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RESEARCH ARTICLE

STUDY OF PLASMA FIBRINOGEN LEVELS IN ACUTE STROKE

Dr. Lalit Jain and Dr. Hemant Kumar Tilgam
Department of Gen. Medicine N.S.C.B. Medical College & Hospital, Jabalpur (M.P.).

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Abstract

Background: Stroke is a disease of paramount public health significance. The role of plasma fibrinogen in determining incidence and severity of stroke has been postulated time and again. Present study was undertaken to determine the correlation between mean plasma fibrinogen level and infarct volume on CT scan in patients with acute stroke.

Methods: Source of data: Plasma fibrinogen of 50 consecutive patients presenting with acute stroke admitted in Netaji Shubhas Chandra Bose Medical College & Hospital, Jabalpur from March 2019 to August 2020 and compared with 50 controls not suffering from stroke with matched age, sex and risk factors (controls) such as heart disease, hypertension, Diabetes and obesity, smoking and use of alcohol. Method of collection of data. The study will be carried out on 50 consecutive patients admitted to N S C B Medical College & Hospital, Jabalpur with acute stroke within 24 hours of the onset of symptoms. Detailed history will be taken to find out the risk factors such as hypertension, diabetes, smoking and alcohol consumption. Hypertension will be diagnosed by JNC VII criteria. Diabetes will be diagnosed by American Diabetes Association criteria. Smoking will be recorded in terms of number of cigarette pack years smoked. Thorough general and systemic examination will be carried out. In addition to routine investigations as per standard protocol in the evaluation of stroke patient, fasting plasma fibrinogen level is estimated and compared to age; sex and risk factors matched controls.

Result: In this study Fibrinogen levels among patients of stroke were estimated. Data on demography (age, sex, habit of smoking, tobacco and alcohol) and clinical parameters (BMI, heart disease, Hypertension and Diabetes) was also collected. All 50 patients of stroke cases was compared with 50 control subjects, matched for age, sex, obesity, clinical parameters like heart disease, hypertension and diabetes and also for habits of smoking, tobacco use and alcohol.

Introduction:-

Cerebrovascular diseases are manifest by the abrupt onset of a focal neurologic deficit in most of the cases, as if the patient was struck by the hand of God. A stroke, or cerebrovascular accident, is defined by this abrupt onset of a neurologic deficit that is attributable to a focal vascular cause globally, stroke is a leading cause of death and

Corresponding Author:- Dr. Hemant Kumar Tilgam
Address:- Department of Gen. Medicine N.S.C.B. Medical College & Hospital, Jabalpur (M.P.).

disability. In India, age- standardized prevalence of cerebrovascular diseases has increased by 12.2% and the number of disability-adjusted life years (DALYS) has increased by 53% from 1990 to 2016. It has been reported as the fifth leading cause for years of life lost and dalys in 2016. Population-based surveys estimated crude prevalence of stroke ranged from 40 to 559/100,000 persons in studies in rural and urban parts of India.[1]

Non-modifiable risk factors for stroke include age, sex, race-ethnicity and genetics, modifiable risk factors are hypertension, current smoking, waist-to-hip ratio, diet risk score, regular physical activity and diabetes mellitus, binge alcohol consumption, psychosocial stress and depression, cardiac disease, and ratio of apolipoprotein B to A_1 were all associated with ischemic stroke risk. Risk factors for intracerebral hemorrhage included hypertension, smoking, waist-to-hip ratio, diet, and heavy alcohol consumption.[2] A High serum fibrinogen levels in high- risk individuals, especially the diabetics, may be used as a predictor for the occurrence of acute ischemic stroke and mortality from stroke as recent studies suggest.[3]

