**95% CI**	**p-value**
CC vs. CG+GG	0.62	0.21 – 1.80	**0.41**
CG vs. CC+GG	0.66	0.30 – 1.49	0.43
GG vs. CC+CG	2.14	0.88 – 5.16	0.13
C vs. G	0.52	0.29 – 0.91	**0.03***
G vs. C	1.64	0.93 – 2.89	0.11

OR – Odds Ratio, CI – Confidence Interval

Genotype Frequencies (Cases who exercise vs. cases who do not exercise)

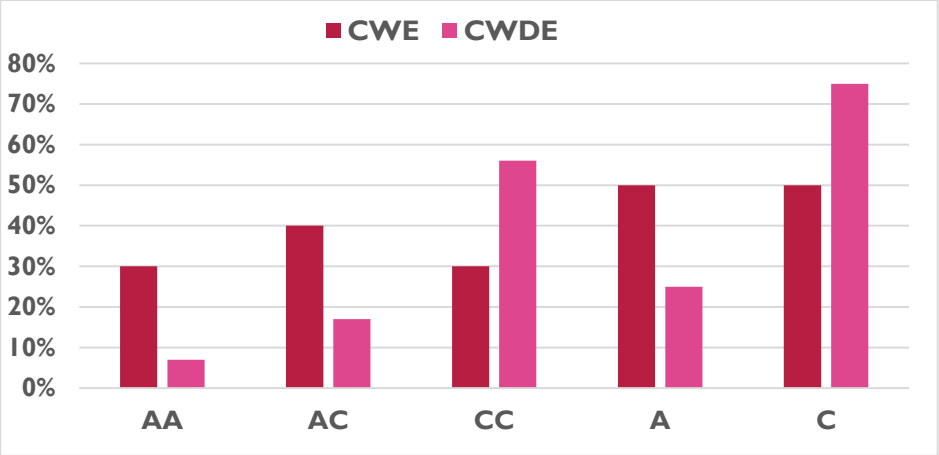
Table 6 describes the percentage distribution of rs838133 polymorphisms among cases who exercise (CWE) and cases who do not exercise (CWDE). The overall genotype frequencies of AA, AC and CC of rs838133 were 30%, 40% and 30% in cases who exercise, while they were 7%, 17 % and 56% in cases who do not exercise respectively. The frequency of A and C alleles were 0.50 and 0.50 in cases who exercise while it was 0.25 and 0.75 in cases who do not exercise respectively. The genotype frequencies did not vary while the allele frequencies differed significantly between the groups ($\chi 2 = 12.29$; $p = 0.0004$*).

The genotype frequencies of CC, CG and GG of rs499765 polymorphism were 20%, 47% and 33% in cases who exercise, while they were 7%, 43% and 50% in in cases who do not exercise respectively. The frequency of C and G alleles were 0.43 and 0.57 in CWE while it was 0.28 and 0.72 in CWDE correspondingly. The genotype did not vary between the groups whereas allele frequencies differed significantly between the groups ($\chi 2 = 4.28$; $p = 0.03$*). [Table 7]

Table 6: Genotype and allelic frequency distribution of FGF21 rs838133 A>Cpolymorphisms among CWE and CWDE groups.

rs838133 A>C	AA N (%)	AC N (%)	CC N (%)	A	C
CWE (30)	9(30)	12(40)	9(30)	0.50	0.50
CWDE (30)	2(7)	11(17)	17(56)	0.25	0.75
	χ^2=5.15; p=0.07			**χ^2=12.29; p=0.0004***	
HWE	CWE	χ^2= 1.2; p = 0.27			
	CWDE	χ^2= 0.014; p = 0.903			

HWE – Hardy Weinberg Equilibrium



Graph 3: Genotype and allelic frequency distribution of FGF21 rs838133 A>Cpolymorphisms among CWE and CWDE

Table 7: Genotype and allelic frequency distribution of FGF21rs499765 C>Gpolymorphisms among CWE and CWDE

rs499765 C>G	CC N (%)	CG N (%)	GG N (%)	C	G
CWE (30)	6 (20)	14 (47)	10 (33)	0.43	0.57
CWDE (30)	2 (7)	13 (43)	15 (50)	0.28	0.72
	χ^2= 1.76; p = 0.41			**χ^2=4.28; p=0.03***	
HWE	CWE	χ^2= 0.074; p = 0.785			
	CWDE	χ^2= 0.134; p = 0.713			

HWE – Hardy Weinberg Equilibrium

Graph 4: Genotype and allelic frequency distribution of FGF21 rs499765 polymorphisms among CWE and CWDE groups

Risk Analysis(Cases who exercise vs. cases who do not exercise)

