“ASSOCIATION OF MEAN PLATELET VOLUME WITH ACUTE ISCHEMIC CEREBROVASCULAR ACCIDENT AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS - A HOSPITAL BASED STUDY”

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ENDORSEMENT

This is to certify that the dissertation entitled **"ASSOCIATION OF MEAN PLATELET VOLUME WITH ACUTE ISCHEMIC CEREBROVASCULAR ACCIDENT AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS - A HOSPITAL BASED STUDY"** is a bonafide research work done by **CANDIDATE REG NO. BG0113006**.

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LIST OF ABBREVIATIONS USED

°C	-	Degree centigrade
ADP	-	Adenosine diphospate
AGEs	-	Advanced Glycosylation End Products
AHA	-	American Heart Association
ANOVA	-	Analysis of variance
APLA	-	Antiphospholipid syndrome
BT	-	Bleeding time
b-TG	-	Beta-thromboglobulin
Ca2+	-	Calcium ion
CAD	-	Coronary artery disease
cAMP	-	Cyclic adenosine monophosphate
CAT	-	Computerized axial tomography
cGMP	-	Cyclic guanosine monophosphate
CHD	-	Coronary Heart Disease
CI	-	Confidence interval
CNS	-	Central nervous system
CT	-	Computed tomography
Cumm	-	Cubic millimeter
CVA	-	Cardiovascular accident
CVD	-	Cardiovascular disease
DALYs	-	Disability adjusted life-years
DM	-	Diabetes mellitus
DNA	-	Deoxyribonucleic acid
DVT	-	Deep venous thrombosis

ED	-	Emergency department
Fig	-	Figure
fL	-	Femto liters
FPG	-	Fasting plasma glucose
GCNKSS	-	Greater Cincinnati/Northern Kentucky Stroke Study
gm	-	Gram
GPE	-	General physical examination
HbA1c	-	Glycosylated haemoglobin
HDL	-	High density lipoprotein
IA	-	Intraarterial
ICH	-	Intracerebral hemorrhage
ITP	-	Idiopathic thrombocytopenic purpura
LAD	-	Large-artery disease
LDH	-	Lactate dehydrogenase
LDL	-	Low density lipoprotein
LOC	-	Level of consciousness
LSR	-	Lausanne Stroke Registry
Mg2+	-	Magnesium ion
MI	-	Myocardial infarction
MK	-	Megakaryocyte
mmol/L	-	Millimole per litre
MPHA	-	Megakaryocyte platelet haemostatic axis
MPV	-	Mean platelet volume
MRI	-	Magnetic resonance imaging
MRM	-	Modified Rankin Morbidity score

n	-	Total number
NIHSS	-	National Institute of Health Stroke Scale
OC	-	Oral contraceptive
OHA’s	-	Oral hypoglycaemic agents
p	-	Probability
PAD	-	Peripheral Arterial Disease
PGI2	-	Prostacyclin
PKC	-	Protein kinase C
ROS	-	Reactive Oxygen Species
SCI	-	Subcortical infarction
SD	-	Standard deviation
SE	-	Standard error
sNIHSS	-	Shortened National Institutes of Health Stroke Scale
SCV	-	Small Cerebral Vessels
SVD	-	Small-vessel disease
TIA’s	-	Transient ischaemic attacks
TXA2	-	Thromboxane A2
TXB2	-	Thromboxane B2
T2DM	-	Type 2 diabetes mellitus
UK	-	United Kingdom
WHO	-	World Health Organization
WMH	-	White Matter Hyperintensity
β	-	Beta

ABSTRACT

Background and objectives

It is reported that, MPV is raised in ischaemic stroke and type 2 diabetes mellitus respectively. Raise in MPV has shown poor outcome of stroke. This study aims at comparing the rise of MPV in diabetic and non diabetic cases with ischaemic stroke and assessing the outcome.

Methodology

This one year hospital based cross sectional study was carried out in the Department of Medicine. A total of 79 patients who presented with acute ischaemic stroke from January 2014 to December 2014 were enrolled (25 patients with diabetes and 54 non diabetics). All the patients underwent NIHSS at the time of admission and MPV was noted. Patients were evaluated for outcome based on MRM score.

Results

Majority of the diabetic (72%) and non diabetic (68.52%) patients were males (p=0.754). The mean age in diabetic patients was 62.04±10.88 years and in non diabetic patients it was 58.11±16.75 years (p=0.217). The commonest presentation was weakness in diabetic (96%) as well as in non diabetic patients (88.89%). History of previous stroke was present in 12% of the patients with DM compared to 1.85% of the non DM (p=0.091). The mean NIHSS scores were significantly high in patients with DM compared to non diabetic patients (20.38±3.19 vs 17.76±3.74; p=0.006). Majority of the patients with DM had raised MPV levels (>9.5) compared to non diabetic patients (72% vs 9.26%;

p<0.001) and mean was also significantly high (10.16±0.89 vs 8.25±0.91;p<0.001) in respective subsets. Majority of the patients with DM had moderate to severe disability compared to non diabetic patients (68% vs 7.41%; p<0.001) and mean MRM scores were significantly high in diabetic population (4.12±0.66 vs 3.00±0.61; p<0.001).

Conclusion and interpretation

Acute ischaemic stroke in diabetic patients is significantly associated with raised MPV level which is likely to be severe with high morbidity and mortality.

Keywords

Acute ischemic stroke; Mean platelet volume; Type 2 Diabetes mellitus;

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INTRODUCTION

A stroke, or cerebrovascular accident, is defined as abrupt onset of a neurologic deficit of vascular origin. World Health Organization defines the clinical syndrome of "stroke" as, rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin.[1]

Majority of stroke are ischaemic (80%); while others result from primary haemorrhage either intracerebral or into the subarachnoid space. Acute ischemic stroke is result of stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke. Ischemic strokes constitute 85–87% of all cases.[2] Hemorrhagic stroke constitute spontaneous intracerebral hemorrhage and subarachnoid hemorrhage, and account for the remainder of cases. According to the Indian Council of Medical Research there were 930,985 cases of stroke in 2004 in India and the National Commission of Macroeconomics and Health has estimated that there will be 1.67 million stroke cases in India by 2015.[2-4]

According to the World Health Organization, stroke is the second leading cause of death world-wide.[3] Thus, cerebrovascular disease is a huge public health problem imposing both as a large disease burden and a large economic burden on our country.[4] The mortality rate of stroke in the acute phase is as high as 20% and it remains higher for several years after the acute event in stroke patients than in the general population.[5] Stroke is an illness of escalating socioeconomic importance, especially among the ageing population.

In some geographical areas or within or some racial and ethnic groups, stroke incidence may be unusually high. Incidence of stroke varies considerably from country to country. Based on the review of available information in India, the prevalence of stroke was estimated as 203 per 100,000 population above 20 years, amounting to a total of about 1 million cases.[7] Upto 85% of all strokes are of ischaemic origin.[8]

Atherosclerosis occurring in arteries supplying the brain, both large and small is the most common cause of ischemic stroke. Atherosclerosis occurring in proximal aorta is also a source of atherogenic brain emboli. Large artery atherosclerotic infarction occurs when there is an impediment to normal perfusion, usually caused by a severe arterial stenosis or occlusion due to atherosclerosis and coexisting thrombosis or artery to artery embolism. Microatheroma, lipohyalinosis, and other occlusive diseases of the small penetrating brain arteries are the most frequent causes of small, sub-cortical "lacunar" infarcts. About 20% of ischaemic strokes are due to cardiogenic embolism, most commonly from atrial fibrillation. A variety of other occlusive disorders may be the primary cause or variably contribute to stroke pathogenesis.[9] Accordingly, stroke is also an important cause of morbidity and long term disability, up to 40% of survivors are not expected to recover their independence and self-care.[5]

Numerous risk factors are involved in the development of stroke, such as hypertension, cigarette smoking, hyperlipidemia and diabetes mellitus.[9] Diabetes mellitus and ischaemic stroke often arise together. People with diabetes have more than double the risk of ischaemic stroke after correction for other risk factors,

relative to individuals without diabetes. Hyperglycaemia occurs in 30-40% of patients with acute ischaemic stroke in diabetic as well as non diabetic patients.[10]

Recent studies have reported raised platelet counts and mean platelet volume (MPV) in diabetics and positive correlation with impaired fasting glucose. Platelets play a major role in integrity of normal haematopoiesis, and MPV is an indicator for its function.[11] The large platelets contain more dense granules and are more potent than smaller platelets and hence more thrombogenic. Increased platelet activity is emphasized to play a role in the development of vascular complications of this disorder.[12] Many studies have shown high MPV as a risk factor for the vascular complications of DM like thromboembolism, stroke and myocardial infarction.[13-17]

Furthermore, an increase in MPV is independently associated with stroke[18] and higher levels of MPV have been found in patients with acute ischemic stroke than in control subjects. Those with the highest quintile of MPV had a >2 fold risk of suffering a severe stroke compared to those within lower quintiles.[19]

These findings postulate the hypothesis that the increase of MPV especially in patients with diabetes mellitus might have a critical role for genesis or worsening of acute ischemic stroke. This prompted us to describe association between MPV and acute ischemic cerebrovascular events which might serve as a valuable predictor of outcome in patients with acute ischemic cerebrovascular events.

OBJECTIVES

The objective of the present study was to study the association between mean platelet volume (MPV) and acute ischemic stroke in patients with type 2 diabetes mellitus (outcome).

REVIEW OF LITERATURE

STROKE

Historical perspectives

The term “Stroke” or “Cerebrovascular accidents” has come to signify the abrupt impairment of brain function caused by a variety of pathological changes involving one (focal) or several (multifocal) intracranial or extracranial blood vessels.[20]

The concept of stroke was first noted from 460 to 370 before the Common Era by Hippocrates. At this time, the symptoms of convulsions and paralysis were referred to as apoplexy. Over the next several hundred years, scholars focused on physical symptoms and potential causes.

The first known description of stroke was given by Hippocrates who took the word “Apoplexy” from common non medical use where it meant **“**Astonished**,** Suddenly benefit of one’s senses**”** and applied it descriptively to stroke.

- Jacob Werter, a Swiss physician was the first person to suggest that apoplexy was caused by disease of blood vessel in the brain.
- Thomas Willis described the circle of wills in 1664.
- Seddicot described spontaneous intracerebral haemorrhage in 1813.
- In 1828 Abberonbie, described the obliterative arterial disease of cerebral arteries.

- Johan Friedrich crell, emphasized the pultaceous or atheromatous elements in some arterial lesions although he did not use the term atheroma.
- Von Haller made similar observations and applying the term “atheroma” to the arterial lesions.
- In 1860, Rudolf Virchow described imbibition theory that states there was deposition of blood constituents on the laminal surface of the arterial wall during the formation and growth of atheromatous plaques. He considered that the early lesions of atherosclerosis were based on a “loosening” of the connective tissue ground substance of the intima as a result of “imbibition” of constituents of the passing blood.
- Von Rokitansky and the thrombogenic theory described the atheromatous deposition is by far the most frequent disease of the arteries and embodies the foundation of aneurysm formation and of many spontaneous arterial obliterations.
- Virchow’s concept of atherogenesis was that, all the structural changes were initiated by an invading stream of plasma. This is the origin of the so called “infiltrative” theory of atherosclerosis which certainly, in so far as lipid accumulation is concerned, appears even now to have much truth in it.
- Vogel in 1847 and Chalatow in 1913 observed that atherosclerotic plaques contained relatively large amounts of cholesterol.
- In 1825, Bonillord described localisation of lesion and aphasia.
- In 1860, Von Graafe used Helmoltz ophthalmoscope.
- In 1895, Hamrich Quinn introduced the technique of lumbar puncture which is so vital in the diagnosis of neurological illness.

- 1877 Osler reported a case of Subarachnoid and intracerebral haemorrhage due to ruptured aneurysm.
- In 1914, Ramasy hunt was the first to describe comprehensive description of spontaneous carotid occlusion without crest disease of the intracranial vessel producing cerebral infarction.
- Dandy performed the first air ventriculogram.
- Denny brown introduced the concept of vascular insufficiency.
- Platelet antiaggregating drugs like aspirin was used in 1971 for TIA's by Karim in 1978.
- Dr. GodFrey Honnsfield, a British physicist in 1972 introduced computerized axial tomography (CAT) technique into neuro radiology which resulted in award of noble prize in 1979. This lead to more precise categorization of ischaemic and hemorrhagic CVA.

Within the last decade, the magnitude of research has grown exponentially. The term apoplexy has faded, and the term stroke has become common place in the medical setting.[21]

Definition

WHO defines stroke as rapid development of clinical signs of focal (or global) brain function disorders, with symptoms which last 24 hours or longer or lead to death, without other clear cause, except signs of blood vessel damage.[22]

Prevalence

Worldwide

It is estimated that approximately 4 million people suffer from stroke annually. Out of that number, approximately 570,000 cases occur in Europe and approximately 500,000 in United States of America. International epidemiological trials show that rates grow exponentially with age, from 0.3‰ in the third and fourth decade of life, all the way to 30‰ in the eighth and ninth decade of life, whichmakes an average of 1–2%. Recent data shows that the incidence of stroke in France is 114 cases per 100,000 persons per year, in Germany 350, in Italy 223, in Spain 141–220, and in UK 161.[23,24]

Although rates of stroke mortality and burden vary greatly among countries, low-income countries are the most severely affected. There has been a 42% decrease in stroke incidence in high-income countries and >100% increase in low- to middle-income countries.[6,25]

Morbidity and Mortality [26]

- 400-800 strokes per 100,000.
- 5.7 million Deaths.
- 16 million new acute strokes every year.
- 28,500,000 DALYs (disability adjusted life-year).
- 28-30 day case fatality ranges from 17%-35%.

Stroke in India

Estimates of the prevalence of stroke in India range from 44 to 843 per 100,000 population.[27,28] Based on the estimates by Dalal et al. in 2008, age adjusted annual incidence per 100,000 population is 152.[29]

Morbidity and Mortality [26]

- Prevalence 90-222 per 100,000.
- 102,620 million deaths.
- 1.44-1.64 million cases of new acute strokes every year.
- 6,398,000 DALYs.
- 12% of strokes occur in the population aged <40 years
- 28-30 day case fatality ranges from 18-41%.

Classification of stroke[30]

Broadly, strokes are classified as either hemorrhagic or ischemic. Acute ischemic stroke refers to stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke.[31]

There are many classifications according to etiology vascular territory and by time course etc.

1. Classification by time course:

    a. Transient ischaemic attack.

    b. Reversible ischaemic neurological deficit.

c. Stroke in evolution.

d. Completed stroke.

2. By arterial territory:

a. Internal carotid artery territory.

b. Vertebrobasilar territory.

c. Lenticulo-striate.

3. By underlying pathology:

a. Atheromatous occlusion of vessels.

b. Atheroembolism.

c. Lipohylinoid necrosis.

d. Charcot Bouchard aneurysm rupture.

4. According to cause:[30]

a. Atherosclerosis.

b. Embolism of cardiac origin.

C. Vasculitis: Primary CNS, PAN, Collagen Vascular Disease, temporal arteritis, infectious vasculitis.

d. Hematological Disorders: Hemoglobinopathies, hyperviscosity syndrome, hypercoagulability states, protein C and S deficiency, APLA syndrome.

e. Drugs: Cocaine, alcohol, amphetamines, OC pills.

f. Others: MoyaMoya, migraine, fibromuscular dysplasia.

g. Cerebral Venous Thrombosis.

h. Intracerebral haemorrhage.