Fibrinogen is a 340 kDa glycoprotein that circulates in healthy humans at 2–4 mg/mL. Fibrinogen is composed of two sets of three polypeptide chains: Aα, Bβ, and γ. Alternative splicing of the γA chain leads to synthesis of a γ′ chain containing a unique 20-amino acid sequence at the C-terminus. Their unadjusted analysis shows a positive association of γ′ fibrinogen with incident coronary heart disease, ischemic stroke, peripheral artery disease, heart failure, and CVD deaths.[4] Fibrinogen γ' (γ') is a natural isoform of fibrinogen, and alters the rate of formation and the properties of clots. It could therefore affect outcome after ischaemic stroke. The γ'/total fibrinogen ratio is associated with unfavorable outcome in patients with ischaemic stroke.[5] The relation between fibrinogen and infarction, and between fibrinogen and stroke, became weaker when blood pressure, serum cholesterol, and smoking habits were taken into account, but was still significant for stroke.[6]There had been studies to evaluate relationship of fibrinogen to stroke but conclusive evidences are still awaiting. Hence this study is designed to investigate the association between plasma fibrinogen levels and acute stroke.

Aims and Objectives:-

1. To detect plasma fibrinogen levels in patients with acute stroke.
2. To compare and correlate the significance of plasma fibrinogen levels in patients with acute stroke with that of age, sex and risk factors matched controls.

Background

Fibrinogen Structure[7]:

The fibrinogen is synthesized by liver and secreted in plasma. The fibrinogen molecule is a large trinodular disulphide bonded glycoprotein composed of two symmetric half molecules. Each half molecule contains three distinct polypeptide chains called Aα, Bβ and γ chains. The entire molecule has a molecular mass of 3,40,000 Dalton and is 45nm long and 9nm in diameter. The central nodule or E-domain is 5nm in diameter and contains the NH-2 terminal of all six polypeptide chains forming the NH-2 terminal disulphide knot.

The outer two D-domain nodules are composed of the C-terminal two thirds of both the Bβ and γ chains. X-ray diffraction studies suggest that the Bβ and γ chain each form an independent sub domain within the D-domain. These two sub domains are located diagonally along the long axis of the molecule. Between the E- and D- domains, there is a stretch of approximately 120 amino acids from each of the three chains that forms an α- helical structure known as the “coiled coil domain”.

Synthesis:[8]

Plasma fibrinogen is synthesized exclusively by the hepatocyte, and the synthesis of the three chains is under the coordinated control of three separate genes localized on chromosome 4(ch4q23-q32). Subsequent to the assembly of the constituent polypeptide chains and the addition of carbohydrate side chain (3%), the mature molecule is secreted into the circulation, where it manifests the half-life of 72-108 hours and fractional catabolic rate of 25% per day. The turnover rate of fibrinogen is about 1.7-5 gm/day (30-60mg/kg/day).

Function[7,8]:

Fibrinogen plays the central role in three major functional processes.

1.The soluble fibrinogen molecule is converted into insoluble fibrin during the process of blood coagulation.

2.The polymerized fibrin serves as a template for the localized assembly and activation of the fibrinolytic system, which modulates fibrin deposition and clot dissolution.

3.Fibrinogen binds to vascular cells such as platelets, where it supports platelet aggregation by binding to platelet GP IIa-IIIb receptors and to endothelial cells, where it participates in tissue repair.

Measurement of Fibrinogen[9]:
A variety of different tests and assays of fibrinogen have been used by clinical laboratories.

The assays vary in the degree of expertise and time required and the equipment available. Some tests are designed for emergency situation, where an exact fibrinogen level may not be required, but merely an estimate of whether the levels are normal or grossly decreased.

In the last ten years, there has been a massive expansion in the range of coagulation automation and reagents available. The automated coagulometers rely on different types of end point technology to detect the fibrin clot. Some employ mechanical principles involving the movement of a metal hook, or clot impedance of a ball bearing magnetic field; others use photo optical devices to measure changes in light transmission or light scatter through 90°.

