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A study on the correlation between serum levels of fibroblast growth factor-19 and cardiovascular risk factors in patients with metabolic syndrome

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***Abstract*---**Metabolic syndrome is a major global threat nowadays due to urbanization, sedentary life style and increased incidence of obesity. FGF-19 has recently been introduced as a novel marker regulating metabolism, reversing diabetes mellitus, hyper lipidemia, hepatic steatosis and adiposity. Aim & Objective: To compare the serum Fibroblast Growth Factor 19 levels of metabolic syndrome patients with healthy individuals. To analyze the correlation between serum FGF 19 and the components of metabolic syndrome. Materials & Methods: A total of 50 patients and 50 controls were

included in the study. After obtaining informed consent, anthropometric measures (Height, Weight, BMI & Waist circumference) were taken. Blood investigations such as FGF 19, TC, HDL-cholesterol were estimated and LDL, VLDL & AIP levels were calculated. Statistical Analysis: Student's t-test was employed for the statistical analysis and data were expressed in terms of mean and standard deviation. 'p' value less than 0.05 is considered as statistically significant. Correlation between the measured parameters was assessed using Pearson's correlation coefficient. Result & Conclusion: Serum levels of FGF 19 were low in patients with metabolic syndrome. The negative relationship obtained between FGF 19 and the cardiovascular risk factors like TGL and log (TGL / HDL-C) suggests that FGF 19 can be used as a novel marker in assessing cardiovascular risk in patients with metabolic syndrome at an earlier stage.

***Keywords*---**Metabolic syndrome, Fibroblast Growth factor 19 (FGF 19), Total Cholesterol (TC), HDL-cholesterol, Anthrogenic index of plasma (AIP).

Introduction

The Metabolic syndrome is a major global threat nowadays due to urbanization, sedentary life style and increased incidence of obesity.[1] Metabolic syndrome is a state of dysregulation of normal body metabolism. It is a cluster of Insulin resistance, glucose intolerance, Obesity, Hypertension and Atherogenic Dyslipidemia, which are potential risk factors for Type 2 Diabetes Mellitus, Cardiovascular diseases and Stroke.[2,3,4]

Fibroblast Growth Factor 19 (FGF-19) is a unique member of the Fibroblast Growth Factor family of secreted proteins.[5] It is a hormone like protein that regulates Carbohydrate, Lipid and Bile acid metabolism. FGF - 19 is synthesized from the small intestine and secreted in to the circulation when bile acids are taken up into the ileum after a meal and then acts on CNS to elicit its metabolic effects. [6,7,8] This hormone-like postprandial protein has recently been shown to stimulate glycogen synthesis and inhibit gluconeogenesis through Insulin independent pathways.[7,6] It stimulates Hepatic protein synthesis and Glycogen synthesis.[8]

FGF-19 has recently been introduced as a novel regulator of metabolism, reversing diabetes mellitus, hyper lipidemia, hepatic steatosis and adiposity[9]. In this study, the aim is to estimate Serum levels of FGF-19 in patients with Metabolic Syndrome and to evaluate the relationship between FGF-19 and other cardiovascular risk factors, there by predicting future cardiovascular complications.

Aim & Objective of the study

- To measure serum Fibroblast Growth Factor 19 in patients with metabolic syndrome and to compare the serum level of FGF 19 with healthy individuals.
- To analyze the correlation between serum FGF 19 and the components of metabolic syndrome.

Materials and Methods

The study was conducted after being approved by the Institutional Ethics committee. Participants of the study group were selected from the Outpatient Department of Medicine. The study included 50 patients with metabolic syndrome (25 males, 25 females) and 50 age and sex matched healthy controls (25 males, 25 females), in the age group of 20-70 years. Informed consent was obtained from all the participants.

Inclusion criteria:
Patients with components of metabolic syndrome were included in the study.

Exclusion criteria:
- History of Myocardial infarction
- Coronary bypass surgery
- Chronic hepatic disease
- Chronic renal disease
- Cancer
- Alcohol abuse
- Pregnant females.

The participants of the study were routinely measured for height and weight. BMI was calculated with the formula weight/height^2 (kg/m^2). All the participants were informed about the study and informed consents were obtained from them. Waist circumference was measured for each subject.

Sample collection
Estimation of FGF 19 and other serum parameters:

Venous blood samples were drawn from each subject, under aseptic precautions, after an overnight fast of 12 hours. The samples were allowed to clot for 30 minutes and were centrifuged at 3000g for 10 minutes. The sera for estimating FGF 19 were stored in the deep freezer, until the estimation was done.

The following cardiovascular parameters were estimated immediately after the serum separation. Fasting lipid profile: (Total cholesterol (Cholesterol oxidase-Peroxidase Enzymatic, endpoint method)[10], HDL cholesterol (Phosphotungstic acid method, Endpoint) & Triacylglycerol (GPO-PAP method, Endpoint)[11]. LDL VLDL cholesterol & AIP levels were calculated from the estimated parameters using Friedewald formula[12,13.] AIP (Atherogenic Index of Plasma) was calculated as log (TG/HDL-C). Fasting serum FGF 19 was measured in all the samples within

one month of collecting the samples by Sandwich Enzyme – Linked Immuno Sorbent Assay using standard methods[14].