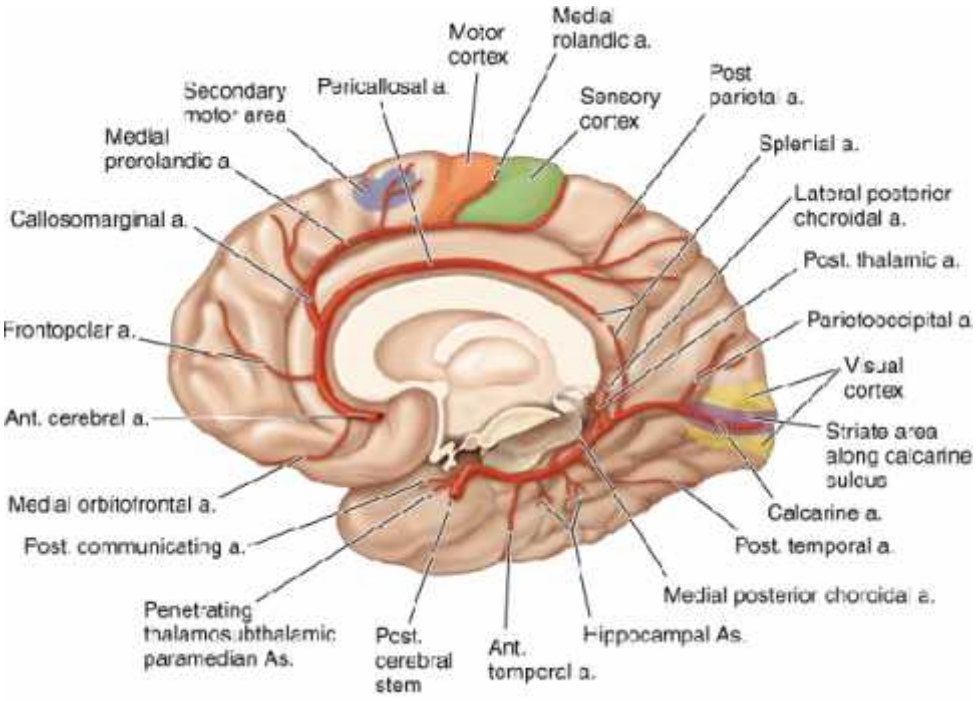


Figure 1. Cerebral hemisphere showing medial aspect - Branches of ACA[32]

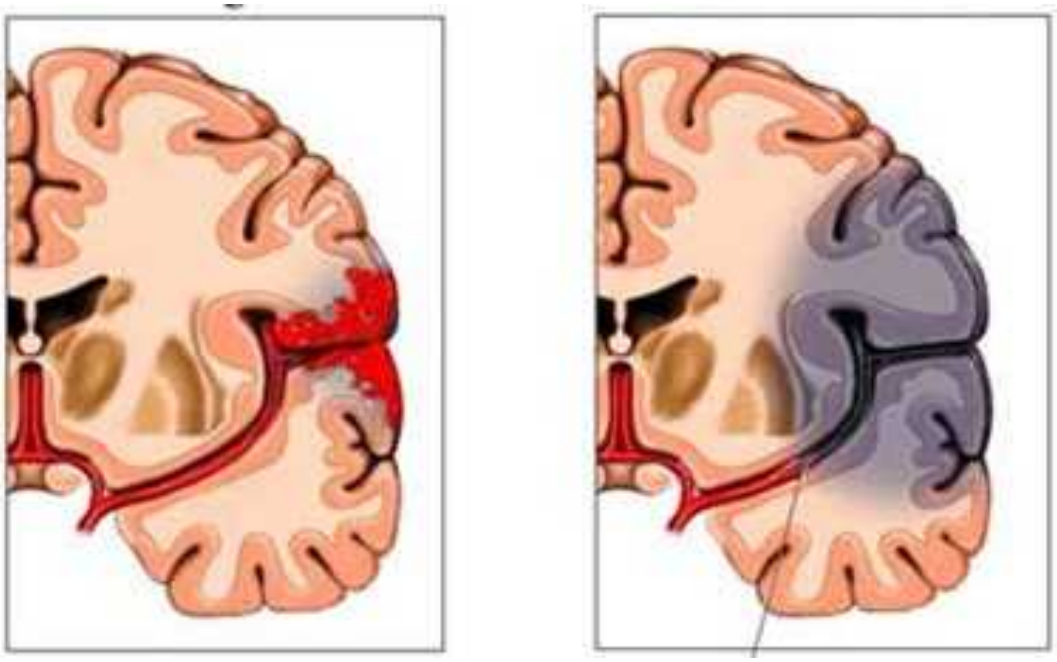


Figure 2. Pathology of haemorrhagic and ischaemic stroke[33]

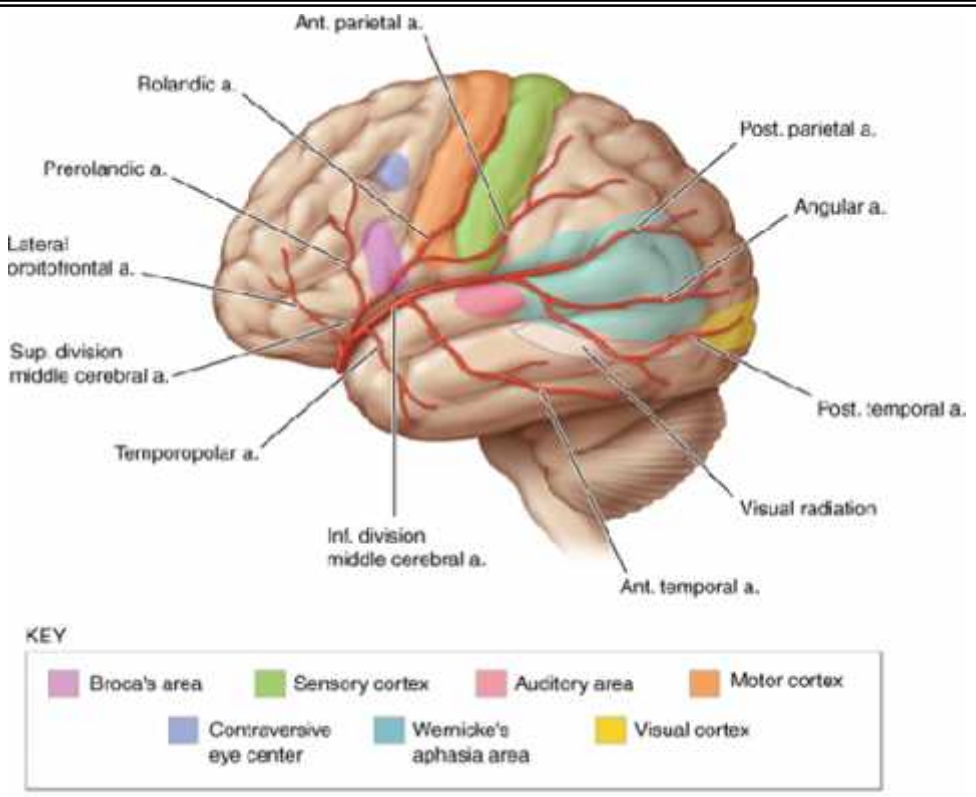


Figure 3. Cerebral hemisphere showing lateral aspect with branches of middle cerebral artery

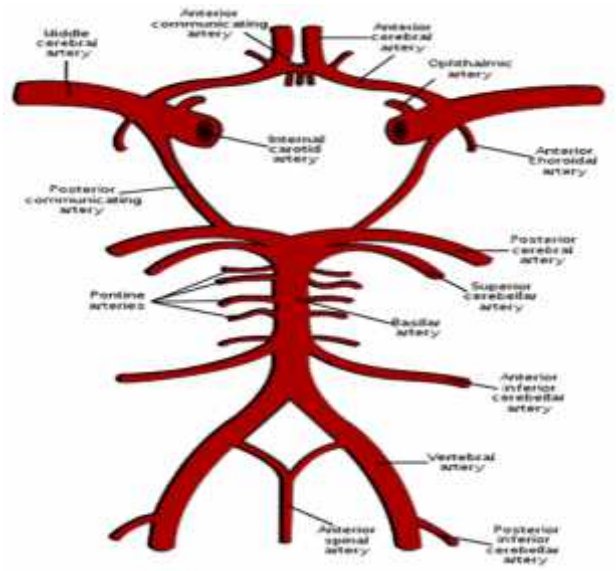


Figure 4. Schematic representation of the circle of Willis, arteries of the brain, and brainstem[34]

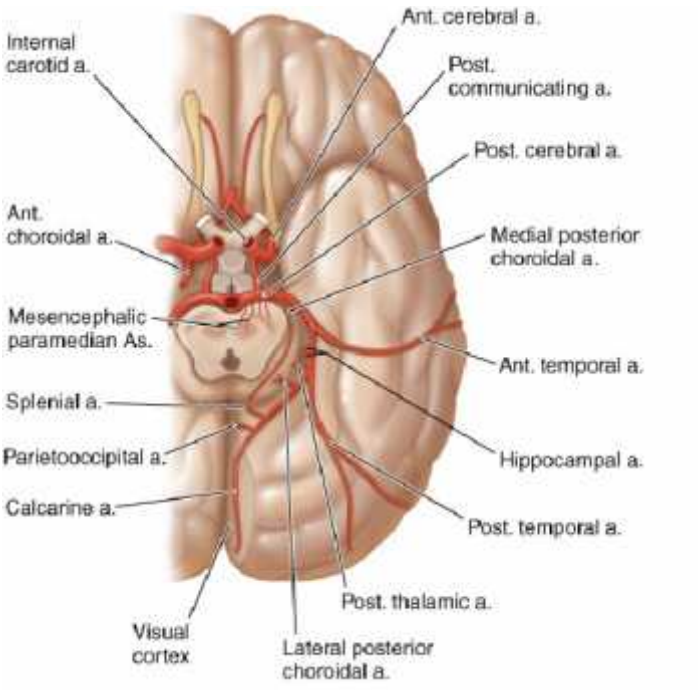


Figure 5. Inferior aspect of the brain with branches of posterior cerebral artery[32]

ISCHEMIC STROKE

Thrombotic cerebral infarction results from the atherosclerotic obstruction of large cervical and cerebral arteries, with ischemia in all or part of the territory of the occluded artery. This can be due to occlusion at the site of the main atherosclerotic lesion or to embolism from this site to more distal cerebral arteries.

Embolic cerebral infarction is due to embolism of a clot in the cerebral arteries coming from other parts of the arterial system, for example, from cardiac lesions, either at the site of the valves or of the heart cardiac cavities, or due to rhythm disturbances with stasis of the blood, which allows clotting within the heart as seen in atrial fribrillation.

Lacunar cerebral infarctions are small deep infarcts in the territory of small penetrating arteries, due to a local disease of these vessels, mainly related to chronic

hypertension. Several other causes of cerebral infarction exist and are of great practical importance for patient management. As they are relatively rare they can be ignored for most epidemiological purposes.

In India, frequency of ischaemic stroke is between 60 to 80%.[28,35-37] Further, lacunar, large vessel and cardioembolic types occur at 18%, 41%, 10% respectively[38] while other determined and undetermined types occur in 10% and 20 respectively.[37]

Etiology[39]

Ischemic strokes result from events that limit or stop blood flow, such as extracranial or intracranial thrombo-embolism, thrombosis in situ, or relative hypoperfusion. As blood flow decreases, neurons cease functioning, and irreversible neuronal ischemia and injury begin at blood flow rates of less than 18 mL/100 g of tissue/min.

Pathophysiology

When an ischemic stroke occurs, the blood supply to the brain is interrupted, and brain cells are deprived of the glucose and oxygen they need to function. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations. Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic in origin, and others have an unknown cause.[40]

Thrombosis can form in the extracranial and intracranial arteries when the intima is roughened and plaque forms along the injured vessel. The endothelial injury (roughing) permits platelets to adhere and aggregate, then coagulation is activated and thrombus develops at site of plaque. Blood flow through the

extracranial and intracranial systems decreases, and the collateral circulation maintains function. When the compensatory mechanism of collateral circulation fails, perfusion is compromised, leading to decreased perfusion and cell death.[40]

During an embolic stroke, a clot travels from a distant source and lodges in cerebral vessels. Microemboli can break away from a sclerosed plaque in the carotid artery or from cardiac sources such as atrial fibrillation, patent foramen ovale, or a hypokinetic left ventricle. Emboli in the form of blood, fat, or air can occur during surgical procedures, most commonly during cardiac surgery, but also after long bone surgeries.[40]

Less common causes of ischemic stroke include carotid dissection and the presence of coagulopathies, such as those resulting from antiphospholipid antibodies. Other causes include arteritis, infection, and drug abuse, such as the use of cocaine. While still not completely understood, the presence of periodontal disease and tooth loss is also an associated risk for ischemic stroke.[40]

As a thrombosis or emboli cause a decrease in blood supply to the brain tissue, events occur at the cellular level, referred to as the ischemic cascade. Neurons and support cells require a careful balance of variables such as temperature, pH, nutrition, and waste removal in their environment to function optimally. Intensive basic scientific research during the last two decades has given healthcare professionals an increased understanding of the ischemic cascade in the format of the precise environmental alterations involved in the pathophysiology of ischemic injury at the cellular level. Understanding the ischemic cascade has led to the concept of a therapeutic time window for treatment possibilities. Often, there is a

core region of dead cells surrounded by an area of hypoperfused tissue. The hypoperfused area may be rescued; this area is referred to as the penumbra region.[40]

Neuroprotection is a broad term that refers to pharmacological and nonpharmacological treatments used to halt the cellular events in the ischemic cascade, forming the theoretical basis for many of the acute stroke therapies under study[41] as well as the rationale for intervening within a therapeutic time window following ischemic stroke.

History and clinical presentation

Assessment of the patient with a stroke begins with recognition of the event as a stroke in the prehospital phase of care and continues throughout care. Emergency medical technicians and ambulance staff members need training in the recognition of signs and symptoms of stroke. Tools such as the Face Arm Speech Test[42] and the shortened National Institutes of Health Stroke Scale[43] have been tested and found to be effective in increasing the diagnostic accuracy of ambulance staff. The National Association of EMS Physicians has published standards for acute stroke prehospital care[44] which the AHA did not seek to duplicate but continued to emphasize the need for immediate diagnosis and evaluation.[45]

In the emergency department (ED), as the patient arrives, preferably by ambulance, a suspected stroke is treated as an acute event until diagnostic evidence suggests otherwise. Neurological assessment is based on both subjective and objective data, and a careful medical history is crucial to establish the exact time of onset of stroke signs and symptoms. Essential data to include are a quick history of

timing of the event, pertinent past medical history, and risk factors. The full NIHSS can be used to guide the neurologic assessment.[45]

NIH Stroke Scale

	Category	**Description**	**Score**
1a	level of consciousness (LOC)	Alert	0
		Drowsy	1
		Stuporous	2
		Coma	3
1b	LOC questions (month, age)	Answers both correctly	0
		Answers 1 correctly	1
		Incorrect on both	2
1c	Answers both correctly Answers 1 correctly Incorrect on both	Obeys both correctly	0
		Obeys 1 correctly	1
		Incorrect on both	2
2	Best gaze (follow finger)	Normal	0
		Partial gaze palsy	1
		Forced deviation	2
3	Best visual (visual fields)	No visual loss	0
		Partial hemianopia	1
		Complete hemianopia	2
		Bilateral hemianopia	3
4	Facial palsy (show teeth, raise brows, squeeze eyes shut)	Normal Minor	0
		Partial Complete	1
5	Motor arm left* (raise 90°, hold 10 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4

	Category	Description	Score
6	Motor arm right* (raise 90°, hold 10 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4
7	Motor leg left* (raise 30°, hold 5 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4
8	Motor leg right* (raise 30°, hold 5 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4
9	Limb ataxia (finger-nose, heel-shin)	Absent	0
		Present in 1 limb	1
		Present in 2 limbs	2
10	Sensory (pinprick to face, arm, leg)	Normal	0
		Partial loss	1
		Severe loss	2
11	Extinction/neglect (double simultaneous testing)	No neglect	0
		Partial neglect	1
		Complete neglect	2
12	Dysarthria (speech clarity to "mama, baseball, huckleberry, tip-top, fifty-fifty")	Normal articulation	0
		Mild to moderate dysarthria	1
		Near to unintelligible or worse	2
13	Best language** (name items, describe pictures)	No aphasia	0
		Mild to moderate aphasia	1
		Severe aphasia	2
		Mute	3
	Total		0-42

* For limbs with amputation, joint fusion, etc, score 9 and explain.
** For intubation or other physical barriers to speech, score 9 and explain. Do not add 9 to the total score.

Symptoms of ischemic stroke according to the areas of cerebral circulation are shown below.

Symptoms of Ischemic Stroke According to Cerebral Circulation[40]

Brainstem

- Hemiparesis or quadriparesis
- Motor or sensory loss in all four limbs
- Eye movement abnormalities, such as diploplia and dysconjugate gaze
- Oropharyngeal weakness
- Vertigo, tinnitus
- Nausea, vomiting
- Dysmetria

Cerebellurn

- Ipsilateral limb ataxia
- Gait ataxia

Vetebrobasilar circulation

- Symptoms correlate with brainstem and cerebellar functions as above
- Cranial nerve deficits in cranial nerves III – XII

Anterior Circulation Symptoms

- Carotid artery
- Contralateral motor and sensory loss
- Amaurosis fugax or transmonocular blindness (caused by emboli to retinal artery)

Anterior Cerebral Artery

- Confusion
- Personality change
- Incontinence

- Contralateral motor or sensory loss in leg greater than arm

Middle Cerebral Artery

- Contralateral motor or sensory loss (arm greater than leg)
- Contralateral motor loss in lower face
- Contralateral visual field loss
- Language deficit (dominant hemisphere)
- Spatial-perceptual deficit (nondominant hemisphere)

Posterior Cerebral Artery

- Contralateral sensory loss
- Ipsilateral visual field deficit
- Cortical blindness

In addition to these symptoms, determining dominance is important as the dominant hemisphere is primarily responsible for language function. Handedness determines dominance for most people. Right-handed people are left-hemisphere dominant; left-handed people are also left-hemisphere dominant about 60% of time. The clinical features that are more common with a dominant left cerebral hemisphere lesion include aphasia, agraphia, acalculia, apraxias, a left gaze preference, a right visual field deficit along with right-sided hemiparesis, and a right-sided hemisensory loss. Common features of a nondominant right cerebral hemisphere include neglect (left-sided hemiinattention), right gaze preference, left visual field deficit, dysarthria, flat affect, left-sided hemiparesis, and left-sided hemisensory loss.[40]

The presence of a transient ischemic attack or other conditions need to be ruled out to ensure that patients receive the appropriate treatment for their condition.

