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Impact of Glycemic Control on Ischemic Stroke Severity and Outcomes: A Prospective Single Centre Study

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Abstract: ***This study investigates the relationship between glycemic status and ischemic stroke severity and functional outcomes in patients admitted to Deenanath Mangeshkar Hospital, Pune. It categorizes patients into diabetic and non-diabetic groups based on HbA1c levels and random blood sugar, further dividing diabetics into well-controlled and poorly controlled subgroups. The research analyzes clinical parameters, stroke severity, and functional outcomes, concluding that there is no significant correlation between glycemic status at admission and stroke severity or functional outcome. The findings highlight the need for more comprehensive studies to understand the role of glycemic control in stroke management.***

Keywords: ischemic stroke, glycemic status, functional outcome, stroke severity, HbA1c levels

1. Introduction

A stroke or cerebrovascular accident is defined as the abrupt onset of a neurologic deficit that is attributable to a focal vascular cause[1]. A stroke occurs when the blood supply to part of our brain is interrupted or severely reduced, depriving brain tissue of oxygen and nutrients.

The Stroke Council of the American Heart Association/ American Stroke Association convened a writing group to develop an expert consensus document for an updated definition of stroke for the 21st century. Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury[2]. Stroke broadly includes ischemic and hemorrhagic stroke.

Diabetes mellitus is a metabolic disorder, resulting from a defect in insulin production, impaired insulin action or both. It is one of the major non- communicable diseases on the rise worldwide, causing 4.8 million deaths and morbidity in 371 million people every year[3].

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. In India, DM is becoming leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.

Glycosylated hemoglobin A1c (HbA1c) indicates long-term uncontrolled hyperglycemia in the body, which in diabetic patients leads to various vascular complications as a part of generalised atherosclerosis culminating ultimately into ischemic stroke. Several prospective community based epidemiological studies conducted in various parts of world suggest that approximately one fifth of stroke patients have DM [4].

Diabetes mellitus, the metabolic disorder can interact with atherosclerosis in ischemic strokes to initiate activate and propagate events. To formulate effective preventive measures, it is mandatory to understand the impact of glycemic status on severity and functional outcome of acute ischemic stroke in patients with diabetes.

The stroke severity at admission was assessed based on National Institutes of health stroke scale[5] (NIHSS) and patients were followed up to discharge and at one month subsequently. The stroke functional outcome at 1 month was assessed by Modified Rankin Scale[6] (MRS).

National Institutes of health stroke scale (NIHSS)
NIHSS is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

Table 1: Stroke severity based on NIHSS

Score	Stroke severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

Modified Rankin Scale (MRS)
The scale runs from 0-6, running from perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

Broadly MRS is divided into three sub groups-MRS score 0-2 good functinal outcome, 3-4 moderate functional outcome and 5-6 poor functional outcome.

Glycemic status in acute ischemic stroke patients with diabetes mellitus was evaluated by measuring the HbA1c level and random blood sugar levels .Glycosylated hemoglobin Hb A1c was done to ascertain whether it was stress hyperglycemia or true diabetes.

HbA1c a marker of chronic hyperglycemia, is associated with uncontrolled diabetes and its complications and has been recommended as a diagnostic test[7, 8]. It is an indicator of average blood glucose concentration over the period of 3 months. Studies[9] have shown that HbA1c rise in the blood and HbA1c continually accumulate in the vessel wall, which lead to rise of thromboxane A2 and protein kinase ,which lead to excessive collagen cross-link by reducing release of nitric oxide , this course result in hardening of vessel wall and decline of artery compliance and a higher content of hbA1c allows oxygen dissociation curve to the left, resulting in oxygen dissociation barrier, nerve tissue ischemia, hypoxia, myelin loss, nerve degeneration, dysfunction and necrosis.

Increased blood glucose concentration at or around the time of cerebral ischemic event may worsen the outcome.

2. Aims and Objectives

Aim:
The aim of this study is to explore the relationship of glycosylated hemoglobin levels and neurological impairment and one month prognosis in patients with acute ischemic stroke.

Objectives:
1) To study the association between glycemic status and severity of acute ischemic stroke at the time of admission in patients with and without diabetes.
2) To compare the functional outcome at discharge and at the end of one month in acute ischemic stroke patients with and without diabetes.
3) To study the effect of glycemic status (i.e poorly controlled and well controlled) on the severity and functional outcome in acute ischemic stroke among patients with known diabetes mellitus.

3. Review of Literature

The term Diabetes, a Greek word meaning siphon, was first used by Aretaeus a disciple of Hippocrates. The Latin word for honey, mellitus was added by William Cullen in 1769, although the ancient Hindus coined “honey urine” the urine that attracted bees and flies[10]. Sushruta has defined “Madhumeha” the condition resembles honey and acquires a sweettaste.

The pathophysiology of type 2 diabetes mellitus is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining β-cell function, eventually leading to β -cell apoptosis .The primary events are believed to be an initial deficit in insulin secretion and, in many patients, relative insulin deficiency in association with peripheral insulin resistance[11].

The pathophysiology in diabetes type 1 is a destruction of beta cells in the pancreas, regardless of which risk factors or causative entities have been present. Individual risk factors can have separate pathophysiological processes too, in turn, causing this beta cell destruction. Still, a process that appears to be common to most risk factors is an autoimmune response towards beta cells, involving an expansion of auto-reactive CD4+ T helper cells and CD8+ T cells, autoantibody-producing B cells and activation of the innate immune system[12].

Table 2: ADA criteria for diagnosis of diabetes mellitus

Criteria for Diabetes Diagnosis-ADA: 4 options
FPG ≥126 mg/dL (7.0 mmol/L)*   Fasting is defined as no caloric intake for ≥8 hours
2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)*   Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
A1C ≥6.5% (48 mmol/mol)*   *Performed in a lab using NGSP-certified method and standardized to DCCT assay*
Random PG ≥200 mg/dL (11.1 mmol/L)   In individuals with symptoms of hyperglycemia or hyperglycemic crisis

The above table shows the ADA criteria for diagnosis of Diabetes mellitus[13].

The International Federation of Clinical Chemistry newly defines HbA1c as hemoglobin that is irreversibly glycated at one or both of the β-chain N- terminal valines, and it does not exclude hemoglobin that is additionally glycated at other sites on the α or β chains[14]. HbA1c could reflect universal tissue protein glycation and might be a much better index of the overall biological effects of glucose above and beyond its predictive value for the 3-month averages of circulating glucose level [15]

Although there are many studies that report the utility of HbA1c in predicting cardiovascular disease and diabetes, there are few that investigate the usefulness of HbA1c as a predictor of ischemic stroke.

Pathophysiology of Hyperglycemia and Acute Ischemic Stroke: Hyperglycemia may be directly toxic to the ischemic brain. Accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism)[16] promotes and accelerates ischemic injury by enhancing lipid peroxidation and free radical formation[17], and impairing mitochondrial function[18]. These neurotoxic effects may be particularly important in the ischemic penumbra where neurons are injured but still viable[19].

Hyperglycemia facilitates the development of cellular acidosis in the ischemic penumbra and results in a greater infarct volume, thus promoting the recruitment of potentially salvageable neurons into the infarction.

Hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose (increasing the amount of glucose available to diffuse into brain) and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation[20].

A) Hyperglycemia-Associated Reduction in Perfusion
Hyperglycemia causes 24% reduction in regional blood flow, reduction in blood circulation to the marginal ischemic areas and converts ischemic penumbra to infarct[21]. CO2-induced increase in cerebral blood flow is decreased in diabetics[22]. CO_2-induced cerebral vasodilatation is mediated through NO, and diabetics are known to have decreased endothelial NO production.

B) Hyperglycemia-Associated Impaired Calcium Homeostasis Excitatory amino acids, notably glutamate, play a central role in neuronal death by activation of postsynaptic glutamate receptors, particularly N- methyl D-aspartate (NMDA) receptors. This leads to an excessive influx of calcium through ion channels, mitochondrial injury, and eventual cell death. Thus, hyperglycemia, by increasing the availability of glutamate, may induce calcium-mediated neuronal cell death. Hyperglycemia may also be harmful to calcium recovery during the early perfusion period after focal cerebral ischemia, thereby increasing intracellular calcium for a longer time[23].

C) Inflammation and free radical associated injury
Hyperglycemia is known to be associated with inflammation and oxidative stress. Glucose intake results in comprehensive inflammation as reflected in an increase in nuclear factor *k*B (NF- *k*B) binding and a decrease in inhibitor kappa B (I *k*B) expression[24]. NF-*k*B is a nuclear transcription factor that normally stays in the cytoplasm in association with I *k*B [25].

In response to an inflammatory stimulus, there is an increase in I *k*B kinase- α and I *k*B kinase-ß, which phosphorylate I *k*B and result in its ubiquitination and proteosomal degradation. Degradation of I *k*B results in release of NF- *k*B and in its translocation from the cytoplasm to the nucleus, where it stimulates the transcription of proinflammatory cytokines. Activation of NF- *k*B and superoxide generation has been shown to be involved in tissue injury after occlusion of middle cerebral artery. NF- *k*B activation leads to increased production of inflammatory cytokines and chemokines such as tumor necrosis factor- and monocyte chemoattractant protein (MCP-1). This attracts leukocytes to the ischemic area. Superoxide radicals can cause direct cell damage through lipid peroxidation, protein carbonylation, and DNA damage. Superoxide also neutralizes NO produced by endothelium by converting NO to peroxinitrite. NO is critical in maintenance of blood flow to the ischemic brain tissue by causing vasodilatation of arteries.

D) Hyperglycemia and Thrombosis
Multiple studies have identified a variety of hyperglycemia related abnormalities in hemostasis, favoring thrombosis . Human studies in patients with type 2 diabetes have shown platelet hyperactivity indicated by increased thromboxane biosynthesis. Hyperglycemia induced elevations of interleukin (IL-6) levels have been linked to elevated plasma fibrinogen concentrations and fibrinogen messenger ribonucleic acid (mRNA) [26, 27].

Increased platelet activation as shown by shear-induced platelet adhesion and aggregation on extracellular matrix has been demonstrated in patients with diabetes[28].

In the healthy state, the vascular endothelium maintains the vasculature in a quiescent, relaxant, anti thrombotic, anti oxidant and anti adhesive state. Acute hyperglycemia may directly alter endothelial cell function by promoting chemical inactivation of nitric oxide, triggering production of reactive oxygen species (ROS) or activating other pathways.

Insulin Treatment in Acute Ischemic Stroke
Insulin therapy reduces ischemic brain damage and can be neuroprotective. Insulin reduces neuronal necrosis regardless of its effect on glucose levels[29].

Insulin has recently been shown to possess a potent anti-inflammatory effect in vitro and in vivo. It suppresses several proinflammatory transcription factors, such as NF- κB, early growth response -1 (Egr-1), and Activator protein -1 (AP-1), and the corresponding genes regulated by them that mediate inflammation[30, 31].

Insulin suppresses ROS generation. In addition to its inhibitory effect on AP-1 and Egr-1, insulin suppresses their regulated gene products as indicated by a fall in plasma concentration of Matrix metalloproteinase (MMP-9), Tissue factor (TF), and Plasminogen activator inhibitor-1 (PAI-1) [32, 33], an effect diametrically opposite to that of glucose. MMP-9 is a cardinal mediator and a reduction in its activity or expression by insulin could be a rational therapeutic approach in the prevention or the limitation of ischemia-related damage to the brain.

High catecholamine levels in the circulation during acute stroke can increase the production of free fatty acids. Free fatty acids decrease the generation and the stability of Prostacyclin[34], which is important for not only vasodilatation but also for preventing platelet aggregation. Insulin inhibits lipolysis, leading to a decrease in plasma-free fatty acids and thus may exert an antiplatelet effect.In addition, insulin has a direct inhibitory effect on platelet aggregation, mediated through the NO– guanylate cyclase-c Guanosine monophosphate (GMP) pathway activated by NO generated by NOS in platelets [35].

Insulin increases endothelial NO release and the expression of NO synthase (NOS) in the endothelial cells[36]. Generation of NO would potentially help in vasodilatation and improved blood flow to the penumbra.

Amit shankar et al., 2013 have found that Several prospective, community based epidemiologic studies conducted in the various parts of world suggest that approximately one fifth of stroke patients have DM[4].

A study on the clinical profile of stroke in relation to glycaemic status of patients (K G hanachandra singh et al. 2014) have followed 50 cases of stroke in the age of 30-75years for a period of 1 year and found that prevalence of stroke in known diabetics is 17 %[37].

Selvin et al., 2010 reported that the HbA1c level would be a strong predictor for cerebrovascular disease (CVD) in next 10 years[38].

Syed Arslan et al., 2013 found that Chronic hyperglycemia as indicated by elevated HbA1c levels is associated with a 17% increase in the risk of stroke with each 1% rise of HbA1c[393].

A study conducted by Geberhiwot et al., found strong association between HbA1c and stroke[40].

Guo shuangxi etal., 2012 found that blood HbA1c can be one of the important predictors of occurrence, development and prognosis of patients with ischemic stroke[41].

Amit shankar et al., 2013 found that people with diabetes have higher Carotid intima-media thickness (CIMT) than the healthy population and significant association between high CIMT and presence of carotid plaques in diabetic stroke patients[42].

Hyung Geun oh et al., 2011 found that subjects with a baseline level of HbA1c between 5.0% and 5.5% were compared with subjects having higher HbA1c values, and their risk for ischemic stroke linearly increased as the baseline level of HbA1c increased. These significances were more prominent in HbA1c values compared with fasting glucose[38].

Stead LG et al., studied the differences in outcome between diabetics and non- diabetic subjects visiting the emergency room with acute ischemic stroke and high blood glucose. They reviewed 447 patients reported to emergency room with acute ischemic stroke and blood glucose had been checked on the arrival. More stroke severity in those with hyperglycemia (p= 0.002) and higher functional impairment among the hyperglycemic group than those with normal blood glucose (p= 0.004), mortality at 90 days was seen to be 2.3 times more among the hyperglycemic group compared to the normoglycemic patients (p<0.001). Stroke severity and functional impairment were more pronounced in those with hyperglycemia and no past history of diabetes. They concluded that hyperglycemia at the onset of acute ischemic stroke is linked to poor outcome in those without history of diabetes than those with Diabetes[43].

