DISSERTATION

On

"LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS"

Submitted in partial fulfillment of
Requirements for

MD DEGREE EXAMINATION

BRANCH-I GENERAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation **titled "LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS"** is a bonafide work done by **Dr. RAVINDRAN.R,** Post Graduate student, Institute of Internal Medicine, Madras Medical College, Chennai – 600003, in partial fulfillment of the university rules and regulations for the award of MD DEGREE in GENERAL MEDICINEBRANCH-I, under our guidance and supervision, during the academic period from April 2011 to April 2014.

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DECLARATION

I solemnly declare that the dissertation titled **"LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS"** was done by me at Madras Medical College, Chennai – 600003, during the period July 2013 to November 2013 under the guidance and supervision of **Prof. R.PENCHALAIAH, MD,** to be submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I.

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ABBREVIATIONS

CVA	Cerebro Vascular Accident
TIA	Transient Ischemic Attack
MI	Myocardial Infarction
ATP	Adenosine Triphosphate
ADP	Adenosine Diphosphate
NOs	Nitric Oxide synthase
CNS	Central Nervous System
ACA	Anterior Cerebral Artery
PCA	Posterior Cerebral Artery
AICA	Anterior Inferior Cerebellar Artery
PICA	Posterior Inferior Cerebellar Artery.
ICA	Internal carotid artery.
DALY	Disability Adjusted Life Year
CT	Computed Tomography
MRI	Magnetic Resonance imaging

LACS	Lacunar Syndrme
DM	Diabetes Mellitus
SHT	Systemic Hypertension
CAD	Coronary Artery Disease
VLDL	Very low density lipoprotein
LDL	Low density lipoprotein
HDL	High density lipoprotein
Lp (a)	lipoprotein (a)
TC	Total cholestrole
TG	triglyceride

CONTENTS

“LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS”

ABSTRACT

AIMS:

This study is done to compare lipoprotein (a) level in Type II diabetic and non-diabetic patient with ischemic stroke, to know any significant association present with lipoprotein (a) levels and ischemic stroke , to identify whether diabetic patients have significantly high lipoprotein (a) value compared non diabetic and to evaluate whether lipoprotein (a) level can use as an early marker to assess severity of ischemic stroke.

STUDY METHODS:

This is a cross sectional study done on 100 patients with ischemic strokewho attended Rajiv Gandhi government general hospital over a period of 6 months from June 2013 to November 2013 . Patients with age above 40 years were studied. Of the 100 patients studied 50 patients under group 1 weretype II diabetic and 50 patients under group 2 were non diabetic. Diagnosis of stroke was made clinically and radiologically CT proven .Lipoprotein(a) levels were measured for all these patients.The disease morbidity was assessed using the Scandinavian scoring system.

RESULTS AND OBSERVATION:

33 patients under group 1(diabetic population) and 23 patients under group 2 (non-diabetic population) had lipoprotein levels in the high risk category [Lp(a)= 30 to 50 mg/dl]. There is a significant difference in the association of Lp(a) levels and ischemic stroke p value 0.044 and there is significant association between diabetic and non-diabetic population(p value=0.047).The rise in Lp(a) levels to assess the disease severity by Scandinavian scoring system was not significant(p value=0.099)

CONCLUSION :

High lipoprotein (a) level significantly associated with ischemic stroke. The Lp(a) levels were significantly higher inpatients with type II diabetes than those without diabetes. Lp(a) cannot be used as a marker to assess the severity of ischemic stroke.

KEYWORDS:

Lipoprotein (a), typeII diabetics, non-diabetics, Scandinavian score .

INTRODUCTION

INTRODUCTION

Stroke is defined as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting for 24 hours or more, it is the most common neurological disorder worldwide. Stroke is also known as Cerebrovascular Accident (CVA), derived from Greek word which means 'Struck Down with violence'[1].

According to the World Health Organization, 15 million people suffer from stroke worldwide every year. Of these, 5 million die and another 5 million are permanently disabled[2].

Stroke kills more than 1,37,000 people a year, 1 of every 18 deaths. Every 40 seconds a stroke occurs every 4 minutes someone dies of stroke .

The incidence of stroke is higher in men than in women. Every year there are about approximately 700,000 cases of stroke, roughly 600,000 ischemic lesions and 100,000 hemorrhages, with 175,000 fatalities from these causes.[3]

It is estimated that by the year 2020 stroke will become the 4th leading cause of disability adjusted life years.[4] The prevalence of stroke in India is estimated to be 203/100000 population above 20 years of age. The disability and morbidity is higher in elderly with doubling of death due to stroke in United States by the year 2030.[5]

Cerebrovascular Accident is defined as the abrupt onset of focal neurological deficit. It was described as if the patient was struck by the hand of God. Stroke may be due to ischemia or hemorrhage, 85% of the stroke are ischemic. Occurrence of stroke leads to a lot of physical disability and also cognitive and behavioral impairment. The most important risk factors that contribute to stroke are Systemic hypertension, Diabetes mellitus, dyslipidemia, and Cigarette smoking and heart diseases. These risk factors causing stroke when modified and kept under strict control have substantial influence in preventing its occurrence and reducing its severity.

Type 2 diabetes is a major risk factor; dyslipidemia also plays a major role as risk factor for ischemic stroke. Studies in the past demonstrated that patient with increased lipoprotein (a) and diabetes as risk factor for ischemic stroke. High lipoprotein (a) predicts risk of early atherosclerosis independently of other risk factor including LDL[6]

So here we analyze whether there exists a relationship between lipoprotein (a) in type 2 diabetic patients in comparison with non-diabetic patients with ischemic stroke, whether lipoprotein (a) can act as an early marker or early predictor for worse prognosis in diabetic patients with ischemic stroke when compared to non-diabetics.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

To compare lipoprotein (a) level in type 2 diabetic and non-diabetic patients with ischemic stroke

SECONDARY OBJECTIVE:

To evaluate lipoprotein (a) levels as an early marker to assess the severity of ischemic stroke in type 2 diabetic patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Stroke is defined according to the standard WHO clinical criteria as “a rapidly developed sign of focal or global disturbance of cerebral function lasting longer than 24 hours (unless interrupted by death), with no apparent nonvascular cause.

Stroke is the second leading cause of death worldwide, next to cardiac death before cancer accounting for 11% of total death. It is the third most common cause for morbidity.

From 1990 to 2010, there is a significant decrease in incidence of stroke by 12% (95%CI 6-17) in countries of high income and increase in the incidence of stroke by 12% in countries with low income and middle income, albeit non significantly. There is a significant fall in mortality rates in both high income (37% ,31-41) and low and middle income countries(20%,15-30). In 2010, the absolute numbers of people with first stroke (16·9 million), stroke survivors (33 million), stroke-related deaths (5·9 million), and DALYs lost (102 million) were high and had significantly increased since 1990 (68%, 84%, 26%, and 12% increase, respectively), with most of the burden (68·6% incident strokes, 52·2% prevalent strokes, 70·9% stroke deaths, and 77·7% DALYs lost) in low-income and middle-income countries.[7]

More than 62% of new strokes, 69·8% of prevalent strokes, 45·5% of deaths from stroke, and 71·7% of DALYs lost because of stroke were in people younger than 75 years.[7]

If these trends in stroke incidence, mortality, and DALYs continue, by 2030 there will be almost 12 million stroke deaths, 70 million stroke survivors, and more than 200 million DALYs lost globally.[7]

Stroke occurs more in men than women, elder than younger.

In India, though only less official records are available stroke and its social and economic impact is more worrisome than other developed countries.

History:

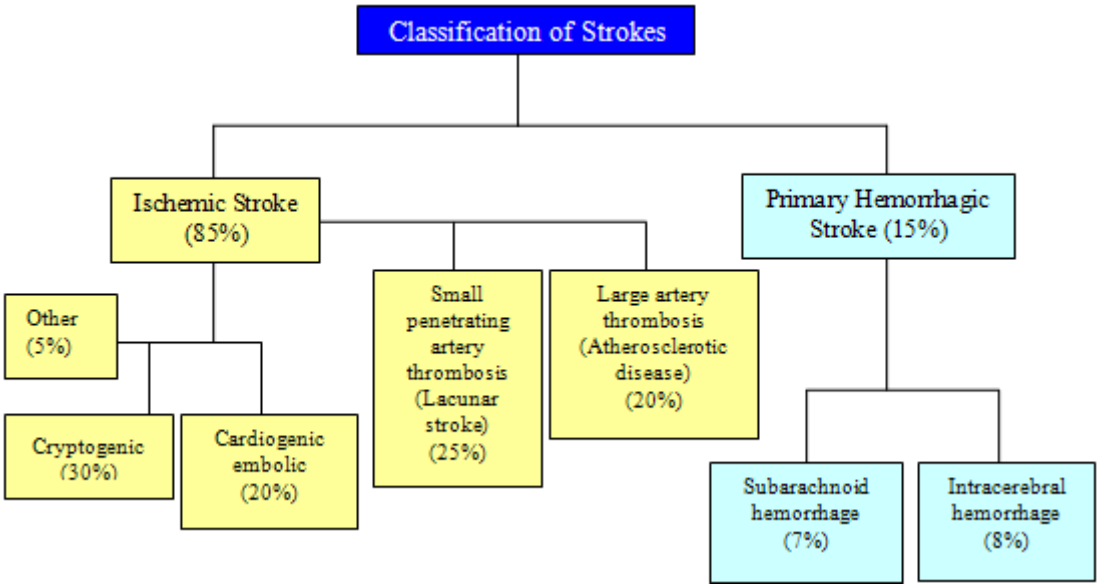
Hippocrates (460-370BC) is the one who first described the stroke events as an acute onset of paralysis. The word stroke used with other meaning of Greek word apoplexy meaning a form of seizure literally means struck down with violence was used in 1599 itself.[8]

In mid-15thcentury JOHANN JACOB WEPFER first described people who died of bleeding inside brain and he is one who explained about blood supply of brain.[9]

Latter in 1927 term cerebrovascular accidents was introduced and been used till now.

Stroke may be due to ischemia or hemorrhage.

85% of all strokes are ischemic.



RISK FACTORS

- The most important risk factor that ranks first in association with stroke is Systemic Hypertension. It has been proved that the control of blood pressure will decrease the risk of occurrence of stroke in an individual.
- The other risk factors are
  - Diabetes.
  - Hyperlipidemia.
  - Smoking – Increase the rate of Carotid atherosclerosis
  - Atrial fibrillation – mainly due to cardiac cause.

- Infective endocarditis (Bacterial and Nonbacterial) leading on to embolic stroke.
- Right to left shunts
- Systemic – Hypercoagulable conditions like APLA.
- Usage of Oral Contraceptive Pills.
- Symptomatic Carotid Artery Stenosis-70-99% of patients develop stroke.

ISCHEMIC STROKE

Ischemic Stroke refers to occurrence of stroke due to decreased cerebral perfusion due to thrombosis or embolism.

ETIOLOGY:

The following table enlists the common and uncommon causes.

COMMON CAUSES	UNCOMMON CAUSES
Thrombosis	**Hypercoagulable disorders**
Lacunar stroke (small vessel)	Protein C deficiency
Large vessel thrombosis	Protein S deficiency
Dehydration	Antithrombin III deficiency
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation
Carotid bifurcation	Prothrombin G20210 mutation
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardio embolic	Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematous
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias
Mechanical valve	Nephrotic syndrome
Bacterial endocarditis	Inflammatory bowel disease
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinus thrombosis
Patent foramen ovale	Fibro muscular dysplasia / Vasculitis
Atrial septal aneurysm	Primary CNS vasculitis
Spontaneous echo contrast	Systemic vasculitis

Few rare causes of ischemic stroke include:

Hypercoagulable disorders:

A variety of disorders are associated with increased risk of thrombosis. Protein C and S deficiency cause arterial thrombosis. SLE, Libman Sacs endocarditis causes embolic stroke. Sickle cell anemia is a common cause of stroke in children.

Fibromuscular Dysplasia:

Fibromuscular Dysplasia affects the vertebral arteries commonly and is more common in women. Usually an incomplete occlusion occurs. Renal artery involvement is common and may cause hypertension. Usually asymptomatic but may be associated with audible bruit, Stroke.

Temporal (Giant Cell) Arteritis:

Temporal (Giant Cell) arteritis is common in old age. Temporal arteries undergoes granulomatous inflammation with giant cells.

Takayasu Arteritis:

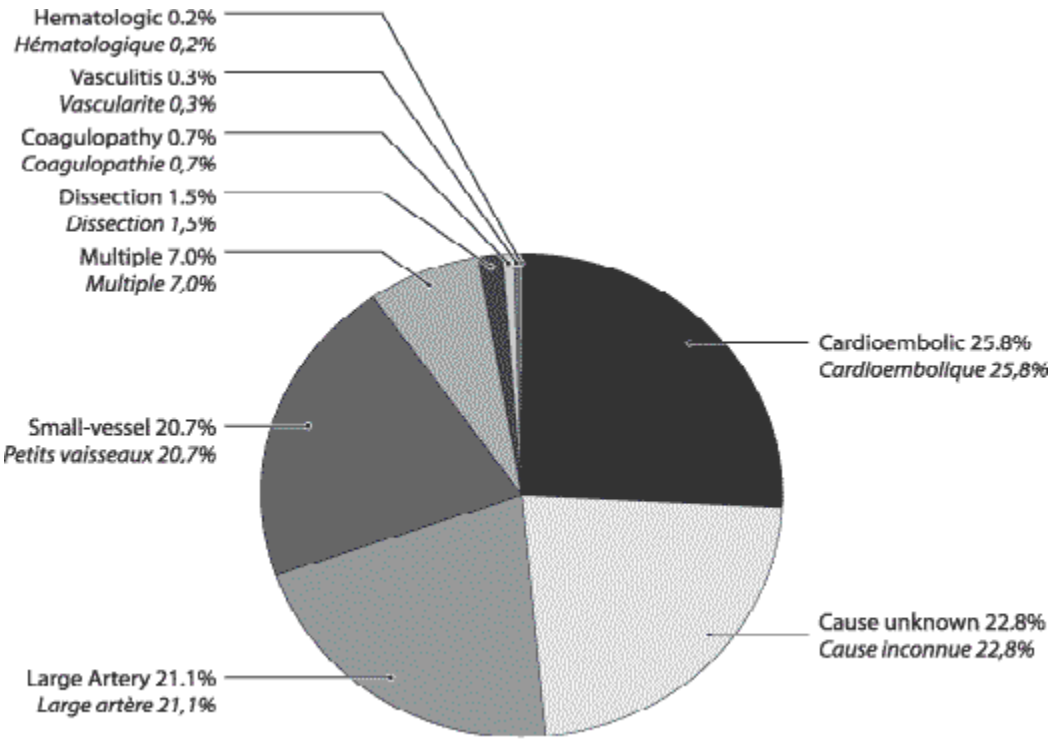
Takayasu arteritis or idiopathic giant cell arteritis involves the great vessels like aortic arch, carotid or vertebral artery leading to thrombosis.

MoyaMoya Disease:

MoyaMoya disease involves the large arteries commonly. The occlusion occurs at the stem of Middle Cerebral Artery and Anterior Cerebral Artery. The presence of collateral circulation gives the appearance of puff of smoke.

Reversible Posterior Leukoencephalopathy:

There is an extensive cerebral segmental vasoconstriction leading to cerebral ischemia. The pathophysiology is uncertain but the ischemia is reversible completely.



Leukoaraiosis:

Leukoaraiosis or Periventricular white matter disease causes multiple small vessel infarcts within the subcortical white matter. It is due to lipohyalinolysis of small penetrating arteries. It commonly occurs in chronic SHT.

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) most commonly presents as small vessel stroke.