The A allele and AA revealed an OR value of 0.16 and 0.33 respectively ($p<0.05$) while the C allele was showing an OR value of 3.0 ($p<0.05$) conferring its protective and predisposing role towards disease susceptibility. The genotypic distributions of the two polymorphisms were in accordance with Hardy Weinberg equilibrium in both patients and controls ($p> 0.05$).[Table 8]

Table 8: Risk analysis of FGF21 rs838133 and rs499765polymorphisms among CWE and CWDE groups

Comparison of groups	**OR**	**95% CI**	**p-value**
AA vs. AC+CC	0.16	0.03 – 0.85	0.04*
AC vs. AA + CC	0.86	0.30 – 2.46	1.0
CC vs. AA + CC	3.1	1.05 – 8.83	0.06
A vs. C	0.33	0.18 – 0.61	**0.0004***
C vs. A	3.0	1.64 – 5.45	**0.0004***
Comparison of groups	**OR**	**95% CI**	**p-value**
CC vs. CG+GG	0.28	0.05 – 1.54	0.25
CG vs. CC+GG	0.87	0.31 – 2.41	1.0
GG vs. CC+CG	2.0	0.70 – 5.67	0.29
C vs. G	0.51	0.28 – 0.92	**0.03***
G vs. C	1.93	1.07 – 3.49	**0.03***

OR – Odds Ratio, CI – Confidence Interval

3. DISCUSSION

Fibroblast growth factor 21 (FGF21) is a peptide, synthesized by several organs and regulates energy homeostasis. FGF-21 signalling has been suggested to affect glucose, lipid, cholesterol, and bile acid metabolism (9,10), which has turned FGF-21 into a reasonable candidate directly affecting the pathophysiology of the metabolic syndrome and T2DM. The present study was aimed to understand more about the disease pathogenesis improve treatment choices, and to identify persons who

are at high risk of acquiring diabetes. Two flanking SNPs (rs499765 and rs838133) of the FGF21 gene were investigated among type 2 diabetes cases and age matched healthy controls. Several studies have reported increased serum FGF21 levels in individuals with obesity, the metabolic syndrome and type 2 diabetes [11-15]. In our study, serum FGF21 was significantly higher in individuals with type 2 diabetes compared with age-matched control participants. Further categorization of cases with respect to physical activity, revealed higher levels of FGF21 among cases who do not exercise than cases who exercise. A similar tendency for higher serum FGF21 levels in the basal state was observed in type 2 diabetes in previous studies. Previous studies have reported that insulin promotes FGF21 expression and release in human muscle cells, and serum of healthy young individuals [11, 16-18].

Variation in FGF21 gene was reported to be involved in regulating glucose and lipid metabolism, and the rs838133 variant may influence these processes by affecting FGF21 levels or activity. Our findings suggest a strong association of rs838133 variant with diabetes susceptibility similar to the findings of Alginabi et al., in Iranian population and dissimilar to the observations of Yu et al., and Faryling et al., where they did not any significant association between these SNPs and susceptibility to type 2 diabetes and diabetes kidney disease respectively [19-21]. Frayling et al., in the year 2018 reported the association of A allele with higher blood pressure and waist-hip ratio, despite an association with lower total body-fat percentage, than it is with BMI or type 2 diabetes [21]. The rs838133 variation is also linked to increased intake of alcohol and cigarettes, as well as other types of reward seeking behaviour [22].Soberg et al in 2017 concluded that rs838133 variant do not do not correlate with obesity, T2DM, or glucose intolerance, however the A allele was associated with lower BMI, waist circumference and better glycemic control [23]. The rs499765 polymorphism did not reveal any association similar to the findings of Alginabi et al and Jiang et al., [19,24]. The G allele was conferring around two fold risk towards disease complications among cases who do not exercise. This finding was contradictory to the observations of Jiang et al., where C allele was conferring a higher risk (OR around 1.5) among nonalcoholic fatty liver disease cases [24].

The FGF21 is expressed in numerous tissues, including liver, adipose tissue, muscle, stomach, brain and pancreas [25]. The serum FGF21 concentrations in persons with poorly managed diabetes are substantially higher than in those with healthy controls and well-controlled diabetes. Our findings demonstrated increasedconcentrations of FGF21 among type 2 diabetes mellitus cases and poorly managed diabetes individuals than controls. Both healthy controls and diabetes case who exercise had lower FGF21 serum levels similar to the findings of Panahi et al., 2016 [26]. High blood levels of FGF21 were linked to insulin resistance and impaired glucose metabolism in patients with type 2 diabetes which may indicate a role in the pathogenesis of T2DM[14, 27-28]. Finally, it can be assumed that the FGF 21 levels are elevated to counter balance any pathophysiological condition. In T2DM, FGF-21 is known to beincreased in fatty liver disease [29], whichin turn is known to precede the metabolicsyndrome and T2DM. Thus, FGF-21 might be considered as a marker of very early metabolicdisturbances preceding T2DM andthe metabolic syndrome.