Kuwashiro and colleagues[44] conducted a study looking at the predisposing factors for the outcome 1 year post stroke among patients with diabetes. They had enrolled 452 diabetic patients and their characteristics and outcome 1year post stroke were reviewed prospectively. Modified Rankin Scale >2 represents the poor outcome 1year post stroke. 286 patients were with good outcome, 166 patients with poor outcome. Increasing age per 1- year increase, NIHSS score on presentation per 1- point increase, diabetic nephropathy and A1C, per 1% increase were regarded as independent risk factors for poor outcome after 1 year post stroke in diabetics.

Diabetes mellitus, through chronic hyperglycemia, has been linked with accelerated development of both microvascular disease and atherosclerosis throughout the body. Consequently, diabetes mellitus increases the combined risk of stroke and myocardial infarction by about 2.5 times[45] and the risk of stroke alone 1.7 to 2.1 times[46, 47], compared with otherwise similar patients without diabetes.

In recently published observation of 5017 patients with different types of ischemic stroke, the prevalence of diabetes was significantly higher in subjects with small vessel cerebrovascular accidents (35.5%) compared to patients with large vessel atherosclerosis (29.0%) or cardio-embolic (28.1%),while it was less common in subjects with other combined etiologies of stroke.(9.4%)[48].

A high proportion of stroke patients might have developed hyperglycemia even in the absence of pre-existing diabetes since acute stroke itself is an acute stress condition[49, 50].

The initial level of plasma glucose is significantly correlated with poor poststroke outcomes. Acute hyperglycemia increases brain lactate production, reduces salvage of penumbral tissue and causes greater final infarct size. In the middle cerebral artery occlusion animal model, hyperglycemia increases the volume of mean lesion size in diffusion- weighted imaging by 118% and hemispheric cerebral blood volume is reduced by 37% in hyper-glycemic rats compared with normoglycemic rats[51].

Hyperglycemia further aggravates the stroke consequences through augmented reperfusion injury by increasing oxidative stress, stimulating systemic inflammation and increasing barrier permeability. Patients with acute ischemic stroke with both diabetes and hyperglycemia have an increase in aggregation and adhesion of platelets to the endothelium. A study conducted in Glasgow showed that higher plasma glucose predicted a poorer prognosis (relative HR = 1.87; 1.43–2.45) even after correcting for age, stroke severity and stroke subtype[52].

In tPA-treated patients, acute hyperglycemia delays reperfusion of the ischemic penumbra and decreases tPA-induced recanalization rates. Among patients with stroke who were treated with intravenous thrombolysis, hyperglycemia was associated with significantly lower rates of desirable clinical outcomes, higher rates of symptomatic ICH and reduced benefits from recanalization with thrombolytic therapy. In the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial, the odds for symptomatic intracerebral hemorrhage (ICH) increased to 75% when the admission glucose increased every 100 mg/dL[53].

A study that aimed to assess total antioxidant capacity and oxidative stress in diabetic and nondiabetic acute stroke patients with 2 different stroke subtypes, large and small vessel disease strokes, concluded that oxidative stress and counter balancing antioxidant capacity are more pronounced in diabetic acute stroke patients than in non diabetics [54].

The mechanism by which poor glycemic control before onset is associated with unfavourable outcome of ischemic stroke

is unclear. Persistent hyperglycemia is thought to be associated with the expansion of infarct volume and worse functional outcome[55]. Admission hyperglycemia has been independently associated with bad outcome both in patients with and without diabetes[56]. One of the proposed mechanisms is that hyperglycemia itself probably results in neurotoxicity and induces a procoagulant state[57].

Hyperglycemia arises in 30–40% of people with acute ischemic stroke both in patients with diabetes mellitus and in patients without a previous history of diabetes and, although in some patients 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. These include the altered recanalization that has been attributed to disorders in coagulation and in fibrinolytic pathways mediated by hyperglycemia[58, 59], 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[60]. 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.

Data from the large prospective European multicenter study showed that stroke in patients with diabetes mellitus was different from stroke in non diabetic 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 handicap 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. [61] 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).

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 hyperglycemia and vascular risk factors such as hypertension and dyslipidemia[62, 63]. In addition to these also genetic, demographic, and lifestyle factors contribute in varying degrees to the overall risk of people with diabetes[64- 68]. As a whole, all these factors, contribute to the characteristic atherogenic profile of the patients with diabetes mellitus, in which there is a complex interplay of several variables with inflammatory metabolic disorders and their effects on the cardiovascular system that may accelerate the atherosclerotic process both in intracranial that extracranial vessels.

Stress hyperglycemia might be a marker of impaired glucose regulation in patients with insulin resistance and is known to be associated with poor outcome after stroke[69, 70]. The association between FBS level and stroke severity in the patients of our study with a relatively normal HbA1c might indicate the effect of stress hyperglycemia; however, stress hyperglycemia might be understood as a protective response that may help survival[71]. The pathophysiological or clinical implications of stress hyperglycemia should be revealed by future studies.

Randomised clinical trials (RCTs) and meta-analysis have failed to show the benefit of intensive glucose control on rates of stroke[72]. Often, females are under represented in RCTs[73], thus there is a need for more observational data to assess whether there is a sex-specific association between HbA1c and the risk of stroke.

Tight Glycemic control appears to be safe in acute ischemic stroke. However, the effectiveness for improving outcome has not been proven, despite positive relationship between glucose level and stroke outcomes in clinical setting. An older trial of glucose potassium insulin infusion in acute ischaemic stroke found that it lowered blood glucose, but it did not affect cerebral growth, was associated with a high incidence of asymptomatic hypoglycemia[74].

Two more recent trials using very developed monitoring protocols found no significant safety concerns[75, 76]. In Acute stroke, treat persistent hyperglycemia (>140mg/dl) with insulin and monitoring to avoid hypoglycemia[77].

Intensive versus Standard Control

There is no evidence that tighter chronic glycemic control prevents first or recurrent stroke even among high risk persons. Three large secondary prevention trials have examined tight control, compared with conventional control, for prevention of macrovascular events in type 2 diabetes.

In the Action in Diabetes and vascular disease: Preterax and Diamicron MR controlled Evaluation (ADVANCE)study , no difference was found between the invasive versus standard control group with respect to the rate of non fatal stroke (3.8% in both treatment groups), major cerebrovascular events (4.3% vs 4.4%), or all cerebrovascular events (6.3% vs. 5.9%) [78]

In the Action to control cardiovascular risk in Diabetes (ACCORD) study, there is no difference in nonfatal or fatal stroke rate between the two treatment groups[79, 80]. The third trial, the Veteran's Affairs Diabetes Trial (VADT) showed no difference in cardiovascular events or all cause mortality, including stroke, between the two treatment groups[81].