TRANSIENT ISCHEMIC ATTACK (TIA):

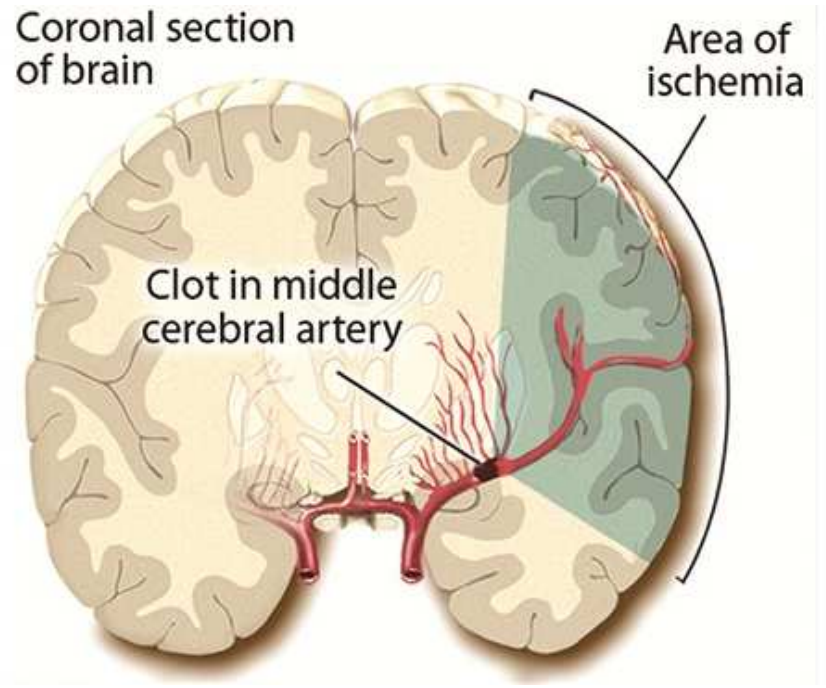
If the neurological signs and symptoms resolve within 1 day (24 hours), irrespective of imaging evidence of new brain changes , it's termed as Transient IschemicAttack.[10]

One third of TIA occurs in patients with hypertension. They are preceded or proceeded by stroke. In 20% of TIA stroke occurs within one month and in 50% within one year.[11] TIA is the warning sign of an impending blood vessel occlusion. TIA of longer duration, multiple episodes each with different pattern is most probably due to embolism, whereas recurrent brief attacks with similar pattern are mostly due to atherosclerosis and thrombosis.

TIA can also occur due to increased viscosity of the blood, as in hypercoagulable states, polycythemia vera & Leukemia. It occurs most commonly in vertebrobasilar system rather than in the carotid system.[12] The risk of occurrence of myocardial infarction is high after transient ischemic attack.

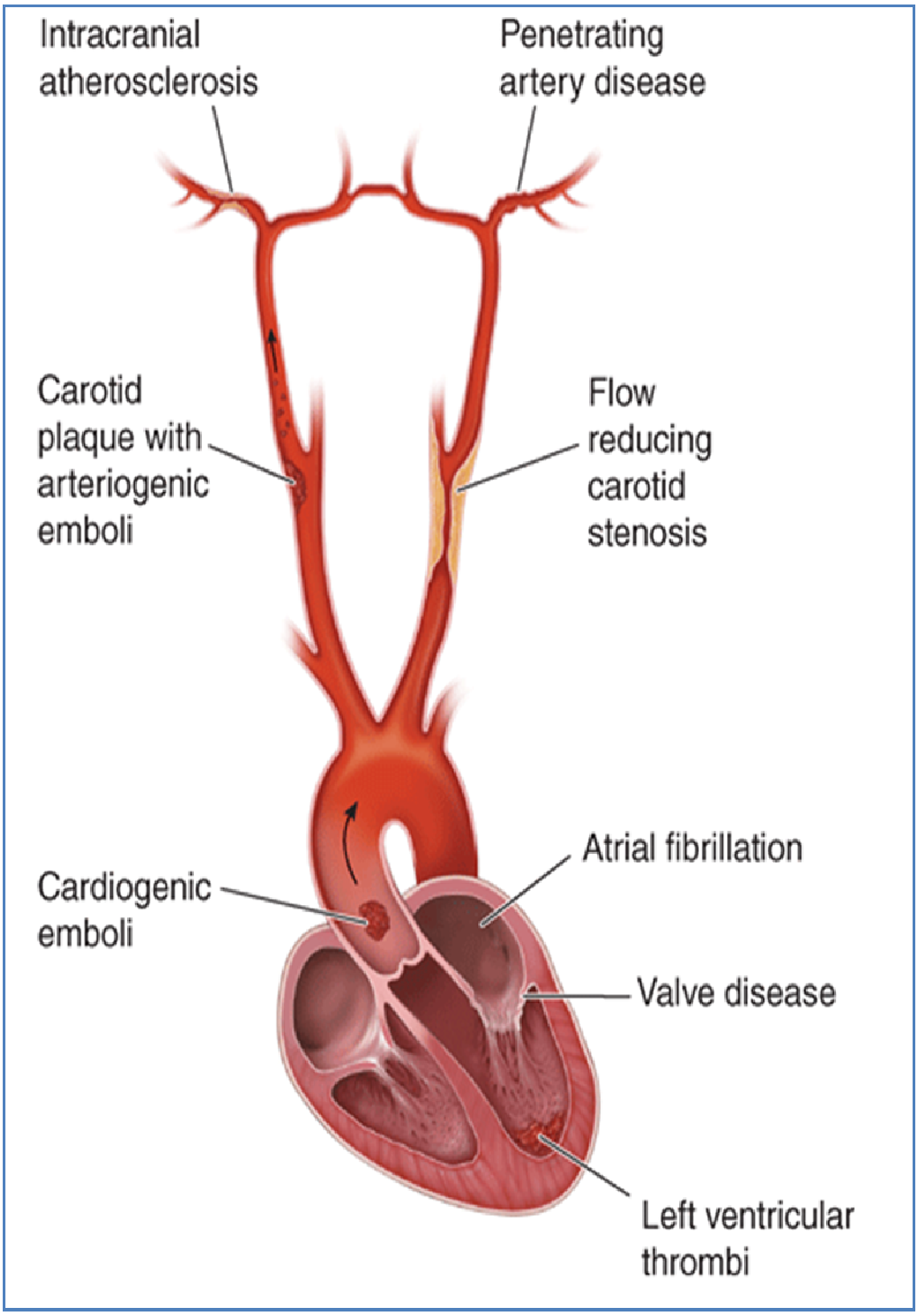
PATHOPHYSIOLOGY OF ISCHEMIC STROKE:

The pathophysiology of occurrence of ischemic stroke depends on its etiology and risk factors. The pathology may be either due to thrombus or embolism or decreased perfusion due to stenosis in arterial system causing occlusion.



- Altered permeability of vessel wall
- Change in the viscosity mainly increased viscosity of the blood
- Blood vessel rupture
- Atherosclerosis
- Aneurysmal dilatation
- Hypertension
- Arteritis and vasospasm
- Developmental malfunction.

It is difficult to distinguish the lesion of an embolism or thrombosis. Embolic stroke occurs suddenly and the neurological deficit is to the maximum at the onset. Thrombotic stroke occurs less abruptly and takes longer time for the stroke to evolve. Thrombosis of vessels may lead to artery to artery embolism. The stenosis occurs most commonly due to atherosclerosis and plaque deposition.



Stenosis, Embolism and Thrombosis are shown in this diagram.

The extent of ischemia depends on degree and duration of occlusion and also the presence or absence of other associated factors like

- **Blood pressure:**

Systemic blood pressure determines the cerebral perfusion pressure. When blood pressure is lowered the cerebral perfusion pressure also decreases leading to global cerebral ischemia.

- **Hyperthermia:**

Ischemic injury is much severe if there is elevated body temperature.

- **Glucose level:**

Both hypoglycemia and hyperglycemia are associated with a poorer outcome.

- **Hypercoagulable state:**

If there is an associated hypercoagulable state there is an increase in micro thrombi formation and worsening of blood vessel occlusion.

NEURONAL DEATH:

Neuronal death occurs by two ways:

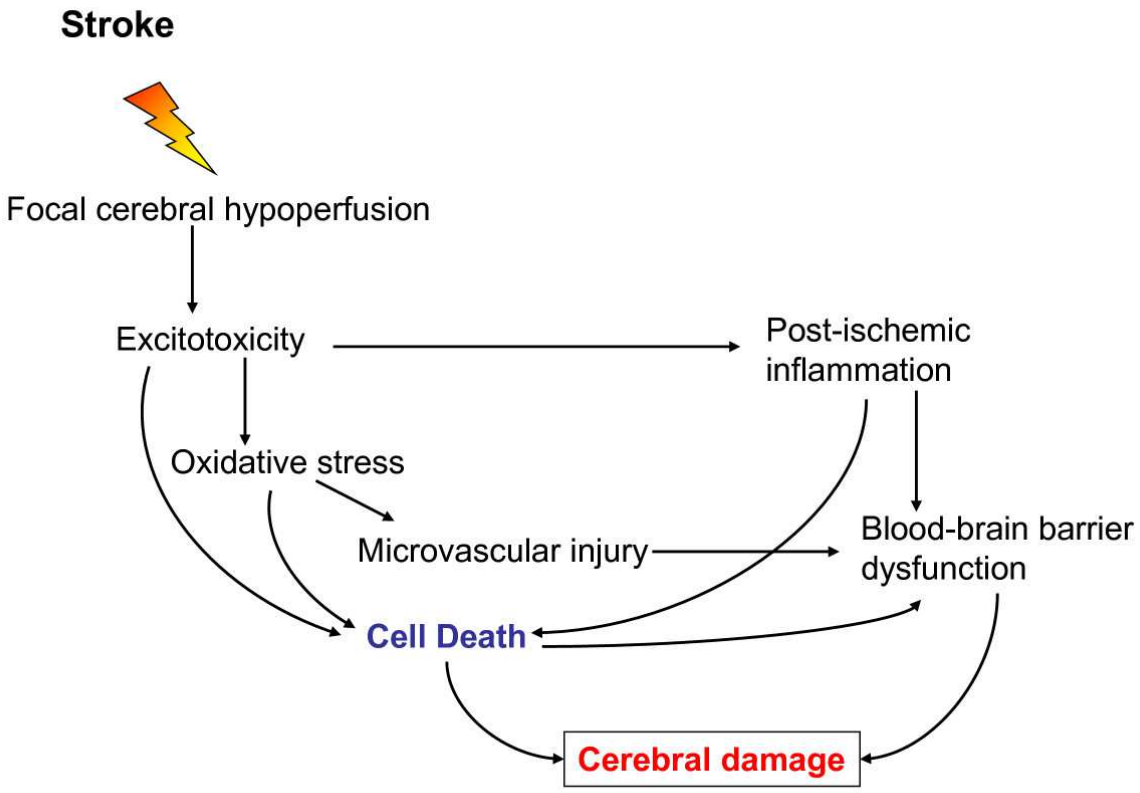
- **Apoptosis:**

Apoptosis is defined as programmed cell death that occurs in neurons in certain conditions like ischemia. The nucleus is damaged first followed by activation of suicide proteins in the nuclei that begins the autolytic process resulting in cell death. This process is mediated by DNA cleavage. The process of apoptosis takes only 1 hour.[13]

- **Coagulation Necrosis:**

Coagulation necrosis is a process by which cell death occurs without inflammation. This is due to damage to the plasma membrane by physical and chemical stimuli. The cell initially swells then shrinks. This process takes 6-12 hours to evolve. By 24 hours there is complete necrosis.[12]

The morphology of cell death in apoptosis is different from cell death due to coagulation necrosis.[14]



- **Thrombosis:**

Atherosclerosis is the most common pathological cause for the occlusion of blood vessel that leads to thrombosis. The plaque that is formed may be fractured, ulcerated or calcified. Damage to the endothelium activates vasoactive enzymes and releases various factors that contribute to thrombosis and occlusion[15].

The other pathological causes of thrombosis is hypercoagulable state by formation of clot, micro thrombi that occurs in conditions like Giant cell Arteritis, APLA.

- **Lacunar Infarcts:**

Lacunar Infarct is due to the occlusion of small penetrating arteries arising from the cerebral arteries. These may be 100-400 mm in diameter. The size of the infarct is about 20mm in diameter. The pathology is due to lipohyalinolysis.[16,17] The incidence is around 10-30% of all strokes. In people with chronic hypertension, the small arterioles are tortuous, long and forms micro aneurysm that makes the arteriole susceptible to occlusion.

- **Embolism:**

Embolization of artery may be due to various causes and the most common cause is Cardiac source. Most of the emboli occlude the middle cerebral artery, because 80% of blood flow occurs through this artery.[18] Apart from this the superficial branch of cerebral and cerebellar arteries are involved though less frequently. The embolic occlusion can also cause vasospasm by acting as an irritant to the blood vessel. Vasospasm more frequent in younger than the elder patients, because blood vessels in younger individuals are not much atherosclerotic.

The important determinants of pale or hemorrhagic infarct are

a. The size of the infarct

b. The adequacy of the collaterals

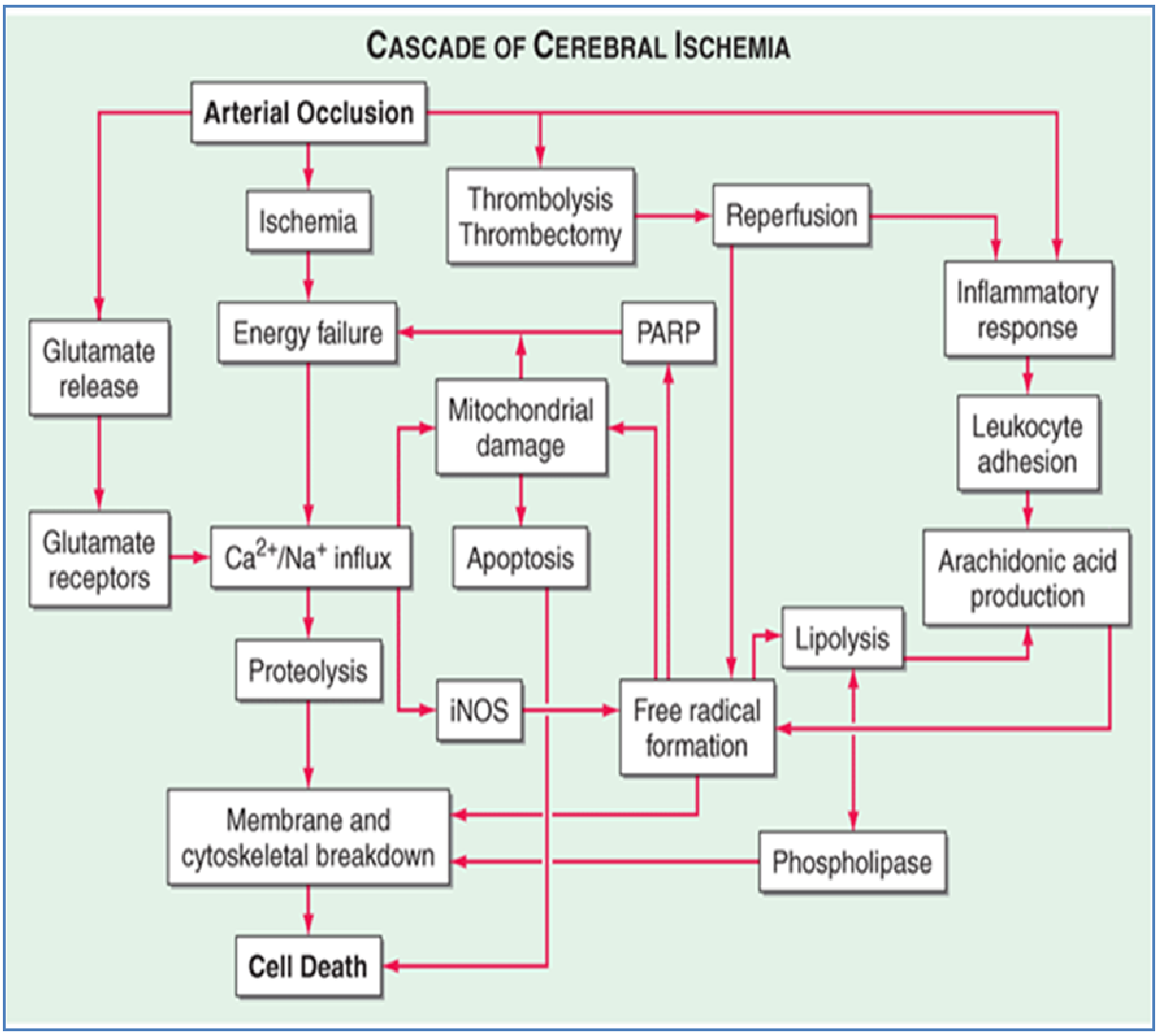
c. The initiation of therapy like anticoagulants and thrombolysis

Hypertension is not the independent risk factor for hemorrhagic infarct.[19,20]

- **Global Ischemia:**

Global Ischemia is also known as the Hypotensive stroke. Systemic hypotension due to any cause can lead to global ischemia. The most commonly affected cells are pyramidal cell layer of hippocampus and the purkinje cell layer of cerebral cortex. The grey matter in cerebrum is also susceptible to this ischemia. It occurs most frequently in the water shed area that is present at the junction of anterior, middle and posterior cerebral arteries. 10% of the infarcts are water shed infarcts. It occurs due to carotid stenosis in 40%.[21]

The clinical presentation of water shed infarct is weakness, sensory involvement involving the upper limb more than the lower limb, face is usually spared and the speech is not affected.



