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Hyperfibrinogenemia In Type Ii Diabetes Mellitus

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Aim: *- To estimate and interpret the Fibrinogen Levels in Type II Diabetes Mellitus.*
Materials*: - 50 patients of established NIDDM in King George Hospital, Visakhapatnam were taken. 25 control subjects without history of NIDDM and who are age and sex matched were taken.*
Plasma Fibrinogen along with Blood Glucose, HbA_1 C, Total Cholesterol and Serum Triglycerides were estimated.
Results: *- In Control Group the mean values of FBS (60-90 mg/dl), HbA_1 C(6-5 %)Serum Cholesterol (140-240 mg/dl), Serum Triglycerides (80-180 mg/dl), Post Prandial Sugar (110-150 mg/dl), Urinary AIb excretion rate(0-70mg/min) and Plasma Fibrinogen (200-400 mg/dl) are within normal range. The mean + SD + SE. Fibrinogen, HbA_1 C and Urinary AlbuminExcretion Rate are 350 + 56.16 + 11.23, 5.08 + 0.377 + 0.08 and 13.8 + 3.77+ 0.76 respectively.In cases there is significant correlation between fibrinogen and age, Hypertension, Triglycerides and Cholesterol levels,FBI,PPBS, HbA,C, and Urinary Albumin excretion rate with 'V' Values 0.677, 0.729,0.87003, 0.9646, 0.9281, 0.9871, 0.8797 and 0.9342 respectively*.
Conclusion*: - In cases there is significant fibrinogen and HbA_1C and Urinary Albumin excretion rate Fibrinogen continues to be important risk factors inNIDDM patients which is an acute phase reactant, an Independent risk factors of cardio Vascular decrease.*

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I. Introduction

Diabetes Mellitus is a chronic disease which results due to deficiency in Insulin.
The Metabolic defects includes:-
1. Impaired Insulin secretion[1].
2. Prephal Insulin[2].
3. Increased basal hepatic glucose output.

All the above contribute to Hyperglycemic[3].NIIDM has various causative factors[4]..The circulatory system has an inherent self sealing process[5].. The mechanism of clotting[6]. is of two types intrinsic and extrinsic.

Material and Methods: - 50 cases of NIDDM in King George Hospital, Visakhapatnam were taken during the period Jan 2017 to Aug 2017 from the Medical Out Patients Department. All Ethical Clearance were done.

Inclusion Criteria:
1. Age > 50 yrs.
2. Both Male and Female
3. Cases included both Smoker and Non Smoker
4. All Patients with 5yrs L/o NIDDM was taken.

Exclusion Criteria:
1.Subjects with BIood Glucose greater than 110 mg/dl were excluded
2.Age < 50 were excluded.
3.Patients with duration of NIDDM < 5 Yrs were excluded

Controls: - Healthy controls subjects who are age and sex matched with the cases and with no family L/o Diabetes Mellitus were taken.
Parameters Estimated

1. Blood Glucose by GOD POD method the fully automated Bio system Analyser.
2. Sr.Cholesterol by Zaks method.
3. Plasma Fibrinogen by modified cullen and Van Styke method
4. Urinary Albumin Excretion Rate by Micral test Strip Method.

II. Results:

Various Parameters Studied In Controls And Diabetics (Mean ± S.D)

TABLE IV

VARIABLES	CONTROLS	DIABETES
Number (%)	25(100)	40(100)
Age (Yrs)	57.16 ± 3	58.6 ± 8
Duration of Diabetes (Yrs)	-	5 ± 3.2
Triglycerides (mg%)	150.68 ± 21.79	193.96±14.36
Cholesterol (mg%)	234.92 ± 17.61	275.15±12.88
Fasting Blood Sugar (mg%)	59.02 ± 48.99	168.35±15.89
PPBS (mg%)	139.4 ± 12.24	197.7±15.82
HbA1C (%)	5.08 ± 0.377	7.18 ±1.22
Fibrinogen (mg/dl)	350 ± 56.16	509.4 ± 104.2
Albumin Excretion Rate in Urine (µg	13.8 ± 3.77	148.56±89.22