It is important to note that none of these trials were designed specifically to examine secondary prevention of stroke in patients with diabetes. Instead they examined stroke as one in a composite of macrovascular outcomes .In the setting of acute stroke, hyperglycemia aggressive management of glucose has also failed to demonstrable benefit .The largest trial to date, the Glucose Insulin in Stroke Trial (GIST), did

not show benefit in 90 day mortality, which was primary end point, or severe disability, the secondary end point[82].

4. Materials and Methods

Study Site: Deenanath Mangeshkar Hospital and Research Centre, Erandawane, Pune -411004.

Study Population: All patients of acute Ischaemic stroke.

Study Design: Prospective comparative study.

Sample size with Justification: A sample size of 70 ischemic stroke patients suffering from diabetes (cases; HbA1c>=6.5) at the time of stroke with 70 non-diabetic ischemic stroke patients (controls; <6.5) at the time of the stroke is needed to detect 3a difference of 16% in the % patients with functional dependency (on the basis of MRS>=3) at 1 month of stroke follow-up between the controls (non-diabetic patients, 4%) and cases (diabetes patients, 20%) based on previous studies, with 80% power (two-sided) at a significance level of α=5%.

Time frame to address the Study: June 2017 to June 2018.

Inclusion criteria
All acute Ischemic stroke patients of age more than 18 years treated conservatively, with intravenous thrombolysis and intravascular interventions (i.e intra-arterial thrombolysis, mechanical thrombectomy).

Exclusion criteria:
1) Cardioembolic strokes.
2) Transient ischemic attacks.
3) Patients with recurrent cerebrovascular events.
4) Patients with proven etiology other than atherosclerosis e.g. Vasculitis, hypercoagulability status.
5) Patients who were discharged against medical advice or atrequest.

4.1 Methodology

Methodology of data collection and procedure:
Every consecutive consenting patient admitted between 15th June 2017 to 15th June 2018 with established Ischemic stroke at study site included in the study group. HbA1c and random blood sugar levels of these patients sent on admission. Consenting patients were classified into 2 groups at inclusion: Diabetics and non-diabetics until sample size of 70 is achieved in each group.

Diabetics were further subclassified into diabetics with good glycemic control (HbA1c < 7) and with poor glycemic control (HbA1c >7).

All patients with acute ischemic stroke were enrolled after fulfilling inclusion and exclusion criteria in our study after a detailed informed consent.

A proforma has been prepared which includes detailed history, clinical examination and all necessary investigations.

History: Includes all the symptoms pertaining to the ischemic stroke in detail with emphasis on all the risk factors including glycemic status at the time of admission.

The stroke severity at admission was assessed with the help of NIHSS score and patients were followed up at the time of discharge and at the end of one month subsequently. The stroke functional outcome at the time of discharge and at the end of month was assessed by modified Rankin scale.

Clinical data was entered in AHIS (Amrita) software used by the hospital. Random blood sugar was checked by glucometry (Capillary sugar level). HbA1C level was measured in the biochemistry Laboratory by high performance liquid chromatography at Deenanath Mangeshkar Hospital. The data of the patients in both groups was compiled in a tabular form for the ease of application of statistical methods.

5. Statistical Methods

Statistical analysis was carried out with the help of SPSS (version 20) for Windows package (SPSS Science, Chicago, IL, USA). The description of the data was done in form of arithmetic mean +/- SD for quantitative data while in the form of frequencies (%) for qualitative (categorical) data. P-values of < 0.05 was considered significant. For quantitative data, Unpaired Student's t-test was used to test statistical significance of difference between means of variables among two independent groups (Diabetics & Non-diabetics). Significance of the differences between more than 2 group means (diabetic patients with good glycemic control & poor glycemic control & non-diabetics) was tested using ANOVA followed by Post-hoc test for multiple comparisons. For comparison of categorical variables (i.e to examine the associations between qualitative/ quantitative variables), chi-square test was used if the number of elements in each cell are 5 or higher and Fisher's exact test, otherwise. Categorical variables where more than two categories are present, was analysed using a $\chi 2$ test; p values from Fishers exact test was presented where appropriate due to small counts. To compare proportions between two independent groups Z test of proportions was used.

6. Observation and Results

The data was arranged in tabular form as observations and was analysed using statistical tests.

Table 3: Gender wise distribution of study subjects

Gender	Number of patients	Percentage (%)
Male	93	66.4
Female	47	33.6
Total	140	100.0

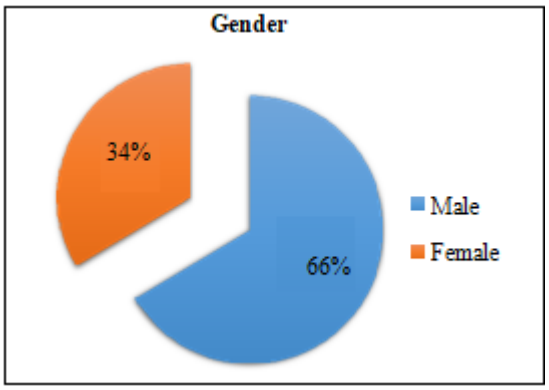

Figure 1

The above table and figure represent the gender distribution of subjects in our study, there were 93 males (66.4%)and 47 females (33.6%).

Table 4: Age wise distribution of study subjects

Age group (years)	Number of patients	Percentage (%)
≤ 40	7	5.0
41 - 50	12	8.6
51 - 60	26	18.6
61 - 70	42	30.0
71 -80	36	25.7
> 80	17	12.1
Total	140	100.0

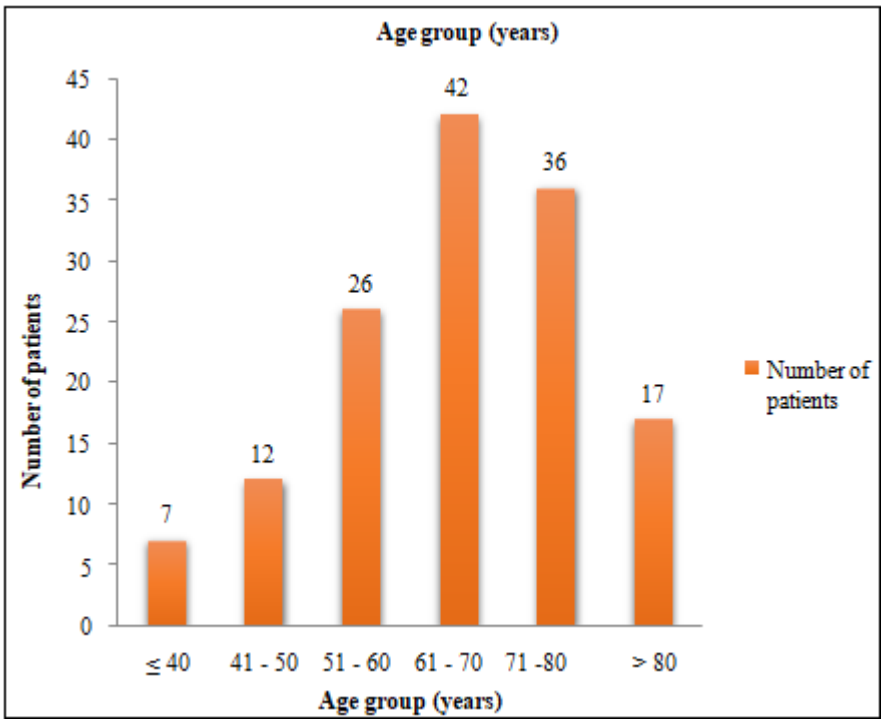

Figure 2

The above table and figure represent the age distribution of subjects in our study, there were 7 subjects < 40 years (5%),12 subjects 41-50 years (8.6%), 26 subjects 51-60 years (18.6%),42 subjects 61-70 years(30%), 36 subjects 71-80 years (25.7%),17 subjects >80 years (12.1).