Unlike any other organs, Brain depends entirely on glucose for its metabolism as it lacks Glycogen which stores glucose, and brain also lacks the anaerobic metabolism. The centers in the lower brain stem regulate the constant blood supply to the brain by stimulation of Vasomotor reflexes and Baroreceptors. Decrease in blood flow for even 4 to 10 minutes produces a rapid symptom of neurological deficit.[22]

The normal cerebral blood flow is 50-60 ml/100 gm/min.[23] Below this level there is cerebral vasodilatation, the collaterals get opened and the oxygen extraction from the other cells increases. When it is less than 20ml/100gm/min, the cerebral auto regulatory mechanism gets impaired. The brain tissue goes for infarction over an hour, if the blood flow is 16-18ml/100gm/min. And finally irreversible neuronal injury occurs if blood flow is less than 10ml/100gm/min.[24]

Once the infarction had occurred there is increased water accumulation immediately both intracellular and in intercellular spaces leading to swelling of the infarcted area. There is a release of inflammatory mediators and leucocyte gets recruited .These released mediators cause vasodilation and platelet aggregation. The immunoregulated platelets, erythrocytes and leukocytes gets adhered to the vessel wall leading to occlusion and ischemia.

When brain tissue is completely deprived of the blood flow leading to irreversible neuronal destruction, it’s termed as Global Ischemia. If the collaterals are able to maintain the blood flow and oxygen it is known as focal ischemia.

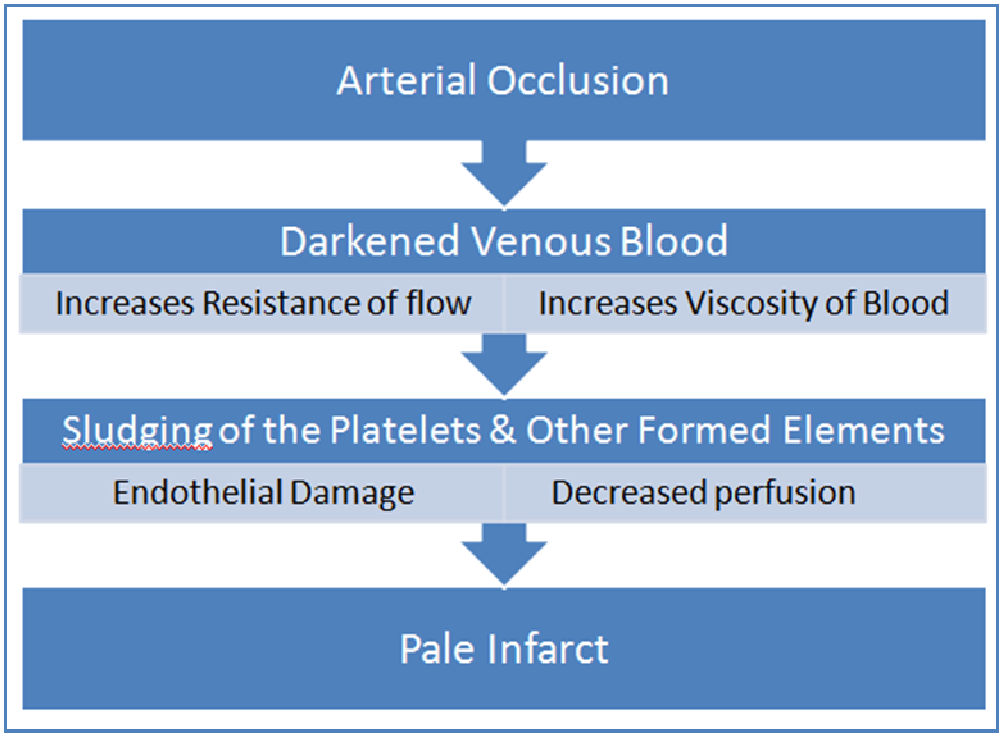
The core region surrounding infarcted area is ischemic. This zone is known as ischemic penumbra, which has viable neurons and marginal perfusion.[25]Maintaining the blood flow to this ischemic penumbra is the targeted factor in ischemic stroke because this ischemia area recovers from

injury once the flow is re-established but when the flow is not reversed it goes for infarction leading to worsening of the clinical status and outcome. Ischemic penumbra is seen in MRI / CT – perfusion- diffusion imaging. The newly emerging modalities of treatment like Revascularization therapies are aimed at saving the ischemic penumbra to prevent further infarction.

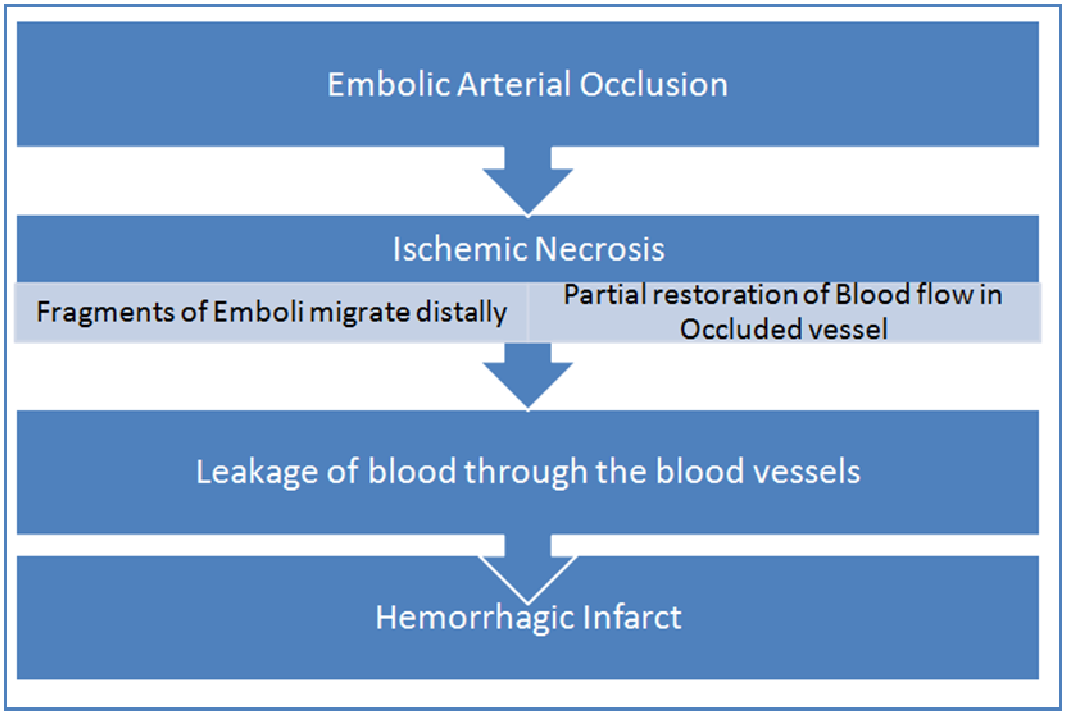
There are two types of infarct

- Pale Infarct
- Hemorrhagic Infarct

PALE INFARCT



HEMORRHAGIC INFARCT

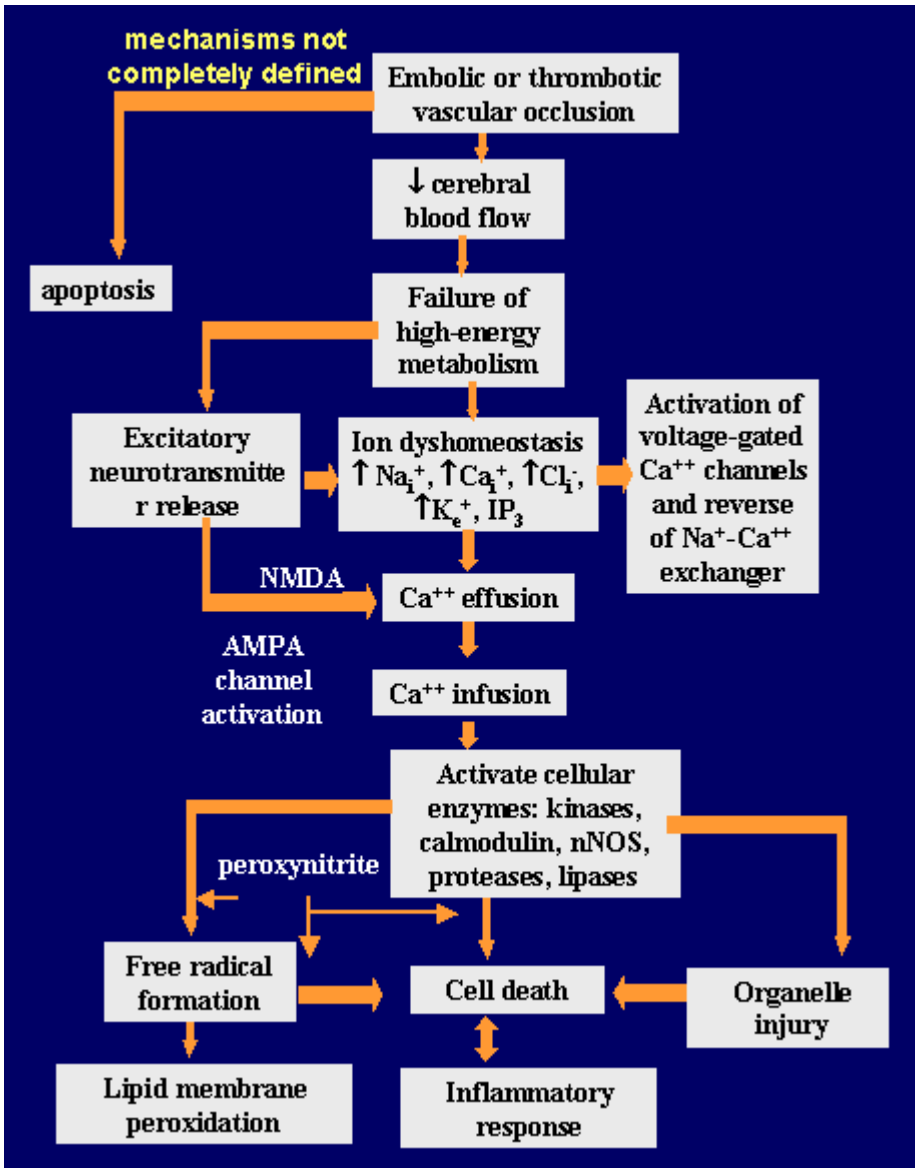


BIOCHEMICAL CHANGES:

These depolarized cells when injured produce efflux of potassium, depletion of ATP and Creatine kinase. Groen et al proposed that low serum potassium increases the stroke rate[26]. Accumulation of free fatty acids destroys the phospholipids in cell membranes of neurons, which alters the calcium homeostasis. These changes lead to histological features of necrosis. The increased extracellular potassium and intracellular calcium causes cellular acidosis.

The cells swell due to accumulation of cytokines and other inflammatory mediators like prostaglandins leading to cytotoxic edema.[27]

CHANGES DUE TO ALTERED METABOLIC FACTORS



GLUTAMATE:

Glutamate is an excitatory neuron transmitter that is cleared by glutamate transporters from the extracellular space. Following stroke the glutamate transporters release glutamate. Glutamate is excitotoxic, so its release causes brain damage following stroke. Glutamate also increases calcium influx leading to persistent depolarization and activation of enzymes, release of cytokines and loss of cellular integrity.

- **Mitochondrial Dysfunction:**

Activation of neuronal NOS, inducible nitric oxide in glial cells lead to Mitochondrial damage and causes ischemia of the brain.

TYPES OF ISCHEMIC STROKE :

Acute stroke is classified by various classification systems,

The Oxford Community Stroke Project classification (OCSP, also known as the Bamford or Oxford classification) relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as-

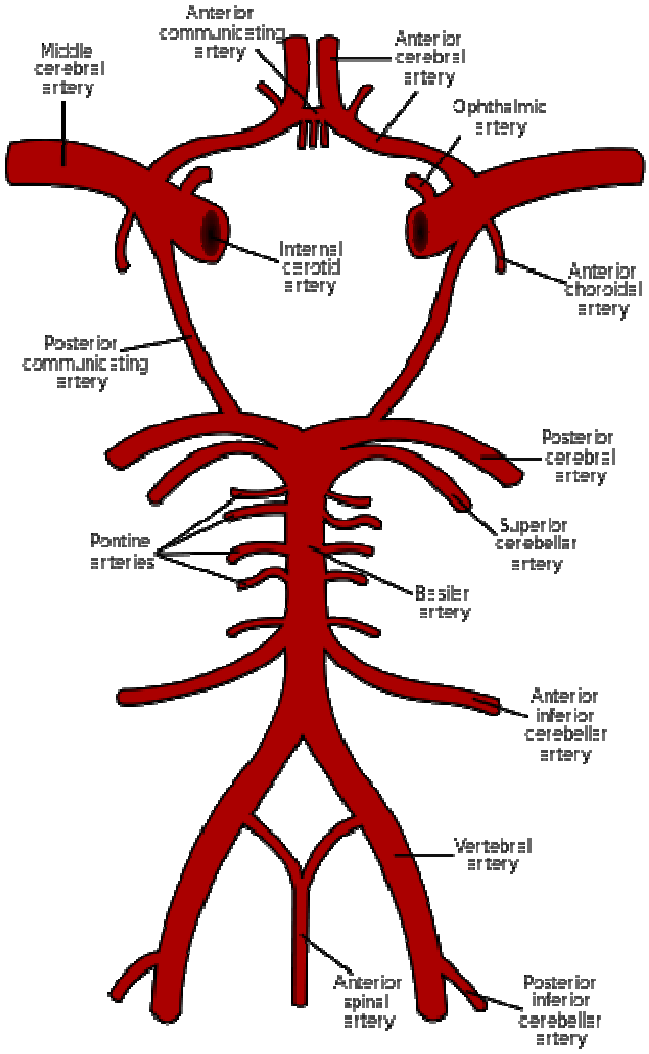
a) Total anterior circulation infarct (TACI).

b) Partial anterior circulation infarct (PACI).

c) Lacunar infarct (LACI).

d) Posterior circulation infarct (POCI).

These four entities predict the extent of the stroke, the part of the brain affected the underlying cause, and the prognosis.



CIRCLE OF WILLIS

ANTERIOR CIRCULATION STROKE (ACS):

- The major blood vessels involved in ACS are
    - Carotid Artery mainly internal carotid artery (ICA)
    - Middle cerebral artery (MCA)
    - Anterior cerebral artery
    - Anterior choroidal artery
- When ACA and MCA are occluded at the top of carotid artery – abulia or stupor / occur with aphasia, anasognosia, hemiplegia, hemianisocoria and amaurosis fugax.

Middle Cerebral Artery (MCA):

MCA involvement causes symptoms of contralateral hemiplegia, homonymous hemianopia, hemianaesthesia, gaze preference to same side and Wernicke's aphasia.

Anterior cerebral artery (ACA):

ACA involvement causes bilateral pyramidal signs, profound abulia, paraparesis or quadriparesis and urinary incontinence.