Stroke
Historical Review[10]: Hippocrates was probably the first to write about the medical aspects of stroke. He and his followers were mostly interested in prognosis, predicting for the patient and family the outcome of an illness. Hippocrates wrote in his aphorisms on apoplexy, "persons are most subject to apoplexy between the ages of forty and sixty", and attacks of numbness might reflect "impending apoplexy". A few hundred years after Hippocrates, Galen (131-201 AD) described the anatomy of the brain and its blood vessels from dissections of animals. During the last half of the seventeenth century, two important physicians Johann Jakob Wepfer and Thomas Willis made important contributions to understand the anatomy of blood circulation and clinical features of stroke. Johann Jakob Wepfer (1629-1695) made further anatomic and clinical observations. Wepfer performed meticulous examinations of the brains of patients dying of apoplexy (stroke). Obstruction of the carotid and vertebral arteries was recognized as a cause of apoplexy. Wepfer was the first to show clearly that bleeding into the brain was an important cause of apoplexy. Thomas Willis, a neuroanatomist best known for his cerebri anatome, which contained a description of a circle of anastomotic vessels at the base of the brain. Willis recognized transient ischemic attacks and the phenomenon of embolism, as well as existence of occlusion of the carotid artery.

Anatomy of Cerebral Circulation[10]:
At rest, the brain which is only 2% of total body weight, receives 20% of the cardiac output of blood and consumes 20% of the total inspired oxygen. This rich blood supply is delivered by the two internal carotid and two vertebral arteries, which anastomose at the base of the brain to form the circle of Willis. The carotid arteries supply the anterior, and the vertebrobasilar arterial system supplies the posterior portions of the brain.

Collateral blood supply to the Brain:
Normally the ICA provides blood to the anterior two-thirds of the ipsilateral cerebral hemisphere. There is rather little mixing of blood via the PoCA and so the posterior circulation is usually supplied by the vertebral, basilar and posterior cerebral arteries. However there are several ways in which collateral blood supply to the brain can develop distal to the occlusion of major arteries in the neck or head.

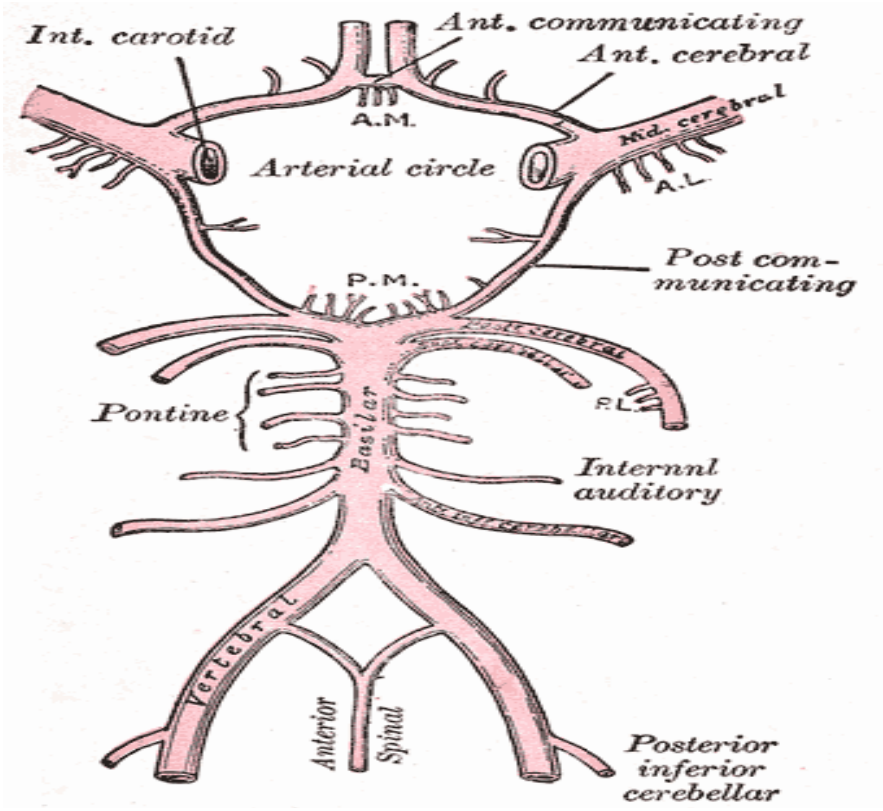

Figure:- Circle Of Willis.