Table 5: Age and gender wise distribution of study subjects

Age group	Gender		Total
	Male	Female	
≤ 40	5	2	7
41 - 50	8	4	12
51 - 60	18	8	26
61 - 70	30	12	42
71 -80	22	14	36
> 80	10	7	17
Total	93	47	140

The above table represents maximum incidence of stroke among males is between 61-70 years, in females the maximum incidence of stroke is between 71-80 years.

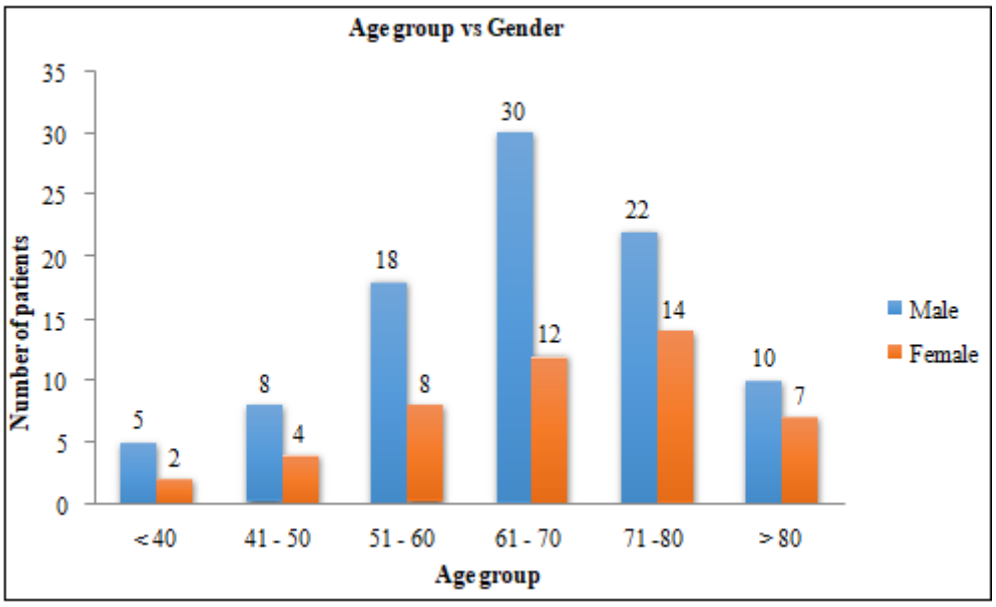

Figure 3

This is the bar chart representation of the above tabular data

Table 6: Diabetes history

Diabetes Mellitus	Number of patients	Percentage (%)
Yes	70	50.0
No	70	50.0
Total	140	100.0

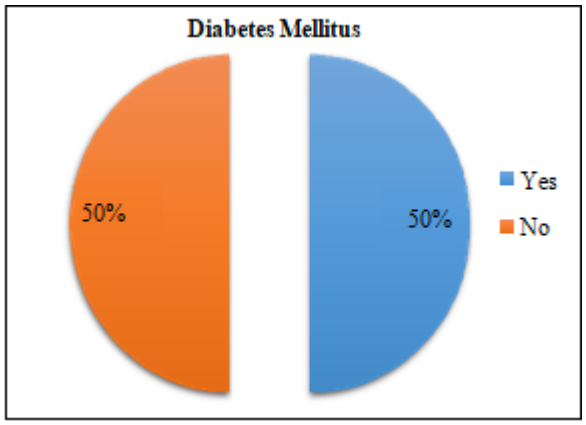

Figure 4

The above table and figure represent 70 diabetics (50%), 70 non diabetics (50%).

Table 7: Other Comorbidities

Other Comorbidities	Number of patients	Percentage (%)
Hypertension	88	62.86
IHD	32	22.86
Peripheral vascular disease	1	0.71

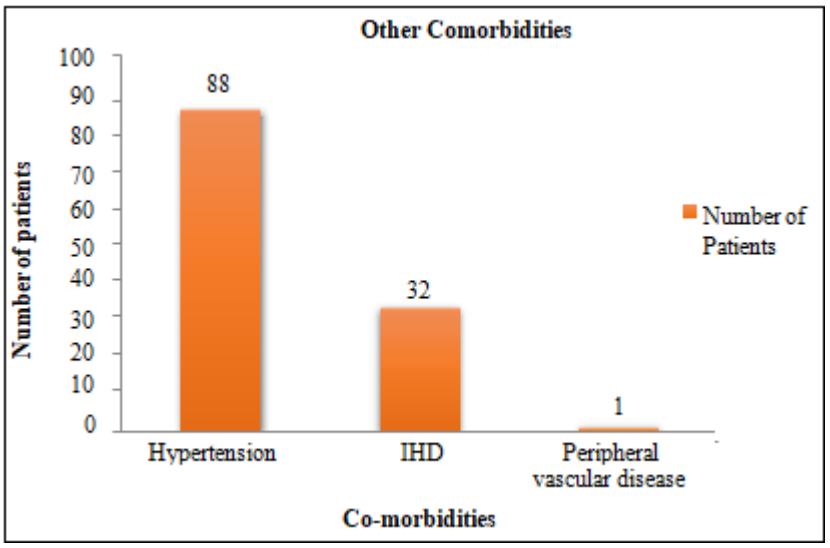

Figure 5

The above table and figure represent the subjects with hypertension 88 (62.86%), Ischemic heart disease 32 (22.86%), Peripheral vascular disease 1(0.71%).

Table 8: Addictions

Addiction	Number of patients	Percentage (%)
No Addiction	133	95.0
Alcohol	4	2.9
Tobacco	3	2.1
Total	140	100.0

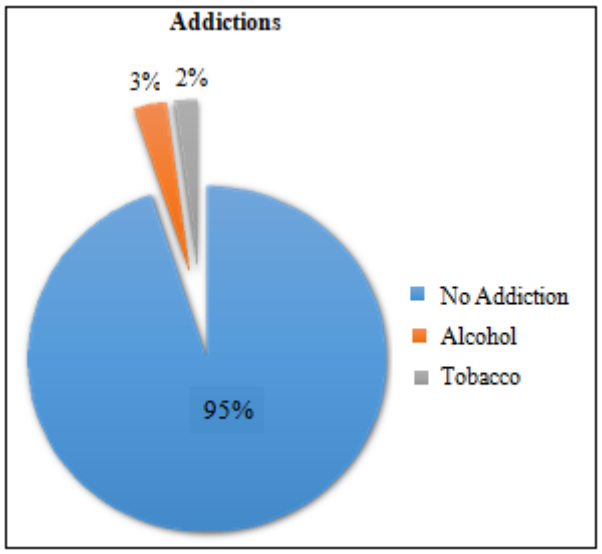

Figure 6

The above table and figure represent the subjects with addictions: Alcohol 4(2.9%), Tobacco 3 (2.1%), No addictions 133 (95%).