A wide range of abnormalities can mimic a stroke, including hypoglycemia, migraine, seizure, and trauma.[40]

Conditions that Mimic Ischemic Stroke[40]

- Unrecognised seizures
- Confusional states
- Syncope
- Toxic or metabolic disorders including, but not limited to the following
    - Hypoglycaemia
    - Drug overdose
    - Hyponatraemia
    - Migrane
    - Concussion with head injury
    - Encephalopathies or encephalitis
    - Eclampsia
    - Brain tumors
    - Subdural hematoma

Diagnosis

Diagnostic studies help to confirm stroke, detect early potentially life-threatening complications, and direct specific care given; those recommended in the AHA guidelines are shown in Figure. These diagnostic tests are available in most

EDs 24 hours a day. Blood glucose can be checked in the ambulance with a finger stick or upon ED arrival and is helpful in ruling out hypoglycemia as a cause for the event or hyperglycemia as a compounding factor.[40] A computed tomography (CT) scan without contrast is recommended to rule out the presence of a hemorrhagic stroke that would preclude the use of thrombolysis.[47] Adjunct studies may include a CT angiogram, magnetic resonance imaging (MRI), and cerebral angiography. A CT angiogram can be used to identify large vessel stenoses or occlusion. MRI allows for better visualization of possible infarcted areas, and angiography is used when intraarterial (IA) thrombolysis is indicated or when surgical interventions are being considered.[40]

Recommended Tests in Evaluation of Acute Ischemic Stroke[40]

All Patients

- CT of the brain without contrast
- MRI can be considered at qualified centers
- Electrocardiogram
- Complete blood count with platelet count
- Serum electrolytes
- Blood glucose
- Prothrombin time, activated partial thromboplastin time, and international normalized ratio
- Renal function tests
- Oxygen saturation

Selected Patients

- Chest X ray
- Hepatic function tests
- Arterial blood gas levels (if hypoxia suspected)
- Markers of cardiac ischemia
- Lumbar puncture (if subarachnoid hemorihage is suspected and CT is negative)
- Erythrocvte sedimentation rate (ESR), syphilis serology
- Lipid profile
- Toxicology screen
- Blood alcohol level
- 2D echocardiography
- Pregnancy test
- Electroencephalogram (when seizures suspected)

Risk factors of stroke[39]

A risk factor is a characteristic of an individual or population associated with increased risk of disease compared to those without it. Multiple risk factors are associated with cerebral infraction and have been studied in great detail. Risk factor profile for ischaemic stroke differs and is variable in young and elderly patients. Various proatherothrombotic processes leading to macrovascular complications are well known. Diabetes mellitus, hypertension, smoking, alcoholism and dyslipidemia are some of the prominent modifiable risk factors for atherothrombotic ischaemic stroke. Other risk factors of stroke are raised homocystein, obesity, inadequate physical activity, migraine,

oral contraceptives and hormonal supplements, fibrinogen and clotting factors, vasculitis, collagen vascular diseases and cardiac disorders to name a few. Age, gender, ethnic and geographical background, genetic inheritance and familial predisposition are some of the non-modifiable risk factors of ischaemic stroke. In spite of the adequate control of these conventional risk factors, the incidence of cerebral infarction is not curbed, emphasizing a need to look into novel and unrecognized risk factors. Risk factors for ischemic stroke include modifiable and nonmodifiable etiologies. Identification of risk factors in each patient can uncover clues to the cause of the stroke and the most appropriate treatment and secondary prevention plan. Nonmodifiable risk factors include the following:

- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches
- Sickle cell disease
- Fibromuscular dysplasia
- Heredity

Modifiable risk factors include the following:

- Hypertension
- Diabetes mellitus
- Cardiac disease - Atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right to left shunting, such as a patent foramen ovale and atrial and ventricular enlargement

- Hypercholesterolemia
- Transient ischemic attacks (TIAs)
- Carotid artery stenosis
- Hyperhomocystinemia
- Lifestyle issues - Excessive alcohol intake, tobacco use, illicit drug use, obesity, physical inactivity
- Oral contraceptive use

Among the types of cardiac disease that increase stroke risk are atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right-to-left shunting, such as a patent foramen ovale and atrial and ventricular enlargement. Since present study is aimed to find the relationship of stroke in diabetic and non diabetic patients the review of risk factors is limited to the literature on diabetes mellitus.[39]

Diabetes and Ischemic Stroke

Diabetes mellitus comprises a group of metabolic disorders that share the phenotype of hyperglycemia. India is frequently referred to as the diabetic capital of the world. Diabetes mellitus is widely prevalent in our country and its incidence is rising in alarming proportions. The worldwide prevalence of diabetes has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals worldwide will have diabetes by the year 2030.[32]

Diabetes mellitus is one of the most common endocrine disorders affecting almost 6% of the world's population and represent one of the most important public

health challenges to all nations. It can be defined as a metabolic disorder characterized by chronic hyperglycemia associated with impaired glucose, lipid and protein metabolism and it is a leading cause of renal failure, coronary heart disease, non-traumatic lower limb amputations, and visual impairment. Diabetes and ischemic stroke are common diseases that frequently occur together. Diabetes is an important risk factor for ischemic stroke and the association between these two conditions has been analyzed by several studies.[48-50]

Previously the Framingham study[49] found a 2.5-fold incidence of ischemic stroke in men with diabetes mellitus and a 3.6-fold one in women with diabetes mellitus.

A multicenter cohort study from Italy, the DIA study[50] (including 14.432 participants) conducted with the aim to assess the prevalence and incidence of stroke and the role of other risk factors in unselected type 2 diabetes mellitus populations showed that during a 4-year follow-up, 296 incident stroke events were recorded. In persons with no history of cardiovascular disease, the age-standardized incidence of stroke (per 1000 person-years) was 5.5 (95% confidence interval, 4.2 to 6.8) in men and 6.3 (95% confidence interval, 4.5 to 8.2) in women. In persons with a history of cardiovascular disease, it was 13.7 (95% confidence interval, 7.5 to 19.8) in men and 10.8 (95% confidence interval, 7.3 to 14.4) in women. These results underline that the incidence rates of stroke that were observed in this study confirm the importance of this event in subjects with diabetes mellitus. Indeed the incidence of stroke in this cohort was 2-3 times higher than that observed in the populations without diabetes. In addition, authors have also found that the combined role of Hba1c, microvascular complications, low HDL cholesterol, and treatment with insulin plus oral agents

highlights the importance of diabetes mellitus history and clinical background in the development of stroke.

The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS),[51] conducted with the aim to describe the epidemiology of ischemic stroke in a biracial population of patients with diabetes residents in the Greater Cincinnati/Northern Kentucky region, which includes two southern Ohio counties and three contiguous northern Kentucky counties that border the Ohio River, showed that diabetes is clearly one of the most important risk factors for ischemic stroke, especially in those patients less than 65 years of age.

Furthermore some authors,[52] with the aim to quantify the associations of diabetes mellitus and fasting glucose concentration with risk of Coronary Heart Disease (CHD) and major stroke subtypes, have conducted a meta-analysis of individual records of diabetes, fasting blood glucose concentration, and other risk factors in people without initial vascular disease from 102 prospective studies (including 530083 participants). They found that diabetes confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes, independently from other conventional risk factors. In this analysis the reported hazard ratio for ischemic stroke was 2·3 (95% CI 2·0–2·7) in people with versus those without diabetes and assuming a population-wide prevalence of diabetes of around 10%, these findings indicate a diabetes-attributable risk of stroke of around 12%.

The risk of stroke in patients with type 1 diabetes has been assessed in few epidemiological studies and usually with limited sample size, and the results have

been inconsistent.[48] Nevertheless with regard of this issue Janghorbani et al.[53] conducted a study with the aim to examine the relationship between type 1 and type 2 diabetes and risk of stroke subtypes in women. In this study authors showed that both type 1 and type 2 diabetes are associated with substantially increased risks of total and most subtypes of stroke and also that the association between stroke and type 1 diabetes was stronger and this was probably attributable to younger age at onset, longer duration of diabetes, insulin deficiency, and development of hypertension with diabetic nephropathy, disturbances of coagulation, fibrinolytic parameters, increased platelet adhesiveness, or episodes of hypoglycemia. Therefore, the results of this study[53] as well as others[54] that enable the direct confrontation between the two types of diabetes have shown that the relative risk of stroke in people with type 1 diabetes is at least similar or perhaps even higher in subjects with type 2 diabetes.

The results of all these studies[48-52] confirm that subjects with diabetes mellitus have approximately twice the risk of ischemic stroke compared with those without diabetes and thus underline that diabetes mellitus is an important risk factor for ischemic stroke.[48]

Furthermore, an important concept to emphasize is that the association between ischemic stroke and diabetes is bidirectional. Moreover, acute stroke may lead to abnormalities in glucose metabolism, which in turn could influence the outcome.[48]

In addition, in the context of cerebrovascular disease, diabetes may contribute to a more insidious brain damage represented by the diseases of Small

Cerebral Vessels (SVD) such as lacunae or White Matter Hyperintensity (WMH) increasing the risk of cognitive decline and dementia suggesting that the relationship between impaired glucose metabolism and cerebrovascular disease is not limited to acute ischemic stroke.[55]

Risk Factors of Stroke Associated with Diabetes

Among patients with diabetes several risk factors play a role together to promote the development of ischemic stroke. In the analysis of these risk factors can be identified diabetes-specific factors such as uncontrolled blood sugars and vascular risk factors such as hypertension and dyslipidemia.[56-58]

In addition to these also genetic, demographic, and lifestyle factors contribute in varying degrees to the overall risk of the subjects with diabetes mellitus.[48] However the risk of ischemic stroke in patients with diabetes is twice those without diabetes, even after adjustment for risk factors listed above (hazard ratio 2.2, 95% CI 1.9–2.6).[52]

Role of Chronic Hyperglycemia

As is well known, prolonged hyperglycemia is associated with microvascular complications, such as retinopathy, neuropathy, and nephropathy, and with macrovascular complications such as cerebrovascular and cardiovascular events and Peripheral Arterial Disease (PAD) caused by atherosclerosis.[48]

Hyperglycemia contributes to the pathogenesis of macrovascular complications through several possible pathways including the generation of large amounts of Reactive Oxygen Species (ROS) such as superoxide anions which may

lead to the endothelial dysfunction by reducing the bioavailability of endothelium-derived NO, formation of Advanced Glycosylation End Products (AGEs) that by binding to their receptors accelerates the atherosclerotic process by promoting LDL uptake and oxidation leading to foam cell formation and finally the diversion of glucose into the aldose reductase pathway and the activation of one or more isozymes of protein kinase C (PKC).[48]

These changes, in their complexity, leading to the typical diabetic milieu that is characterized by a chronic state of low-grade inflammation, endothelial dysfunction, hypercoagulability, dyslipidemia and insulin resistance. However, although it is well known that the harmful role of prolonged hyperglycemia in the development of micro and macrovascular complications of diabetes, until now there is no evidence to show that stroke prevention will be improved by intensive glucose-lowering treatment, in people with either type 1 or type 2 diabetes.[48]

Role of Hyperglycemia in Acute Ischemic Stroke

The pathogenetic and prognostic role of hyperglycemia in the acute phase of ischemic stroke needs to be emphasized in this study. Hyperglycemia arises in 30–40% of people with acute ischemic stroke irrespective of previous history of diabetes. Although in some patients it reflects a pre-existing and unrecognized diabetes, more often it can be considered as a stress reaction resulting in the increased production of stress hormones such as cortisol and epinephrine following the activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system which finally results in an increased production of glucose through the gluconeogenesis, glycogenolysis, lipolysis and proteolysis. In animal models of

reversible focal brain ischemia, hyperglycemia consistently increased infarct size and several mechanisms have been identified through which hyperglycemia could aggravate cerebral damage in ischemic stroke. This has been attributed to disorders of coagulation and fibrinolytic pathways mediated by hyperglycemia, the decreased reperfusion of the damaged brain area caused by the disturbances in metabolism of endothelium-derived nitric oxide and last but not the least the increased reperfusion injury which is the result of the detrimental effects of oxidative stress and inflammation.[48]

The effects of the above mentioned mechanisms alter the recovery of the ischemic penumbra that is the part of the ischemic area which may still potentially recover if proper reperfusion is restored within hours after stroke onset.[48]

On this basis, some authors[59] systematically reviewed the published literature to summarize the available evidence and to estimate the strength of association between admission hyperglycemia and both short-term mortality and functional recovery after stroke with the aim to evaluate if stress hyperglycemia may be associated with increased mortality and poor recovery in people with diabetes and in patients without diabetes after stroke. They found that compared with patients with normo glycaemia, the unadjusted relative risk of in-hospital or 30-day mortality after an ischemic stroke in individuals who are hyperglycemic at admission is 3.3 (95% CI 2.3–4.7) in those without known diabetes and 2.0 (0.04–90.1) in those with a known history of diabetes and concluded that acute hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke in patients without diabetes and increased risk of poor functional recovery in non-diabetic stroke survivors.

Furthermore other studies[60] suggest that the association between hyperglycemia and poor outcome after stroke is stronger in patients with large-vessel thromboembolic stroke than in those with lacunar stroke and this is understandable considering that hyperglycemia primarily exerts its detrimental effects at the level of the ischemic penumbra which is usually not present in lacunar subtype. The detected relationship between hyperglycemia and poor outcome in patients with ischemic stroke arouses the question of whether the outcome may be improved by glucose-lowering treatment. In fact, although it is true that the concentrations of glucose can be reduced by several treatment regimens of insulin, one has to consider that in the early days after the onset of stroke the realization of normal blood glucose concentrations may be difficult probably because the intake of oral food causes fluctuations in the levels of glucose. Therefore, the achievement of stable normoglycemia in the acute phase of stroke can be difficult and the possibility of hypoglycemia remains a concern, because even with intensive monitoring, many patients may experience one or more episodes of hypoglycemia.[48]

Findings of randomized controlled trials specifically targeting individuals with stroke have failed to show beneficial effects. In a meta- analysis of 1296 patients with acute stroke from seven trials, intensively monitored intravenous insulin treatment (aimed at maintenance of glucose concentrations between 4·0 and 7·5 mmol/L) was compared with usual care.[61] No difference was seen with respect to poor outcome (odds ratio 1.0, 95% CI 0.8–1.3), and the risk of symptomatic hypoglycemia was significantly higher in the group treated with insulin (25.9, 9.2–72.7). Therefore, there is evidence suggesting that glucose-lowering treatment improves clinical outcome in patients with acute ischemic stroke and to date

uncertainty persists about the issue of whether glucose-lowering treatment for early stroke can improve clinical outcome.[48]

Patterns of Stroke Type Associated with Diabetes Mellitus

Diabetes and ischemic stroke are common diseases that frequently occur together. Several studies[49-52] that have analyzed the relationship between these two disorders have shown that subjects with diabetes mellitus have approximately twice the risk of ischemic stroke compared with those without diabetes underlying that diabetes mellitus is a well-established independent risk factor for stroke and is associated with high mortality. It is well known that diabetes mellitus may contribute to systemic and intracranial atherosclerotic disease and this increased risk has been linked to the pathophysiological changes seen in the cerebral vessels of patients with diabetes.[62]

With the purpose to characterize stroke patterns in stroke patients with and without diabetes mellitus Salah-Eddine Megherbi et al.[63] conducted a study in a large European sample of hospitalized stroke patients. Data from this large prospective European multicenter study showed that stroke in patients with diabetes mellitus was different from stroke in non patients from several perspectives in fact in stroke patients with diabetes mellitus, the frequency of intracerebral hemorrhage was lower, the rate of lacunes was higher, recovery of morbidity by Rankin Scale score was worse, and mortality was not increased. Therefore the great contribution of this study was to demonstrate that the subtype of stroke that is mainly found among patients with diabetes is the lacunar type.