Venous Drainage:

Venous blood flows centrally via the deep cerebral veins and peripherally via the superficial cerebral veins into the dural venous sinuses which drain into the internal jugular veins. The cerebral veins are thin walled, have no valves and the blood flow is often in the same direction as in neighboring arteries.[10]

Stroke

Definition of stroke:

Stroke is defined as a sudden, non- convulsive, focal neurologic deficit. The World health organization definition of stroke is "Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting for 24 hours or longer, or leading to death with no apparent cause other than of vascular origin[11]

Epidemiology of stroke:

Stroke has an annual incidence in the United States of America of approximately 4,00,000 cases per year. It is the most common serious neurological disorder in the world and accounts for half of all acute hospitalizations for neurological disease. The age specific incidence of stroke however varies dramatically over the life course.

Classification of cerebrovascular disease:

A detailed classification comprising all the problems involved in cerebrovascular disease is as yet not available. The principle cause of cerebral abnormalities from disease of cerebral arteries and veins are

1. Atherosclerotic thrombosis
2. Transient ischemic attacks.
3. Embolism
4. Ruptured or unruptured saccular aneurysm or AVM.
5. Arthritis

Risk factors for stroke

The three main classes of stroke that concern us are ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage. Although blood pressure is related to each of these types, other risk factors are not shared.

Blood pressure
Hypertension is a major risk factor for stroke, whether hemorrhagic or not. About 40% of strokes can be attributed to a systolic blood pressure of more than 140 mm hg[12]

Smoking
The Multiple Risk Factor Intervention Trial data shows that smoking is related to all forms of stroke with about the same strength as it is to coronary heart disease. The Framingham study showed three fold increases of ischemic strokes in smokers as compared to non-smokers. The effect was greater at younger ages and paralleled the number of cigarettes smoked.[13]

Obesity
The Whitehall study showed that body mass index was predictive of stroke in both smokers and non smokers. It was estimated that being overweight having a body mass index above 25 kg/m2 and smoking account for 60% of strokes in men up to 65 years.[14]

Diabetes Mellitus
Diabetes is a well-established risk factor for stroke. It can cause pathologic changes in blood vessels at various locations and can lead to stroke if cerebral vessels are directly affected. Additionally, mortality is higher and post stroke outcomes are poorer in patients with stroke with uncontrolled glucose levels.[15]

Transient Ischemic Attacks
It is one of the important risk factor for ischemic stroke. By and large one might expect that after 2-4 years, one out of six patients with TIA would have suffered a thrombotic stroke.[16]

Cardiovascular Disease
Electrocardiographic changes of left ventricular hypertrophy increases the risk of ischemic stroke by ten fold, nonspecific ST changes and T changes by four fold and congestive cardiac failure by nine fold according to the Framingham study. Hypertension and peripheral vascular disease, myocardial infarction, cardiac arrhythmias, valvular and congenital heart diseases are the risk factors for embolic stroke.

Clinical features of acute stroke:
Ischemic stroke may either be thrombotic or embolic. The major etiologic factors are the atherosclerosis and hypertensive disease. Systolic blood pressure is as important a risk factor as diastolic blood pressure. Diabetes mellitus, hyperlipidemia and smoking are other well recognized risk factors. Various pathogenic mechanisms and the effect of Ischemic modification due to collateral influx, influence the mode of presentation and evolution of the stroke. Most often the main part of the stroke is preceded by episodes of prodromal TIAs lasting for usually less than 10 minutes indicating evolving thrombus of the major arteries. Stroke may be preceded by one or two attacks or hundred or more and it may follow the onset of the attack by hours, weeks or months.