Statistical analysis

Student's t-test was employed for the statistical analysis of data. The data were expressed in terms of mean and standard deviation. 'p' value less than 0.05 was taken as the significant value. Correlation between the measured parameters was assessed using Pearson's correlation coefficient.

Results

A total of 100 participants were included in the study. Out of these, 50 were grouped under controls and 50 were under cases. The serum value of Total Cholesterol, HDL and TGL were estimated for all the samples in both the groups. BMI, VLDL, LDL and AIP were calculated. The values obtained for the cases and controls are represented in tables.

Table 1: statistical analysis of BMI between cases and controls

T-test			
BMI (kg/m^2)	Mean	SD	Statistical inference
Control (n=50)	22.305	1.5341	P value = .000 <0.05 – significant

Table 1 shows student's t-test analysis of BMI between cases and controls. There is increase in the mean BMI in cases (34.37 ± 3.13), when compared to the mean BMI in controls (22.31 ± 1.53), which is statistically significant. (p value < 0.05).

Table 2: Statistical analysis of waist circumference between cases and controls

T-test			
WC (cm)	Mean	SD	Statistical inference
Control (n=50)	86.620	4.9193	P value = .000 <0.05 – significant
Cases (n=50)	95.380	5.7743	

Table 2 shows student's t-test analysis of Waist circumference between cases and controls. There is increase in the mean Waist circumference in cases (95.38 ± 5.77), when compared to the mean Waist circumference in controls (86.62 ± 4.92), which is statistically significant. (p value < 0.05).

Table 3: Statistical analysis of systolic BP between cases and controls

T-test			
Systolic BP (mmHg)	Mean	SD	Statistical inference
Control (n=50)	121.920	7.6127	P value = .000

Cases (n=50)	133.840	4.3064	<0.05 – significant

Table 3 shows student's t-test analysis of Systolic BP between cases and controls. There is increase in the mean Systolic BP in cases (133.84 ± 4.31), when compared to the mean Systolic BP in controls (121.92 ± 7.61), which is statistically significant. (p value < 0.05).

Table 4: Statistical analysis of diastolic BP between cases and controls

T-test			
Diastolic BP (mmHg)	Mean	SD	Statistical inference
Control (n=50)	77.640	4.4020	P value = .000
Cases (n=50)	88.380	3.9790	<0.05 – significant

Table 4 shows student's t-test analysis of Diastolic BP between cases and controls. There is increase in the mean Diastolic BP in cases (88.38 ± 3.98), when compared to the mean Diastolic BP in controls (77.64 ± 4.4), which is statistically significant. (p value < 0.05).

Table: 5 statistical analysis of serum FGF 19 between cases and controls

T-test			
FGF 19 (pg/ml)	Mean	SD	Statistical inference
Control (n=50)	266.340	65.5070	p value = .000 <0.05 – Significant
Cases (n=50)	135.020	20.7556	

Table 5 Shows student's t-test analysis of serum FGF 19 level between cases and controls. There is decrease in the mean serum FGF 19 in cases (135.02 ± 20.76 pg/ml), when compared to the mean serum FGF 19 in controls (266.34 ± 65.5 pg/ml), which is statistically significant. (p value < 0.05).

Table 6: Statistical analysis of TC between cases and controls

T-test			
TC (mg/dl)	Mean	SD	Statistical inference
Control (n=50)	157.880	12.1834	p value = .000 <0.05 – Significant
Cases (n=50)	233.840	19.1326	

Table 6 shows student's t-test analysis of serum TC between cases and controls. There is increase in the mean TC in cases (233.84 ± 19.13), when compared to the mean TC in controls (157.88 ± 12.18), which is statistically significant. (p value < 0.05).

Table 7: Statistical analysis of TGL between cases and controls

T-test			
TGL (mg/dl)	Mean	SD	Statistical inference
Control (n=50)	106.880	14.7864	P value = .000 <0.05 – significant

Table 7 shows student's t-test analysis of serum TGL between cases and controls. There is increase in the mean TGL in cases (230.16 ± 37.8), when compared to the mean TGL in controls (106.88 ±14.79), which is statistically significant. (p value < 0.05).

Table 8: Statistical analysis of HDL between cases and controls

T-test			
HDL (mg/dl)	Mean	SD	Statistical inference
Control (n=50)	46.320	3.9354	P value = .000 <0.05 – significant

Table 8 shows student's t-test analysis of serum HDL between cases and controls. There is decrease in the mean HDL in cases (36.76 ± 3.79), when compared to the mean HDL in controls (46.32 ± 3.94), which is statistically significant. (p value < 0.05).