These results are consistent with those of Th. Karapanayiotides et al.[64] that assessed the risk factors, etiology, lesion topography, clinical features, and outcome of all the subjects with diabetes mellitus in the Lausanne Stroke Registry (LSR). They found that diabetes mellitus was associated with lower relative prevalence of intracerebral hemorrhage (ICH; odds ratio [95% CI]: 0.63 (0.45 to 0.9); p = 0.022), higher relative prevalence of subcortical infarction (SCI; 1.34 [1.11 to 1.62]; p = 0.009), and higher relative frequency of small-vessel (SVD; 1.78 [1.31 to 3.82]; p = 0.012) and large-artery (LAD; 2.02 [1.31 to 2.02]; p = 0.002) disease. The results of this large population study mentioned above show that stroke patients with diabetes mellitus are associated with specific patterns of stroke type, especially with lacunar infarcts which are defined as non cortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery accounting for a quarter of all ischemic stroke. Lacunar stroke also represent the major cause of progressive motor deficits and may contribute to increase the risk of dementia and lead to a steeper decline in cognitive function constituting a significant disease, with important clinical implications. The pathogenic plausibility of the relationship between diabetes and lacunar stroke is supported by pathological and autopsy reports.[48]

Although diabetes mellitus increases the risk of stroke, and the pathophysiological changes of diabetic cerebral vessels may differ in comparison with non-diabetic ones, the clinical and prognostic profile of stroke in people with diabetes is not yet fully understood. On this basis, Tuttolomondo et al.[65-69] conducted a study to evaluate cerebrovascular risk factor prevalence in stroke patients with diabetes mellitus in comparison with subjects without diabetes with the aim to analyze whether subjects with diabetes mellitus have a different prevalence of

stroke subtypes as classified by the TOAST classification, and to determine whether people with diabetes and patients without diabetes have a different prognosis. The authors found a higher prevalence of lacunar stroke subtype and of hypertension among patients with diabetes and they also observed that after correction for other risk factors and TOAST subtype, the association between diabetes and lacunar stroke remains statistically significant underlying how the relationship between diabetes and lacunar strokes could exist in diabetic subjects with ischemic stroke, partially independent from hypertension.

This is an interesting finding in the light of several studies that have underlined the role of hypertension as the first risk factor for lacunar subtype but this is actually true in patients without diabetes, whereas in diabetic ones hypertension could represent only a cofactor of lacunar stroke determinism.[48]

Furthermore, Pinto et al.[70,71] with the purpose to evaluate the cerebrovascular morbidity both on a retrospective and a prospective evaluation in patients with diabetic foot in comparison to patients without diabetic foot complications showed a worse cerebrovascular risk profile in subjects with diabetes mellitus with diabetic foot compared to patients with diabetes mellitus without foot ulceration. They also observed a higher prevalence of both the lacunar and large artery atherosclerosis subtype with a slight higher prevalence of lacunar subtype in patients with diabetic foot suggesting the putative role of both microvascular disease and atherosclerosis in determining cerebrovascular morbidity in patients with diabetic foot. Finally, the stroke subtype which is mainly observed among patients with diabetes is the lacunar type, probably because diabetes may accelerate the atherosclerotic process both in intracranial that extracranial vessels contributing to the pathogenesis of lacunae

consistent with the classical Fisher's hypotesis of a lypohyalinotic or atherothrombotic occlusion of the small cerebral vessels and therefore it is associated with a more insidious ischaemic damage to the brain, mainly manifesting as SVD and increased the risk of cognitive decline and dementia.[48]

Mean platelet volume

Platelets play an important role in the integrity of normal homeostasis, and mean platelet volume (MPV) is the indicator for its function. The large platelets contain more dense granules, are more potent than the smaller platelets, and are hence more thrombogenic. Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelet. Increase in MPV has been documented in patients with metabolic syndrome, stroke and diabetes mellitus (DM).[11,72]

MPV, a determinant of platelet function, is a newly emerging risk factor for atherothrombosis.[72] Counter flow centrifugation can be used to separate platelets into fractions by differences in platelet volume. These differences in platelet volume correlate with differences in density, dense body content, enzymatic activity of LDH (lactate dehydrogenase), platelet aggregation to ADP (adenosine diphospate), and serotonin uptake and release, supporting the relevance of the mean platelet volume (MPV) as a measure of platelet functional capability.[73,74]

Platelet size (MPV), a marker (and possibly a determinant) of platelet function is a physiological variable of haemostatic importance. Large platelets are metabolically more reactive, produce more prothrombotic factors and aggregate more easily. They also contain more dense granules and release more serotonin and

beta thromboglobulin than do small platelets.[73] Mean platelet volume, as well as platelet count, are an index of haemostasis and its dysfunction i.e. thrombosis. Larger platelets are metabolically and enzymatically more active,[75] and have greater prothombotic potential.[76]

Mean platelet volume (MPV), the most commonly used measure of platelet size, is a potential marker of platelet reactivity. MPV is routinely available laboratory test in the panel of haemogram easily available with no added cost.[77]

Changes in MPV play a more important role in haemostasis than platelet count6. Platelet volume is regulated by various intrinsic and extrinsic factors. The mean lifespan of light platelets is shorter than that of heavy platelets.[73]

Elevated MPV is associated with other markers of platelet activity, including increased platelet aggregation, increased thromboxane synthesis and β-thromboglobulin release, and increased expression of adhesion molecules. Furthermore, higher MPV is observed in patients with diabetes mellitus, hypertension, hypercholesterolemia, smoking, and obesity, suggesting a common mechanism by which these factors may increase the risk of thrombosis.[77]

Perturbed megakaryocyte platelet haemostatic axis (MPHA), results in the formation of hyper-functional platelets, which may contribute to the development of vascular disease or an acute thrombotic event such as ischemic stroke or myocardial infarction. Increase in platelet volume has been reported as a risk factor for acute myocardial infarction, acute cerebral ischemia, transient ischemic attacks, and for death or recurrent vascular events after myocardial infarction. Moreover, increased platelet size has been reported in patients with vascular risk factors such as diabetes,

hypercholesterolemia, smoking, metabolic syndrome and in patients with renal artery stenosis. Higher levels of MPV in patients with acute ischemic stroke have been demonstrated than in control subjects.[73]

The megakaryocyte-platelet-haemostatic axis

Platelets are anucleate cells and, as such, have little or no protein synthetic capacity. Platelets are heterogeneous regarding their size, density and haemostatic potential. Platelet size (mean platelet volume, MPV) is a marker (and possibly determinant) of platelet function, large platelets being potentially more reactive. For example, they contain more dense granules, undergo greater in vitro aggregation in response to agonists such as ADP and collagen, and release more serotonin and b-thromboglobulin (b-TG). They also produce more thromboxane A2 (TXA2) per unit volume and are associated with a decreased bleeding time (BT; a measure of in vivo haemostatic function). It used to be thought that platelet size decreased with age, but more recent evidence suggests that MPV and other platelet parameters and, therefore, platelet protein content and reactivity, are determined primarily at or before thrombopoiesis by the platelet precursor cell, the MK.[78]

MKs are unique amongst mammalian cells in that they are polyploid. That is to say they can redouble their chromosomal DNA content without subsequent full mitotic cell division, a process termed endomitosis. MKs undergo varying numbers of endomitotic cycles to produce a population of cells whose ploidy ranges from 4N to 128N (where 2N represents the normal diploid state), with 16N being the modal ploidy in the majority of mammals studied thus far. Each MK produces about 1000

to 2000 platelets, probably by cytoplasmic fragmentation of MKs in the pulmonary circulation.[78]

Measurements of platelet and MK parameters in man suggest that they are so closely linked that they can be considered a single system: the megakaryocyte-platelethaemostatic axis (MPHA).[78,79]

For example, in normal individuals the platelet count is inversely proportional to MPV; platelet mass (the product of MPV and platelet count) is a near constant; platelet mass correlates with BT; and BT is inversely proportional to MK ploidy and size.

Variation in MPV is a result of a change in the rate of platelet destruction, whereas altered MK ploidy, and concomitant changes in MK size and cytoplasmic volume are associated with a change in the rate of platelet production.[78] Although platelets are incapable of de novo protein synthesis they are very active metabolically and respond rapidly to vascular injury or trauma by undergoing a series of reactions (adhesion, release of granule contents, shape change and aggregation), which ultimately result in the formation of a platelet–fibrin plug.[80]

In normal haemostasis, platelet activation, and for this reason the extent of thrombus formation, is controlled by extrinsic (for example, endothelial cell-derived prostacyclin and nitric oxide) and intrinsic factors.

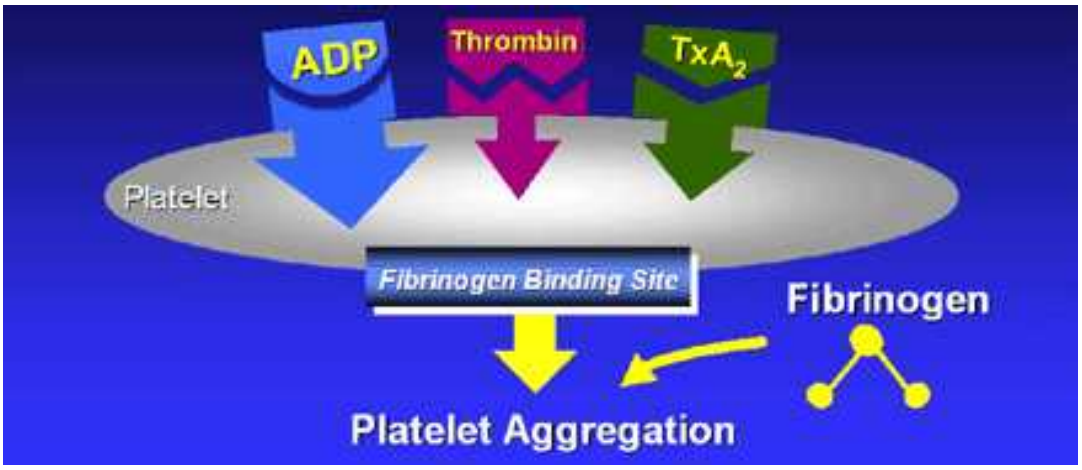


Figure 6. Platelet aggregation[81]

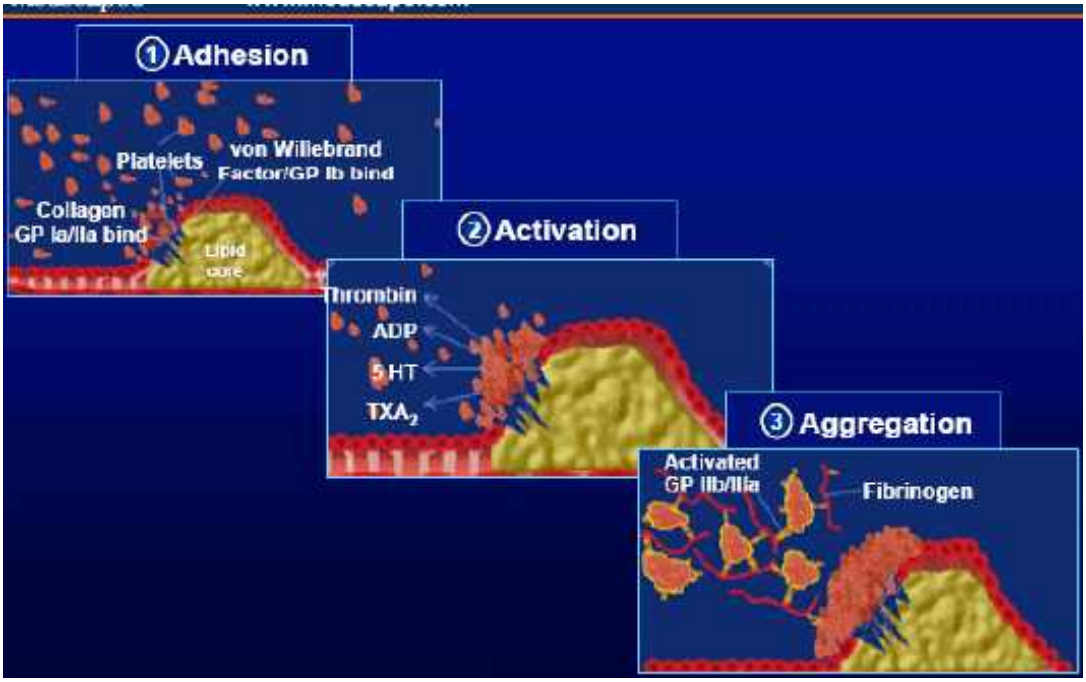


Figure 7. Platelet activation cascade[32,82]

O'Brien and colleagues[83] have conducted aggregation experiments which indicate that shear stress alone can cause platelet activation and aggregation followed shortly afterwards by the platelets returning to the quiescent state – a phenomenon they termed 're-bleeding'.

However, in some pathologic conditions the MPHA is chronically or acutely perturbed resulting in the production of hyperfunctional platelets which may be involved in subsequent vascular disease or an acute thrombotic event such as stroke. There is evidence that platelet function is accentuated in acute ischaemic stroke. Therefore, a fundamental issue is whether this increase in platelet reactivity precedes the stroke, and plays a part in initiating the event, or represents a reactive change to it. The development of atherosclerosis involves local platelet adhesion, but whether widespread systemic activation of platelets is present is open to question. The study of MKs and platelets in the acute stage (within 36 h of onset) of stroke would yield valuable information on this subject.[78]

MPV measured at this stage may well reflect (at least in part) the potential reactivity of platelets prior to the stroke. However, the dynamics of platelet consumption and production in the acute phase of stroke are not yet understood well enough to rule out the possibility that MPV is being modified to some extent by the acute destruction of platelets and subsequent change in the fragmentation of MK cytoplasm. If MK parameters could be shown to be abnormal shortly following the stroke this would strongly suggest that the MPHA was chronically perturbed prior to the stroke.[78]

Increased platelet function and, in some cases, a shift in MK indices in a prothrombotic direction has been shown in stroke risk factors such as hypertension, hypercholesterolaemia, diabetes mellitus and smoking, and in vascular conditions associated with stroke, such as atherosclerosis, MI and peripheral vascular disease. Thus, it would seem probable that in patients with certain risk factor profiles systemic platelet activation precedes the onset of stroke.[78]

PGI2 and NO increase levels of cAMP and cGMP respectively, resulting in activation of cAMP- or cGMP-dependent protein kinases and inhibition of the platelet activation pathways. The substances released following platelet activation act on platelets and other cells, thereby reinforcing and amplifying thrombus formation. Aspirin irreversibly inactivates cyclo-oxygenase and thus inhibits endoperoxide- and thromboxane-dependent platelet activation. Clopidogrel and ticlopidine act by reducing ADP binding to a G-protein-linked receptor (not shown). Dipyridamole raises platelet cAMP and cGMP levels by inhibition of cyclic nucleotide phosphodiesterases.[78]

Relationship of mean platelet volume in patients with acute ischaemic stroke

The majority of studies have found that the MPV is significantly increased in acute iscahemic stroke, with a concomitant decrease in platelet count.[84] The exceptions to this include a study by Tohgi et al[85] in which MPV was significantly lower in patients with IS than in controls.

D'Erasmo et al[86] found a significantly lower platelet count in patients that died, whereas O'Malley et al.[18] found that platelet changes were not associated with clinical outcome after 6 months. It has been found that patients that do badly

(determined as death or dependency) have a significantly higher MPV in the acute phase of stroke than those who do well (independence) and tend to have a lower platelet count.[87]

It has also been found that MPV remained elevated 3 months post-stroke. The significance of this has yet to be established, but since MPV measured 6 months post-acute myocardial infarction predicts recurrent coronary events and all-cause mortality,[88] a persistently raised MPV following ischaemic stroke may well be associated with recurrent vascular events and death. This has been assessed as a substudy of the PROGRESS trial.[89]

Accentuated platelet function is probably important in the pathophysiology of cortical (and some cases of brainstem) stroke but not lacunar stroke. A number of different aspects of platelet function have been studied in subtypes of ischaemic stroke.

There are conflicting results regarding MPV. O'Malley et al found MPV to be raised in all subgroups of ischaemic stroke,[18] whereas another study found that, MPV was raised in cortical but not lacunar stroke.[87]

O'Malley et al.[18] found no significant differences in platelet count between subtypes; results that concur with our own. Fisher and Zipser[90] found that urinary TXB2 levels were raised in large vessel and cardiogenic but not lacunar strokes compared with normal controls.

However, a study[91] has shown no difference in urinary 11-dehydro-TXB2 excretion in cortical and lacunar infarcts. Secreted a-granule proteins have been studied in stroke subtypes by several groups of workers.

Woo and colleagues[92] found that plasma b-TG was raised following large vessel atherosclerotic and cardioembolic strokes but not lacunar infarcts.

Shah et al.[93] made similar findings and additionally found that plasma PF4 was increased after thromboembolic but not cardioembolic or lacunar strokes. In contrast, Iwamoto and colleagues[94] found elevated levels of b-TG in all subgroups of patients compared with controls.

It is found that sP-selectin levels were significantly higher in large cortical strokes than in lacunar infarcts. Shear-induced platelet aggregation has been shown to be significantly increased following atherothrombotic stroke but not after cardioembolic or lacunar stroke.[78]

So, it can be seen that the bulk of the evidence points to there being greater platelet activity following cortical than lacunar stroke and it is probable that this is related to their respective pathophysiologies.