Material and Methods:-

Source of data: Plasma fibrinogen of 50 consecutive patients presenting with acute stroke admitted in Netaji Shubhas Chandra Bose Medical College & Hospital, Jabalpur from March 2019 to August 2020 and compared with 50 controls not suffering from stroke with matched age, sex and risk factors (controls) such as heart disease, hypertension, Diabetes and obesity, smoking and use of alcohol.

Method of collection of data. The study will be carried out on 50 consecutive patients admitted to N S C B Medical College & Hospital, Jabalpur with acute stroke within 24 hours of the onset of symptoms.

Detailed history will be taken to find out the risk factors such as hypertension, diabetes, smoking and alcohol consumption. Hypertension will be diagnosed by JNC VII criteria.

Diabetes will be diagnosed by American Diabetes Association criteria. Smoking will be recorded in terms of number of cigarette pack years smoked. Thorough general and systemic examination will be carried out. In addition to routine investigations as per standard protocol in the evaluation of stroke patient, fasting plasma fibrinogen level is estimated and compared to age, sex and risk factors matched controls. Patient will be followed up till they are discharged from the hospital.

Controls will be taken who are not suffering from stroke and are age, sex and risk factor matched.

Inclusion Criteria
1) Patients presenting with acute stroke within 24 hours of onset of symptoms.
2) Patients of acute cerebrovascular accident in whom CT scan shows cerebral infarct or hemorrhage.

Exclusion Criteria
1. Patients with evidence of uremia.
2. Patients with evidence of infection.
3. Patients with evidence of active hepatic disease.
4. Patients who have suffered from myocardial infarction in last three months.
5. Patients who have undergone surgery in last three months.

Result:-

In this study Fibrinogen levels among patients of stroke were estimated. Data on demography (age, sex, habit of smoking, tobacco and alcohol) and clinical parameters (BMI, heart disease, Hypertension and Diabetes) was also collected. All 50 patients of stroke cases was compared with 50 control subjects, matched for age, sex, obesity, clinical parameters like heart disease, hypertension and diabetes and also for habits of smoking, tobacco use and alcohol. Proportional representation of demographic and clinical parameters and comparison of mean Fibrinogen levels for all these parameters are as follows:

Table No. 1:- Distribution of patients according to age.

Age group	Cases (N=50)	Control (N=50)
≤30	6 (12 %)	6 (12 %)
31-40	8 (16 %)	8 (16 %)
41-50	9 (18 %)	9 (18 %)
51-60	14 (28 %)	14 (28 %)
61-70	7 (14 %)	7 (14 %)
71-80	4 (8 %)	4 (8 %)
>80	2 (4 %)	2 (4 %)
TOTAL	**50 (100 %)**	**50 (100 %)**

Most of the patients were in 51-60 years of age group, followed by younger cohort 41-50 years and older 61-70 years of age. While least common age groups were more than 71 years of age in our study.

Table No. 2:- Distribution of patients according to sex.

Sex	Cases (N=50)	Control (N=50)
Male	25 (50 %)	25 (50 %)
Female	25 (50 %)	25 (50 %)
TOTAL	**50 (100 %)**	**50 (100 %)**

There were 50% males and 50% of the patients were females.

Table No. 3:- Distribution of patients according to status of hypertension.

Hypertension	Cases (N=50)	Control (N=50)
Present	22 (44 %)	22 (44 %)
Absent	38 (76 %)	38 (76 %)
TOTAL	**60 (120 %)**	**60 (120 %)**

There were 22 (44 %) patients with hypertension in our cases of stroke and similar proportion of the controls were having hypertension.

Table No. 4:- Distribution of patients according to status of diabetes.