Correlation Between Various Parameters To Fibrinogen In Cases And Controls

TABLE V

VARIABLES	CONTROLS	DIABETES
Age (yrs)	r = 0.723	r = 0.672
Sex	p > 0.01	p > 0.01
Family History	p = 0.04	p = 0.10
Duration of DM(yrs)	–	r = 0.24
Smoking	p = 0.05	p = 0.15
Hypertension	–	r = 0.729
Triglycerides (mg%)	r = 0.6715	r = 0.87003
Cholesterol (mg%)	r = 0.7231	r = 0.9646
PPBS (mg%)	–	r = 0.9871
FBS (mg%)	–	r = 0.9281
HbA1C (%)	–	r = 0.8797
Urinary Albumin excretion rate(µg/Min)	–	r = 0.9342

III. Discussion:

As per the result obtained it is found that patients with NIDDM have elevated levels of fibrinogen and the plasma fibrinogen levels was independently associated with glycosylated hemoglobin and urinary albumin excretion rate.

Many studies of Kannel et al, lee AJ et al and the present study except the study of Ganda et al, found that plasma fibrinogen has positive correlation with diabetes. Higher fibrinogen levels in diabetics than in controls signifies the increased cardiovascular risk.

Total number of cases studied in the present study were 50, out of which 25 were men and 25 were women with a mean age of 57. 16 + 3 Yrs (Mean + SD) and 25 age and sex matched controls. In 50 cases 8 are controlled on diet. 27 on oral hypoglycemic agents (OHA). 13 on insulin and 2 on both insulin and OHAs. Mean duration of diabetes was 5+3. 2 Yrs in diabetics. Family history of diabetes were seen in 30 of diabetics and 8 of controls. In diabetes 11 are smokers, 8 are former smokers and 31 are non- smokers and in controls 5 are smokers, 5 are former smokers and 15 are non- smokers. 27 out of 50 diabetes and hypertensive and all controls are normotensive.

As per the results obtained the study is discussed under the following categories:

1.Hyperfibrinogenemia in NIDDM.
2.Relation of fibrinogen with glycosylated hemoglobin.
3.Relation of fibrinogen with urinary albumin excretion rate.
4.Relation of fibrinogen with other biochemical parameters.

1.Hyperfibrinogenemia in NIDDM:

Year	Name of the Study	FBS in mg/dl	PPBS in mg/dl	Fibrinogen in g/dl
1996	G.Bruno et al[7].	151+ 59	279+ 32	4.9+ 3.1
1999	Barszzoni et al[8].	143+ 62	256+ 43	5.3+ 2.8
2001	AnjulaJain et al[9].	191+ 83	235 + 179	7.3 + 5.8
2003	Present Study	168 + 15.9	197.7+ 15.8	5.09 +1.04

Comparative Study:

The Values obtained in the present study are consistent with the data of above mentioned studies. The possible mechanism for hyperfibrinogenemia in diabetics could be.

A. Fibrinogen is an acute phase reactant and it increases with early atherosclerosis:

Clinical disease resulting from large vessels atherosclerosis is responsible for most of the increased mortality of NIDDM. The risk of clinical macrovascular disease is increased twofold to three fold in subjects with diabetes. So fibrinogen which is an acute phase reactant also rises in the early atherosclerosis along with other acute phase reactants. Any damage to the vessel wall stimulates platelets (unpigmented enucleated blood cells really fragments of much larger progenitor cells named megakarocytes) to adhere to damaged blood vessels and then to each other so as to form a plug that can stop minor bleeding. This association is mediated by von Willerbrandt factor, a large (up to 10000 KD) multimeric plasma glycoprotein of subunit mass 225D. Fibrinogen binds to both a specific receptor on the platelet membrane and to the collagen and possibly other components of the subendothelial membrane exposed by vascular injury. Then, as the platelets aggregate, they release several physiologically active substances. Including serotonin and thromboxane A_2 that stimulate vasoconstriction, thereby reducing the blood flow at the injury site. Finally the agreegating platelets and the damaged tissue initiate the formation of blood clot. Thus, fibrinogen plays important role starting from the stage of plaque formation till formation of occlusive thrombus over a ruptured atherosclerotic plaque which is the main precipitating causes for Myocardial Infarction. The mechanisms by which fibrinogen is found to promote atherosclerosis and thrombosis are:

Hyperfibrinogenemia increases plasma viscosity.
It includes reversible RBC aggregation.
It binds to the receptors on platelet membrane and causes platelet aggregation.All these factors results in increased atherogenesity in patients of hyperfibrinogenemia which causes coronary artery disease.