Anterior choroidal artery:

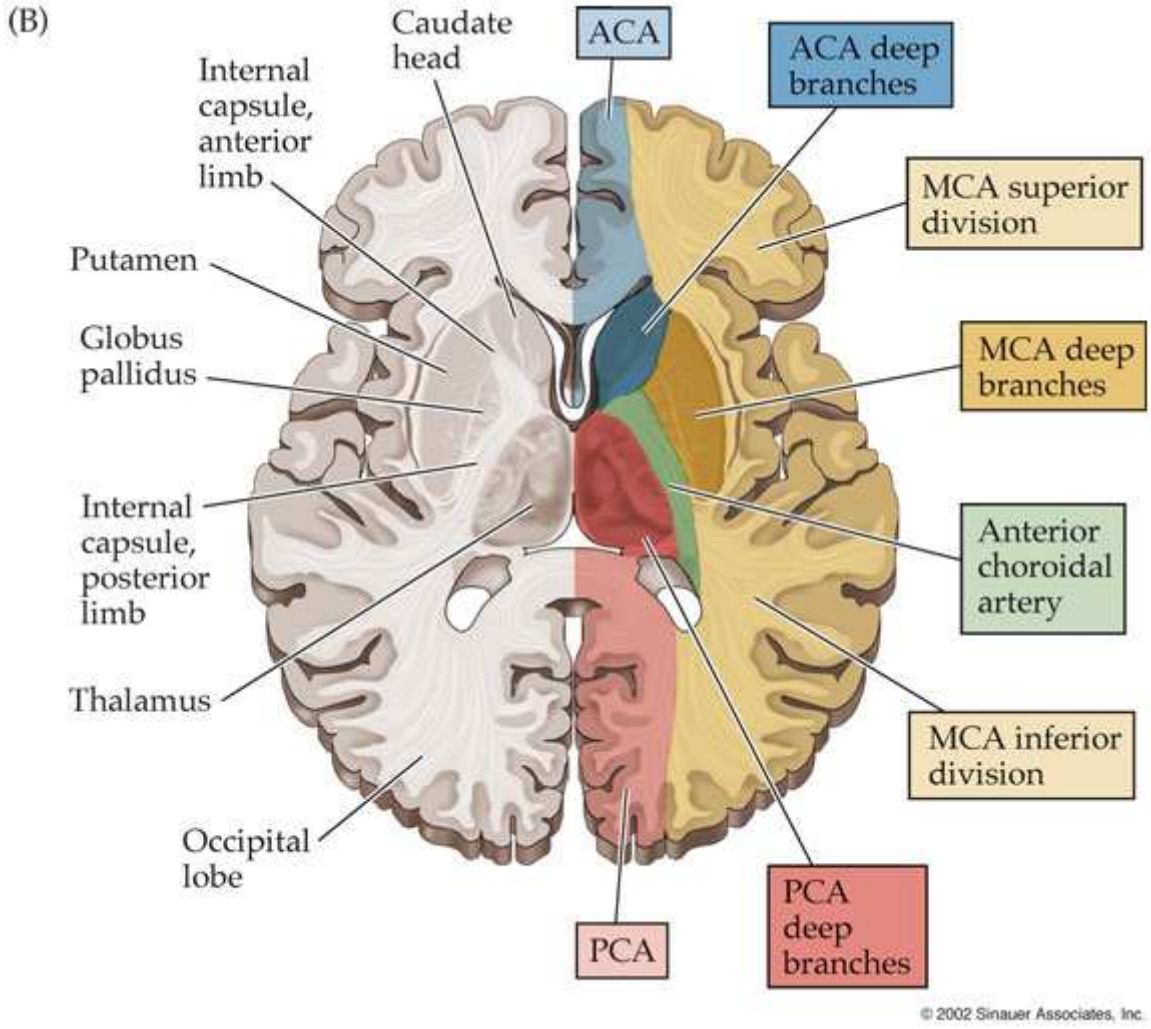
Anterior choroidal artery involvement leads to contralateral hemiplegia, homonymous hemianopia and hemianaesthesia.

Common carotid artery:

Common carotid artery involvement causes Jaw claudication.

POSTERIOR CIRCULATION STROKE (PCS):

The arteries involved are posterior cerebral artery, posterior inferior cerebellar artery, Vertebral Artery, Basilar Artery. Posterior circulation syndromes are because of emboli / atheroma formation, at the top of basilar artery. P1 Syndrome and P2 Syndrome are due to posterior cerebral artery occlusion.



BLOOD SUPPLY TO BRAIN

The features are

- Contralateral homonymous hemianopia with macular sparing.
- Bilateral infarction of distal PCA
- Cortical blindness
- Anton’s Syndrome
- Balint’s syndrome - Balint’s syndrome occurs due to infarction in water shed area between MCA and PCA.
- Embolic occlusion of top of basilar artery - Bilateral signs, ptosis, pupillary asymmetry, absence of light reflex and somnolence.
- Vertebral and Posterior ICA - Lateral medullary Syndrome,
- Medial medullary Syndrome.
- Hemiparesis is not the feature of vertebral artery occlusion, but quadriparesis can result from occlusion of anterior spinal artery.

INVESTIGATIONS:

CT Brain:

Brain CT scans obtained in the first several hours after an infarction generally show no abnormality, and the infarct may not be seen reliably for 24–48 hours.

MRI:

MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface.

Conventional x-ray cerebral angiography:

Conventional x-ray cerebral angiography is the gold standard for identifying and quantifying atherosclerotic stenosis of the cerebral arteries.

Ultrasound Techniques:

Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity ("duplex" ultrasound). Transcranial Doppler (TCD) assessment of MCA, ACA, and PCA flow and of vertebrobasilar flow is also useful. This latter technique can detect

stenotic lesions in the large intracranial arteries because such lesions increase systolic flow velocity. Furthermore, TCD can assist thrombolysis and improve large artery recanalization following rtPA administration.

Perfusion Techniques:

Both xenon techniques (principally xenon-CT) and PET can quantify cerebral blood flow. These tools are generally used for research but can be useful for determining the significance of arterial stenosis and planning for revascularization surgery. Single-photon emission computed tomography (SPECT) and MR perfusion techniques report relative cerebral blood flow.

Disability adjusted life year (DALY):

Disability adjusted life year is used to measure the global burden of disease. It's the healthy time lost by the patient due to early mortality and life with morbidity. Scandinavian stroke scale is commonly used in India to evaluate DALY.[28]

SCANDINAVIAN STROKE SCALE

Patient Name: _____

Rater Name: _____

Date: _____

Function	Score	Prognostic Score	Long Term Score
Consciousness:			
-fully conscious	**6**	____	
-somnolent, can be awaked to full consciousness	**4**		
-reacts to verbal command, but is not fully conscious	**2**		
Eye movement:			
-no gaze palsy	**4**	____	
-gaze palsy present	**2**		
-conjugate eye deviation	**0**		
Arm, motor power *:			
-raises arm with normal strength	**6**	____	____
-raises arm with reduced strength	**5**		
-raises arm with flexion in elbow	**4**		
-can move, but not against gravity	**2**		
-paralysis	**0**		
Hand, motor power *:			
-normal strength	**6**		____
-reduced strength in full range	**4**		
-some movement, fingertips do not reach palm	**2**		
-paralysis	**0**		
Leg, motor power *:			
-normal strength	**6**	____	____
-raises straight leg with reduced strength	**5**		
-raises leg with flexion of knee	**4**		
-can move, but not against gravity	**2**		
-paralysis	**0**		

Orientation:			
-correct for time, place and person	**6**		___
-two of these	**4**		
-one of these	**2**		
-completely disorientated	**0**		
Speech:			
-no aphasia	**10**		___
-limited vocabulary or incoherent speech	**6**		
-more than yes/no, but not longer sentences	**3**		
-only yes/no or less	**0**		
Facial palsy:			
-none/dubious	**2**		___
-present	**0**		
Gait:			
-walks 5 m without aids	**12**		___
-walks with aids	**9**		
-walks with help of another person	**6**		
-sits without support	**3**		
-bedridden/wheelchair	**0**		
Maximal Score	___	**22**	**48**

* Motor power is assessed only on the affected side.

It is one of the commonly used clinical outcome measures in patients with stroke

Diabetes mellitus:

Diabetic patients have 2 to 3 times greater risk of stroke than non-diabetic population according to Framingham survey .28 .and a number of other surveys too proved this greater risk.

ICMR study also suggested that uncontrolled hyperglycemia as an important risk factor for CVD.

Dyslipidemia:

Serum lipid abnormities is associated with increased risk of stroke and carotid atherosclerosis. 4s trial, WOSCOPS &CARE study all show an association between serum lipids and increased stroke risk.

Diabetic dyslipidemia:

In type 2 diabetes and insulin resistance the dyslipidemia pattern is as follows

HDL – (decreased) – increased Clarence of Apo A

Decreased proportion of large HDL

Triglyceride enrichment

Diminished reveres cholesterol transport

LDL – (qualitative abnormalities) – increased production Apo B

Decreased Receptor mediated clearance

Smaller (more denser) particle distribution

VLDL –(increased) – increased production of triglyceride and Apo B

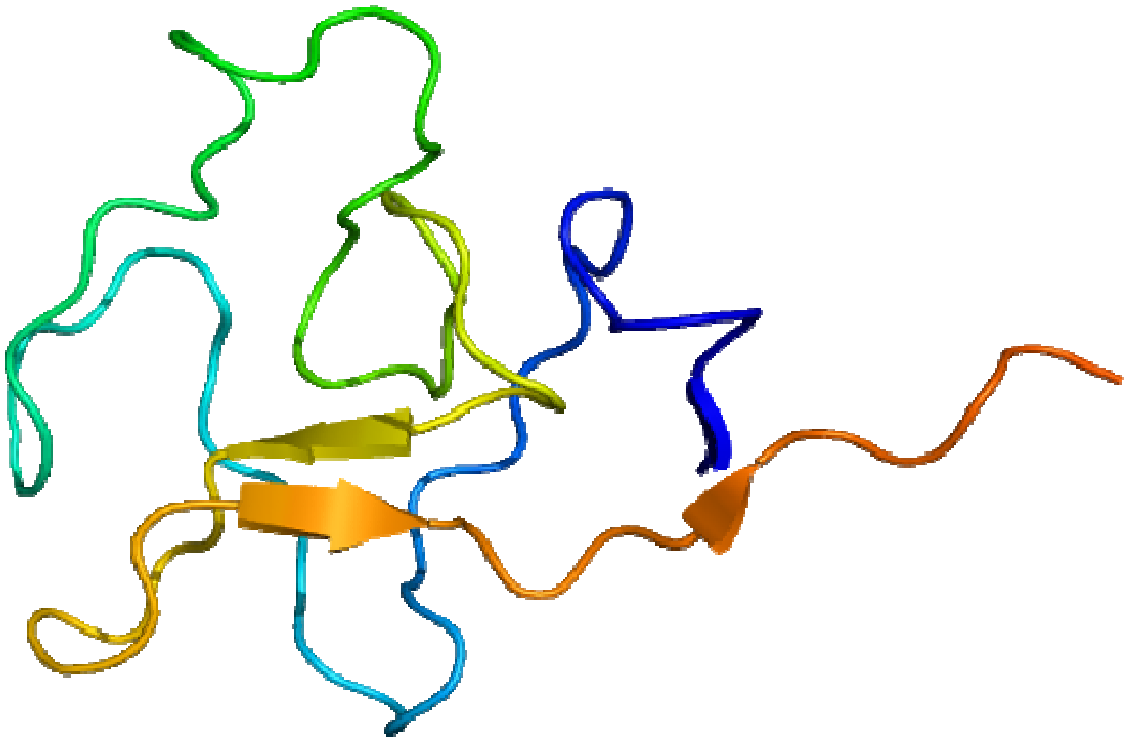
Decreased clearance of triglyceride and Apo

Triglyceride - (increased)

Lipoprotein (a) Lp (a) – (increased)

THE STRUCTURE OF LP(a):

Lipoprotein (a) is a molecule that resembles LDL. It is made of Apo B100 and Apo (a) linked by a disulfide bridge. Plasminogen, macrophage stimulating factor, tissue plasminogen activator, prothrombin and factor XII are a group of kringle containing proteins and Apo (a) is a member of it. The sequence of LP (a) is much identical to that of plasminogen. Nearly 34 different alleles have been identified for the highly polymorphic Apo (a) gene. Corresponding isoforms with molecular weights ranging from 187 to 648 kDa were identified in human serum. The number of kringle IV type 2 repeats determine the size polymorphism of Apo (a).[29]



LIPOPROTEIN (A) STRUCTURE

Function

The physiological function of Lp (a)/Apo(a) is still unknown. Plasminogen gene duplication derives LPA gene leads to homologues between Apo (a) and plasminogen leads to possible function within coagulation system

Other functions are helping in angiogenesis and wound healing by recruitment of inflammatory cells by interaction with Mac1 integrin.

In GULO (l- gulonolactone oxidase)deficiency, lipoprotein a used as vitamin c for arterial wall repair by a poorly understandable mechanism

Pathology

- Lp (a) is structurally similar to plasminogen and tPA.
- It competes with plasminogen during resolution of blood clot.
- It reduces fibrinolysis and forms a hypercoaguable state leading to thrombogenesis as it secretes PAI-1.
- It helps in atherosclerosis by being a carrier of cholesterol.
- It causes recruitment of proinflammatory cells.

- Thus it causes inflammation and smooth muscle proliferation in vessel wall.

Lipoprotein (a) and disease

- High Lp (a) in blood is a risk factor for
- Coronary heart disease (CHD),
- Cerebrovascular disease (CVD),
- Atherosclerosis, Thrombosis.
- Lp(a) concentrations may be affected by disease states, (for example renal failure), but are only slightly affected by diet, exercise, and other environmental factors.
- High Lp (a) predicts risk of early atherosclerosis independent of other cardiac risk factors, including LDL.
- Lp (a) indicates a coagulant risk of plaque thrombosis.

Diagnostic testing

The European Atherosclerosis Society recommends that patients with a moderate or high risk of atherosclerosis and cardio and cerebrovascular events have their lipoprotein (a) levels checked. Patients with following risk factors must be screened

- premature cardiovascular disease
- familial hypercholesterolemia

- family history of elevated lipoprotein (a)
- recurrent cardiovascular disease

If the level is elevated, treatment should be initiated and the goal will be of bringing the level below 50 mg/dl

The Atherosclerosis Risk in Communities (ARIC) followed 3467 African Americans and 9851 whites for 20 years. The research shows that an elevated Lp (a) has the same risk in each group. However, African Americans had roughly three times the level of Lp (a), and Lp(a) also predicted an increased risk of stroke.[32]

A standardized international reference material has been developed and is accepted by the WHO Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine.

- Lipoprotein (a) – Lp (a) level [37]
- Desirable: < 14 mg/dl (< 35 nmol/l)
- Borderline risk: 14 - 30 mg/dl (35 - 75 nmol/l)
- High risk: 31 - 50 mg/dl (75 - 125 nmol/l)
- Very high risk: > 50 mg/dl (> 125 nmol/l)

LIPOPROTEIN(A), DIABETES AND ISCHEMIC STROKE :

Dyslipidemia, lipoprotein(a) and diabetes are risk factors for ischemic stroke . Lipoprotein (a) has atherogenic and thrombotic properties. This potential of lipoprotein (a) could be increased in diabetic patients.

Atherogenicity of lipoprotein (a) at molecular and cellular level is caused by

- Interference with fibrinolytic system,
- Affinity to secretory phospholipase A2,
- Interaction with extracellular matrix glycoprotein and
- Binding scavenger receptor on macrophage.

Little evidence in previous studies shows that there is correlation between increased risk of atherogenicity and lipoprotein(a)among diabetic patients.

Lipoprotein a is an important factor that links micro vascular and macro vascular complications of diabetes.

In previous studies contribution of lipoprotein (a) to enhanced risk of vascular disease in diabetes mellitus population is not clearly defined.

Lipoprotein a can promote thrombosis, inflammation, and foam cell formation.

EPK study already clearly discussed that lipoprotein (a) and risk of CAD and stroke is well established and also added

Lipoprotein (a) associated with Peripheral arterial disease, Coronary artery disease and ischemic stroke.

All these previous studies clearly shows high lipoprotein (a) is an independent risk factor for the development of cerebral infarction .

Lp (a) must measure by uniform methods in future and its involvement in pathogenesis of stroke sub types is still unsettled.

This study is to evaluate the lipoprotein (a) level as an early marker to assess the severity of ischemic stroke in Type II diabetic patients

Whether lipoprotein (a) can act as an early marker (or) early predictor for worse prognosis in diabetic patients with ischemic stroke when compared to non-diabetics was unclear. Studies have also shown that high lipoprotein (a) predicts risk of early atherosclerosis independently of other stroke risk factors including LDL cholesterol.

LIPID VARIABLES AND THE RISK OF STROKE

TOTAL CHOLESTEROL AND STROKE;

Total cholesterol level is a risk factor for stroke, TIA and ischemic heart diseases .The raise in total cholesterol is directly proportional to IHD but not to stroke as different blood vessel with different pressure gradients are involved. Only highest level of TC directly increases non-hemorrhagic stroke not the intermediate level cholesterol .[30]

HDL CHOLESTEROL AND STROKE

Majority of the studies shows an inverse relationship between HDL level and risk of stroke

Lipoprotein (a) and atherosclerosis

Following studies done in the past supports lipoprotein (a) association with stroke/atherosclerosis

- Jurgens and Koltringer (1987) [-31]
- Lindgren et al (1992)- [32]
- Vavernova et al (1993)[33]
- Jurgens et al (1995)[34]
- Peynet et al (1999)[35]
- Van Kooten et al (1996)[36]
- Margaglione et al (1996)[37]
- Nagayama et al (1994)[38]
- Peng et al (1999)[39]
- Kario et al (1996)[40]
- ARIC study* (1994)[41]
- Ichinose et al (1998)[42]

All these following studies are supporting the role of lipoprotein (a) with stroke and atherosclerosis association.

Lipid profile of 131 stroke patients studied by Lindgren et el 6 month later showed elevated LP (a) and TG levels and decreased LDL HDL TC level than the controls.

Van Kooten's study on stroke patients showed significantly raised Lp(a) values but stroke characteristics prognosis and CVD risk profile has got no association with Lp(a) level.[43]

Lipoprotein A in acute ischemic stroke; In the atherosclerosis risk in communities (ARIC) study,

In this study conducted on 15160 stroke patients showed Lp (a) as risk factor for stroke and TIA in all races (blacks and whites) but stroke morbidity does not show any racial difference. Lp(a) concentration is directly proportionate to the incidence of ischemic stroke .