Diabetes Mellitus	Cases (N=50)	Control (N=50)
Diabetic	16 (32 %)	16 (32 %)
Euglycemic	34 (68 %)	34 (68 %)
TOTAL	**60 (120 %)**	**60 (120 %)**

There were 16 (32 %) patients with diabetes and 34 (68 %) euglycemic patients among stroke cases group and similar proportion of matched controls.

Table No. 5:- Distribution of patients according to status of smoking.

Habit of smoking	Cases (N=50)	Control (N=50)
Present	14 (28 %)	14 (28 %)
Absent	36 (72 %)	36 (72 %)
TOTAL	**50 (100 %)**	**50 (100 %)**

Fourteen (28%) patients were smokers and 36 (72 %) were non-smokers in the cases group of stroke, while same proportion of matched control subjects were also smokers.

Table No. 6:- Distribution of patients according to status of alcohol use.

Habit of Alcohol	Cases (N=50)	Control (N=50)
Present	5 (10 %)	5 (10 %)
Absent	45 (90 %)	45 (90 %)
TOTAL	**50 (100 %)**	**50 (100 %)**

Five (10%) of the patients had a habit of alcohol among 50 cases. A similar proportion of matched controls was also having habit of alcohol use.

Table 7:- Mean fibrinogen levels between study groups.

Study Group	Cases (N=50) (Mean±SD)	Control (N=50) (Mean±SD)	Student's t- test (p-value)
Fibrinogen	526.2±163.1	343.6±142.7	**<0.0001**

Mean fibrinogen levels for cases 526.2 mg/dl, which was significantly ($p<0.0001$) higher than the mean fibrinogen levels of control group (343.7 mg/dl).

Table No. 8:- Mean fibrinogen levels for different age groups.

Age group (years)	Cases (N=50) (Mean±SD)	Control (N=50) (Mean±SD)	Student's t-test (p-value)
≤30	426.2±188.7	246.5±130.4	0.084
31-40	452.6±143.3	241.5±97.2	**0.0039**
41-50	469.4±73.14	317.8±77.37	**0.0006**
51-60	593±204.9	413.9±172.9	**0.0191**
61-70	603.6±147.9	419.4±125.9	**0.0275**
71-80	546.3±66.51	319.5±105.8	**0.011**
>80	597±12.73	450.5±33.23	**0.0283**

Fibrinogen shown a positive linear co-relation with age in both of the groups of cases and controls ($p<0.05$). Fibrinogen increased with age and highest mean values were seen for the age group of 61-70 years of age than showed a slight decline in cases. While in the control group the rise in continued till last highest age group studied that is >80 years of age, was with highest mean fibrinogen value. Mean fibrinogen levels were higher in all the age groups for cases compared to control. Where mean fibrinogen levels were significantly ($p<0.05$) higher in all the age group from 31-40 to >80 years of age for cases compared to control, except for the youngest age group of ≤30 years which showed comparable mean fibrinogen values between cases and control.

Table No. 9:- Mean fibrinogen levels for sex of patients.

Sex	Cases (N=50) (Mean±SD)	Control (N=50) (Mean±SD)	Student's t-test (p-value)
Male	544±162.4	342.5±143.6	**<0.0001**
Female	508.4±165.2	344.7±144.8	**0.0005**
Student's t-test			

(p-value)	0.4464	0.9572	

Mean fibrinogen levels were significantly ($p<0.05$) higher in cases, compared to control groups when compared for the both sexes of males and females. In intra group analysis between males and females of cases and controls, males and females showed a comparable mean fibrinogen levels ($p>0.05$),

Table No. 10:- Mean fibrinogen levels for status of hypertension.

