Original Article

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Plasma Fibrinogen in Type 2 Diabetic Patients with Metabolic Syndrome and its Relation with Ischemic Heart Disease (IHD) and Retinopathy

Biochemistry Section

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ABSTRACT

Introduction: Metabolic syndrome or Syndrome X is characterized by hyperlipidemia, increased blood pressure, abdominal obesity and hyperglycemia, which increases the risk of cardiovascular complications. In addition to these, it is also associated with nontraditional risk factor like C- reactive protein, Plasminogen activator and fibrinogen. Various studies have documented association of these nontraditional risk factor, in Type 2 diabetes mellitus. Thus patients with diabetes mellitus are higher risk of developing micro and macro vascular complications like ischemic heart disease (IHD) and diabetic retinopathy. Diabetic retinopathy is the leading cause of decreased visual acuity, which is associated with maculopathy and profierative complications of it. Chronic hyperglycemia and its associated nonenzymatic glycation play an important role in the development of microangiopathy.

Aims and Objectives: To study the prevalence of the metabolic syndrome in type 2 diabetes mellitus. To study the plasma fibrinogen and its relationship with IHD and retinopathy in type 2 Diabetes mellitus patients with metabolic syndrome.

Materials and Methods: Patients of type 2 diabetes Mellitus were recruited based on the inclusion and exclusion criteria. History of IHD and ECG evidence of ischemia was obtained. Retinopathy was diagnosed by direct opthalmoscopy. Fasting glucose, lipid profile and plasma fibrinogen were analyzed. Stastical analysis was carried by Chi square test and student't' test.

Results: The prevalence of metabolic syndrome in study population of 100 type 2 diabetic patients is 58% and is significantly associated with duration of the disease ($p<0.001$). Fifty eight patients have hyperfibrinogenemia and mean fibrinogen level is significantly high in diabetic patients with metabolic syndrome when compared to diabetic patients without metabolic syndrome ($p<0.001$). Diabetic patient with metabolic syndrome and hyperfibrinogenemia have higher prevalence of IHD and retinopathy in comparison with diabetic patients without metabolic syndrome ($p<0.05$).

Conclusion: The prevalence of metabolic syndrome is higher in type 2 Diabetes mellitus patients. The combination of metabolic syndrome and hyperfibrinogenemia increases the risk of developing micro and macro vascular complications.

Keywords: Diabetes mellitus, Fibrinogen, Metabolic syndrome

INTRODUCTION

Diabetes is one of the most common chronic hyperglycemic syndrome, affecting nearly 200 million people worldwide. If unchecked, by 2025, it is expected that diabetes will reach epidemic proportions, affecting 333 million people globally. Much of this increase is expected to occur in developing countries including India [1,2].

The metabolic syndrome is a cluster of various risk factors like hyperglycemia, hyperlipidemias and obesity. It is estimated that around a quarter of the world's adult population has metabolic syndrome [3] and these people are twice as likely to die from, and three times a likely to have IHD or stroke compared with people without this syndrome [4].

Fibrinogen is the major coagulation protein in blood. It is glycoprotein and circulates as a dimer composed of three pair of polypeptide chain. And it is the nontraditional risk factor for the development of cardiovascular complications [5]. It is an acute phase protein, increases during the inflammatory process. Inflammation plays an important role in the development of atheromatous plaque. Monocytes infiltrating the plaque differentiate into macrophages that release cytokines, such as interleukin-6, which increase plasma fibrinogen. Fibrinogen, by virtue of its role in platelet crosslinking, thrombus formation, and increased blood viscosity, may enhance plaque progression,which in turn may lead to IHD [6].

A significant inverse relationship between plasma levels of fibrinogen and thickness of fibrous cap of atheroma has been observed, which results in greater incidence of plaque rupture and thrombosis in subjects with increased fibrinogen levels [7].

Various population-based studies have documented hyperfibrinogenemia in subjects with metabolic syndrome, since it characterized by high blood pressure, Dyslipidemia and hyperglycemia, which may predispose to earliest development of cardiovascular events. Since there is lack of literature regarding metabolic syndrome and plasma fibrinogen in this part of state, we had an impetus to study the same in type 2 diabetes mellitus.

Thus, the study was designed to know the prevalence of metabolic syndrome in type 2 diabetic patients and to study the relation of plasma fibrinogen with metabolic syndrome and diabetic retinopathy.