Table 9: Glycemic status based on HbA1c Level

Diabetes Mellitus Status	Number of patients	Percentage (%)
Poorly controlled DM	56	40.0
Good controlled DM	14	10.0
No Diabetes	70	50.0
Total	140	100.0

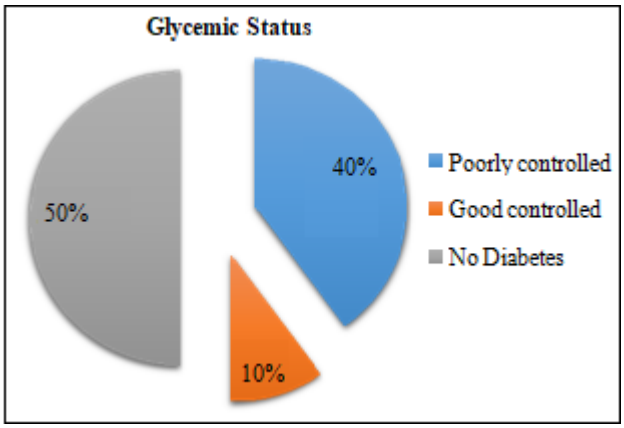

Figure 7

The above table and figure represent the subjects with poorly controlled DM 56 (40%), Good controlled DM 14 (10%), No Diabetes 70 (50%).

Table 10: Stroke severity based on NIHSS score

NIHSS score	At Admission		At Discharge	
	Number of patients	Percentage (%)	Number of patients	Percentage (%)
Mild	44	31.4	79	56.4
Moderate	90	64.3	59	42.1
Moderate to Severe	4	2.9	2	1.4
Severe	2	1.4	0	0
Total	140	100.0	140	100.0

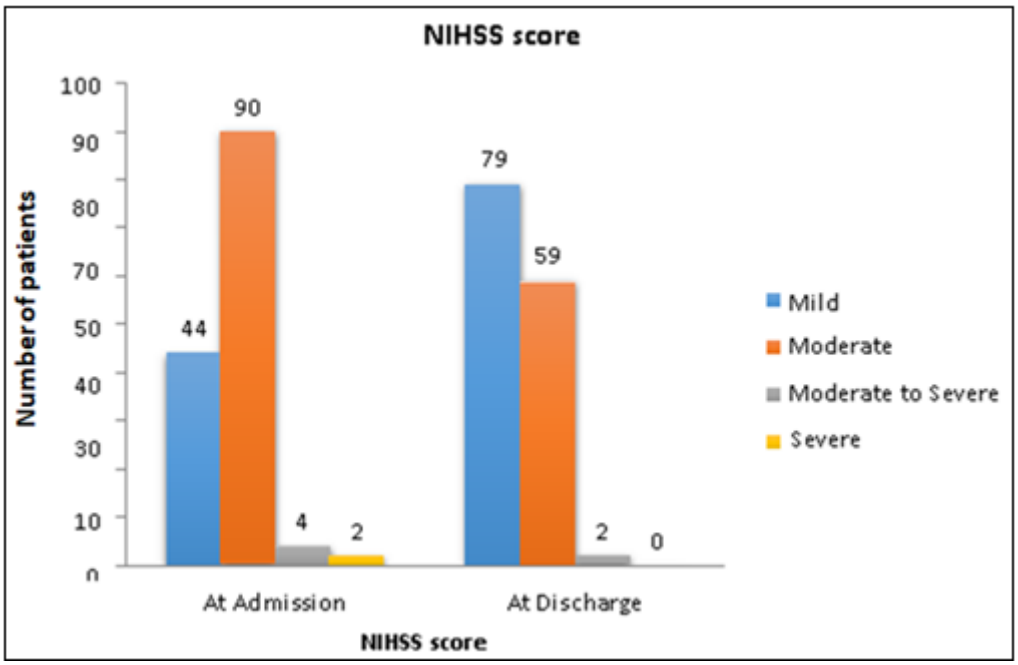

Figure 8

The above table and figure represent the subjects with stroke, severity is classified based on NIHSS score 44 subjects had mild stroke (31.4%), 90 Subjects had moderate stroke (64.3%),4 Subjects had moderate to severe stroke (2.9%),2

subjects had severe stroke 1.4%).

Table 11: Functional outcome based on MRS (At the end of one month)

Functional outcome	Number of patients	Percentage (%)
Poor	7	5.0
Moderate	26	18.6
Good	107	76.4
Total	140	100.0

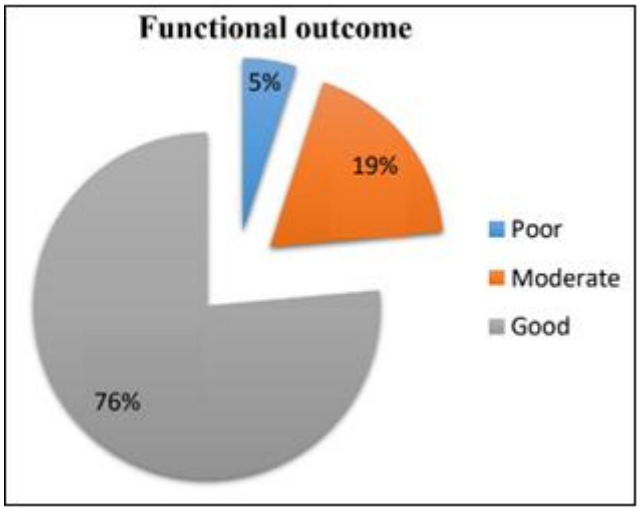

Figure 9

The above table and figure represent the subjects in which functional outcome at one month was assessed based on MRS, 7 patients had poor outcome (5%), 26 patients had moderate outcome (18.6%), 107 patients had good outcome (76.4%).

Table 12: Gender predisposition to Diabetes mellitus

Gender	Diabetes Mellitus (DM) status			Total	p-value
	Poorly Controlled DM	Good Controlled DM	No DM		
Male	41	12	40	93	0.048
Female	15	2	30	47	
Total	56	14	70	140	

The above table represents statistical significance regarding gender predisposition to Diabetes mellitus by using chi-square test ($P<0.05$).

Out of 93 males, 41 had poorly controlled DM, 12 had good controlled DM, 40 do not have DM.

Out of 47 females, 15 had poorly controlled DM, 2 had good controlled DM, 30 do not have DM.