The severity and poor outcome of ischemic stroke patients with increased MPV has been reported in the literature. Stroke patients with high mortality have been found to have low platelet count. Again, ischemic stroke patients with higher MPV tend to have poor outcome than their counterparts with low MPV.[73]

Mean platelet volume in patients with diabetes mellitus

Platelets of diabetic patients are characterized by dysregulation of several signaling pathways and have been suggested to be hyperreactive, showing increased adhesion, activation, and aggregation. Platelets from patients with type 1 and type 2 diabetes exhibit enhanced platelet activity early in the disease course that may

precede the development of CVD. Several mechanisms may account for the increased platelet activity in diabetes. The glycation of platelet surface proteins reduces membrane fluidity and increases platelet adhesion, causing incorporation of glycated proteins into the thrombi. An increase in calcium mobilization from intracellular storage pools, resulting in increased intracellular calcium levels, has been correlated with reduction in membrane fluidity. Platelet dysfunction in diabetes may be found even before development of visible damage to the vessel wall. Platelets in diabetes respond more frequently even to subthreshold stimuli, and thus contribute to accelerated thrombosis and release of fresh hyperreactive platelets.[95]

Insulin has a direct inhibitory effect on platelet aggregation. Insulin binds to platelet membrane receptor and reduces platelet response to thrombin, ADP, arachidonic acid, collagen, and platelet activating factor. Diabetic platelets are less sensitive to the inhibitory action of insulin. There is a decrease in platelet insulin receptor number and affinity in type 2 diabetes, which suggest that reduced insulin sensitivity may account for platelet hyperreactivity in this condition.[95]

<u>Possible mechanism of platelet hyperreactivity in diabetic patients</u>[95]

- Reduced membrane fluidity
- Altered Ca2+ and Mg2+ homeostasis
- Nonenzymatic glycation of platelet surface proteins
- Increased adhesion and activation
- Increased arachidonic acid metabolism
- Increased thromboxane A2 synthesis
- Increased numbers of glycoprotein receptors

- Increased platelet volume
- Enhanced generation of reactive oxygen species
- Decreased antioxidant levels
- Decreased prostacyclin and nitric oxide production
- Decreased sensitivity to insulin

Larger platelets are more active hemostatically and enzymatically, and they contain more prothrombotic molecules, such as platelet factor 4, serotonin, and platelet-derived growth factor, and possess greater aggregability in response to ADP. Mean platelet volume (MPV), which is used to measure platelet size, can reflect platelet activity. Increased MPV may lead to a prothrombotic condition with increased thromboxane A2 (TXA2) and B2 and adhesion molecule expression, such as P-selectin and glycoprotein IIb/IIIa, and β-thromboglobulin release.[95]

Previous studies have shown that MPV is increased in diabetes and prediabetes.[88,96-98] Additionally, increased MPV has been associated with poor glycemic control in diabetes, the duration of diabetes, microalbuminuria, coronary heart disease, and an increase in the number of diabetic complications. Increased MPV can be restored to normal level through improved glycemic control.[95]

However, Shah et al.[99] reported a significant correlation between MPV and the degree of glycemic control only in diabetic patients. This result suggests that the positive relationship between an increased glucose level and increased MPV is a unique phenomenon of diabetes itself. Recent data supported this possibility. A study found contrasting relationship between MPV and fasting plasma glucose (FPG) in the presence and absence of diabetes in a Korean general population. After

adjusting for confounding variables, MPV was only positively correlated with FPG in newly diagnosed diabetic women (β±SE, 0.097± 0.037; P=0.016). Interestingly, MPV showed a significant inverse relationship with FPG in intermediate hyperglycemia (men: β±SE, -0.072±0.027, P=0.007; women: β±SE, -0.111± 0.035, P=0.002) and normal glucose tolerance status (men: β±SE, -0.112±0.033, P<0.0001; women: β±SE, -0.102±0.034, P=0.003). The underlying mechanism behind this finding is unclear. Possible explanations include osmotic swelling due to increased blood glucose or other metabolites and lack of a physiological inverse relationship between MPV and platelet count in diabetes, although increased platelet counts by increased glucose levels may lead to a subsequent decrease in MPV.[95]

We have reviewed several studies[95-99] showing rise in MPV in diabetics and several other studies showing rise in MPV in ischaemic CVA[73-77] but there are no much studies correlating role of MPV in diabetic and non diabetic ischaemic strokes.

METHODOLOGY

This study was done at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was a one year cross sectional study.

Study period and duration

This study was conducted for the period of one year, from January 2014 to December 2014.

Place

The present study was done in the Department of General Medicine and Department of Neurology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum, a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

This study comprised of patients presenting with acute ischemic brain stroke with or without prior history of diabetes mellitus.

Sample size

Based on inverse sampling method, all the patients who presented with acute ischemic stroke fulfilling the selection criteria during the study period were included

in the study till sample size of patients presenting with acute ischaemic stroke with history of type 2 diabetes mellitus was 25.

Sampling procedure

$$n = 2\ Z_{1-\alpha/2}\ (SD_1^2 + SD_2^2) / d^2$$

Where,

SD_1 – Mean ± Standard deviation (SD) of MPV type 2 diabetes mellitus.[100]

SD_2 – Mean ± Standard deviation (SD) of MPV in stroke.[101]

Z – Constant i.e. 1.96 at 95% confidence interval.

d – Standard error

Hence considering n=25 allows "d" to be at maximum where sample size in any of two groups does not overlap.

Selection criteria

Inclusion

- All patients with acute ischemic brain stroke identified based on radiological evaluation that is, magnetic resonance imaging or computed tomography admitted in KLES Dr. Prabhkar Kore Hospital and Medical Research Centre, Belgaum.

Exclusion

- Patients with anemia that is, haemoglobin levels < 12 gm% in males and 10 gm% in females.
- Patients with

- Coronary artery disease
- Diagnosed for any malignancy
- ITP
- Acute post streptococcal GN
- Renal failure
- Valvular heart disease
- Cyanotic congenital heart disease
- DVT.

Ethical clearance

The ethical clearance was obtained from Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Patients were screened for the eligibility and those fulfilling the selection criteria were briefed about the nature of the study. In case of comatose patients, the relatives / caretakers were informed about the study. The patients/caregivers expressing their willingness to participate in the study were enrolled after obtaining a written informed consent (Annexure I).

Method of collection of data

Demographic data such as age and sex were recorded. History of other co-morbid conditions such as, hypertension, diabetes mellitus, previous stroke, personal history such as habits of alcohol consumption, smoking, were noted. A thorough physical examination was conducted for vitals (pulse rate, blood pressure and respiratory rate) followed by systemic examination. The diagnosis of stroke was

entertained after fulfilling WHO definition of stroke by the patient (27). The ischemic nature of stroke was established by computed tomographic / magnetic resonance imaging scan. Evaluation of stroke severity was carried out based on NIHSS. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The patients were evaluated for the tests.

- Haemoglobin
- Platelet count
- Mean platelet volume
- HbA1c
- Imaging studies - Magnetic resonance imaging or computed tomography scan of brain.

Estimation of mean platelet volume

Under all aseptic precautions 2ml of blood sample was obtained from antecubital vein of the patient at admission were collected in EDTA vials and transported for analysis at laboratory. The mean platelet volume was estimated on Beckman and Coulter LH 780 haematology analyzer and ≥ 9.5 fL was considered as raised.[102]

Figure 8. Beckman and Coulter LH 780 haematology analyzer

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The data was analysed using SPSS statistics software version 20.0. The categorical data was expressed in terms of rates, ratios and proportions and comparison was done using chi-square test or Fisher's exact test. The continuous data was expressed as mean ± standard deviation (SD) and the comparison was done using independent sample 't' test. In case of more than two means one way ANOVA was used to compare the data. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

RESULTS

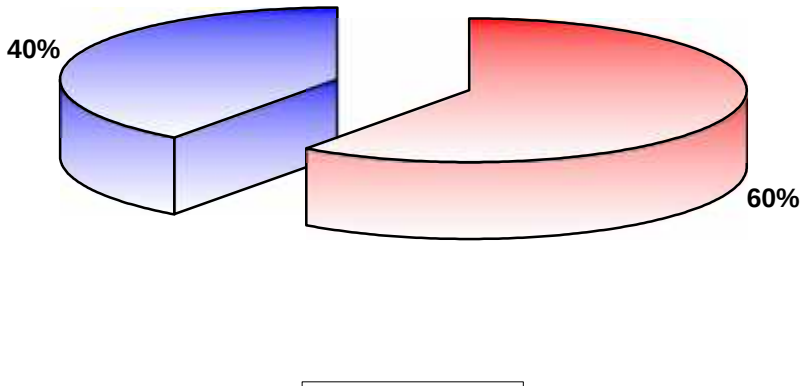
The present one year hospital based cross sectional study was conducted in the Department of Medicine from January 2014 to December 2014. A total of 79 patients presented with acute ischaemic stroke during the study period. Among them, 25 patients (31.6%) had history of diabetes which formed the diabetic subset and the remaining 54 (68.35%) were considered in non diabetic subset.

The data obtained was coded and analysed. The final results and interpretations were tabulated as below.

Table 1. Distribution of diabetic patients according to the duration of diabetes

Duration (Years)	Distribution (n=25)	
	Number	**Percentage**
5 or less	15	60.00
> 5	10	40.00
Total	**25**	**100.00**

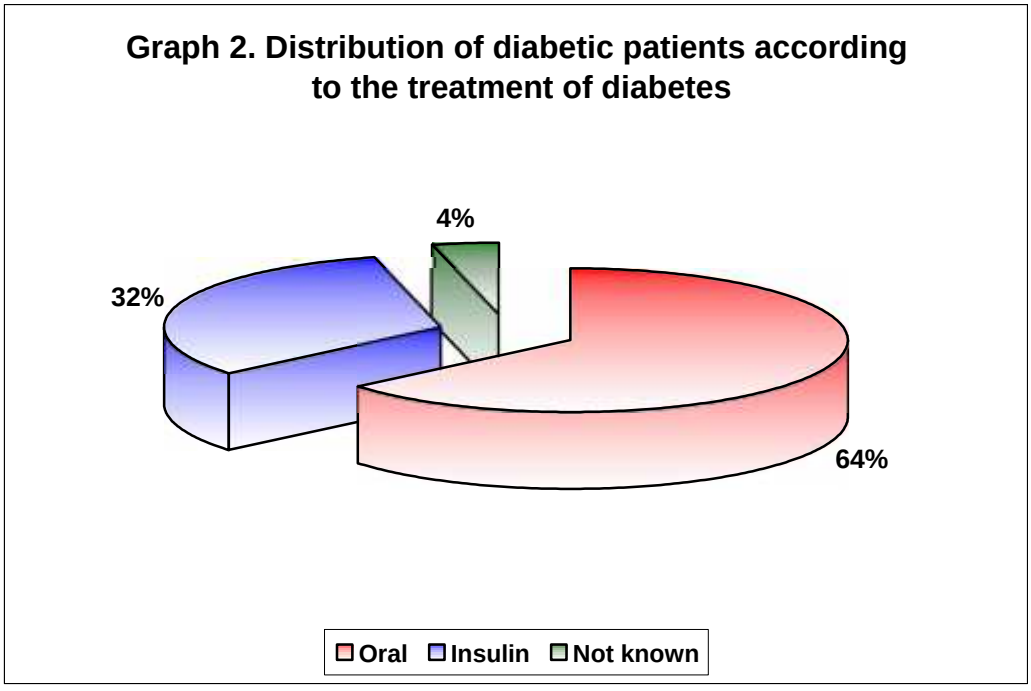
Graph 1. Distribution of diabetic patients according to the duration of diabetes



In the present study among the patients with diabetes the duration of diabetes was 5 years or less in 60% of the patients.

Table 2. Distribution of diabetic patients according to the treatment of diabetes

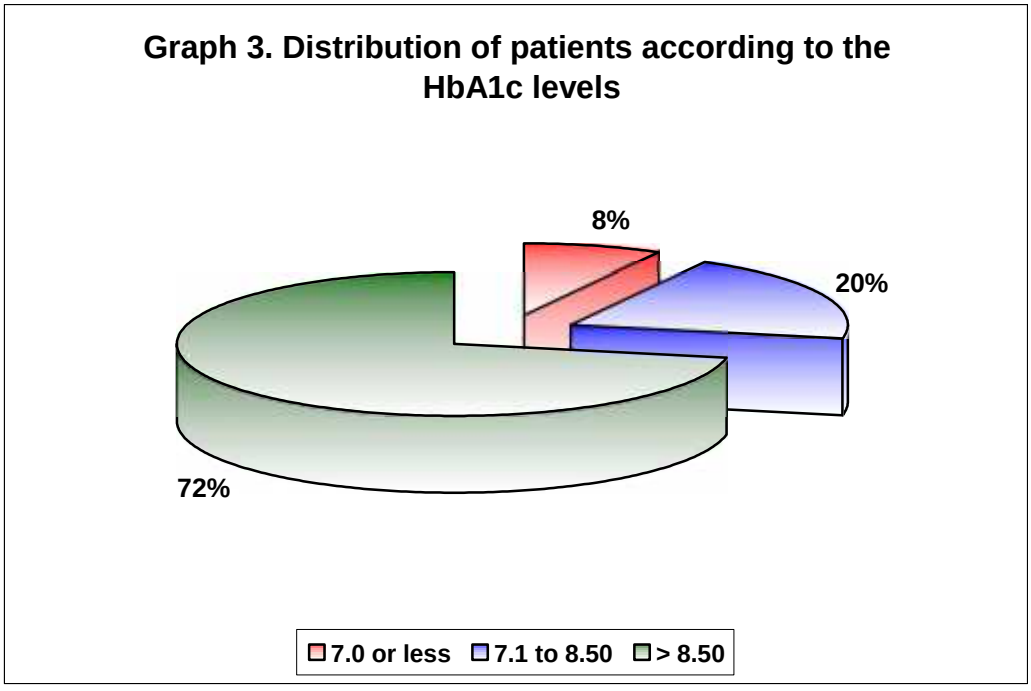
Treatment	Distribution (n=25)	
	Number	**Percentage**
Oral	16	64.00
Insulin	8	32.00
Not known	1	4.00
Total	**25**	**100.00**



In this study 64% of the patients were on oral hypoglycaemic agents while 32% had insulin.

Table 3. Distribution of patients according to the HbA1c levels

Glycaemic control	Distribution (n=25)	
	Number	**Percentage**
7.0 or less	2	8.00
7.1 to 8.50	5	20.00
> 8.50	18	72.00
Total	**25**	**100.00**

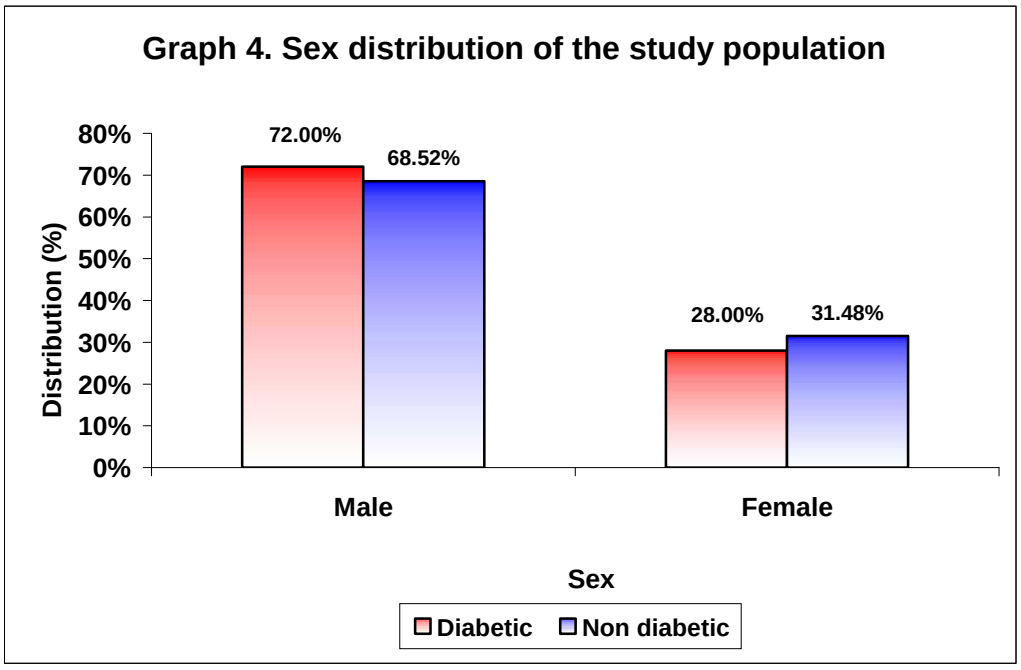


In the present study most of the patients (72%) had the HbA1c levels > 8.50.