B.Glycosylated Fibrinogen is less susceptible to plasmin degradation: Fibrinogen is extensively post-translationally modified, e.g. by glycosylation phosphorylation, sulfation, hydroxylation, oxidation and proteolytic processing. Mutations in the genes encoding the human fibrinogen chains present in diabetic patients led to novel glycosylation sites. In some patients it was studied, a mutation caused an Ala->Thr substitution in

position 335 of the B beta chain, leading to a complete glycosylation of the Asn residue in position 333, i.e. two residue before the incorrectly encoded residue. In other patients a mutation caused a Met>Thr substitution in position 310 of the chain, leading to a complete glycosylation of the Asn residue in position 308, i.e. two residues before. Even though both types of patients were heterozygous for the mutation, their blood plasma fibrinogens showed a considerable functional abnormality, such as highly prolonged coagulation time, most likely due to the presence of the excessive carbohydrate component and not to the amino acid exchange. Also these findings indicate the importance of the correct carbohydrate structure in glycoproteins. This glycosylated fibrinogen is less susceptible to plasmin degradation.
Relative Insulin Deficiency in Diabetes increases the Fibrinogen Synthesis[10].
II. Relation of Fibrinogen with Glycosylated Hemoglobin[11].: From the results it was found that as the concentration of glycosylated hemoglobin increases the mean plasma fibrinogen levels also increases.In addition to relationship between fibrinogen and glycosylated hemoglobin, there is direct relation with fibrinogen (r=0.8797).

The table shows the relationship between fibrinogen and glycosylated hemoglobin:

HbAIC	Patients(n)	Plasma Fibrinogen Level (g/dl)
5-6%	11	3.58 + 0.14
6-8%	23	5.39 + 0.13
>8%	16	5.98 + 0.15
(G.Bruno et al study)		
<6.8%	25	3.44 + 0..4
6.8-8.8%	51	3.60 + 0.04
>8.8%	27	3.80 + 0.04

The present study is compared with the study of G.Bruno et al where the levels of fibrinogen rise in the levels of glycosylated hemoglobin. The reason for this correlation may be due to:

1. Glycosylated fibrinogen is less susceptible to plasmin degradation[12]..
2. Relatively insulin deficiency in diabetes increases the fibrinogen levels.

The application of glycosylated hemoglobin measurements in assessing or predicting the long term complications of Diabetes has not been studied in detail, through it has been presumed by various authors. That glycation maylead to abnormal structure and functions which may be responsible for the complications that occur in Diabetes. Spiro et al noted that the sequelac of Diabetes are associated with those tissues that are not insulin dependent. The altered function resulting from the glycosylation leads to cellular abnormalities seen in Diabetes Mellitus.

Assessment of "Rapid changes of HbAIC fraction following alteration of diabetic control" was done by karamanous et al. They studied the temporal relationship of glycosylated hemoglobin concentrations to glucose concentrations. While the minimum period of time over which change in the blood glucose concentration must be sustained to produce this response is not clear. Karamanous et al stated that it may be of the order of a week or less. While the mechanism by which these relatively rapid changes are produced in HbAIC is not known Peterson et al, ruled out the reduced red cell survival as a factor contributing to this P.J.Dunn et al, pronuced that the observed reduction in the life span is not adequate to explain the rapid changes. The dissociation of glycosylated haemoglobin in the stable ketoamine form also seems unlikely. The possibility of disproportionate increase in the reversible Schiff's base moiety in diabetics has not been excluded. A third theoretical possibility is a disproportionately accelerated systhesis of glycosylated haemoglobin at higher blood glucose concentrations, which may be purely conjectural.