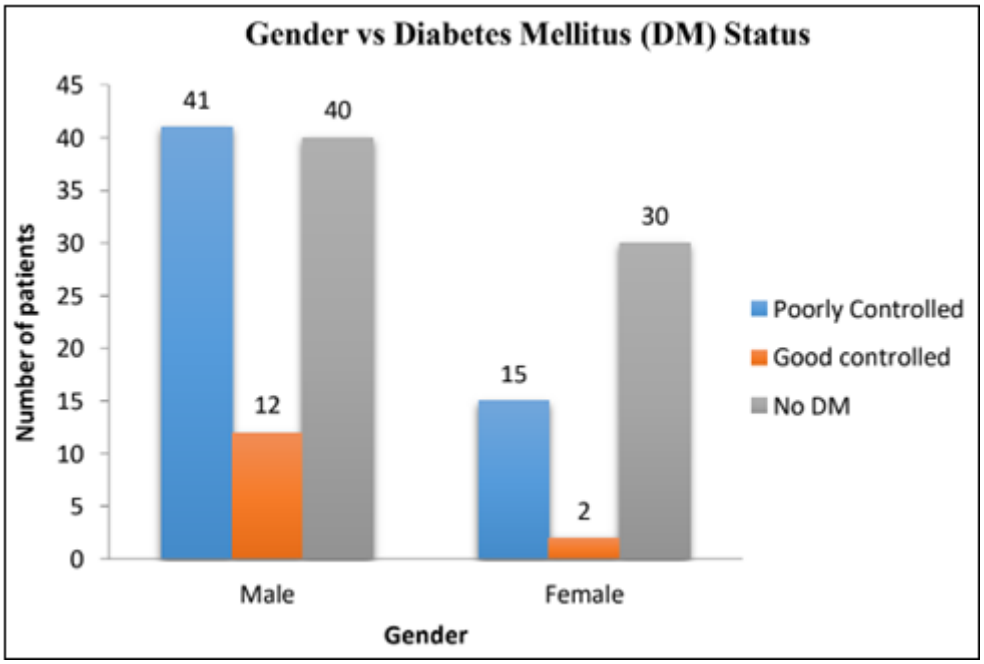

Figure 10

This is the bar chart representation of the above tabular data

Table 13: Diabetic status based on age group

Age group	Diabetes Mellitus (DM) status			Total	p-value
	Poorly Controlled DM	Good Controlled DM	No DM		
≤ 40	1	0	6	7	0.173
41 - 50	4	2	6	12	
51 - 60	13	2	11	26	

61 - 70	22	6	14	42	
71 -80	11	2	23	36	
> 80	5	2	10	17	
Total	56	14	70	140	

The above table represents status of DM did not show any statistical significance with age group (P>0.05 using Fisher's exact test).

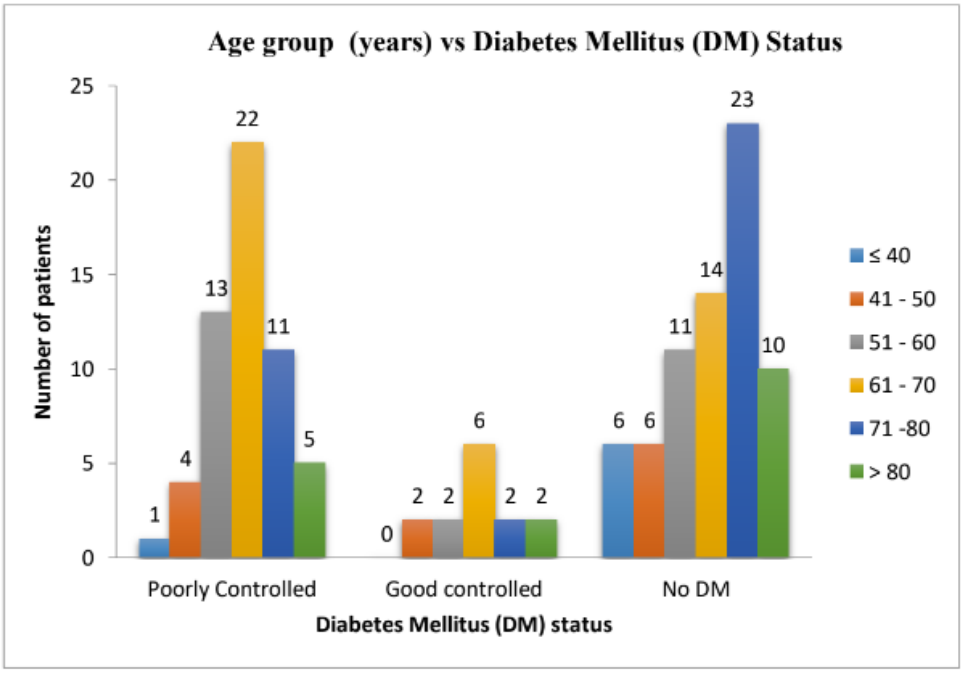

Figure 11

This is the bar chart representation of the above tabular data**.**

Table 14: Corrrelation of NIHSS at admission with DM status

NIHSS score at admission	Diabetes Mellitus (DM) status			Total	p-value
	Poorly Controlled DM	Good Controlled DM	No DM		
Mild	18	5	21	44	0.35
Moderate	33	9	48	90	
Moderate to Severe	4	0	0	4	
Severe	1	0	1	2	
Total	56	14	70	140	

The above table represents NIHSS at admission did not show any statistical significance with status of DM (P>0.05 using Fisher's exact test).

Table 15

Diabetes Mellitus (DM) status	Number of patients	NIHSS score at admission	
		Mean	SD
Poorly Controlled DM	56	7.55	4.27
Good controlled DM	14	6.07	3.58
No Diabetes mellitus	70	7.30	4.05

The above table represents 56 poorly controlled DM patients had mean of 7.55 , SD of 4.27, 14 good controlled DM had mean of 6.07, SD of 3.58, 70 non diabetic patients had mean of 7.30 and SD of 4.05.

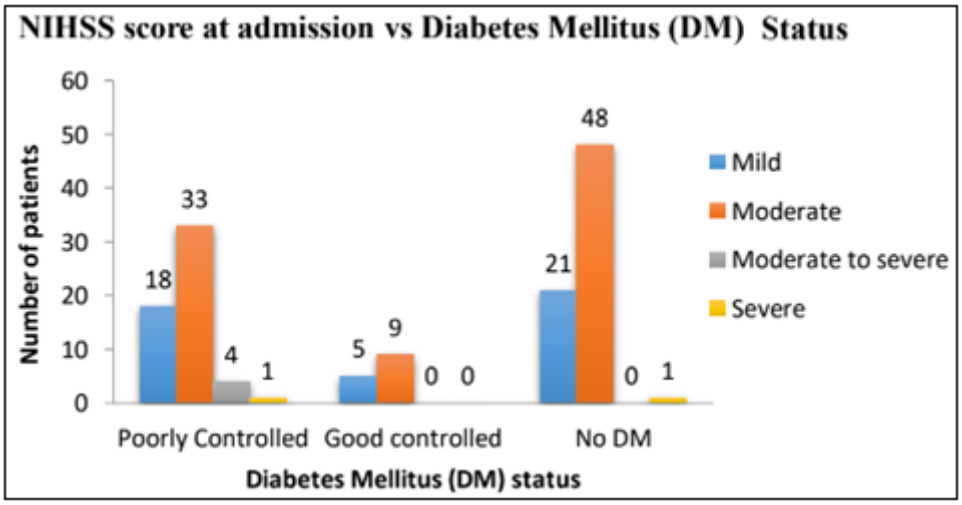

Figure 12

This is the bar chart representation of the above tabular data.