Table 4. Sex distribution of the study population

Sex	Diabetic (n=25)		Non diabetic (n=54)	
	Number	**Percentage**	**Number**	**Percentage**
Male	18	72.00	37	68.52
Female	7	28.00	17	31.48
Total	**25**	**100.00**	**54**	**100.00**

p = 0.754

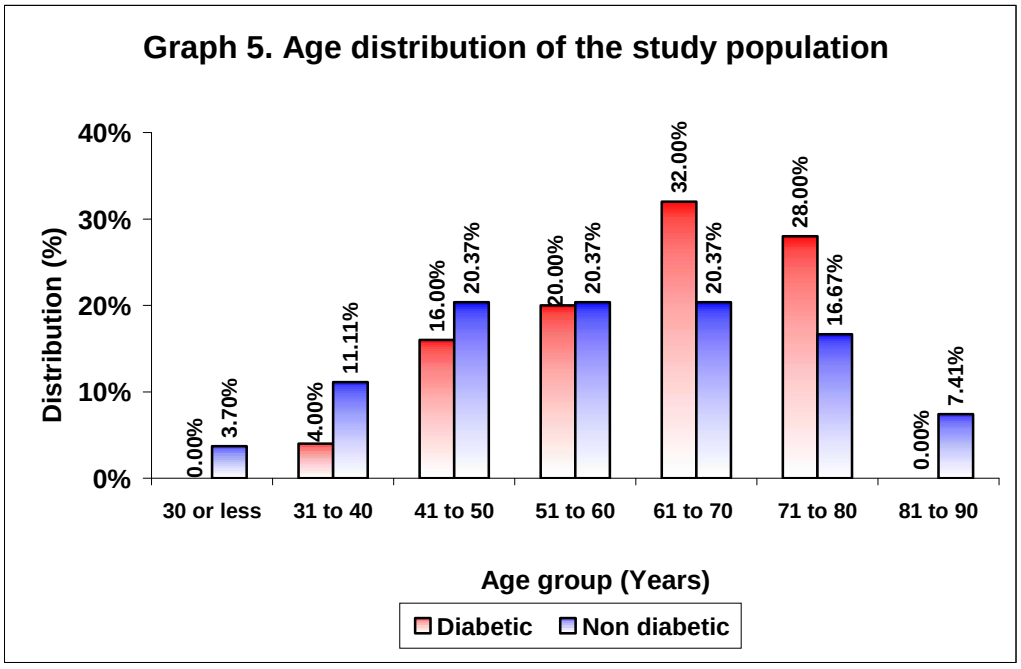


In this study 72% of the diabetics were males compared to 68.52% non diabetics. However the difference was statistically not significant (p=0.754).

Table 5. Age distribution of the study population

Age group (Years)	Diabetic (n=25)		Non diabetic (n=54)	
	Number	Percentage	Number	Percentage
30 or less	0	0.00	2	3.70
31 to 40	1	4.00	6	11.11
41 to 50	4	16.00	11	20.37
51 to 60	5	20.00	11	20.37
61 to 70	8	32.00	11	20.37
71 to 80	7	28.00	9	16.67
81 to 90	0	0.00	4	7.41
Total	**25**	**100.00**	**54**	**100.00**

p = 0.551



In the present study the commonest age group was 61 to 70 years (32%) in patients with diabetes compared to 20.37% of the patients without history of diabetes. However the difference was statistically not significant (p=0.551)

Table 6. Comparison of mean age

Variables	Diabetic (n=25)		Non diabetic (n=54)		p value
	Mean	SD	Mean	SD	
Age (Years)	62.04	10.88	58.11	16.75	0.217

In this study the mean age among diabetic patients was 62.04 ± 10.88 years compared to 58.11 ± 16.75 years. However this difference was statistically not significant (p=0.217).

Table 7. Comparison of clinical presentation

Presentation	Findings	Diabetic (n=25)		Non diabetic (n=54)		p value
		No.	%	No.	%	
Dysarthria	Present	1	4.00	10	18.52	**0.077**
	Absent	24	96.00	44	81.48	
	Total	**25**	**100.00**	**54**	**100.00**	
Ataxia	Present	6	24.00	5	9.26	**0.082**
	Absent	19	76.00	49	90.74	
	Total	**25**	**100.00**	**54**	**100.00**	
Weakness	Present	24	96.00	48	88.89	**0.284**
	Absent	1	4.00	6	11.11	
	Total	**25**	**100.00**	**54**	**100.00**	
Tingling	Present	1	4.00	1	1.85	**0.536**
	Absent	24	96.00	53	98.15	
	Total	**25**	**100.00**	**54**	**100.00**	
Global aphasia	Present	2	8.00	4	7.41	**0.623**
	Absent	23	92.00	50	92.59	
	Total	**25**	**100.00**	**54**	**100.00**	
Burning	Present	1	4.00	1	1.85	**0.536**
	Absent	24	96.00	53	98.15	
	Total	**25**	**100.00**	**54**	**100.00**	
Drowsiness	Present	1	4.00	1	1.85	**0.536**
	Absent	24	96.00	53	98.15	
	Total	**25**	**100.00**	**54**	**100.00**	
Inability to speak	Present	2	8.00	7	12.96	**0.410**
	Absent	23	92.00	47	87.04	
	Total	**25**	**100.00**	**54**	**100.00**	
Imbalance	Present	1	4.00	0	0.00	**0.316**
	Absent	24	96.00	54	100.00	
	Total	**25**	**100.00**	**54**	**100.00**	
Motor aphasia	Present	4	16.00	15	27.78	**0.255**
	Absent	21	84.00	39	72.22	
	Total	**25**	**100.00**	**54**	**100.00**	
Deviation angle of mouth	Present	1	4.00	3	5.56	**0.623**
	Absent	24	96.00	51	94.44	
	Total	**25**	**100.00**	**54**	**100.00**	
Loss of consciousness	Present	2	8.00	4	7.41	**0.623**
	Absent	23	92.00	50	92.59	
	Total	**25**	**100.00**	**54**	**100.00**	
Slumping	Present	0	0.00	6	11.11	**0.093**
	Absent	25	100.00	48	88.89	
	Total	**25**	**100.00**	**54**	**100.00**	
Swaying	Present	1	4.00	2	3.70	**0.686**
	Absent	24	96.00	52	96.30	
	Total	**25**	**100.00**	**54**	**100.00**	

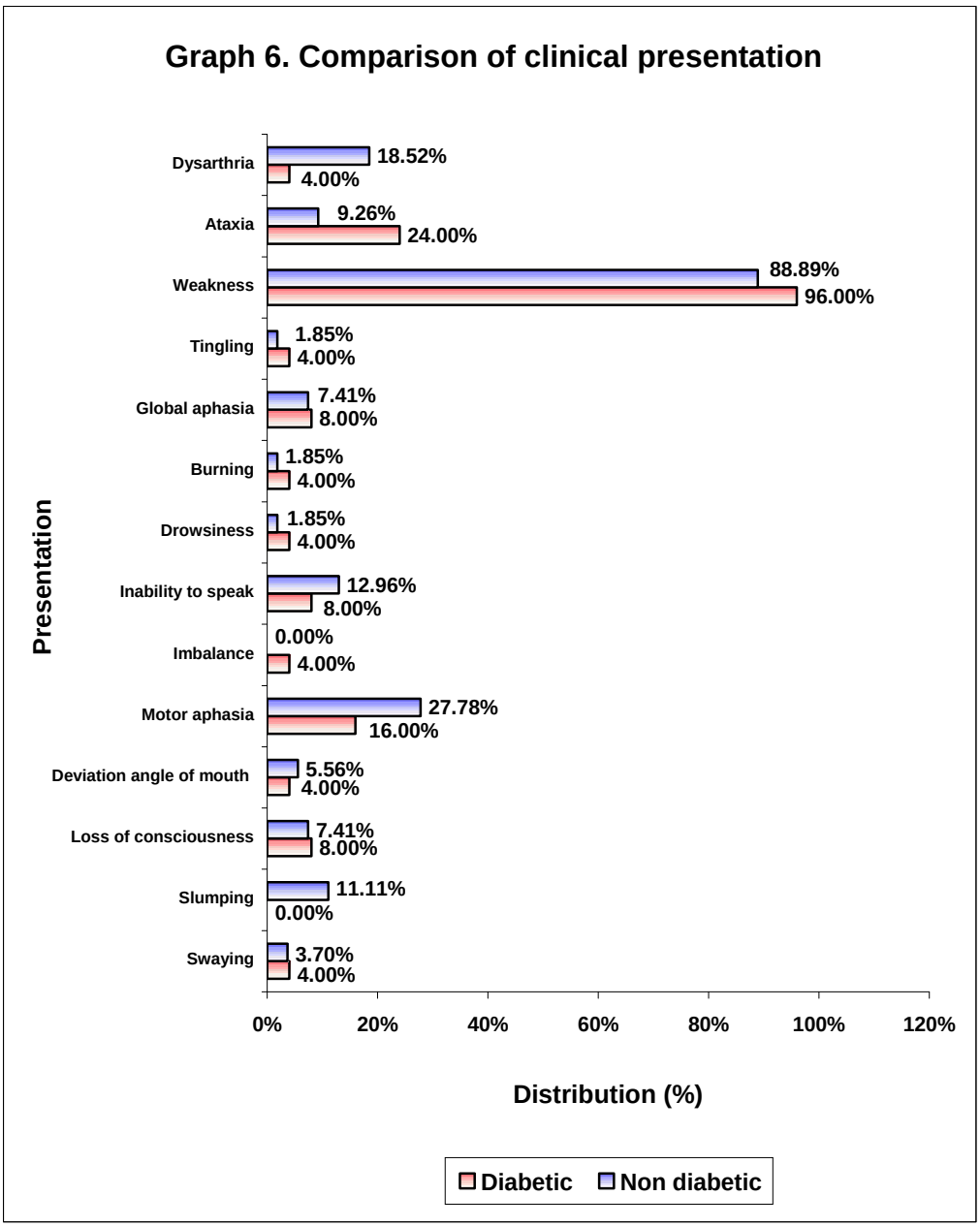
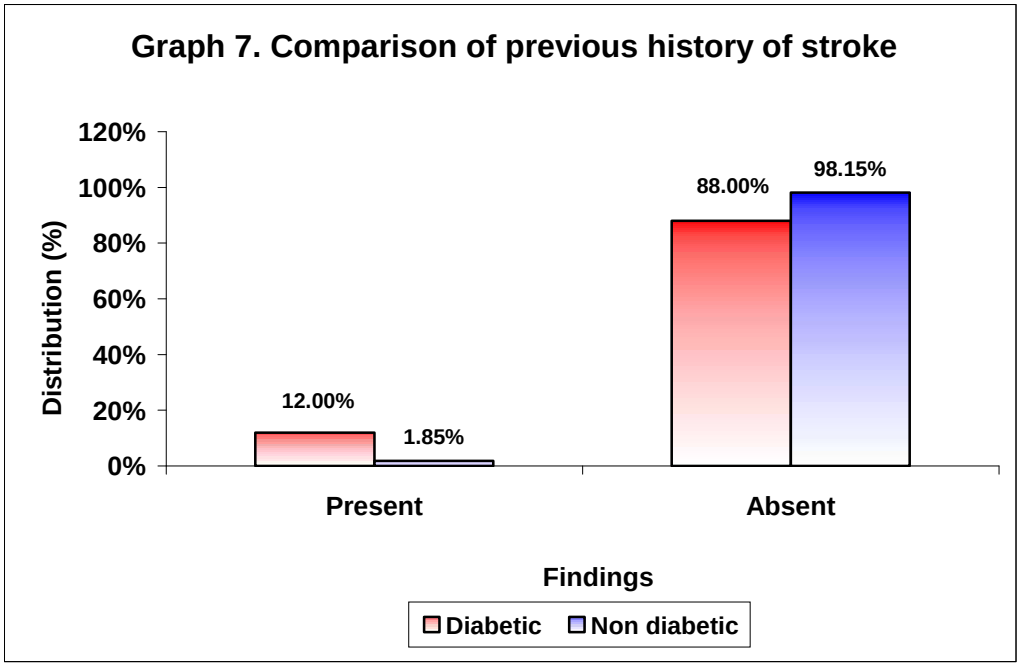


Table 7 and graph 6 shows clinical presentation among the patients with and without the history of diabetes mellitus. It was observed that the commonest presentation was weakness noted among 96% of the patients with diabetes and 88.89% of the non diabetics. The clinical presentation of the patients with history of diabetes mellitus was comparable with those who did not had history of diabetes mellitus.

Table 8. Comparison of previous history of stroke

Findings	Diabetic (n=25)		Non diabetic (n=54)	
	Number	**Percentage**	**Number**	**Percentage**
Present	3	12.00	1	1.85
Absent	22	88.00	53	98.15
Total	**25**	**100.00**	**54**	**100.00**

p = 0.091

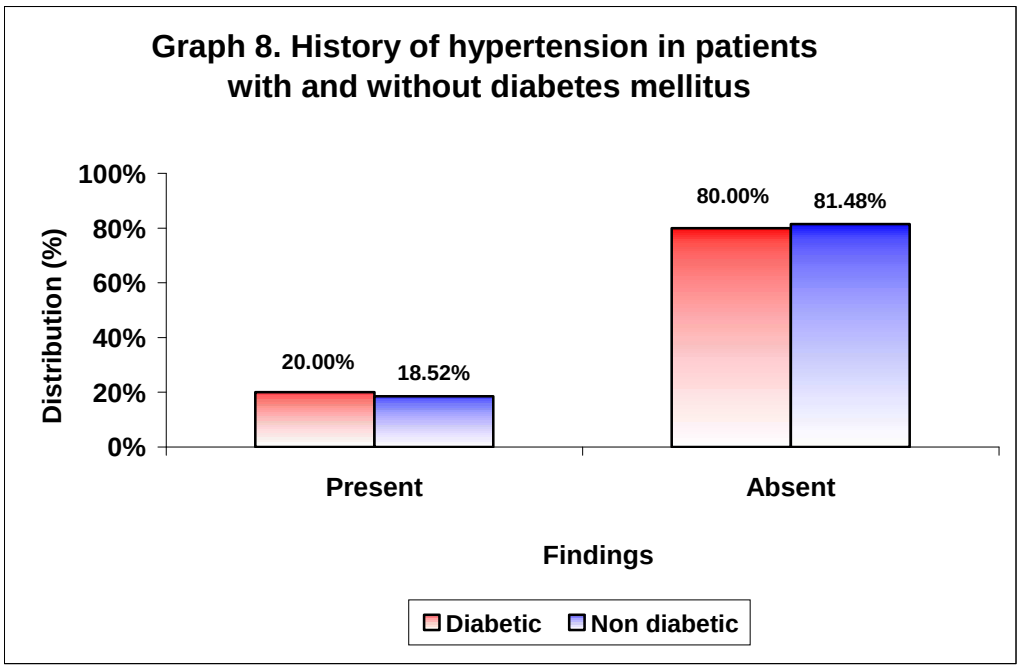


In the present study history of previous stroke was present in 12% of the patients with diabetes mellitus compared to 1.85% of the patients who did not had diabetes mellitus (p=0.091)

Table 9. History of hypertension in patients with and without diabetes mellitus

Findings	Diabetic (n=25)		Non diabetic (n=54)	
	Number	**Percentage**	**Number**	**Percentage**
Present	5	20.00	10	18.52
Absent	20	80.00	44	81.48
Total	**25**	**100.00**	**54**	**100.00**

p = 0.551



In this study history of hypertension was comparable among the patients with diabetes mellitus (20%) and non diabetics (18.52%) (p=0.551).

Table 10. Comparison of mean blood pressure levels

Blood pressure	Diabetic (n=25)		Non diabetic (n=54)		p value
	Mean	SD	Mean	SD	
Systolic (mm Hg)	160.37	15.78	161.60	12.81	0.714
Diastolic (mm Hg)	94.07	7.90	95.60	5.07	0.305

The mean blood pressure levels among diabetic and non diabetic patients is as shown in table 10. However no statistically significant difference was observed between the two groups ($p>0.050$).

Table 11. Distribution of patients according to the arterial supply

Location	Diabetic (n=25)		Non diabetic (n=54)	
	Number	**Percentage**	**Number**	**Percentage**
ACA	2	8.00	5	9.26
ACA/MCA	2	8.00	4	7.41
MCA	17	68.00	31	57.41
MCA/PCA	1	4.00	6	11.11
PCA	3	12.00	8	14.81
Total	**25**	**100.00**	**54**	**100.00**

p=0.890

In the present study the commonest location was MCA in 68% of the patients with history of diabetes mellitus compared to 57.41% non diabetic patients.