AIMS AND OBJECTIVES

- To study the prevalence of metabolic syndrome in Type 2 diabetes mellitus.
- To compare the levels of plasma fibrinogen in Type 2 diabetes mellitus patients with and without metabolic syndrome.
- To study the relationship of plasma fibrinogen with IHD and retinopathy in diabetic patients with metabolic syndrome.

MATERIALS AND METHODS

This study was conducted at, JN medical College and hospital, Belgaum, Karnataka, India. A cross-sectional study, which includes 100 type 2 Diabetes mellitus patients, both newly diagnosed and known cases were included. Endocrine causes of hyperglycaemia and patients with acute and chronic infections were excluded. The study was approved by Institute ethical committee and written informed consent was obtained from the patients.

Metabolic syndrome was diagnosed based on guidelines of National Cholesterol Eradication Program Adult Treatment Panel III. Following are the criteria to diagnose:

Waist circumferences in Men >102 cm and in Women >88 cm, HDL Cholesterol in Men <40 mg/dl and in Women < 50 mg/dl, Triglycerides ≥ 150 mg/dL, Blood pressure ≥ 130/85mmHg and Fasting glucose ≥ 110 mg/dl. Presence of three or more criteria is diagnostic of metabolic syndrome.

Data Collection

Hundred patients with type 2 diabetes mellitus were included in the study. Detailed history including duration of diabetes and physical examination was done. Retinopathy was assessed by direct ophthalmoscope. IHD was diagnosed with history of ischemia in past or ECG changes suggestive of ischemia. Waist circumference was taken at the level of umbilicus.

After 8-12 hours fasting, 5ml of venous blood was collected from anticubital vein under aseptic precaution; 3ml of blood was transferred to tube containing EDTA for estimation of plasma glucose and plasma fibrinogen. Another 2ml of blood was allowed to clot and serum separated for the assay of Triglycerides and HDL-cholesterol. Only fasting blood glucose,TG and HDL were analyzed to identify the patients with metabolic syndrome as per criteria of NCEP ATP III. Fasting glucose was assayed by glucose oxidase -Peroxidase (GOP-POD) method and Triglyceride by glycerol phosphate oxidase (GPO) method, HDL cholesterol by cholesterol oxidase method was analyzed by using commercially available reagent kits adopted to fully automated analyzer. Plasma fibrinogen was estimated by immunoturbidometric method.

STATISTICAL ANALYSIS

Data were expressed as mean ±SD, chi-square test and student unpaired 't' test was carried out. p-value <0.05 was considered as significant for all statistical tests. All analyses were performed using SPSS software version 17.

RESULTS

Out of 100 patients of type 2 Diabetes mellitus 67(67%) were men, 33 (33%) were women, and their average age was 59.9±7.87. Majority of the patients 47(47%) were in the age group of 51-60 years [Table/Fig-1].

Prevalence of metabolic syndrome in study population is 50% using NCEP ATP III criteria and 58% using Revised NCEP ATP III guidelines with waist circumferences modified for South East Asians, abdominal obesity (waist circumference ≥90 cm for Asian men and ≥80 cm for Asian women) [Table/Fig-2]. Among 58 patients with metabolic syndrome 32 (55.17%) were male and 26 (44.83) were female [Table/Fig-3].

Mean duration of diabetes is 7.86 ±4.799 (years). As the duration of diabetes increase, prevalence of metabolic syndrome increases. The relationship of duration of diabetes with metabolic syndrome is found to be highly significant. (x^2 value is 16.997 and p value 0.0007) [Table/Fig-4].

Mean plasma fibrinogen is significantly high (p<0.001) in type 2 Diabetes mellitus patients with metabolic syndrome, when compared with type 2 Diabetes mellitus patients without metabolic syndrome [Table/Fig-5].

The 95% confidence limits for fibrinogen (mg/dl) among metabolic syndrome cases are 353.27 and 393.71, patients without metabolic syndrome 95% confidence limits are 265.96 and 295.76.

Hyperfibrinogenemia (>400mg/dL) was found in 33 (56.89%) patients of type 2 diabetes mellitus with metabolic syndrome whereas 4 (9.52%) patients with type 2 diabetes mellitus without metabolic syndrome was having plasma fibrinogen level >400mg/dL and this difference was statistically significant. (x^2 21.464, p< 0.0001) [Table/Fig-6].