Diabetes Mellites	**Cases (N=50) (Mean±SD)**	**Control (N=50) (Mean±SD)**	**Student's t-test (p-value)**
Diabetic	648.6±127.9	470.8±116.3	**0.0003**
Euglycemia	468.6±146.2	283.8±112.1	**<0.0001**
Student's t-test (p-value)	**0.0001**	**<0.0001**	

In inter group analysis between cases and controls both kind of patients whether with Diabetic or Euglycemics showed a significantly ($p<0.001$) higher mean fibrinogen levels for the cases compared to control group. On Intra group analysis for both the group, mean fibrinogen levels were significantly higher ($p<0.05$) in Diabetic patients compared to that of Euglycemic patients.

Discussion:-

In present study of fibrinogen in stroke patients 51-60 years of age group was the most common group of patents presented which was younger than most of the western data.[17] There were 50% males and 50% of the patients were females in our study while suggest otherwise where Stroke has a greater effect on women than men because women have more events and are less likely to recover. Age-specific stroke rates are higher in men, but, because of their longer life expectancy and much higher incidence at older ages, women have more stroke events than men.[18]

We had seen 15 (30 %) were overweight and had a BMI of ≥25 while rest 70% cases were having a BMI of <25 kg/m^2. While reported 64% overweight and 26% obese patients among stroke patients. At another center in same study prevalence of obesity was 15 to 30%.[19]

Use of smokeless tobacco was 12% in our study suggested similar findings where smokeless tobacco was an important etiological factor for young ischemic stroke.[20] Use of alcohol was 10% and smoking was 28% in our study. A study by reported 10 and 6 fold increase in risk with alcohol and smoking respectively. Although similar results were observed on smoking where smokers had an increased risk of overall stroke compared with nonsmokers, with a pooled or of 1.61 (95% CI: 1.34–1.93). A subgroup analysis was conducted based on smoking status: the ORs were 1.92 (95% CI: 1.49–2.48) for current smokers and 1.30 (95% CI: 0.93–1.81) for former smokers.[20]

Fibrinogen:

The present study of estimation of fibrinogen levels among stroke patients, 50 stroke patients (cases) and 50 controls were enrolled. The mean fibrinogen level amongst cases is 526.2 mg/dl in case group; in controls mean fibrinogen is 343.6 mg/dl which is statistically significant. Also reported comparable results to our study; a significantly increased (531.73±74 mg%) levels of fibrinogen compared to those of the age and sex matched control group (445.78±92.28mg%).[21]While mean fibrinogen levels in ischemic stroke were 584±62mg/dl which was significantly higher ($p<0.05$) than normal range of (200-400mg/dl). There was significant correlation between infarct volume and fibrinogen levels.[22] while showed that Hyperfibrinogenemia at the beginning of ischemic stroke is associated with poor outcome.[23]

Age and Fibrinogen:

Reported that about half (55%) of stroke patients were in the age group 41-60 years.[24] Most common age group affected with stroke was 51-60 years of age. Age is an important nonmodifiable risk factor for stroke. The mean age of stroke onset in India (i. e., 63 years) is lower than that in Western countries (68 years in the USA and 71 in Italy). This is due to inadequate control of the common modifiable risk factors and also due to added existence of nontraditional risk factors.[17]

Fibrinogen levels increases with age.[25]The contrasting fact that synthesis albumin and Fibrinogen decreases with age but it decrease disposal or degradation of fibrinogen that is responsible for age related increment.[26] Our study is also in synopsis with age related increase in fibrinogen concentration thus increase incidences of stroke in older age. As age advances there is change in orientation of gpIIa/IIIb receptor causing decreased fibrinolytic activity which accounts for increased plasma fibrinogen levels as age advances.

Sex and fibrinogen:
Reported that cerebrovascular strokes are more common in males (59.7%) than females (40.3%).[26] Showed even higher male ratio than our study with 172 (71.67%) males and 68 (28.33%) females (M: F = 2.53:1).24 Demonstrated presence of higher grade of cerebrovascular plaques being associated with higher concentration of fibrinogen in females.[27] was consistent .