Table 12. Distribution of patients according to the circulation

Location	Diabetic (n=25)		Non diabetic (n=54)	
	Number	**Percentage**	**Number**	**Percentage**
Anterior	21	84.00	40	74.07
Posterior	4	16.00	14	25.93
Total	**25**	**100.00**	**54**	**100.00**

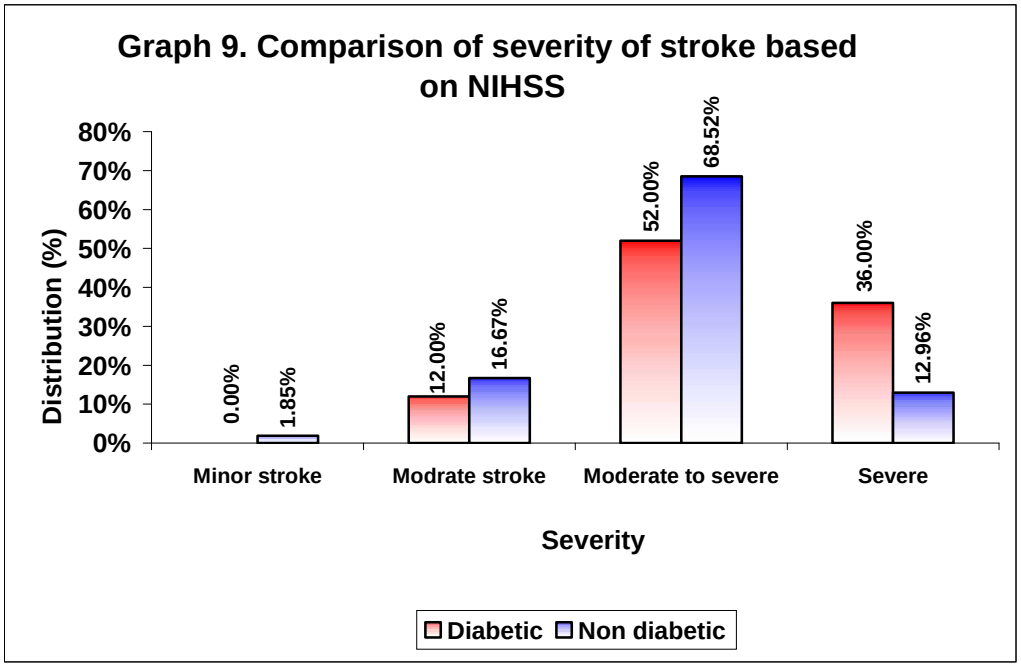
p=0.328

In this study anterior location was involved in 84% of the patients with history of diabetes compared to 74.07% of the non diabetic patients.

Table 13. Comparison of severity of stroke based on NIHSS

Severity	Diabetic (n=25)		Non diabetic (n=54)	
	Number	Percentage	Number	Percentage
Minor stroke	0	0.00	1	1.85
Moderate stroke	3	12.00	9	16.67
Moderate to severe	13	52.00	37	68.52
Severe	9	36.00	7	12.96
Total	**25**	**100.00**	**54**	**100.00**

p = 0.095



In the present study severity of stroke based on NIHSS scale revealed 52% of the patients with diabetes had moderate to severe stroke compared to 68.52% non diabetics while severe stroke was present in 36% compared to 12.96% respectively. However this difference was statistically not significant (p=0.095).

Table 14. Comparison of mean NIHSS scores

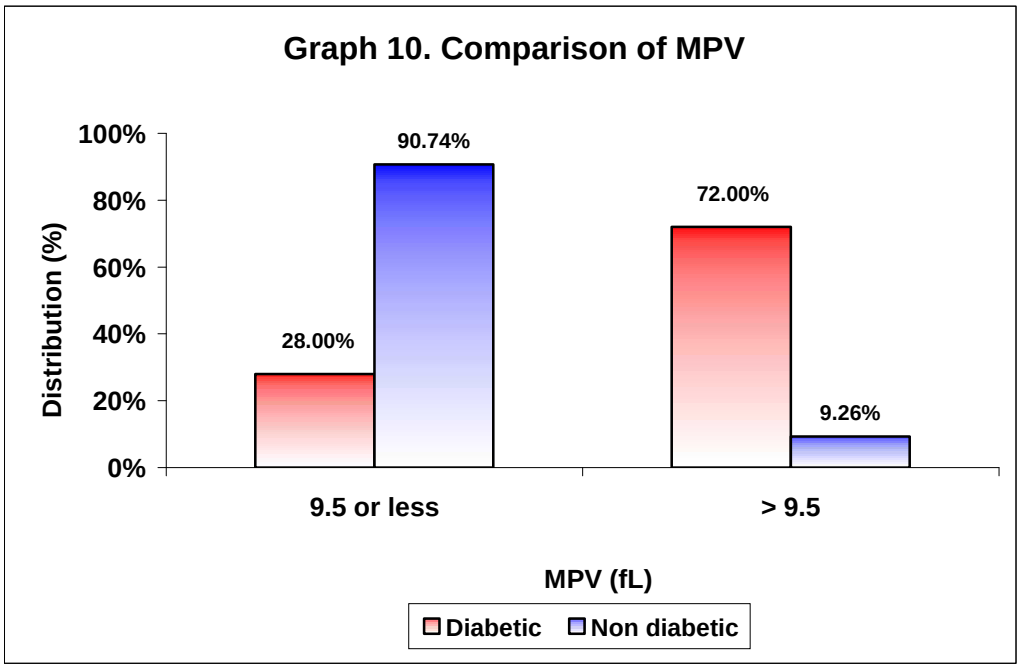
Variables	Diabetic (n=25)		Non diabetic (n=54)		p value
	Mean	SD	Mean	SD	
NIHSS score	20.08	3.19	17.76	3.74	0.006

In the present study mean NIHSS scores were significantly high among the patients with history of diabetes mellitus (20.38 ± 3.19) compared to non diabetic patients (17.76 ± 3.74) (p=0.006).

Table 15. Comparison of MPV

MPV (fL)	Diabetic (n=25)		Non diabetic (n=54)	
	Number	**Percentage**	**Number**	**Percentage**
9.5 or less	7	28.00	49	90.74
> 9.5	18	72.00	5	9.26
Total	**25**	**100.00**	**54**	**100.00**

p < 0.001



In this study, 72% of the patients with diabetes mellitus had MPV levels of >9.5 fL compared to 9.26% non diabetic patients. This difference was statistically significant (p<0.001).

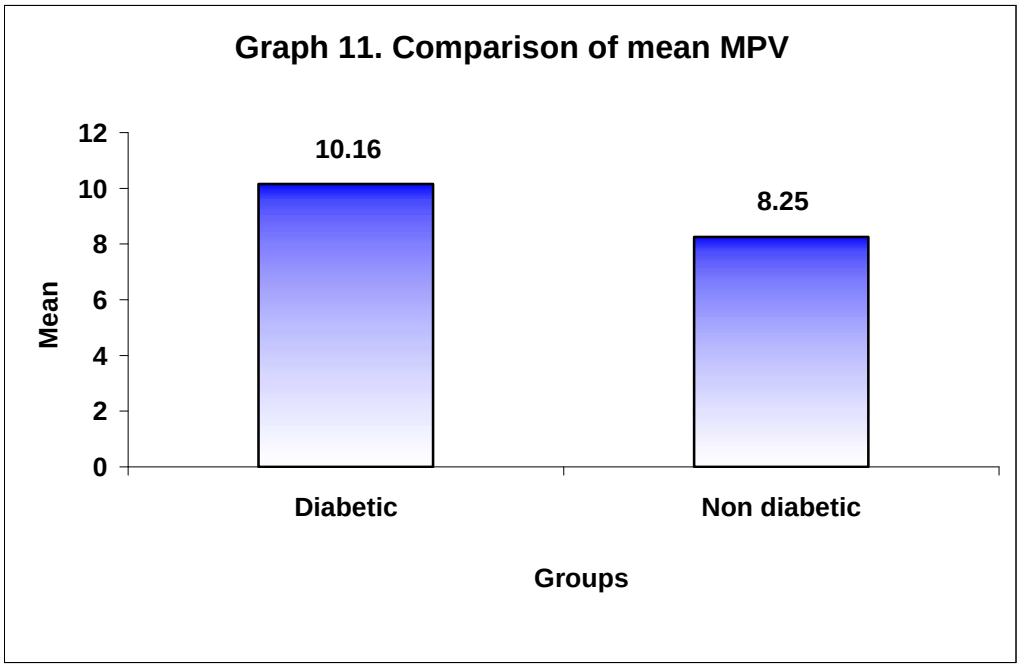
Table 16. Comparison of mean haemoglobin and platelet count

Variables	Diabetic (n=25)		Non diabetic (n=54)		p value
	Mean	SD	Mean	SD	
Haemoglobin (gm%)	13.86	1.06	13.87	1.64	0.968
Platelet count (Lakhs/Cumm)	2.61	0.51	2.76	0.64	0.290

The mean haemoglobin and platelet count among the diabetic and non diabetic patients is as shown in table 16. It was observed that, mean haemoglobin and platelet count were comparable in both the groups ($p>0.050$).

Table 17. Comparison of mean MPV

Variables	Diabetic (n=25)		Non diabetic (n=54)		p value
	Mean	SD	Mean	SD	
MPV (fL)	10.16	0.89	8.25	0.91	<0.001

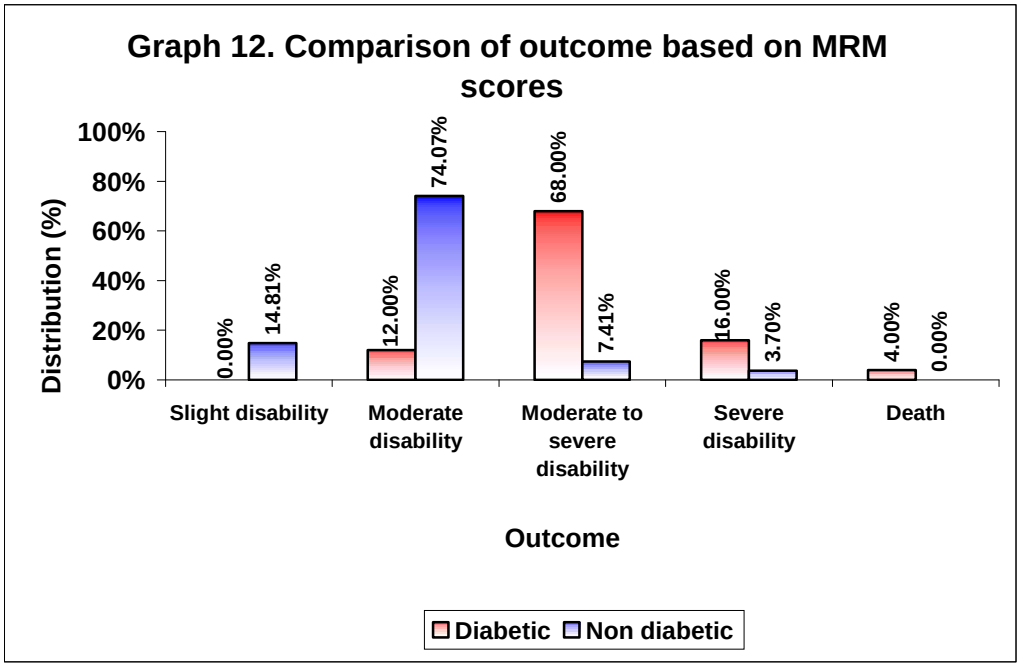


In the present study the mean platelet volume in patients with diabetes mellitus was significantly high (10.16 ± 0.89 fL) compared to non diabetic patients (8.25 ± 0.91 fL) ($p<0.001$).

Table 18. Comparison of outcome based on MRM scores

Outcome	Diabetic (n=25)		Non diabetic (n=54)	
	No.	%	No.	%
Slight disability	0	0.00	8	14.81
Moderate disability	3	12.00	40	74.07
Moderate to severe disability	17	68.00	4	7.41
Severe disability	4	16.00	2	3.70
Death	1	4.00	0	0.00
Total	**25**	**100.00**	**54**	**100.00**

p < 0.001



In the present study 68% of the patients with diabetes mellitus had moderate to severe disability and 16% had severe disability compared to 7.41% and 3.70% of the patients in non diabetic subset and this difference was statistically significant ($p<0.001$)

Table 19. Comparison of mean MRM scores

Variables	Diabetic (n=25)		Non diabetic (n=54)		p value
	Mean	SD	Mean	SD	
MRM score	4.12	0.66	3.00	0.61	<0.001

In this study the mean MRM scores were significantly high in patients with diabetes mellitus compared to non diabetic patients (4.12 ± 0.66 vs 3.00 ± 0.61; $p<0.001$).

Table 20. Association of MPV with diabetic characteristics

Parameters	Sub groups	MPV (fL)				Total		p value
		> 9.5		9.5 or less				
		No.	%	No.	%	No.	%	
Duration	5 or less	11	73.33	4	26.67	15	100.00	0.601
(Years)	> 5	7	70.00	3	30.00	10	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	
Treatment	Oral	12	75.00	4	25.00	16	100.00	0.746
	Insulin	5	62.50	3	37.50	8	100.00	
	Unknown	1	100.00	0	0.00	1	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	
HbA1c	≤ 7.0	1	50.00	1	50.00	2	100.00	0.807
	7.1 to 8.5	4	80.00	1	20.00	5	100.00	
	> 8.5	13	72.22	5	27.78	18	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	

In the present study, among the diabetic patients, no association was found between duration of diabetes mellitus and the raised MPV as well as treatment of diabetes ($p>0.050$).

Table 21. Association of MPV with history in patients with diabetes mellitus

History	Findings	MPV (fL)				Total		p value
		> 9.5		9.5 or less				
		No.	%	No.	%	No.	%	
Previous	Present	2	66.67	1	33.33	3	100.00	0.645
Stroke	Absent	16	72.73	6	27.27	22	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	
Hypertension	Present	4	80.00	1	20.00	5	100.00	0.564
	Absent	14	70.00	6	30.00	20	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	

In this study, prior history of stroke (p=0.645) and hypertension (p=0.564) were not associated with raised MPV levels in patients with diabetes mellitus.

Table 22. Association of MPV with stroke severity and outcome in patients with diabetes mellitus

Variables	Findings	MPV (fL)				Total		p value
		> 9.5		9.5 or less				
		No.	%	No.	%	No.	%	
NIHSS score	Moderate	3	100.00	0	0.00	3	100.00	0.564
	Moderate to severe	8	61.54	5	38.46	13	100.00	
	Severe	7	77.78	2	22.22	9	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	
MRM score	Moderate disability	2	66.67	1	33.33	3	100.00	1.000
	Moderate to severe disability	12	70.59	5	29.41	17	100.00	
	Severe disability	3	75.00	1	25.00	4	100.00	
	Death	1	100.00	0	0.00	1	100.00	
	Total	**18**	**72.00**	**7**	**28.00**	**25**	**100.00**	

In the present study raised MPV levels were not associated with severity of stroke based on NIHSS score and outcome based on MRM scores (p>0.050).

Table 23. Comparison of mean MPV in different durations of DM

Variables	5 years or less		> 5 years		p value
	Mean	SD	Mean	SD	
MPV	10.07	0.80	10.29	1.04	0.585

In this study the mean MPV levels in diabetic patients with duration of ≤ 5 years and > 5 years were comparable (p=0.585).

Table 24. Comparison of mean MPV in different treatment modalities of DM

Variables	Oral		Insulin		p value
	Mean	SD	Mean	SD	
MPV (fL)	9.98	0.75	10.36	1.09	0.404

In the present study mean MPV levels among diabetic patients who were on treatment with OHA's and insulin were comparable (p=0.404).

Table 25. Comparison of mean MPV in HbA1c levels

HbA1c	Distribution (n=25)	
	Mean	SD
7.0 or less	9.75	0.35
7.01 to 8.50	9.98	0.74
> 8.50	10.39	1.00
F value	0.395	
p value	0.678	

In the present study the mean MPV levels among the patients with HbA1c levels ≤ 7.0, 7.01 to 8.50 and > 8.50 were comparable (p=0.678).

DISCUSSION

DM is a complex metabolic syndrome characterized by chronic hyperglycemia resulting in micro- and macrovascular complications.[32] Diabetes and ischemic stroke are common diseases that frequently occur together. The relationship between these two disorders have shown that subjects with diabetes mellitus have approximately twice the risk of ischemic stroke compared with those without diabetes. Diabetes mellitus is a major risk factor for ischemic stroke and is associated with high mortality. It is well known that diabetes mellitus may contribute to systemic and intracranial atherosclerotic disease and this increased risk has been linked to the pathophysiological changes seen in the cerebral vessels of patients with diabetes.[48] Preventing vascular complications and monitoring of DM is the need of the hour as the prevalence of DM and its vascular burdens are increasing day by day.

Mean platelet volume (MPV), the most commonly used measure of platelet size, is a potential marker of platelet reactivity. Increased platelet function has been shown in stroke risk factors such as hypertension, hypercholesterolaemia, diabetes mellitus and smoking, and in vascular conditions associated with stroke, such as atherosclerosis, MI and peripheral vascular disease. Platelet size is determined at the level of the progenitor cell (ie, the megakaryocyte), and recent studies reported that cytokines such as interleukin-3 or interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets.[78] It is therefore reasonable to speculate that a proinflammatory state before the cerebrovascular

event may confer a higher MPV and a prothrombotic condition. This prompted us to evaluate the association between mean platelet volume (MPV) and acute ischemic stroke in patients with type 2 diabetes mellitus.

This one year hospital based cross sectional study was done in the Department of Medicine, KLES Dr. Prabhkar Kore Hospital and Medical Research Centre, Belgaum. A total of 79 patients who presented with acute ischaemic stroke from January 2014 to December 2014 were studied.