Twenty-five (43.10%) and 43 (74.14%) out of 58 patients of type 2 diabetes mellitus with metabolic syndrome was found to have

Age group (years)	Male	Female	Total
41-50	6	3	9
51-60	32	15	47
61-70	22	12	34
71-80	7	3	10
	67	33	100

[Table/Fig-1]: Age and the sex distribution of study subjects

Number of criteria	NCEP-ATP III	Modified for south Asians
3/5	23	25
4/5	17	15
All 5	10	18
	50	58

[Table/Fig-2]: Prevalence of metabolic syndrome in patients with Type 2 Diabetes mellitus

Sex	Number	Percentage (%)
Males	32	55.17
Females	26	44.83
	58	100

[Table/Fig-3]: Sex distribution of Type 2 Diabetic patients with metabolic syndrome

Duration (years)	Number of cases	Cases with metabolic syndrome	Cases without metabolic syndrome
<5	36	12	24
6-10	41	27	14
11-15	16	12	04
>15	7	7	00
Total	100	58	42

[Table/Fig-4]: Relation between duration of Type 2 Diabetes mellitus and metabolic syndrome
X^2=16.997 , p=0.007 highly significant

Diabetic patients	Number of cases	Mean fibrinogen level (mg/dL)
With metabolic syndrome	58	373.44±17.29
Without metabolic syndrome	42	280.56±57.23

[Table/Fig-5]: Plasma fibrinogen levels in Type 2 Diabetic patient with and without metabolic syndrome

Diabetic patients	Number of cases	Plasma Fibrinogen level (>400mg/dL)	Normal fibrinogen level (200-400 mg/dL)
With metabolic syndrome	58	33	25
Without metabolic syndrome	42	04	38
Total	100	37	63

[Table/Fig-6]: Prevalence of hyperfibrinogenemia in Type 2 Diabetic patients with and without metabolic syndrome
X^2 =21.464 p<0.0001 highly significant

Diabetic patients	Number of cases	Cases with Ischemic heart disease	Cases without ischemic heart disease	Cases with Retinopathy	Cases without Retinopathy
With metabolic syndrome	58	25	33	43	15
Without metabolic syndrome	42	07	35	09	33
Total	100	32	68	52	48

[Table/Fig-7]: Relation between Ischemic heart disease and diabetic retinopathy in type 2 Diabetic patients with and without metabolic syndrome
*X^2 =6.613, p<0.001 significant (Ischemic heart disease relation with and without Metabolic syndrome)
** X^2=25.04, p<0.001 highly significant. (Diabetic Retinopathy relation with and without Metabolic syndrome)

Metabolic syndrome	Number of cases	Cases with Ischemic heart disease	Cases without ischemic heart disease	Cases with Retinopathy	Cases without Retinopathy
Hyperfibrinogenemia	33	17	16	29	04
Normal fibrinogen	25	08	17	14	11
Total	58	25	33	43	15

[Table/Fig-8]: Relation between Type 2 diabetes mellitus with metabolic syndrome and hyperfibrinogenemia with ischemic heart disease and retinopathy
*X^2 =1.485 p>0.05 insignificant (Type 2 Diabetes Mellitus with metabolic syndrome and hyperfibrinogenemia with ischemic heart disease)
** X^2=5.969 p<0.0146 significant. (Type 2 Diabetes Mellitus with metabolic syndrome and hyperfibrinogenemia with retinopathy)

IHD and diabetic retinopathy respectively and only 7 (16.67%) and 9 (21.43%) patients was found to have IHD and retinopathy in patients of type 2 diabetes mellitus without metabolic syndrome. The association of metabolic syndrome with IHD and Retinopathy was found to be statistically significant p<0.001 [Table/Fig-7].

IHD was found in 17 (51.51%) and 29 (87.88%) had diabetic retinopathy out of 33 diabetic patients with metabolic syndrome and hyperfibrogenemia where as in patients of diabetes mellitus without metabolic syndrome and normal fibrinogen, 8 (32.00%) patients were found to have IHD and 14 (56%) had retinopathy. The association of hyperfibrogenemia with IHD was found to be insignificant (>0.05) and was statistically significant with diabetic retinopathy (p<0.01) [Table/Fig-8].