III.Relation of Fibrinogen with Urinary Albumin Excretion Rate :

As per the results in the present study and various other studies it is demonstrated that there is increased fibrinogen levels in diabetics with microalbuminuria than with normoalbuminuria.

The table below shows the relationship between fibrinogen and urinary albumin excretion rate (µg/min) with r=0.9342.

Urinary Albumin Excretion Rate	Patients	Plasma Fibrinogen Level (g/dl)
<20 µg/min	8	3.52 + 0.11
20-200 µg/min	32	3.68 + 0.04
>200 µg/min	10	6.56 + 0.11
(G.Bruno et al Study)		
<20 µg/min	38	3.52 + 0.03
20-200 µg/min	63	3.68 + 0.04
>200 µg/min	36	3.77 + 0.06

The possible mechanism for this correlation may be:
1. Fibrinogen increases plasma viscosity.
2. Fibrinogen increases blood volume.
3. Fibrinogen increases pressure in the renal tubules.

All the above factors causes proteinuria.

Iv. Association of Fibrinogen and other parameters:

Fibrinogen levels are found to be associated with age, hypertension, triglycerides and cholesterol in addition to glycosylated Hb and urinary albumin excretion rate in diabetics. The is no correlation with smoking (r=o, 24), sex (p>0.01), family history (p=0.10) and duration of diabetes (r=0.24).

The table IV below shows relationship of fibrinogen with various other parameters in both cases and controls.

VARIABLES	CONTROLS	DIABETICS
Age (Yrs)	R=0.723	R=0.672
Sex	P>0.01	P>0.01
Family History	p=0.04	P=0.01
Duration of DM	-	R=0.24
Smoking	P=0.05	P=0.15
Hypertension	-	R=0.729
Triglycerides (mg %)	R=0.6715	R=0.87003
esterol (mg%)	R=0.7231	R=0.9646
FBS (mg %)	-	R=0.9281
PPBS (mg %)	-	R=0.9871

The 4S studyhad already demonstrated the benefit of cholesterol lowering Type II Diabetes Mellitus. Bretzal et al66 in an epidemiological relationship showed every percentage point decrease of HbAIC reduced risk of microvascular complications by 35%. Kannel et al in their studies proved that reduction in fibrinogen levels decrease the risk of macrovascular complications by 55%. Gaede et al reported that in patients with Type II Diabetes Mellitus multifactorial intervention reduced the risk of progression of nephropathy, retinopathy, autonomic neuropathy and cardiovascular complications. The multifactorial intervention include the decreased fat diet, light to moderate exercises, advice to stop smoking and pharmacotherapy.
Finally it was found that fibrinogen has association with glycemic control and urinary albumin excretion rate.

IV. Summary:

1.A total of 50 patients 25 men and 25 women with Non-Insulin Dependent Diabetes Mellitus and 25 healthy controls were studied.
2.The biochemical parameters estimated were fasting blood sugar, postprandial blood sugar, Serum Triglycerides, Serum Cholesterol, Plasma Fibrinogen, Glycosylated Hemoglobin and Urinary Albumin Excretion Rate as shown in the tables.
3.Fasting blood sugar, postprandial blood sugar, serum triglycerides, serum cholesterol, Glycosylated hemoglobin, plasma fibrinogen and urinary albumin excretion rate are significantly higher in cases when compared to controls.

4.In case there is significant correlation between fibrinogen and glycosylated hemoglobin and urinary albumin excretion rate. As the value of fibrinogen increases there is significant rise in glycosylated hemoglobin and urinary albumin excretion rate.
5.Fibrinogen was found to be significantly related with age, hypertension, triglycerides levels and cholesterol level also, but no correlation with sex family history, smoking and duration of diabetes mellitus.
6.In controls fibrinogen has shown a positive correlation with age, triglycerides, cholesterol and smoking.
7.Fibrinogen continues to be an important risk factor in Non-Insulin Dependent Diabetes Mellitus patients which is an acute phase reactant, an independent risk factor of cardiovascular disease.
8.So Fibrinogen is an important parameter to be estimated along with other parameters in Non-Insulin Dependent Diabetes Mellitus.

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