4. CONCLUSION

In conclusion, our findings revealed a strong association of rs838133 polymorphism in manifestation of T2DM; however, rs499765 polymorphism suggests lack of direct involvement in the genetic predisposition to T2DM and its clinical traits. Further categorization of cases into CWE and CWDE and analysis showed elevated levels of FGF21 among cases who do not exercise compared to cases who exercise. To the best of our knowledge, this is the first report from South India with respect to rs838133 and rs499765 SNPs of FGF21, a hepatokine. The limitation of the present study was the small sample size. Replicative studies on different ethnic groups are warranted to understand the potentiality of FGF21 polymorphisms in the causation of T2DMand in turn may help the clinicians for the better management of the condition. Functional studies of this gene would be required further to gain meaningful insights on the aetiology of FGF21 towards diabetic phenotype.

CONFLICTS OF INTEREST

None.

REFERENCES

[1] Jain, H. R., Shetty, V., Singh, G. S., & Shetty, S. A study of lipid profile in diabetes mellitus. International Journal of Scientific Study, 2016; 4(9): 56-61.

[2] Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020 Oct 13;10(4):174-188. doi: 10.4103/ajm.ajm_53_20. PMID: 33437689; PMCID: PMC7791288.

[3] Goyal S, Rani J, Bhat MA, Vanita V. Genetics of diabetes. World J Diabetes. 2023 Jun 15;14(6):656-679. doi: 10.4239/wjd.v14.i6.656. PMID: 37383588; PMCID: PMC10294065.

[4] Nishimura T, Nakatake Y, Konishi M, Itoh N (June 2000). "Identification of a novel FGF, FGF-21,

preferentially expressed in the liver". BiochimicaetBiophysicaActa (BBA) - Gene Structure and Expression. 1492 (1): 203–6.

[5] von Holstein-Rathlou, S.; BonDurant, L.D.; Peltekian, L.; Naber, M.C.; Yin, T.C.; Claflin, K.E.; Urizar, A.I.; Madsen, A.N.; Ratner, C.; Holst, B.; et al. FGF21 Mediates Endocrine Control of Simple Sugar Intake and Sweet Taste Preference by the Liver. Cell Metab. 2016, 23, 335–343

[6] Berglund ED, Kang L, Lee-Young RS, Hasenour CM, Lustig DG, Lynes SE. et al. Glucagon and lipid interactions in the regulation of hepatic AMPK signaling and expression of PPARalpha and FGF21 transcripts in vivo. American journal of physiology Endocrinology and metabolism. 2010;299:E607-14

[7] Epperlein S, Gebhardt C, Rohde K, Chakaroun R, Patt M, Schamarek I, Kralisch S, Heiker JT, Scholz M, Stumvoll M, Kovacs P, Breitfeld J, Tönjes A. The Effect of FGF21 and Its Genetic Variants on Food and Drug Cravings, Adipokines and Metabolic Traits. Biomedicines. 2021 Mar 29;9(4):345. doi: 10.3390/biomedicines9040345. PMID: 33805553; PMCID: PMC8065804.

[8] Chu, Audrey Y., TsegaselassieWorkalemahu, Nina P. Paynter, Lynda M. Rose, Franco Giulianini, Toshiko Tanaka, Julius S. Ngwa, Qibin Qi, Gary C. Curhan, Eric B. Rimm, David J. Hunter, Louis R. Pasquale, Paul M. Ridker, Frank B. Hu, Daniel I. Chasman, and Lu Qi. 2013. “Novel Locus Including FGF21 Is Associated with Dietary Macronutrient Intake.” Human Molecular Genetics 22(9):1895–1902. doi: 10.1093/hmg/ddt032.

[9] Inagaki T, Dutchak P, Zhao G, et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab 2007;5:415–425

[10] Ito S, Fujimori T, Furuya A, Satoh J, Nabeshima Y, Nabeshima Y. Impaired negative feedback suppression of bile acid synthesis in mice lacking betaKlotho. J Clin Invest 2005;115:2202–2208

[11] Mashili FL, Austin RL, Deshmukh AS et al (2011) Direct effects of FGF21 on glucose uptake in human skeletal muscle: implications for type 2 diabetes and obesity. Diabetes Metab Res Rev 27:286–297.