Table 9: Statistical analysis of VLDL between cases and controls

T-test			
VLDL (mg/dl)	Mean	SD	Statistical inference
Control (n=50)	21.376	2.9573	p value = .000 <0.05 – Significant
Cases (n=50)	46.032	7.5603	

Table 9 shows student's t-test analysis of serum VLDL between cases and controls. There is increase in the mean VLDL in cases (46.03 ±7.56), when compared to the mean VLDL in controls (21.38 ± 2.96), which is statistically significant. (p value < 0.05).

Table 10: Statistical analysis of LDL between cases and controls

T-test			
LDL (mg/dl)	Mean	SD	Statistical inference
Control (n=50)	90.184	11.5157	P value = .000 <0.05 – significant
Cases (n=50)	151.048	16.1828	

Table 10 shows student's t-test analysis of serum LDL between cases and controls. There is increase in the mean LDL in cases (151.05 ± 16.18), when

compared to the mean LDL in controls (90.18 ± 11.52), which is statistically significant. (p value < 0.05).

Table 11: Statistical analysis of AIP between cases and controls

T-test			
AIP	Mean	SD	Statistical inference
Control (n=50)	0.3603	0.06328	P value = .000 <0.05 – significant
Cases (n=50)	0.79287	0.11597	

Table 11 shows student's t-test analysis of serum AIP between cases and controls. There is increase in the mean AIP in cases (0.79± 0.12), when compared to the mean AIP in controls (0.36± 0.06), which is statistically significant. (p value < 0.05).

Table 12: Pearson's correlation between FGF 19 and other parameters

Cases – FGF 19	Correlation value	Statistical inference
BMI	-0.875	P < 0.01 Significant
Waist circumference	-0.864	P < 0.01 Significant
SBP	-0.808	P < 0.01 Significant
DBP	-0.841	P < 0.01 Significant
TC	-0.827	P < 0.01 Significant
TGL	-0.892	P < 0.01 Significant
HDL	+0.773	P < 0.01 Significant
VLDL	-0.892	P < 0.01 Significant
LDL	-0.742	P < 0.01 Significant
AIP	-0.873	P < 0.01 Significant

Discussion

FGF 19 is a newly identified metabolic regulator, influencing homeostasis of glucose and lipid metabolism. It has been concluded that the expression of FGF 19 in liver is induced by FXR (Farnesoid X receptor), a transcription factor[15]. The natural ligand for the FXR receptor was identified as bile acids. So, FXR acts as a "bile acid sensor" inducing the expression of FGF 19. FGF 19 inhibits the enzyme CYP7A1 in liver, thereby inhibiting the rate limiting step of Bile acid synthesis from cholesterol[16]. The repression of bile acid synthesis is the net result of FXR activation. FXR not only regulates bile acid metabolism, but also metabolism of cholesterol, triglyceride, lipoprotein and glucose. The dys-regulations of glucose, cholesterol and triglyceride metabolism lead to metabolic syndrome[17].

Animal studies revealed that recombinant FGF 19 increased the metabolic rate, decreased body weight and reversed diabetes[18]. This led to further research which suggested that FGF 19 increases oxidation of lipids and increases the activity of Carnitine Acyl transferase 1, favoring fatty acid oxidation. Therefore it was concluded that FGF 19 might improve dyslipidemia, reduce adiposity and body weight and also improve insulin sensitivity[19].

In this study, in patients with metabolic syndrome, serum levels of FGF 19 (135.02 ± 20.76 pg/ml) are significantly lower than that of the healthy controls (266.34 ± 65.5 pg/ml). Additionally, Serum TGL and HDL-C also differed significantly between cases and controls. Comparison of mean value of AIP of the controls (0.36± 0.06) and the cases (0.79± 0.12) showed a significant rise in the cases.

Pearson correlation showed negative correlation between FGF 19 and other cardiovascular risk factors like TGL and AIP and a positive correlation with cardio protective factors like HDL. Several studies showed that in patients with metabolic syndrome, obesity is a main factor contributing to insulin resistance, which plays a potent role in the pathogenesis of Cardiovascular diseases[20,21,22]. Obesity also promotes atherogenic dyslipidemia. Dyslipidemia favours development of CVD. Hyper triglyceridemia is an independent risk factor for CVD[23]. FGF 19 increases fatty acid oxidation, which decreases the concentration of triglycerides. Hence, a low FGF 19 level is invariably associated with increased atherogenity of plasma, leading on to cardiovascular diseases[24]. Hence these observations suggest that FGF 19 is a novel marker of metabolic syndrome and is used to assess cardiovascular risk in patients with Metabolic syndrome.

Conclusion

This study shows that serum levels of FGF 19 are low in patients with metabolic syndrome. The negative relationship obtained between FGF 19 and several other known cardiovascular risk factors like TGL and log (TGL / HDL-C) suggests that FGF 19 can be used as a novel marker in assessing cardiovascular risk in patients with metabolic syndrome. Hence, earlier intervention can be taken to reduce the cardiovascular complications.

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