Pedro-Bodet et al, studied Apo E 4 gene in ischemic stroke patients in a case control study. It showed that in ischemic stroke patients there is a higher frequency of Apo E4 gene. [45]

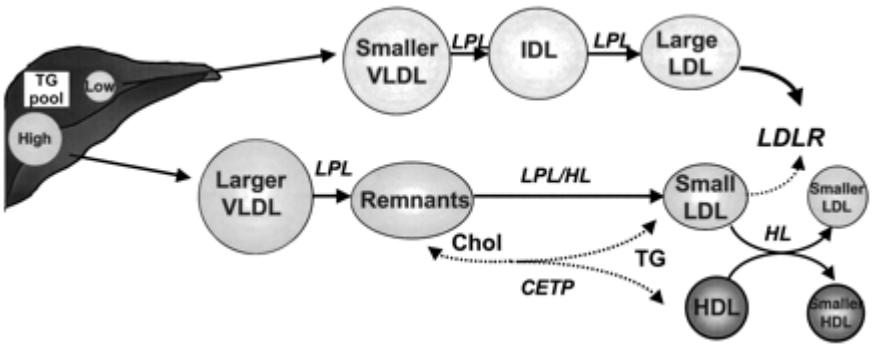
Apo (a) modulates smooth muscle cell proliferation, enhances lipid deposition in vessel wall, and inhibits fibrinolysis and thus causing endothelial dysfunction.

Watts and his colleagues observed the lipid profile in those with TIA. They showed a significant association between Lp (a) concentration and the extent of carotid atherosclerosis.[47]

Lp(A) and diabetes:

A cluster of interrelated plasma lipid and lipoprotein abnormalities associated with alterations in VLDL metabolism contribute to the risk for atherosclerosis and CHD in the majority of patients with type 2 diabetes. Insulin resistance plays a key role in the development of diabetic dyslipidemia. Each of the lipid abnormalities (low HDL, small dense LDL, and elevated triglycerides) is associated with an increased risk of CHD[48]

Diagram showing various pathways linked with dyslipidemia and in diabetics



Hypothetical scheme for the relation of altered metabolism of triglyceride-rich lipoproteins to the development of an atherogenic lipoprotein phenotype.

CETP-cholesterol ester transfer protein; Chol- cholesterol;

HL-hepatic lipase; LDLR-LDL receptor; LPL- lipoprotein lipase; TG-triglyceride.

Each of the lipid abnormalities (low HDL, small dense LDL, and elevated triglycerides) is associated with an increased risk of CHD.

Our aim is to to compare lipoprotein (a) level in Type II diabetic and non-diabetic patient with ischemic stroke

METHODOLOGY

METHODOLOGY

Title	LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS
Aims and Objectives	
Primary Objectives (s)	To compare lipoprotein (a) level in Type II diabetic and non-diabetic patients with ischemic stroke
Secondary Objective(s)	To evaluate lipoprotein (a) level as an early marker to assess severity of ischemic stroke in Type II diabetic patients
Study Centre	Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai
Duration of the Study	6 months
Study Design	Cross sectional study
Sample Size	100 patients

Inclusion Criteria	Patients of stroke diagnosed clinically and proven radio-logically Age above 40 years
Exclusion Criteria	Patients with hemorrhagic stroke Patients with cardio-embolic stroke Patient with liver disease Patient with smoking and alcoholic Patient taking antilipidemic drugs
Data Collection and Methods	Patients have their history taken according to a Questionnaire and subjected to clinical examination
Methodology (Materials and Methods)	Study was conducted in 100 patients of ischemic stroke(CT proven) Subject were divided into two groups Group 1 - 50 patients with type II diabetes Group 2 - 50 patients with non-diabetes Patient are subjected to routine blood investigations CBC,RFT,LFT and fasting lipid profile, lipoprotein(a),fasting blood sugar ,HbA1c, CT brain

	Patients are followed for at least four weeks or until death if earlier and their lipoprotein (a) level in ischemic stroke with type II diabetic and non-diabetic are compared
Product / Procedure / Investigation Details	CT brain, lipid profile, lipoprotein (a)
Analysis Plan	SPSS, Epi INFO
Sponsorship (Yes/ No) If Yes details	No
Conflict of Interest	No

OBSERVATION AND RESULTS

Table 1:

RESULTS AND OBSERVATION :

		Type II DIABETIC		**NON DIABETIC**	
		Count	Table %	Count	Table %
sex	MALE	32	32.0%	30	30.0%
	FEMALE	18	18.0%	20	20.0%
Smoker	YES	25	25.0%	26	26.0%
	NO	25	25.0%	24	24.0%
alcoholic	YES	20	20.0%	14	14.0%
	NO	30	30.0%	36	36.0%
MORIBIDITY	<15	23	23.0%	15	15.0%
	>15	27	27.0%	35	35.0%

Variables for 100 ischemic stroke patients were divided according to their age , gender, smoking ,alcoholic, and their morbidity were compared between both type II diabetic and non-diabetic .

Table 2:

P value for Diabetic patients

AGE GROUP * lipo protein (a) value

		lipoprotein(a) value				Total	
		15 – 30		30 - 50			
		Count	%	Count	%	Count	%
AGE GROUP	40- 50	8	47.1%	6	18.2%	14	28.0%
	50 -60	7	41.2%	11	33.3%	18	36.0%
	60 -70	2	11.8%	13	39.4%	15	30.0%
	above 70	0	.0%	3	9.1%	3	6.0%
Total		17	100.0%	33	100.0%	50	100.0%

P value :0.05 Significant

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	50	42	73	57.06	8.153
Valid N (listwise)	50				

In our study patients with age above 40years were studied. The minimum age was 42 and maximum age was 73 and mean age was 57.06 .

As age increases the risk of stroke also increases (p value 0.05)

42 Table 3

sex * lipo protein (a) value

		lipo protein value				Total	
		15 – 30		30 - 50			
		Count	%	Count	%	Count	%
sex	Male	9	52.9	23	69.7	32	64.0
sex	Female	8	47.1	10	30.3	18	36.0
Total		17	100	33	100	50	100

P value :0.242 Not Significant

In our study there is no gender difference in lipoprotein (a) value (p value 0.242)

Chart 1:

Percentage distribution of gender among ischemic stroke patients compared between diabetic and non diabetic .

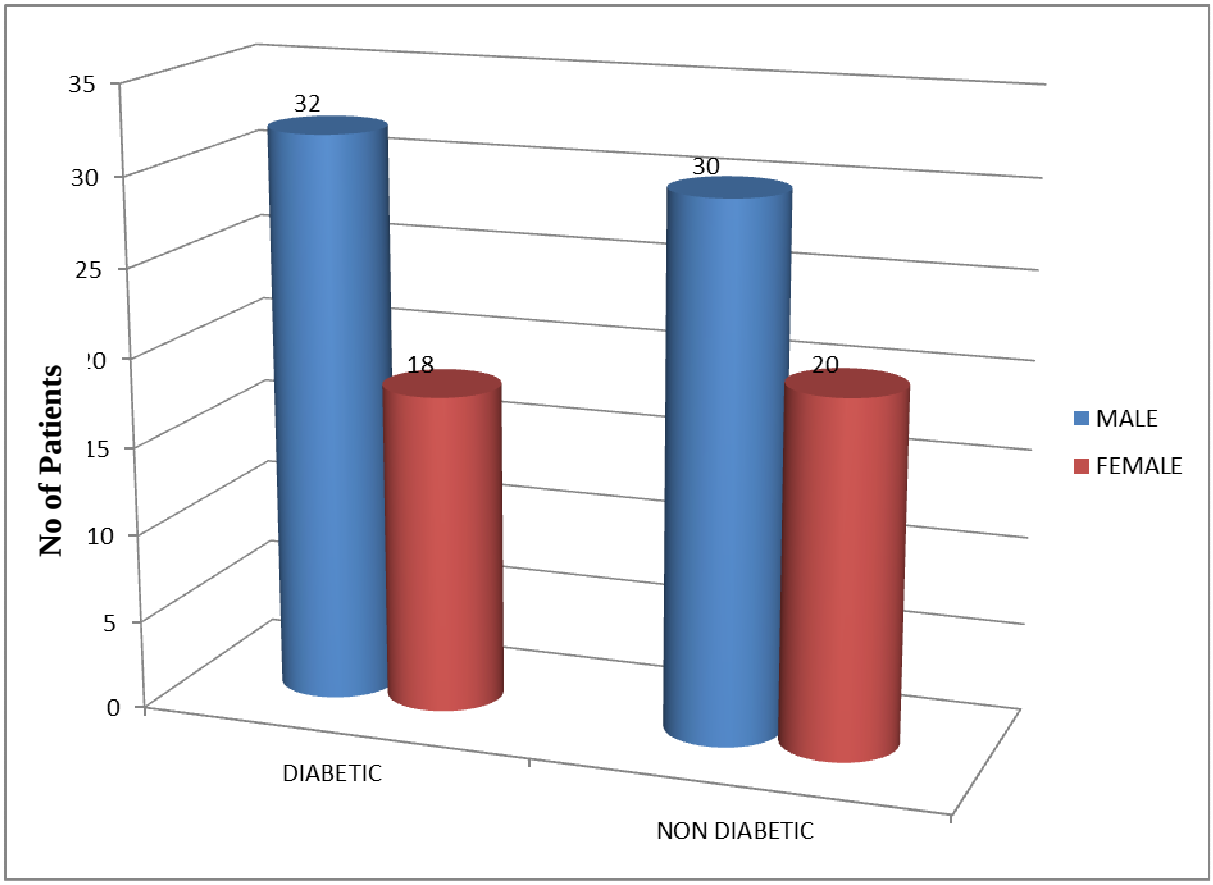


Table 4:

Smoker * lipo protein (a) value

		lipo protein value				Total	
		15 – 30		30 - 50			
		Count	%	Count	%	Count	%
Smoker	Yes	8	47.1%	17	51.5%	25	50.0%
Smoker	No	9	52.9%	16	48.5%	25	50.0%
Total		17	100.0%	33	100.0%	50	100.0%

P value :0.765 Not Significant

In our study there is no relationship between smoker and lipoprotein (a) level as indicated by p value 0.765

Chart:2

Percentage distribution of smoking among ischemic stroke patients compared between diabetic and non diabetic .

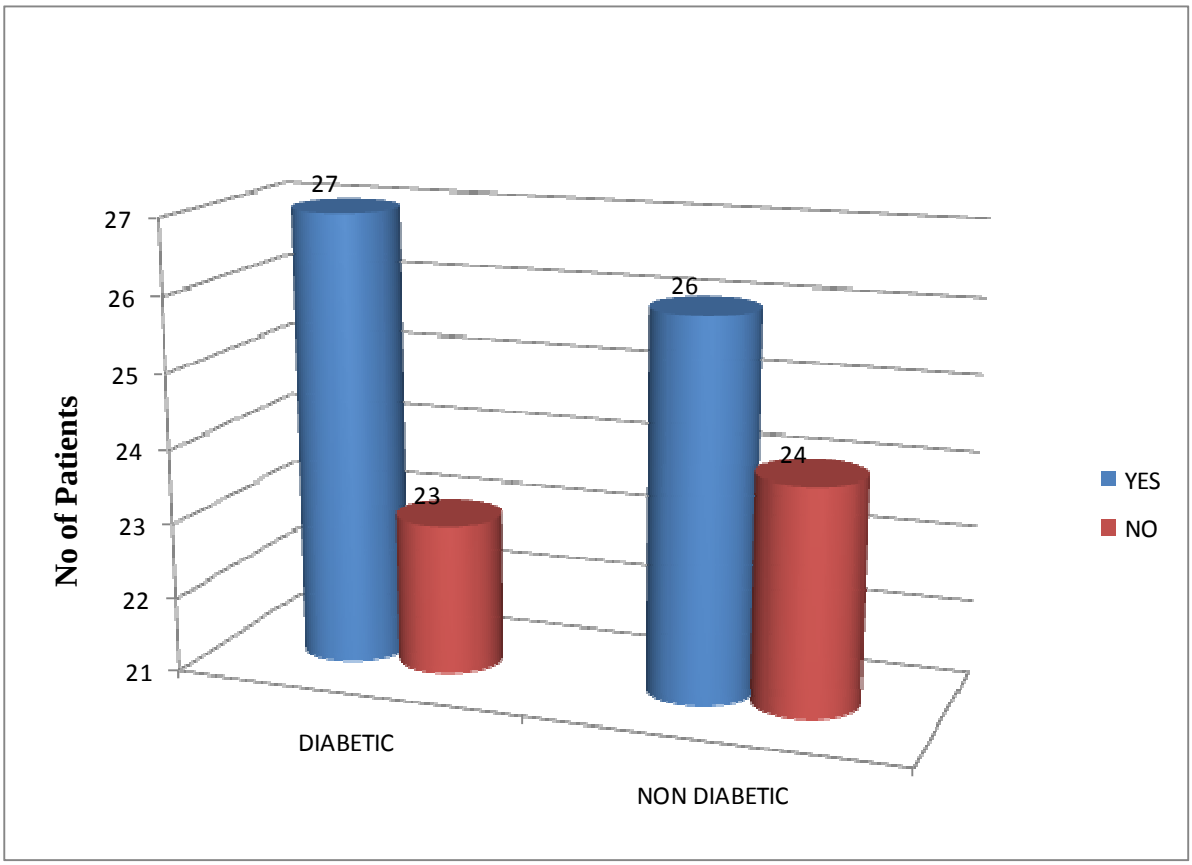


Table 5:

alcoholic * lipo protein (a) value

		lipo protein value				Total	
		15 – 30		30 - 50			
		Count	%	Count	%	Count	%
alcoholic	YES	7	41.2%	13	39.4%	20	40.0%
	NO	10	58.8%	20	60.6%	30	60.0%
Total		17	100.0%	33	100.0%	50	100.0%

P value :0.903 Not Significant

From our study there is no significant difference in lipoprotein (a) level between alcoholic and non alcoholic p value 0.903

Chart 3:

Distribution of alcoholic and non alcoholic ischemic stroke patients

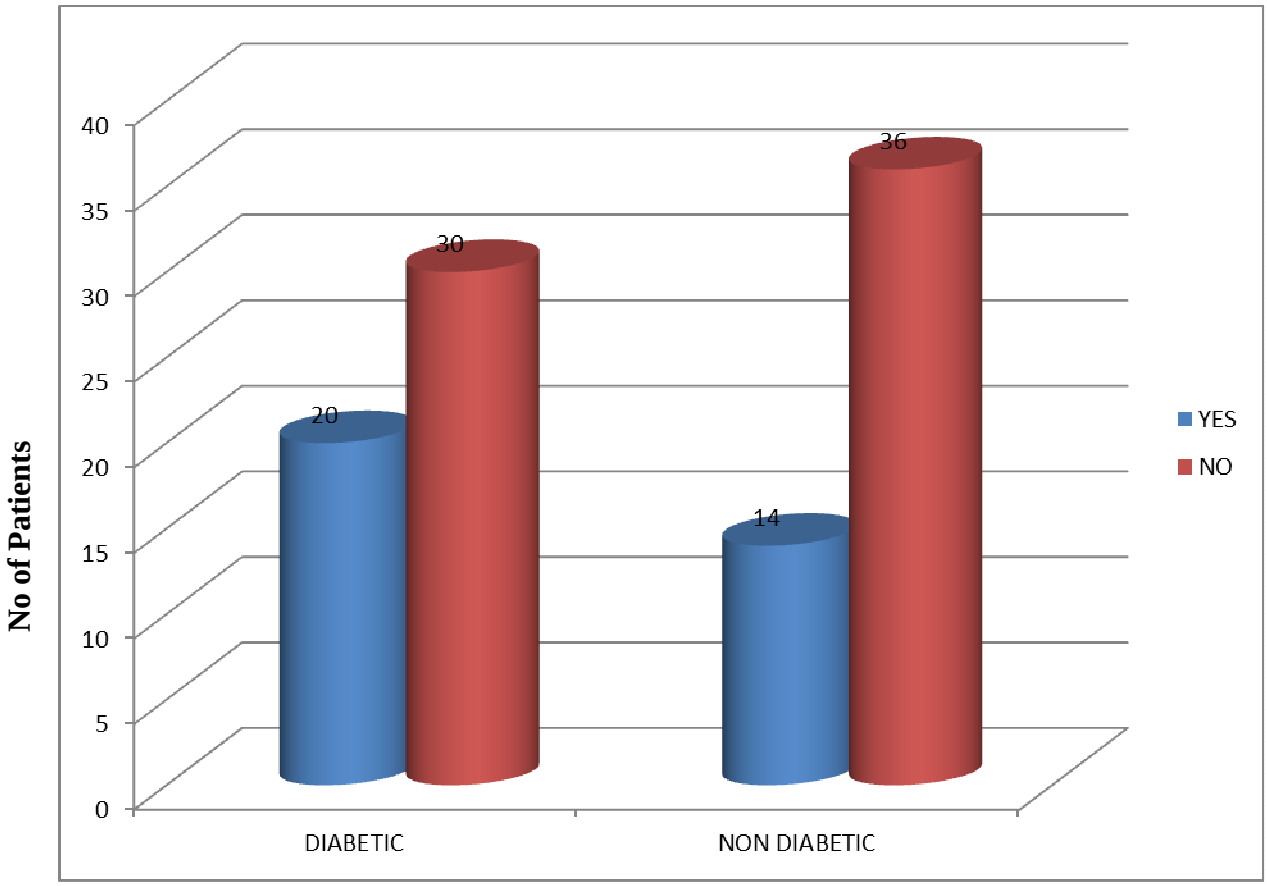


Chart 4:

