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A CROSS SECTION STUDY TO ASSESS THE RELATIONSHIP BETWEEN SERUM LEVELS OF FIBROBLAST GROWTH FACTOR-19 AND FASTING AND POSTPRANDIAL BLOOD SUGAR LEVELS IN PATIENTS WITH METABOLIC SYNDROME

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Abstract: Metabolic syndrome (MetS) refers to the concurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. FGF-19, a peptide with 216 amino acids, including a signal peptide of 22 amino acids was recently introduced as a novel metabolic regulator reversing diabetes mellitus, hepatic steatosis, hyperlipidemia, 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 serum blood glucose levels of patients with MetS. **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, FBS PPBS were estimated. **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 FBS and PPBS suggests that FGF 19 can be used as a novel marker in assessing the risk of developing metabolic syndrome and also can be used to reduce insulin resistance.

Keywords: Metabolic syndrome, Fibroblast Growth factor 19 (FGF 19), Fasting blood sugar (FBS), Post Prandial Blood Sugar (PPBS)

Introduction:

Due to epidemic of obesity, as a direct consequence, the prevalence of metabolic syndrome is rising at an alarming rate. Currently, almost 25% of population is affected by MetS, and the problem is worse in individuals older than 60 years.[1] In diabetic patients, the prevalence was almost around 86%.[2] Decreased physical activities and increased intake of energy dense foods and sugars are the most important contributing factor in the drastic increase in the prevalence of Obesity and hence the Metabolic Syndrome[3]. A huge hike in the prevalence of obesity (BMI > 30.0) is also documented by the NHANES surveys. Metabolic syndrome is a growing health problem, even in countries with lower gross national product, due to ingestion of cheap vegetable oils and increased urbanization rate[3]. In Asian Indians, the prevalence of the metabolic syndrome differs according to the area, the extent of urbanization, patterns of life style and cultural or socio-economic factors. According to a recent data, in large cities in India, the prevalence accounts for about one-third of the urban population[4]. In patients with Metabolic syndrome, the risk of mortality from Cardiovascular problem is about two times compared to normal individuals. Also, there is a fivefold increased risk of developing frank Type 2 Diabetes Mellitus[5,6]. The major risk factors for developing atherosclerosis include the components of MetS like Dyslipidemia, hypertension, diabetes mellitus and smoking. Fibroblast growth factor

19 (FGF19), a hormone expressed by ileal enterocytes, is a member of the FGF family involved in regulating lipid and nutrient metabolism[6]. FGF 19 is a protein that in humans is encoded by the FGF19 gene. It functions as a hormone, regulating bile acid synthesis, with effects on glucose and lipid metabolism[7]. Various research studies have shown that over expression of FGF 19 or treatment with recombinant protein enhanced metabolic rates and decreased fat mass, in addition to demonstrating improvements in glucose metabolism, insulin sensitivity, and lipid profiles[8]. Though reduced synthesis, and blood levels of FGF 19 may be a factor in certain metabolic disorder however, the relationship of endogenous islet beta cell function and FGF 19 is not fully understood. Hence the major purpose of our study is to provide information on the association between FGF 19 levels and serum glucose which signifies the beta cell function.

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 fasting and postprandial blood sugar levels in patients with 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 parameters were estimated immediately after the serum separation.

- 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[9].
- Blood Glucose – fasting and postprandial[10].

Result:

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 2: 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 3: statistical analysis of FBS between cases and controls

T-test			
FBS (mg/dl)	**Mean**	**SD**	**Statistical inference**
Control (n=50)	85.500	7.3158	P value = .000 <0.05 – significant
Cases (n=50)	118.040	5.1109	

Table 4: statistical analysis of PPBS between cases and controls

T-test			
PPBS (mg/dl)	**Mean**	**SD**	**Statistical inference**
Control (n=50)	126.920	8.2853	P value = .000 <0.05 – significant
Cases (n=50)	168.860	13.4271	

Table 5: Pearsons correlation between FGF19 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
FBS	-0.754	P < 0.01 Significant
PPBS	-0.853	P < 0.01 Significant

Discussion

FGF 19 is a newly identified metabolic regulator, influencing homeostasis of glucose and lipid metabolism[11]. It has been concluded that the expression of FGF 19 in liver is induced by FXR (Farnesoid X receptor), a transcription factor. 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. 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[12]. The dysregulations of glucose, cholesterol and triglyceride metabolism leads to metabolic syndrome[13].

In our study there is increase in the mean FBS in cases (118.04 ± 5.11), when compared to the mean FBS in controls (85.5 ± 7.32), which is statistically significant. (p value < 0.05). Also there is increase in the mean PPBS in cases (168.86 ± 13.43), when compared to the mean PPBS in controls (126.9 ± 8.29), which is statistically significant. (p value < 0.05). Also in our study, in patients with Metabolic syndrome where the serum levels of FBS and PPBS were high, the serum levels of FGF 19 (135.02 ± 20.76 pg/ml) are also significantly lower than that of the healthy controls (266.34 ± 65.5 pg/ml). Obesity is a main factor contributing to insulin resistance among patients with metabolic syndrome, which plays a potent role in the pathogenesis of Cardiovascular diseases[11].

Animal studies revealed that Recombinant FGF 19 increased the metabolic rate, decreased body weight and reversed diabetes[14]. Also the analysis of Guo et al., 2022 showed a significant elevation of FGF 19 levels among DM remitters compared with non-remitters. They also suggested that early FGF 19 improvements may predict the complete remission of T2DM for obese patients. Furthermore, our study pointed out a negative linear correlation between FGF 19 levels and the indicators of DM severity, including FBS and PPBS. This implies that FGF 19 may also provide predictive value regarding improvements in insulin resistance and remission of T2DM[15].

In addition Stejskal et al., 2008 demonstrated the relationship between FGF-19 levels and glucose, HDL-c, and TG levels and found a significant correlation between FGF 19 and glucose levels but they found no significant correlation between FGF-19 and BMI. 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[16]. Therefore it was concluded that

FGF 19 might improve dyslipidemia, reduce adiposity and body weight and also improve insulin sensitivity. Hence the observations of our study suggest that FGF 19 is a novel marker of Metabolic syndrome and is used to reduce the insulin resistance among them.

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 FBS and PPBS suggests that FGF 19 can be used as a novel marker in assessing the patients with risk of developing metabolic syndrome and also can be used to reduce insulin resistance.

Limitations of the study

The study has the following limitations:

1. The sample size has small number of patients and controls.
2. Other valuable relevant markers like fasting Insulin, hsCRP, HbA1C were not included in the study.

Future scope of the study

In patients with obesity, metabolic syndrome and non alcoholic fatty liver, FGF 19 serum levels has been decreased [56,61]. Therapies with recombinant FGF 19 is under research to treat diabetes and bile acid disorders[51]. FGF 19 is considered as a new weapon to combat increasing incidence of obesity, metabolic syndrome and type 2 Diabetes. It helps to explore potential targets for treating the metabolic disorders[78].

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