[12] Zhang X, Yeung DC, KarpisekMet al (2008) Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 57:1246–1253

[13] Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, DeFronzo RA, Tripathy D (2009) Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. Diabetes Care 32:1542–1546

[14] Cheng X, Zhu B, Jiang F, Fan H (2011) Serum FGF-21 levels in type 2 diabetic patients. Endocr Res 36:142–148

[15] Jeon JY, Choi SE, Ha ES et al (2016) Association between insulin resistance and impairment of FGF21 signal transduction in skeletal muscles. Endocrine 53:97–196

[16] Hojman P, Pedersen M, Nielsen AR et al (2009) Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. Diabetes 58:2797–2801

[17] IzumiyaY, BinaHA, Ouchi N, Akasaki Y, KharitonenkovA,Walsh K (2008) FGF21 is an Akt-regulated myokine. FEBS Lett 582:3805–3810

[18] Vienberg SG, Brons C, Nilsson E, Astrup A, Vaag A, Andersen B (2012) Impact of short-term high-fat feeding and insulin-stimulated FGF21 levels in subjects with low birth weight and controls. Eur J Endocrinol 167:49–57

[19] Abdulhusein A. F. Algenabi, Majid Kadhum Hussain, Thakra Al-KashwanRasha Mohamed Abood (2021). Association of Common Variants of FGF21 Gene Polymorphism rs499765 and rs838133 with Type 2 Diabetes Mellitus in Iraqi Population. Thi-Qar Medical Journal (TQMJ):Vol.(22),No.(2).

[20] Yu, Weihui, Hong Zhu, Xiong Chen, XuejiangGu, Xingxing Zhang, Feixia Shen, WeipingJia, and Cheng Hu. 2019. “Genetic Variants Flanking the FGF21 Gene Were Associated with Renal Function in Chinese Patients with Type 2 Diabetes.” Journal of Diabetes Research 2019. doi: 10.1155/2019/9387358.

[21] Frayling, Timothy M., Robin N. Beaumont, Samuel E. Jones, HaniehYaghootkar, Marcus A. Tuke, Katherine S. Ruth, Francesco Casanova, Ben West, Jonathan Locke, Seth Sharp, Yingjie Ji, William Thompson, Jamie Harrison, Cecilia M. Lindgren, Niels Grarup, Anna Murray, Rachel M. Freathy, Michael N. Weedon, Jessica Tyrrell, and Andrew R. Wood. 2017. “A Common Allele in FGF21 Associated with Preference for Sugar Consumption Lowers Body Fat in the Lower Body and Increases Blood Pressure.” BioRxiv. doi: 10.1101/214700.

[22] Schumann G,.KLB is associated with alcohol drinking, and its gene product b-Klotho is necessary for FGF21 regulation of alcohol preference. Proc Natl AcadSci USA. 2016;113(50):14372–14377.

[23] Søberg, S.; Sandholt, C.H.; Jespersen, N.Z.; Toft, U.; Madsen, A.L.; von Holstein-Rathlou, S.; Grevengoed,

T.J.; Christensen, K.B.; Bredie, W.L.P.P.; Potthoff, M.J.; et al. FGF21 Is a Sugar-Induced Hormone Associated with Sweet Intake and Preference in Humans. Cell Metab. 2017, 25, 1045–1053.e6.

[24] Jiang, Shan, Rong Zhang, Huating Li, Qichen Fang, Feng Jiang, XuhongHou, Cheng Hu, and WeipingJia. 2014. "The Single Nucleotide Polymorphism Rs499765 Is Associated with Fibroblast Growth Factor 21 and Nonalcoholic Fatty Liver Disease in a Chinese Population with Normal Glucose Tolerance." Journal of Nutrigenetics and Nutrigenomics 7(3):121–29. doi: 10.1159/000367943.

[25] Laeger T, Henagan TM, Albarado DC et al (2014) FGF21 is an endocrine signal ofprotein restriction. J Clin Invest 124:3913–39224.

[26] Y. Panahi1, S. Bonakdaran2, M.A. Yaghoubi.,et al .(2016). Serum levels of fibroblast growth factor 21 in type 2 diabetic patients. General Endocrinology. 10.4183/aeb.2016.257.

[27] Semba RD, Sun K, Egan JM, Crasto C, Carlson OD, Ferrucci L. Relationship of serum fibroblast growth factor 21 with abnormal glucose metabolism and insulin resistance: the Baltimore Longitudinal Study of Aging. J ClinEndocrinolMetab 2012; 97(4):1375-1382.

[28] Kralisch S, Fasshauer M. Fibroblast growth factor 21: effects on carbohydrate and lipid metabolism in health and disease. CurrOpinClinNutrMetab Care 2011; 14(4):354-359.

[29] Li H, Fang Q, Gao F, et al. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. J Hepatol 2010;53:934–940