Fasting blood sugar level in type 2 diabetic and non diabetic patients

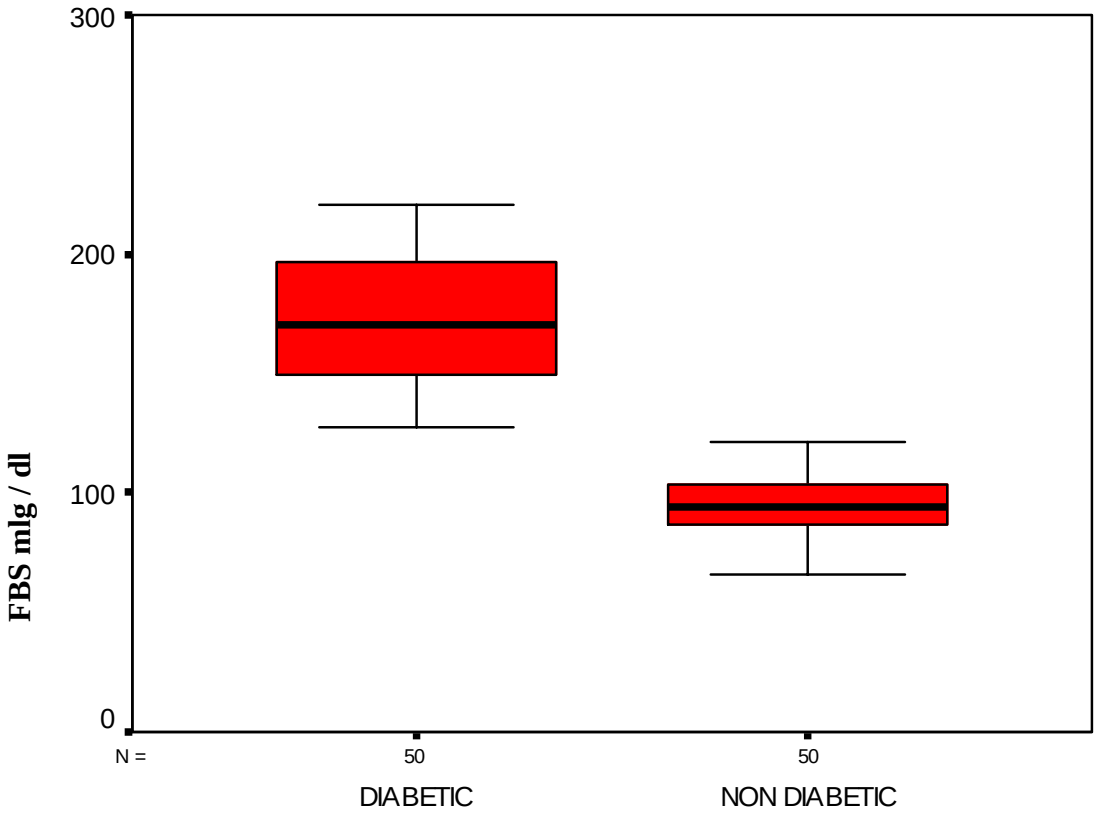


Chart 5:

HbA1c level in type II diabetic and non- diabetic ischemic stroke patient.

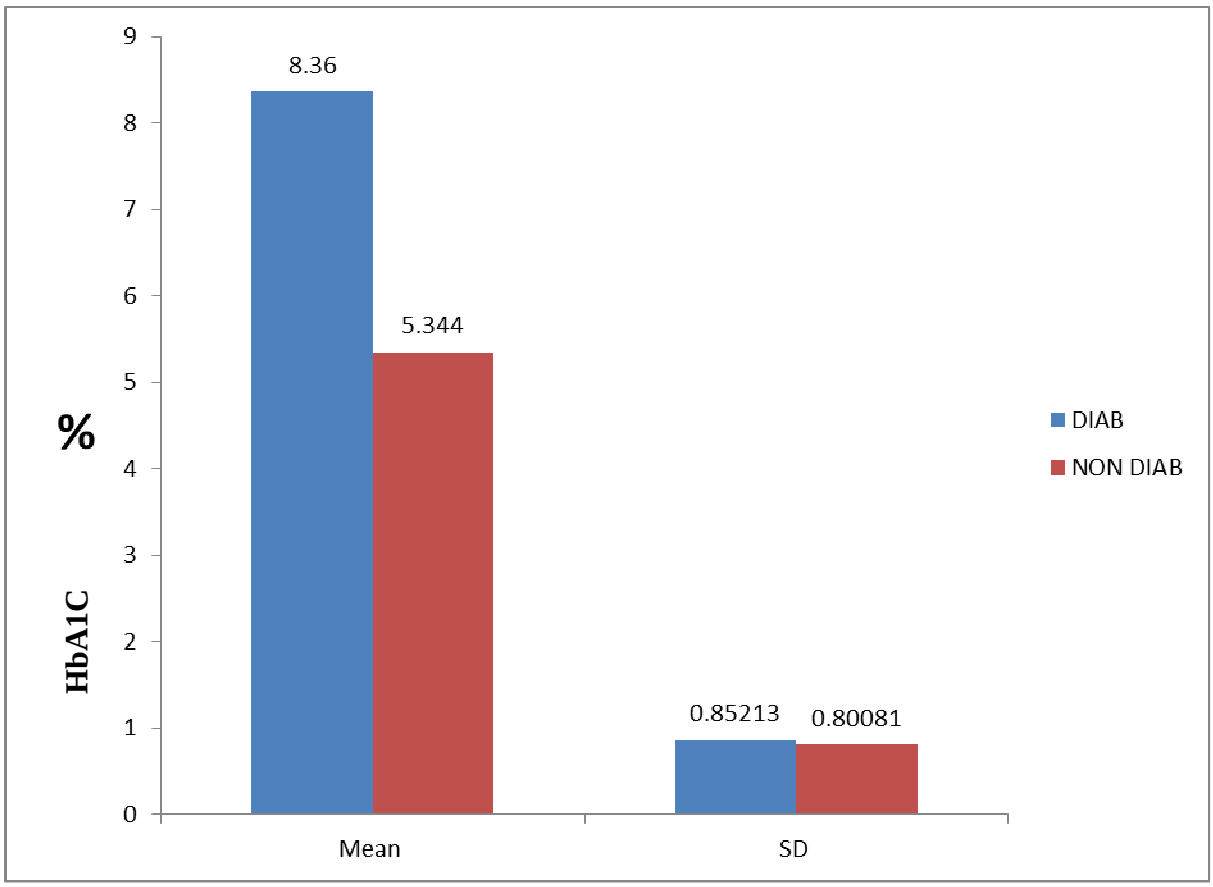


Table 6 :

Lipoprotein (a) levels in Type II diabetic and non-diabetic patients with ischemic stroke

		Type II DIABETIC	**NON DIABETIC**	Total
Lp a value1	<14	0	0	0
	15 - 30	17	27	44
	30 - 50	33	23	56
	>50	0	0	0
Total		50	50	100

	Value	df	P value
Pearson Chi-Square	4.058(b)	1	.044

The association between lipoprotein (a) value and ischemic stroke is significant (p value 0.044)

Table 7:

Comparison of lipoprotein(a) level in both type II diabetic and non-diabetic patients.

Independent Samples Test

t-test for Equality of Means						
t	df	P value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
					Lower	Upper
2.011*	96.954	0.047	3.84	1.910	.049	7.631

There is a significant difference in lipoprotein (a) level between type II diabetic and non-diabetic ischemic stroke patients(p value 0.047)

Chart 8:

Lipoprotein (a) level distribution in type II diabetic and non-diabetic ischemic stroke patients

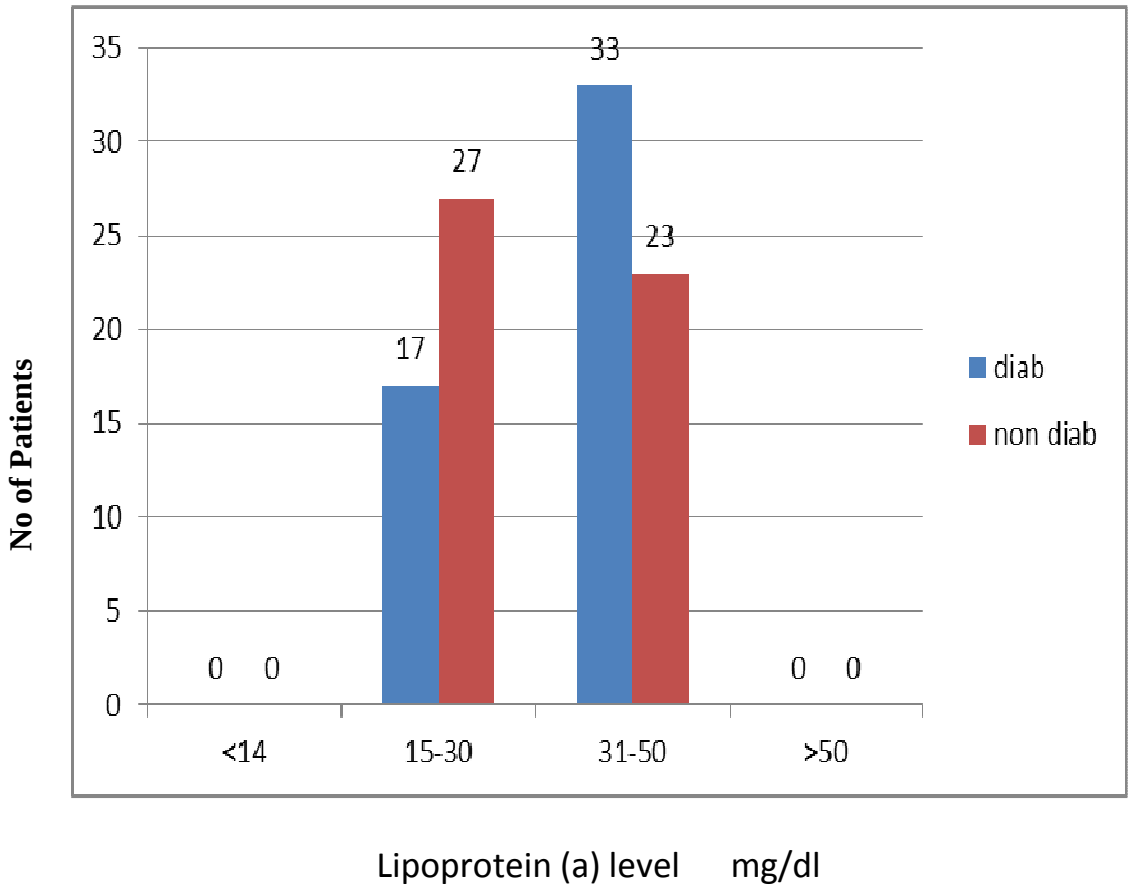


Table 9:

Evaluation of lipoprotein (a) level as a marker to assess severity of ischemic stroke in Type II diabetic and non-diabetic patients using Scandinavian score

					Total	
			TYPE II DIABETIC	NON DIABETIC		
MORIBIDITY	<15	Count	23	15	38	
		% within MORIBIDITY	60.5%	39.5%	100.0%	P= 0.099 Not significant P>0.05
	>15	Count	27	35	62	
		% within MORIBIDITY	43.5%	56.5%	100.0%	
Total		Count	50	50	100	
		% within MORIBIDITY	50.0%	50.0%	100.0%	

Lipoprotein (a) value cannot be used to assess severity of ischemic stroke as our p value 0.099 using Scandinavian score.

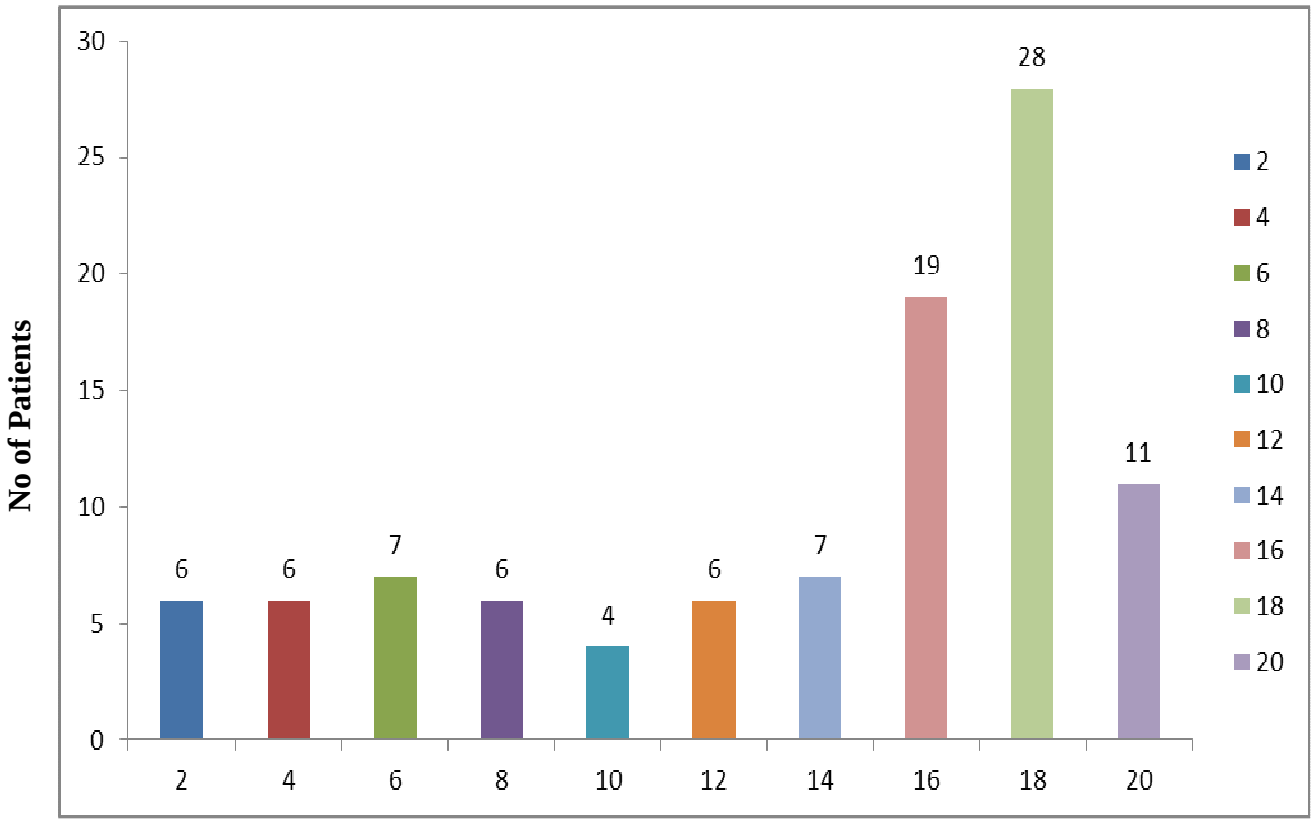
Table 10:

Scandinavian score distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2	6	6.0	6.0	6.0
	4	6	6.0	6.0	12.0
	6	7	7.0	7.0	19.0
	8	6	6.0	6.0	25.0
	10	4	4.0	4.0	29.0
	12	6	6.0	6.0	35.0
	14	7	7.0	7.0	42.0
	16	19	19.0	19.0	61.0
	18	28	28.0	28.0	89.0
	20	11	11.0	11.0	100.0
	Total	100	100.0	100.0	

Chart 9:

Scandinavian score distribution in 100 ischemic stroke patients



Scandinavian score

Chart 10:

Scandinavian sore in 100 ischemic stroke patients to assess severity in type 2 diabetes and non diabetes