In this study, of the 79 patients studied, 25 (31.6%) patients had history of diabetes which formed the diabetic cohort and the remaining 54 patients (68.35%) formed non diabetic subset. Among the diabetic patients most of the patients (60%) reported duration of diabetes as ≤ 5 years, were receiving oral hypoglycaemic agents (64%) and had poor diabetic control (72%). The mean duration of diabetes was 5.05 ± 3.22 years and mean HbA1c level was 9.77 ± 2.11 which was also suggestive of poor diabetic control. MPV was assessed in all subjects.

The male sex has been listed as a risk factor for stroke.[103] In this study acute ischemic stroke widely prevalent among males as 72% of the diabetics and 68.52% of the non diabetics were males. The male to female ratio among diabetics was 2.57:1 while in non diabetic patients it was 2.17:1 but the difference was statistically not significant (p=0.754). These findings suggest male preponderance in acute ischaemic stroke patients which was consistent with a study by Shah PA. et al.[73] who reported that, males constituted 59% of ischemic stroke patients. Similar findings have been reported in other studies from India by Khan et. al.[104]

Age is an important non-modifiable risk factor for stroke. The mean age of stroke onset in the South Asian region (for example, 63 years in India and 59 years in Pakistan) is lower than in Western countries (for example, 68 years in the USA and 71 years in Italy).[28] In the present study nearly one third of the study diabetic patients (32%) were aged between 61 to 70 years compared to one fifth of the non diabetic patients (20.37%). However statistically the age distribution was comparable among the diabetic and non diabetic patients (p=0.551). In this study the mean age among diabetic patients was 62.04 ± 10.88 years compared to 58.11 ± 16.75 years in non diabetic patients. However this difference was statistically not significant (p=0.217). These observations showed that, acute ischemic stroke in this study was common in elderly age group. A study to assess the role of MPV in ischemic stroke by Shah PA. et al.[73] also reported mean age as 58 years

In the present study, commonest clinical presentation was motor weakness in diabetic (96%) and non diabetic patients (88.89%). The next common clinical presentation was ataxia (24% in diabetics and 9.26% in non diabetics). Few patients presented with other presentations which included dysarthria, tingling, global aphasia, burning, drowsiness, inability to speak, imbalance, motor aphasia, deviation angle of mouth, loss of consciousness, slumping and swaying. However, the clinical profile of patients with history of diabetes mellitus was comparable with those who did not have history of diabetes mellitus (p>0.050).

It is hypothesized that higher MPV may predispose to the occurrence of ischemic strokes which is substantiated by other research workers.[73] In the present study, it was observed that, significantly higher number of diabetic patients had raised MPV levels (>9.5) as compared to non diabetic patients (72% vs. 9.26%

respectively; p<0.001). Also the mean the mean platelet volume was significantly high in patients with history of diabetes mellitus compared to non diabetic patients (10.16 ± 0.89 vs. 8.25 ± 0.91 respectively; p<0.001). These findings confirm the positive association between mean platelet volume (MPV) and acute ischemic stroke in patients with diabetes mellitus. The positive association observed between ischaemic stroke with MPV in diabetic patients was independent of treatment of diabetes (p=0.404), duration of diabetes (p=0.585), glycaemic control (p=0.678), prior history of stroke (p=0.645) and hypertension (p=0.564). There is lack of data to comment on these findings as this study is first of its kind to study acute ischemic stroke in diabetic patients and study its correlation with MPV. It's a cross sectional study design having a positive outcome.

The association of ischemic stroke with MPV observed in the present study is in accord with the known facts that there is greater reactivity of larger platelets, the pathophysiological role of platelets in the occurrence of ischemic stroke, and the identified effects of antiplatelet therapy on the risk of ischemic stroke.[97]

Similar findings were reported by PROGRESS collaborative group.[97] In this study, stroke rates were greater among individuals with higher measurements of MPV, both for overall (P for trend across fifths of MPV=0.01) and for ischemic stroke alone (P=0.01). With adjustment for population of recruitment and measurement error, the strength of the overall association was such that each 1-fL increase in usual MPV was associated with a 12% (95% CI, 4% to 20%) increased relative risk of stroke. The study identified MPV as an independent predictor of the risk of stroke among high-risk individuals. The measurement of MPV may add

useful prognostic information for clinicians managing patients with a history of cerebrovascular disease.

Also in our study out of 25 diabetic stroke cases 3 had history of recurrent stroke in whom MPV was highly raised(10, 12 and 11 in pt 1, 2 and 3 respectively) thus associating raised MPV to recurrence of stroke**.** In this study 12% of the patients with diabetes mellitus presented with history of stroke compared to 1.85% of the non diabetic patients. However in the present study there was no association of prior history of stroke (p=0.645) seen due to small sample size. No correlation was seen in hypertension (p=0.564) with ischemic stroke in diabetic patients. History of hypertension was noted in 20% of the diabetic patients compared to 18.52% of the non diabetics. However, no statistically significant difference was noted with regard to history of previous stroke and hypertension among diabetic and non diabetic patients (p=0.091; p=0.551).

A prospective study by Shah PA. et al.[73] on 100 patients each of ischemic stroke with equal number of age and sex matched control group reported that, mean platelet volume and platelet count in control group were lower and higher, in comparison to the study group. This observation is in conformity with bulk of the published data[84,87,105-107] and consistent with the present study.

MPV values in association with both thrombosis and inflammation have become a point of interest in the last few decades, and recent studies have reported MPV values significantly higher in patients with stroke.[87]

Vizoli et al.[108] reported that platelet volumes are determined in bone marrow by thrombopoetin, cytokines and growth factor that may explain changes in MPV

value in vascular and inflammatory events. Increased MPV is considered an indicator of platelet function and an independent predictor of coronary artery disease (CAD), severity of CAD. It also reflects larger infarct volume in stroke patients and can predict severity of strokes.[109]

Slavka et al.[110] showed that subjects with higher MPV (>11.01 fL) had 1.5 times higher vascular mortality risk than patients with low MPV (<8.7 fL) value. In the same study,[110] significant positive relationship between high MPV and the risk of ischaemic heart disease was identified.

Arevalo-Lorido et al.[111] reported that higher MPV levels in stroke patients are associated not only with overall morbidity and mortality.

The present study showed several other implications with regard to severity of stroke and outcome. The severity of stroke is likely to be severe in diabetics based on NIHSS scores (20.38 ± 3.19 vs 17.76 ± 3.74; p=0.006) and are likely to have higher mortality and morbidity based on MRM scores (4.12 ± 0.66 vs 3.00 ± 0.61; p<0.001). Similar findings finding have been reported in other studies also.[87,107,112] A prospective study by Shah PA. et al.[73] also reported that, patients with higher MPV had worse outcome at the end of one week as measured by Modified Rankin scale score and authors reported that, mean platelet volume bears an inverse relationship to immediate outcome from ischemic stroke independent of stroke subtype. However, the present study did not assess the outcome in different stroke types due to smaller sample size.

There are some possible explanations for MPV fluctuations during the acute phase of ischemic stroke. According to the results of the West Birmingham Stroke

Project,[15] the pathophysiology of ischemic stroke potentially involves the platelet and its morphology. In fact, patients presenting with an acute ischemic stroke have activated platelets, as evident by the increased levels of soluble and platelet P-selectin. Also, platelet size is determined at the level of the progenitor cell (namely, the megakaryocyte), and some studies reported that cytokines such as interleukin-3 or interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets.[113] It is, therefore, reasonable to speculate that a proinflammatory state before the cerebrovascular event may confer a higher MPV and a prothrombotic condition.

In addition, it has been suggested that patients with large platelets are more susceptible to some risk factors such as diabetes, and obesity, and therefore have an increased risk of ischemic stroke.[101] Diabetic patients are known to have higher incidence of stroke and myocardial infarction. Presence of high MPV in these patients is an important finding that could increase the risk of thrombotic complications. It has also been shown that among diabetic patients, those with retinopathy and other complications have higher MPV values than those who do not have this complication.[73] Presence of significantly higher MPV in IFG patients as compared to non-diabetic subjects is also reported in the literature.[48]

This is a first study to co-relate MPV in diabetic stroke and non diabetic strokes with a positive outcome. Thus stating MPV was highly raised in diabetic strokes than in non diabetic strokes and has bad prognosis and worst outcome**.**

This study has some limitations that should be taken into account in assessing the results. We measured MPV only at admission, and did not perform

further serial measurements during the evolution of stroke. Therefore, according to our results, we recommended further studies to investigate the role of this index as a predictive factor in the severity of ischemic stroke.

CONCLUSION

Diabetes being a pro coagulant state, patients are at risk of any thrombotic event. Mean platelet volume an indicator of platelet reactivity is a simple test available in panel of haemograms and can serve as a valuable predictor.

Based on findings of this study it may be concluded that, there is positive association between mean platelet volume and acute ischemic stroke in patients with diabetes mellitus. This association is independant of duration of diabetes,mode of treatment for diabetes,glycemic control and hypertension. Also acute ischemic stroke in diabetic patients with raised MPV is likely to be severe (as assessed by NIHSS score) and may results in high morbidity and mortality (as assessed by mrs). Inorder to correlate MPV to predict recurrence of stroke, a larger sample size of diabetic strokes has to be considered.

SUMMARY

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.With such increasing incidence we as physicians have to anticipate the associated microvascular and macrovascular complications.. Atherothrombosis is the main cause for most of vascular complications. Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function and is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A2, platelet factor 4, and thromboglobulin.

Studies in the past have shown MPV to be associated with diabetes and affect its complications. Studies have also shown MPV to predict the severity of ischemic strokes. Therefore, in this study we associated MPV to a cohort of diabetic stroke(cases) and compared it to non diabetic strokes(controls) to assess severity of stroke (NIHSS SCORE) and also predict the outcome of stroke (MRS)

In this one year hospital based cross sectional study, total of 79 patients with acute ischemic stroke were enrolled of which 25 patients (31.6%) had history of diabetes which formed the diabetic subset and the remaining 54 (68.35%) were non diabetics.

In diabetic group 72% were males where as in nondiabetic group 68.52% were males (p=0.754)**.** The mean age among diabetic and non diabetic group was 62.04 ± 10.88 years and 58.11 ± 16.75 years (p=0.217) respectively. It was observed

that the commonest presentation in both the groups was motor weakness which constituted 96% of the patients with diabetes and 88.89% of the non diabetics.

Among the patients with diabetes the duration of diabetes was 5 years or less in 60% of the patients, 64% of the patients were on OHA and most of the patients (72%) had the HbA1c levels > 8.50. History of previous stroke was present in 12% of the patients with diabetes mellitus compared to 1.85% of the non diabetic patients (p=0.091). Here we couldn't comment much on whether MPV could predict the recurrence of stroke in diabetic population as among the 25 diabetic patients only 3 had history of recurrent stroke. Hence there is a need to assess relation between MPV and recurrence of stroke in diabetics in a larger sample size.36% of the diabetics had severe stroke compared to 12.96% in non diabetic group (p=0.095) when assessed by NIHSS score. The mean NIHSS scores were significantly high among the patients with diabetes mellitus (20.38 ± 3.19) compared to non diabetic patients (17.76 ± 3.74) (p=0.006). 72% of the patients with diabetes mellitus had MPV levels of >9.5 compared to 9.26% of non diabetic patients (p<0.001). The mean platelet volume in patients with diabetes mellitus was significantly high (10.16 ± 0.89) compared to non diabetic patients (8.25 ± 0.91) (p<0.001).By MRM score 68% of the patients with diabetes mellitus had moderate to severe disability compared to 7.41% of the patients in non diabetic subset (p<0.001) The mean MRM scores were significantly high in patients with diabetes mellitus compared to non diabetic patients (4.12 ± 0.66 vs 3.00 ± 0.61; p<0.001).

Thus to conclude there is a positive association between mean platelet volume and acute ischemic stroke in patients with diabetes mellitus. Furthermore,

acute ischaemic stroke in diabetic patients with raised MPV is likely to be severe with high morbidity and mortality.

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ANNEXURE I – CONSENT FORM

"ASSOCIATION OF MEAN PLATELET VOLUME WITH ACUTE ISHCHEMIC CEREBROVASCULAR ACCIDENT AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS"- A HOSPITAL BASED STUDY.

Objective and purpose of the study

This research is intended to study the association of MPV and acute ischemic brain strokes in diabetics as MPV can be used as an economical tool for prognosis of acute ischemic CVA in diabetics. This study will be of great help to patients with ischemic brain strokes and diabetics and also predict their complications and recurrences in the future.

Procedure

If you agree to be part of the research study, you will be asked the relevant history pertaining to stroke and diabetes and will be subjected to relevant clinical examination (GPE, systemic examination, nihss, modified rankin score) and investigations (routine investigations for stroke and diabetes). You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from my arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

This study will assess MPV as an economical tool for prognostication of stroke in diabetes and chances of recurrence of stroke.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

In the event of injury, related to the study, treatment will be made available at KLES Dr. PRABHAKAR KORE HOSPITAL AND RESEARCH CENTRE, BELAUM. There is no compensation or payment for such medical treatment by law.

Financial incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the stud will be borne by the investigator.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant, you may call:

DR. *** ********,**
Investigator,
PG in General Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010
Phone No.: ****** *******

DR. ** *********,**
Professor & Head of Unit,
Dept of General Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010
Phone No.: ****** ********

DR. *** *********
**Professor,
Dept. of Neurology,
Jawaharlal Nehru Medical College,
K.L.E University,
Belgaum -.590 010

DR. *** ******
**Professor,
Dept. of Pathology,
Jawaharlal Nehru Medical College,
K.L.E University,
Belgaum – 590 010

CONSENT STATEMENT

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____

Signature / Thumb print: _____

Name of the Witness: _____

Signature/ Thumb print: _____

Investigator Name: _____

Signature: _____

Date:

Place:

ANNEXURE II – PROFORMA

ASSOCIATION OF MEAN PLATELET VOLUME WITH ACUTE ISHCHEMIC CEREBROVASCULAR ACCIDENT AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS"- A HOSPITAL BASED STUDY.

Principal Investigator
Dr. ** *******,**

Guide
Dr. *** ******,**

Co-guide
Dr. *** *******

Type of study - one year cross sectional study

Case Number :

Name :

In Patient Number :

Age / sex :

Address :

Occupation :

Complaints at presentation

History pertaining ischemic brain stroke

Known case of type 2 diabetes mellitus ☐yes ☐ no

If yes,

Duration of illness

Details of treatment

Past history of cerebrovascular events

Past history of angina pain

Myocardial infarction

Ischemic heart disease or on any specific medication.

On examination

General Physical Examination

VITALS

NIHSS SCORE (ON DAY OF ADMISSION)

Instructions	Scale Definition	Score
1a. Level of Consciousness	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	
1b. LOC Questions	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	
1c. LOC Commands	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	
2. Best Gaze	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	

Instructions	Scale Definition	Score
3. Visual	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
4. Facial Palsy	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	
5. Motor Arm	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm	
6. Motor Leg	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg	

Instructions	Scale Definition	Score
7. Limb Ataxia	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____	
8. Sensory	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best Language	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	
10. Dysarthria	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain:_____	
11. Extinction and Inattention (formerly neglect)	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	

Modified rankin score

- 0 No symptoms at all
- No significant disability despite symptoms; able to carry out all usual duties and activities
- 2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3 - Moderate disability; requiring some help, but able to walk without assistance
- 4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 - Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6 - Dead

TOTAL (0–6): _____

Investigations

CT / MRI brain for diagnosis of acute ischemic stroke

HbA1c (to assess glycemic control)-

EDTA blood samples for measurement of MPV

Lipid profile

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
ACA	-	Anterior cerebral artery
Ant	-	Anterior
B/L	-	Bilateral
BG	-	Basal ganglia
BP	-	Blood pressure
CHD	-	Congenital heart disease
DM	-	Diabetes mellitus
DVT	-	Deep vein thrombosis
F	-	Female
fL	-	Femtoliter
gm	-	Grams
GN	-	Glomerulonephritis
GP	-	Globus pallidus
HbA1c	-	Glycosylated haemoglobin
HDL	-	High density lipoprotein
I	-	Insulin
IC	-	Internal capsule
ITP	-	Immune thrombocytopenic purpura
LDL	-	Low density lipoprotein
Lt	-	Left
M	-	Male

MCA	-	Middle cerebral artery
mm Hg	-	Millimeters of mercury
MO	-	Medulla oblongata
MPV	-	Mean platelet volume
MRI	-	Magnetic resonance imaging
MRM	-	Modified Rankin Morbidity Score
nad	-	No abnormality detected
NIHSS	-	National Institute of Health Stroke Scale
NK	-	Not known
nvbs	-	Normal vesicular breath sounds
O	-	Oral hypoglycaemic agents
PCA	-	Posterior cerebral artery
Pos	-	Posterior
Rt	-	Right
S/A	-	Sub-acute
S1	-	First heart sound
S2	-	Second heart sound