Smoking and fibrinogen: Demonstrated that smoking contributes more than additively to the strong influences of single and combined traditional risk factors on fibrinogen levels. These data confirm that smoking is a dominant determinant of fibrinogen levels in the general population.[27] suggest a primary role for increased synthesis in producing the hyper fibrinogenaemia associated with smoking. Moreover, abstention from smoking for a period of only 2 weeks induces a significant decrease in the rate of fibrinogen synthesis by the liver, with a concomitant reduction in the plasma fibrinogen concentration.[28]

This study has shown increased fibrinogen levels in controls amongst smokers as compared to non-smokers. Smoking activates lung macrophages which releases IL-β which increases fibrinogen synthesis. Smoking decreases fibrinolytic activity and causes endothelial damage resulting in activation of coagulation system and release clotting factors.[28]

Hypertension and fibrinogen:
Provide prospective epidemiological evidence of an essential link between plasma fibrinogen level and incident hypertension among men but not among women, a finding consistent with that observed in the Atherosclerosis Risk in Communities Study[29]

In this study hypertensive patients in control group had significantly higher fibrinogen than normotensives. Several plausiblemechanisms could explain an observed association between elevated fibrinogen levels and hypertension such as relation of fibrinogen to increased viscosity and peripheral vascular resistance, markers of inflammation such as IL -6 and IL-8 are elevated in hypertension and causes reduced consumption of fibrinogen, thereby contributing to increased plasma fibrinogen in hypertension, increased platelet activation etc.[29]

Diabetes and fibrinogen:
In this study diabetics had higher fibrinogen than non-diabetics. Studied mean plasma fibrinogen level in diabetics in a case control study, in cases fibrinogen was high (380.03 ± 101.07 mg/dl) as compared to controls (244.43 ± 61.27 mg/dl), which was found to be statistically highlysignificant ($p < 0.0001$).[30] Also that plasma fibrinogenlevels were significantly higher in diabetics than the non diabetic subset (386.04±132.87 vs. 314.38±97.42; $p<0.001$).[31] The exact mechanism of increased fibrinogen levels in diabetics is unknown. Insulin stimulates cholesterol synthesis in smooth muscle cells stimulates the proliferation and migration of smooth muscle cells. It also enhances the formation of fibrinogen. Endothelial dysfunction which is common in diabetics, which causes decreased fibrinolytic activity and hence increased plasma fibrinogen levels. The plasma glucagon concentration is positively related to the plasma fibrinogen concentration. Thus, fibrinogen production is markedly enhanced in diabetic patients, and this alteration is likely to determine the observed hyper fibrinogenemia in these patients.

Hyperglucagonemia may contribute to the increased fibrinogen production. Thus, insulin concentrations (and probably also glucose profiles) may need to be maintained at the lowest attainable level in type 2 diabetes to prevent increased fibrinogen synthesis and concentrations.

Conclusion:-

In this study mean fibrinogen levels were significantly higher in cases of stroke compared when to the match control group for age, sex, obesity, heart disease, hypertension and diabetes habit of smoking, tobacco chewing and alcohol. There was a significant association of fibrinogen levels, increased with age in both cases and controls. Sex seems to have no significant effect on fibrinogen levels. Fibrinogen levels were significantly raised among both groups of

patients of Heart disease, Hypertension, diabetes mellitus and habit of smoking. However the levels were raised in smokers fibrinogen levels were comparable for parameters of tobacco. In obese patients also fibrinogen levels were comparable in cases as well as in controls. Therefore, with my study a conclusion can be made that: In the patients of stroke fibrinogen can be very good biomarker for evaluation of role of developing cardiovascular disease. Patients at risk for the development of fibrinogen related ischemic complications like atherosclerosis can be easily identified and non- pharmacological interventions (cessation of smoking, diet and exercise etc) which seems to lower the raised fibrinogen along with pharmacological treatment can be employed.

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