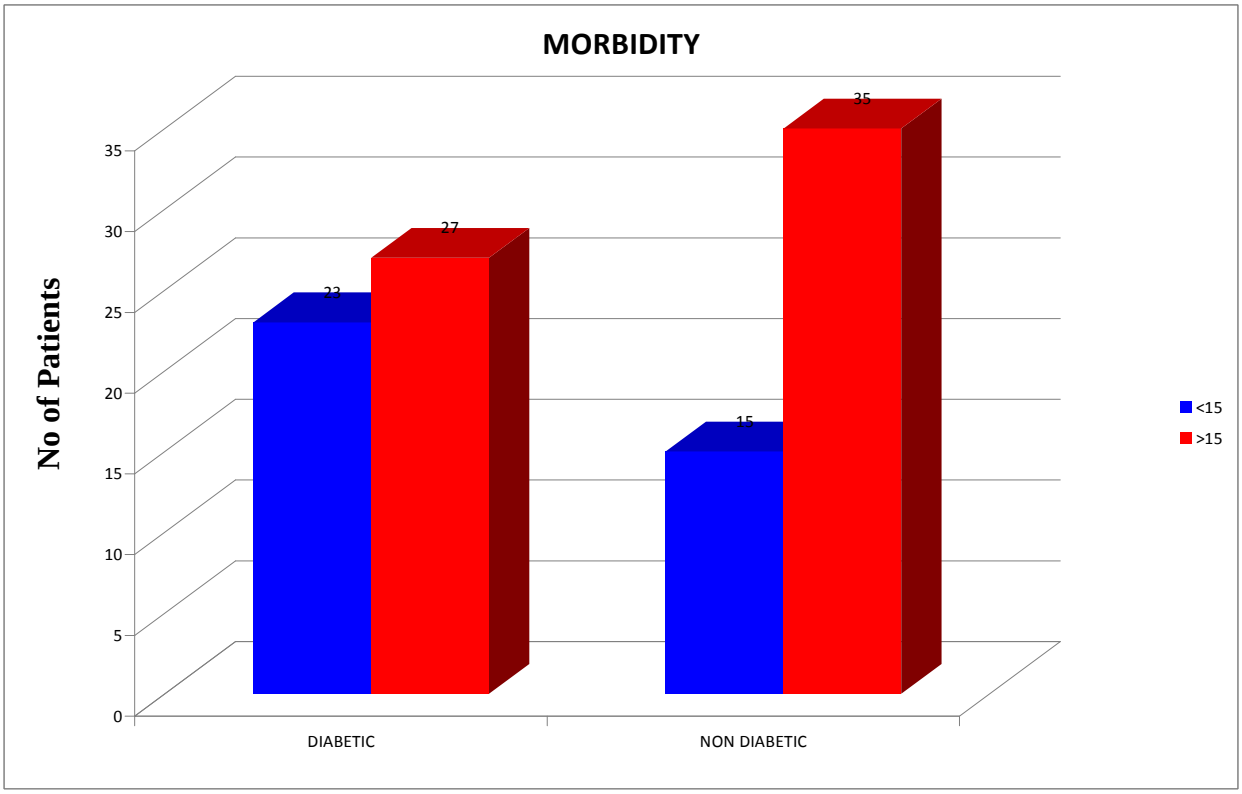


Table 11:

Lipid profile in type 2 diabetic and non diabetic ischemic stroke patients

	Mean	Median	Std.Deviation	Mean	Median	Std.Deviation
LDL	164.1	162.5	40	97.7	96	35
HDL	34	36	7	41	40	7
TC	235	224	38	203	211	26
TG	251	240	50	152.2	115	60

Chart 11:

Serum HDL level in type II diabetic and non diabetic ischemic stroke patients

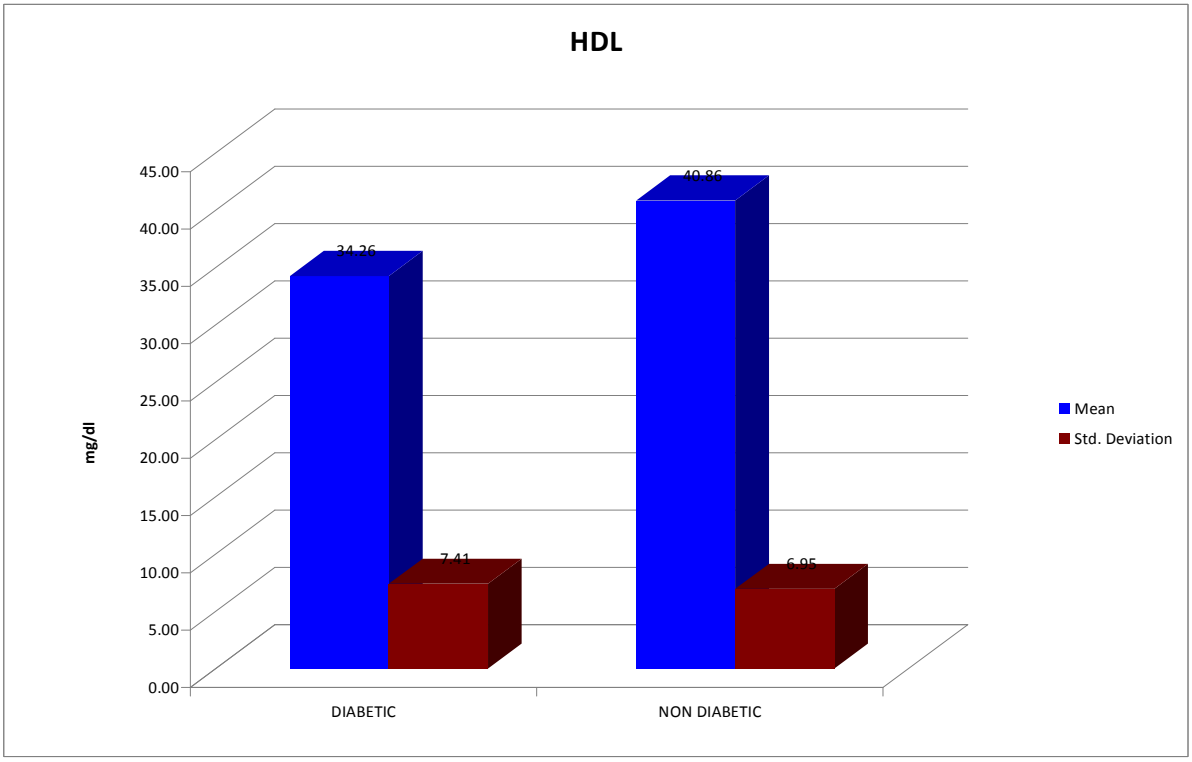
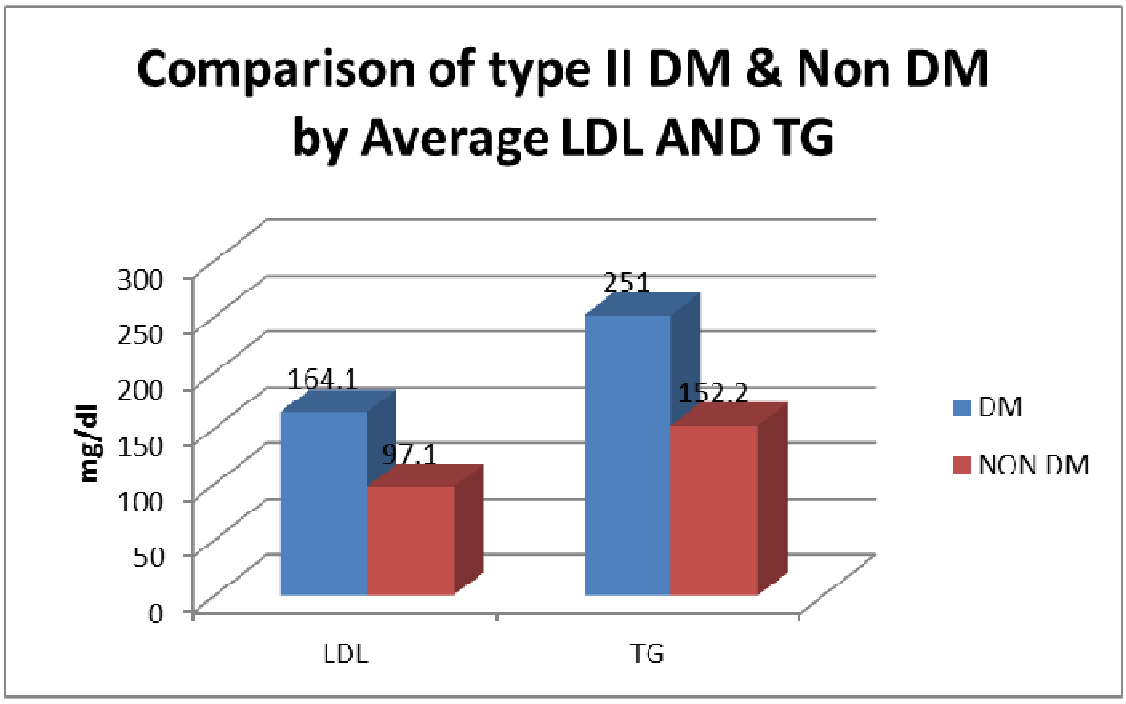


Chart 13:

LDL and Triglyceride level in type 2 diabetic and non diabetic ischemic stroke patient.



DISCUSSION

DISCUSSION

This study was a cross sectional study conducted in 100 Ischemic stroke patients admitted in Rajiv Gandhi government general hospital. These patients were divided into two groups 50 each. Group-1 includes Type II diabetes with ischemic stroke and Group-2 includes non-diabetics with ischemic stroke.

62 were males and 38 were females. Age of the study group was more than 40 years.Mean age of study group 57.06.

The results from this study showed Lipoprotein (a) level to be significantly elevated in ischemic stroke patients who had diabetes, than who were non diabetic.P value 0.044.

This study also showed that patients with elevated Lipoprotein (a) levels had no significant difference in morbidity and mortality between diabetic and non-diabetic patients which shows - p value - 0.099 (p more than 0.05)

In stroke and TIA Lp (a) is observed to be an independent risk factor in ARIC study.

Zenker et al study showed that Lipoprotein (a) is not only a risk factor for CAD but also for CVD.(p value less than 0.01)

Decreased HDL, increased LP (a) ,IDL ,LDL ,TC are seen in patients with ischemic stroke in the study conducted by pedreno j et el Similar results have been concluded in our study which showed decreased HDL in diabetic patients with ischemic stroke.

Naoki nago et al study conducted in Japanese population with 1235 males and 1762 females over 30 years old found mean Lipoprotein (a) level were higher in females than males. Not much study has been conducted in Indian population.

The same study also concluded that LP(a) level is inversely proportional with alcoholics and also with TGL levels.

Increased concentration of TG, Lp (a) and decreased con centration of HDL, TC and LDL pattern of lipoid profile is observed in ischemic stroke in Lindgren et el's study In our study also patient with ischemic stroke has higher lipoprotein (a) , triglyceride level and lower HDL levels. Total cholesterol and serum LDL levels do not show significant abnormal values.

Nagayama et al' studied that Lpa levels were higher in patients with ischemic stroke of less than 70 years. Study conducted by Maurizio margaglione et al ' also showed that LP(a) level is higher in patients less than 70 years with ischemic stroke.In our study patients aged more than 40 years were studied and was found to have elevated lipoprotein (a) levels.

Maurus marques et al' conducted study in 60 patients with ischemic stroke and when compared between diabetics and non-diabetics mean Lipoprotein (a) level was high in diabetics than non-diabetics. I n our study also the mean lipoprotein (a) level was higher in diabetics than non-diabetics - p value in our study 0.047 (p value less than 0.05)

Jenkin' s et al study concluded that vascular complications like ischemic stroke and myocardial infarction are higher in patients with elevated lipoprotein (a) level in our study p value 0.044 (p value less than 0.05) significant association between increasing lipoprotein a level and ischemic stroke . But our study being a retrospective study in ischemic stroke patients with diabetes having significant elevation of lipoprotein (a) level would also serve to suggest that lipoprotein (a) as an independent risk factor to develop ischemic stroke. Further prospective studies could be done to evaluate this.

LIMITATIONS OF THIS STUDY

LIMITATIONS OF STUDY

1. Study sample was small only 100 patients with ischemic stroke 50 patients with type 2 diabetic and 50 patients with non-diabetic.

2. Long term follow up of the patients was difficult, so the follow up study was done for a short duration of 7 days. If the patients were followed up for 6 months as done in other studies, the correlation of lipoprotein a with ischemic stroke with Scandinavian score Scale would be much more ideal.

3. The controls were matched only for age and sex and not for other risk factors which would have been ideal.

4. Seriously ill patients admitted in intensive care units were not included in this study due to difficulty in getting the consent. This might have lead to selection bias.

5. People admitted during our study period only compared, if more patients and if studies conducted for long period then it may be more ideal as other studies are done.

CONCLUSION

CONCLUSION

- In our study, a significant association of lipoprotein (a) concentration with ischemic stroke was inferred- p value -0.044

- Increased levels of lipoprotein(a) in type II diabetic patients was found to have increased predilection to ischemic stroke when compared to non diabetics .(P value -0.047)

- Although study showed increased predilection of lipoprotein (a) in ischemic stroke, Lipoprotein (a) levels skewed towards higher values in both type 2 diabetic and non-diabetics.

- In our study conducted in 100 ischemic patients, 50 diabetic patients were compared with non diabetics and was followed up for 7 days or until death whichever is earlier .The significance inferred was- p value 0.099. So from our study lipoprotein (a) cannot be used as a surrogate marker to assess severity of ischemic stroke.

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BIBLIOGRAPHY

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ANNEXURES

LIPOPROTEIN (a) IN ISCHEMIC STROKE - A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON-DIABETIC PATIENTS

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY :

TREATMENT HISTORY :

DRUG ALLERGY :

GENERAL EXAMINATION :

VITALS :

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM :

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM : Higher motor function

Cranial nerves

Motor system

Sensory system

Cerebellar signs

INVESTIGATIONS :

CBC :

RFT- GLUCOSE

UREA

CRETININE

NA+

K+

LFT- Total bilirubin :

Direct bilirubin

SGOT

SGPT

ALP

Total protein

Albumin

Chest x ray

Echocardiography :

Ultrasound abdomen :

FASTING LIPID PROFILE :

LIPOPROTEIN (a) :

FASTING BLOOD SUGAR :

HbA1C :

CT BRAIN :

INFORMATION SHEET

We are conducting a study on **"LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study to evaluate lipoprotein (a) level as early marker to assess severity of ischemic stroke in diabetic patient

We are selecting certain cases and if you are found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature of Participant

Date:

Place:

PATIENT CONSENT FORM

Study Detail	:	LIPOPROTEIN (a) IN ISCHEMIC STROKE- A COMPARATIVE STUDY BETWEEN TYPE II DIABETIC VS NON DIABETIC PATIENTS
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsors of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and ❑

to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms.

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ❑

Signature/thumb impression
Patient's Name and Address:

Signature of Investigator

Study Investigator's Name:

Dr. R. RAVINDRAN

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970
EC RegNo.ECR/270/Inst./TN/2013

CERTIFICATE OF APPROVAL

To
Dr. R.Ravidran,
MD General Medicine PG,
Madras Medical College, Chennai-3.

Dear R.Ravidran,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Lipoprotein (a) In Ischemic Store – A comparative study Between Type II Diabetic Vs non Diabetic Patients" No.20062013.