DISCUSSION

The present study was conducted in type 2 diabetic patients to know the prevalence of metabolic syndrome. The National Cholesterol Education Program's ATP III report identified the metabolic syndrome as a specific entity deserving more clinical attention. People with the metabolic syndrome, due to presence of multiple risk factors like Hypertension, Dyslipidemia and Hyperglycemia, which may contribute to early development of cardiovascular complications then the risk associated with individual components of the syndrome alone [8].

In the present study, prevalence of metabolic syndrome in type 2 diabetes mellitus is 50% using NCEP ATP III criteria. Our finding is in agreement with the study by Eliasson B et al., who documented prevalence of 77% of metabolic syndrome in diabetic patients [9].

In the present study prevalence increased from 50% to 58% when NCEP ATP III criteria with modified waist circumference for Asian Indians. The study by Tan CE et al., reported low prevalence figures in Asian population using NCEP ATP III criteria, suggesting the need for ethnic specific cut off for waist circumference i.e. 90 cms in males and 80 cms in female [10].

The study by Ranmachandra et al., concludes that the prevalence of metabolic syndrome in non diabetic subjects was found to be 41% by using modified NCEP ATP III criteria for asian population [11] and study by Misra A et al., reported prevalence of 29.9%. The higher rate of prevalence in the present study may be due to the study group comprising of only diabetic patients [12].

The prevalence of metabolic syndrome in men with diabetes mellitus is (55%) and in women was (45%) in our study which is in agreement with study by Marques Vidal et al.who reported, the prevalence of 23% and 12% in males and females respectively [13].

In the present study, we found increased prevalence of metabolic syndrome. Thus long-standing diabetes mellitus may contribute for the development of other components of metabolic syndrome.

In this study, 37 patients had hyperfibrinogenemia. Mean plasma fibrinogen level is significantly higher in diabetic patients with metabolic syndrome then those without metabolic syndrome. This study is in agreement with study by Imperator et al., who reported significantly higher plasma fibrinogen levels in subjects of metabolic syndrome than in those without . The procoagulant plasma fibrinogen is considered to be a component of metabolic syndrome [14].

Increased levels of fibrinogen in patients with metabolic syndrome are mainly due to associated factor like chronic inflammation and insulin resistance. The metabolic syndrome is hypercoagulable state and is associated with increased levels of plasma fibrinogen, factor VII and factor VIII, and also increased levels of PAI-1.Thus leading to a hypofibrinolytic state, all these factors add to development of cardiovascular complications [15].

In the present study prevalence of IHD is 43% in those with metabolic syndrome and 16% in those without metabolic syndrome. This is statistically significant. Our finding is in accordance with the finding by Costa LA et al., and Isomaa B et al., has found that the prevalence of IHD is 53% in patients with metabolic syndrome on comparison without metabolic syndrome 36% [16,17]. If the combination of Metabolic syndrome and hyperfbrinogenemia is considered, this group had a higher prevalence of IHD as compared to the group without this combination. However, the difference is not statistically significant.

The prevalence of diabetic retinopathy in our study was 74.14% with metabolic syndrome and 21.43% without metabolic syndrome. Our study is in accord with the study conducted by Costa LA et al., who reported the prevalence of diabetic retinopathy is 44% in metabolic syndrome in comparison with 20% without metabolic syndrome and also by Isoma B et al.who documented 23% and 7% respectively [16,17]. If the combination of metabolic syndrome and hyperfbrinogenemia is considered, this group had a higher prevalence of retinopathy as compared to the group without this combination and the difference is statistically significant p<0.01. Chronic hyperglycemia and its associated nonenzymatic glycation play an important role in the development of microangiopathy.

LIMITATIONS OF THE STUDY

The main limitations of our study are limited sample size and we have not analyzed C-reactive protein, Plasminogen activator and its association with metabolic syndrome. And other lipid parameters like total cholesterol, LDL and VLDL were not analyzed.

CONCLUSION

The present study concludes that, the prevalence of metabolic syndrome in Type 2 Diabetes mellitus is 58% and plasma fibrinogen is significantly higher in these patients. Macro and micro vascular complications are frequent in long standing patients with type

2 diabetes mellitus, Thus presence of metabolic syndrome and hyperfibrinogenemia may contribute to early development of macro (IHD) and micro (Retinopathy) vascular complications.

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