The following members of Ethics Committese were present in the meeting held on 11.06.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandini 12/7/13
Member Secretary, Ethics Committee

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Author	20111017 . M.d. General Medicine RAVINDRAN R . RAJI
E-mail	dr.ravindran.r@gmail.com
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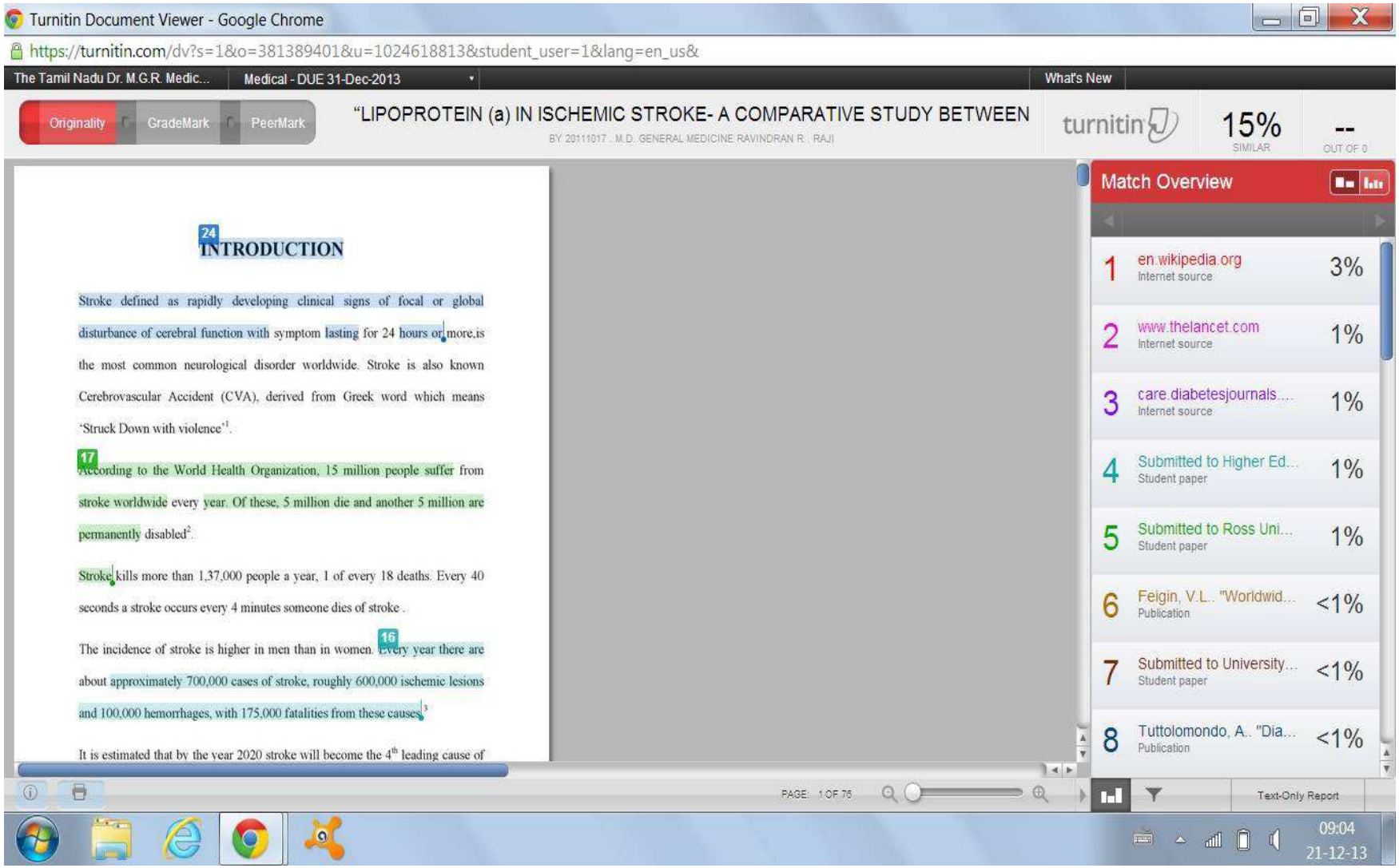
INTRODUCTION Stroke defined as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptom lasting for 24 hours or more,is the most common neurological disorder worldwide. Stroke is also known Cerebrovascular Accident (CVA), derived from Greek word which means 'Struck Down with violence'1. According to the World Health Organization, 15 million people suffer from stroke worldwide every year. Of these, 5 million die and another 5 million are permanently disabled2. Stroke kills more than 1,37,000 people a year, 1 of every 18 deaths. Every 40 seconds a stroke occurs every 4 minutes someone dies of stroke . The incidence of stroke is higher in men than in...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INTRODUCTION
Stroke defined as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptom lasting for 24 hours or more,is the most common neurological disorder worldwide. Stroke is also known Cerebrovascular Accident (CVA), derived from Greek word which means 'Struck Down with violence'[1].
According to the World Health Organization, 15 million people suffer from stroke worldwide every year. Of these, 5 million die and another 5 million are permanently disabled[2].
Stroke kills more than 1,37,000 people a year, 1 of every 18 deaths. Every 40 seconds a stroke occurs every 4 minutes someone dies of stroke .
The incidence of stroke is higher in men than in women. Every year there are about approximately 700,000 cases of stroke, roughly 600,000 ischemic lesions and 100,000 hemorrhages, with 175,000 fatalities from these causes[3]
It is estimated that by the year 2020 stroke will become the 4th leading cause of
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Text-Only Report
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SL.NO	AGE	Sex	SMOKER	ALCOHOLIC	Diabetic Status	FBS mg/dl	HBA1C %	Lipo Protein (a) mg/dl	MORBIDITY	MORTALITY	Scandinavian Score	VAR
1	48	MALE	YES	YES	DIABETIC	132	8.1	16	16	ALIVE	>15	15 - 30
2	54	MALE	NO	YES	DIABETIC	174	9.3	28	12	ALIVE	<15	15 - 30
3	51	MALE	YES	YES	DIABETIC	144	7.3	20	10	ALIVE	<15	15 - 30
4	63	MALE	YES	NO	DIABETIC	169	7.2	31	4	ALIVE	<15	30 - 50
5	66	FEMALE	NO	NO	DIABETIC	134	9.7	31	2	DEATH	<15	30 - 50
6	57	MALE	YES	YES	DIABETIC	164	7.8	31	8	ALIVE	<15	30 - 50
7	62	FEMALE	NO	NO	DIABETIC	128	8.2	26	12	ALIVE	<15	15 - 30
8	49	MALE	YES	YES	DIABETIC	167	9.1	15	4	ALIVE	<15	15 - 30
9	50	FEMALE	NO	NO	DIABETIC	161	8.1	23	6	ALIVE	<15	15 - 30
10	55	FEMALE	NO	NO	DIABETIC	170	7.7	18	14	ALIVE	<15	15 - 30
11	47	MALE	YES	NO	DIABETIC	163	9.2	26	6	ALIVE	<15	15 - 30
12	60	FEMALE	NO	NO	DIABETIC	175	7.3	24	2	ALIVE	<15	15 - 30
13	42	MALE	YES	YES	DIABETIC	174	9.6	20	8	ALIVE	<15	15 - 30
14	61	MALE	YES	NO	DIABETIC	136	7.9	32	16	ALIVE	>15	30 - 50
15	59	FEMALE	NO	NO	DIABETIC	130	8.4	22	4	ALIVE	<15	15 - 30
16	44	MALE	YES	YES	DIABETIC	133	8.9	15	6	ALIVE	<15	15 - 30
17	52	FEMALE	NO	NO	DIABETIC	148	7.6	20	4	ALIVE	<15	15 - 30
18	64	FEMALE	NO	NO	DIABETIC	168	7.7	16	12	ALIVE	<15	15 - 30
19	60	FEMALE	NO	NO	DIABETIC	168	10.8	26	2	DEATH	<15	15 - 30
20	44	MALE	YES	NO	DIABETIC	150	8.7	28	8	ALIVE	<15	15 - 30
21	53	MALE	YES	YES	DIABETIC	150	7.8	50	10	ALIVE	<15	30 - 50
22	59	MALE	NO	YES	DIABETIC	165	8.3	48	12	ALIVE	<15	30 - 50
23	62	MALE	YES	NO	DIABETIC	138	7.1	35	8	ALIVE	<15	30 - 50
24	45	MALE	YES	NO	DIABETIC	172	8.3	33	20	ALIVE	>15	30 - 50
25	56	MALE	NO	YES	DIABETIC	156	7.8	34	16	ALIVE	>15	30 - 50
26	64	FEMALE	NO	NO	DIABETIC	139	7.6	36	20	ALIVE	>15	30 - 50
27	70	MALE	YES	NO	DIABETIC	171	10.2	35	18	ALIVE	>15	30 - 50
28	59	MALE	YES	NO	DIABETIC	164	8.4	34	16	ALIVE	>15	30 - 50
29	61	FEMALE	NO	NO	DIABETIC	131	8.6	35	20	ALIVE	>15	30 - 50
30	48	MALE	YES	YES	DIABETIC	166	7.8	34	18	ALIVE	>15	30 - 50
31	59	MALE	YES	NO	DIABETIC	198	9.2	37	16	ALIVE	>15	30 - 50

SL.NO	AGE	Sex	SMOKER	ALCOHOLIC	Diabetic Status	FBS mg/dl	HBA1C %	Lipo Protein (a) mg/dl	MORBIDITY	MORTALITY	Scandinavian Score	VAR
32	64	MALE	YES	YES	DIABETIC	181	10.2	37	18	ALIVE	>15	30 - 50
33	66	FEMALE	NO	NO	DIABETIC	182	8.3	36	16	ALIVE	>15	30 - 50
34	63	FEMALE	NO	NO	DIABETIC	186	7.8	40	18	ALIVE	>15	30 - 50
35	54	FEMALE	NO	NO	DIABETIC	181	9.4	45	18	ALIVE	>15	30 - 50
36	49	MALE	YES	YES	DIABETIC	206	8.6	40	18	ALIVE	>15	30 - 50
37	52	MALE	YES	YES	DIABETIC	206	9.9	36	18	ALIVE	>15	30 - 50
38	59	MALE	YES	YES	DIABETIC	204	8.3	45	16	ALIVE	>15	30 - 50
39	71	FEMALE	NO	NO	DIABETIC	221	8.0	40	18	ALIVE	>15	30 - 50
40	49	MALE	YES	YES	DIABETIC	201	7.8	48	18	ALIVE	>15	30 - 50
41	73	MALE	NO	YES	DIABETIC	218	8.0	50	18	ALIVE	>15	30 - 50
42	67	FEMALE	NO	NO	DIABETIC	200	7.4	44	16	ALIVE	>15	30 - 50
43	45	MALE	YES	YES	DIABETIC	183	7.1	30	16	ALIVE	>15	15 - 30
44	65	FEMALE	NO	NO	DIABETIC	205	8.4	39	16	ALIVE	>15	30 - 50
45	48	MALE	YES	YES	DIABETIC	218	8.1	42	18	ALIVE	>15	30 - 50
46	73	MALE	NO	NO	DIABETIC	184	8.3	37	20	ALIVE	>15	30 - 50
47	60	FEMALE	NO	NO	DIABETIC	189	8.2	47	18	ALIVE	>15	30 - 50
48	58	MALE	NO	NO	DIABETIC	212	8.5	46	14	ALIVE	<15	30 - 50
49	48	MALE	YES	NO	DIABETIC	200	7.8	38	16	ALIVE	>15	30 - 50
50	65	MALE	NO	YES	DIABETIC	196	8.2	34	8	ALIVE	<15	30 - 50
51	41	FEMALE	YES	YES	NON DIABETIC	98	5.2	16	12	ALIVE	<15	15 - 30
52	62	MALE	YES	NO	NON DIABETIC	112	6.0	17	8	ALIVE	>15	15 - 30
53	67	FEMALE	NO	NO	NON DIABETIC	96	5.9	22	14	ALIVE	<15	15 - 30
54	43	MALE	YES	NO	NON DIABETIC	116	5.5	16	6	ALIVE	<15	15 - 30
55	48	MALE	NO	NO	NON DIABETIC	114	6.2	31	6	ALIVE	<15	30 - 50
56	43	FEMALE	YES	NO	NON DIABETIC	121	6.0	31	14	ALIVE	<15	30 - 50
57	45	MALE	NO	NO	NON DIABETIC	90	4.1	16	14	ALIVE	<15	15 - 30
58	47	FEMALE	NO	NO	NON DIABETIC	87	6.5	21	10	ALIVE	<15	15 - 30
59	53	FEMALE	NO	NO	NON DIABETIC	108	5.2	31	10	ALIVE	<15	30 - 50
60	69	FEMALE	YES	NO	NON DIABETIC	115	6.0	32	6	ALIVE	<15	30 - 50
61	66	FEMALE	YES	NO	NON DIABETIC	120	5.0	41	12	ALIVE	<15	30 - 50
62	50	FEMALE	YES	NO	NON DIABETIC	117	5.3	47	6	ALIVE	<15	30 - 50

SL.NO	AGE	Sex	SMOKER	ALCOHOLIC	Diabetic Status	FBS mg/dl	HBA1C %	Lipo Protein (a) mg/dl	MORBIDITY	MORTALITY	Scandinavian Score	VAR
63	50	FEMALE	NO	NO	NON DIABETIC	95	5.3	42	20	ALIVE	<15	30 - 50
64	44	FEMALE	YES	NO	NON DIABETIC	91	5.0	48	20	ALIVE	<15	30 - 50
65	59	MALE	NO	NO	NON DIABETIC	87	5.2	40	16	ALIVE	>15	30 - 50
66	46	MALE	NO	NO	NON DIABETIC	94	6.4	41	18	ALIVE	>15	30 - 50
67	44	MALE	NO	NO	NON DIABETIC	81	4.1	47	2	DEATH	>15	30 - 50
68	40	MALE	NO	NO	NON DIABETIC	107	6.4	38	18	ALIVE	>15	30 - 50
69	51	MALE	NO	NO	NON DIABETIC	74	4.8	37	18	ALIVE	>15	30 - 50
70	60	MALE	YES	NO	NON DIABETIC	97	5.1	47	18	ALIVE	>15	30 - 50
71	44	FEMALE	YES	NO	NON DIABETIC	107	4.2	36	18	ALIVE	>15	30 - 50
72	41	FEMALE	NO	NO	NON DIABETIC	95	4.2	32	18	ALIVE	>15	30 - 50
73	58	FEMALE	YES	NO	NON DIABETIC	77	4.3	33	18	ALIVE	>15	30 - 50
74	68	MALE	YES	NO	NON DIABETIC	67	5.7	31	16	ALIVE	>15	30 - 50
75	67	FEMALE	YES	YES	NON DIABETIC	90	5.7	28	18	ALIVE	>15	15 - 30
76	43	MALE	YES	YES	NON DIABETIC	100	6.3	26	18	ALIVE	>15	15 - 30
77	53	FEMALE	YES	NO	NON DIABETIC	76	4.9	30	18	ALIVE	>15	15 - 30
78	64	FEMALE	NO	NO	NON DIABETIC	100	4.8	22	16	ALIVE	>15	15 - 30
79	64	FEMALE	YES	NO	NON DIABETIC	103	6.5	24	20	ALIVE	>15	15 - 30
80	63	MALE	NO	NO	NON DIABETIC	75	6.2	33	18	ALIVE	>15	30 - 50
81	58	FEMALE	NO	YES	NON DIABETIC	92	6.1	22	16	ALIVE	>15	15 - 30
82	63	FEMALE	YES	YES	NON DIABETIC	99	4.1	30	16	ALIVE	>15	15 - 30
83	53	MALE	NO	YES	NON DIABETIC	97	4.2	27	20	ALIVE	>15	15 - 30
84	41	MALE	YES	YES	NON DIABETIC	66	5.2	32	2	DEATH	>15	30 - 50
85	61	MALE	YES	YES	NON DIABETIC	107	6.5	29	14	ALIVE	>15	15 - 30
86	46	MALE	NO	NO	NON DIABETIC	102	5.9	30	16	ALIVE	>15	15 - 30
87	48	MALE	NO	YES	NON DIABETIC	69	4.2	25	18	ALIVE	<15	15 - 30
88	69	MALE	YES	NO	NON DIABETIC	88	4.5	23	18	ALIVE	>15	15 - 30
89	49	MALE	NO	YES	NON DIABETIC	77	6.3	34	18	ALIVE	>15	30 - 50
90	54	MALE	YES	NO	NON DIABETIC	73	4.9	28	16	ALIVE	>15	15 - 30
91	54	MALE	NO	NO	NON DIABETIC	87	6.2	20	18	ALIVE	>15	15 - 30
92	67	FEMALE	YES	YES	NON DIABETIC	72	4.4	22	20	ALIVE	>15	15 - 30

SL.NO	AGE	Sex	SMOKER	ALCOHOLIC	Diabetic Status	FBS mg/dl	HBA1C %	Lipo Protein (a) mg/dl	MORBIDITY	MORTALITY	Scandinavian Score	VAR
93	51	MALE	NO	NO	NON DIABETIC	91	4.2	20	20	ALIVE	>15	15 - 30
94	54	MALE	YES	NO	NON DIABETIC	92	5.6	21	18	ALIVE	>15	15 - 30
95	50	MALE	NO	YES	NON DIABETIC	97	5.5	24	2	DEATH	>15	15 - 30
96	44	MALE	NO	NO	NON DIABETIC	102	4.1	21	14	ALIVE	>15	15 - 30
97	54	MALE	YES	NO	NON DIABETIC	109	6.3	22	16	ALIVE	>15	15 - 30
98	61	MALE	YES	NO	NON DIABETIC	93	6.1	30	20	ALIVE	<15	15 - 30
99	47	MALE	NO	YES	NON DIABETIC	83	5.4	34	4	ALIVE	>15	30 - 50
100	62	MALE	YES	YES	NON DIABETIC	89	5.5	31	4	ALIVE	>15	30 - 50