Table 16: Correlation of NIHSS at discharge with DM status

NIHSS score at Discharge	Diabetes Mellitus (DM) status			Total	p-value
	Poorly Controlled DM	Good Controlled DM	No DM		
Mild	29	11	39	79	0.444
Moderate	26	3	30	59	
Moderate to Severe	1	0	1	2	
Total	56	14	70	140	

The above table represents NIHSS at discharge did not show any statistical significance with status of DM (P>0.05 using Fisher's exact test).

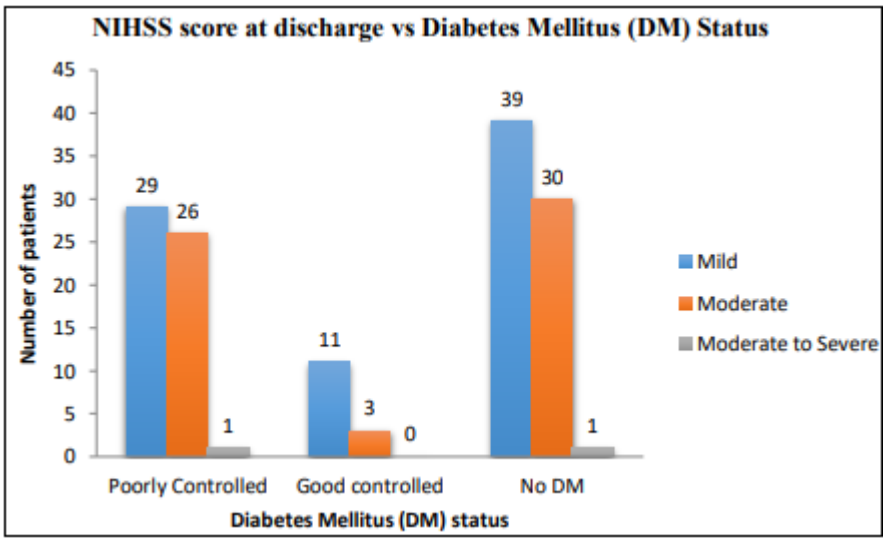

Figure 13

This is the bar chart representation of the above tabular data**.**

Table 17: Correlation of functional outcome with DM status

Functional outcome	Diabetes Mellitus (DM) status			Total	p-value
	Poorly Controlled DM	Good Controlled DM	No DM		
Poor	3	1	3	7	0.751
Moderate	12	1	13	26	
Good	41	12	54	107	
Total	56	14	70	140	

The above table represent functional outcome of stroke at one month did not show any statistical significance with status of DM (P>0.05 using Fisher's exact test).

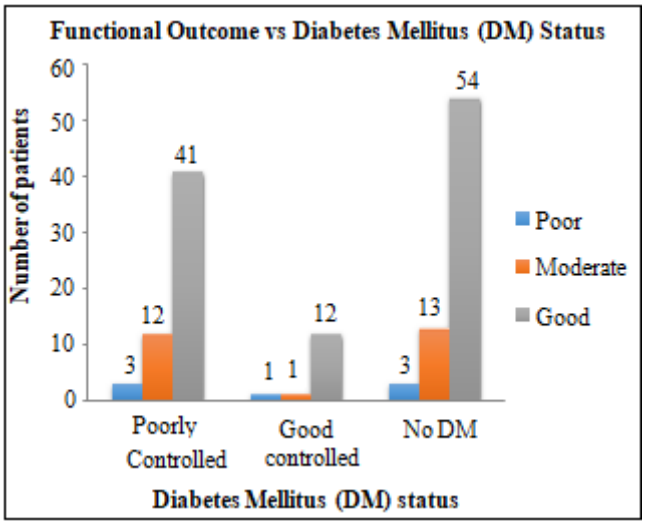

Figure 14

This is the bar chart representation of the above tabular data**.**

Table 18, 19: Correlation of DM status with MRS.(At discharge and one month).

Diabetes Mellitus (DM)	Number of patients	MRS at discharge		p-value
		Mean	SD	
Poorly Controlled DM	56	2.82	1.36	0.213
Good controlled DM	14	2.14	1.23	
No Diabetes mellitus	70	2.59	1.31	

The above table represent DM status did not show any statistical significance with MRS at discharge (P>0.05 using Anova test).

Diabetes mellitus Status	Number of patients	MRS at 1 month		p-value
		Mean	SD	
Poorly Controlled DM	56	2.82	1.36	0.369
Good controlled DM	14	2.14	1.23	
No Diabetes mellitus	70	2.59	1.31	

The above table represent DM status did not show any statistical significance with MRS at one month (P>0.05 using Anova test).

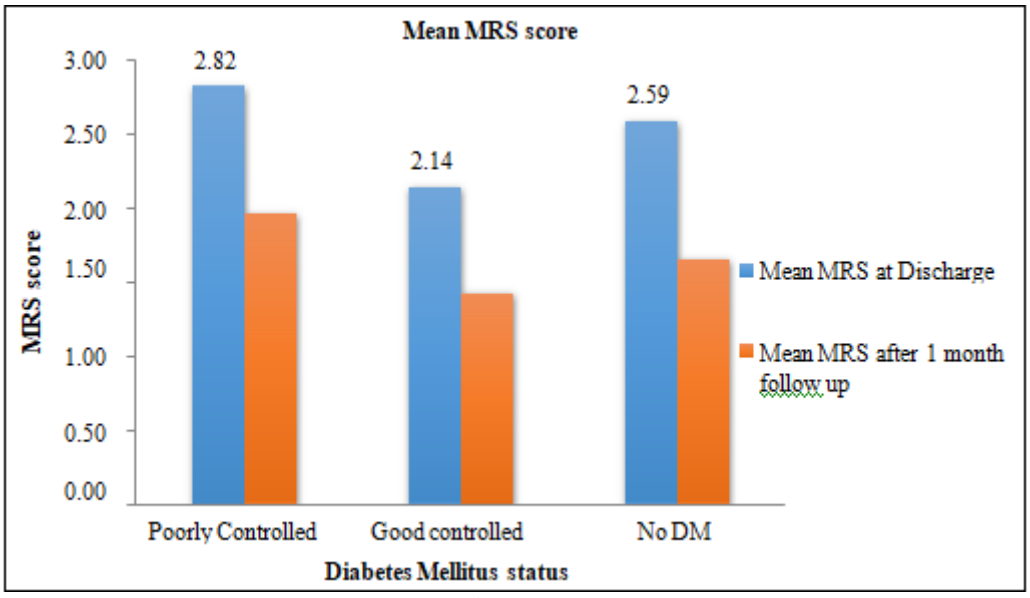

Figure 15

This is the bar chart representation showing mean MRS score.

Table 20: Correlation of NIHSS at admission and random blood sugar

NIHSS score at admission (Stroke severity)	Random Sugar		Total	p-value
	Normal	Abnormal		
Mild	28	16	44	0.761
Moderate	64	26	90	
Moderate to severe	3	1	4	
Severe	1	1	2	
Total	96	44	140	

This table showed that NIHSS at admission (Stroke severity) did not show any statistical significance with random blood sugar (P>0.05 using Fisher's exact test).

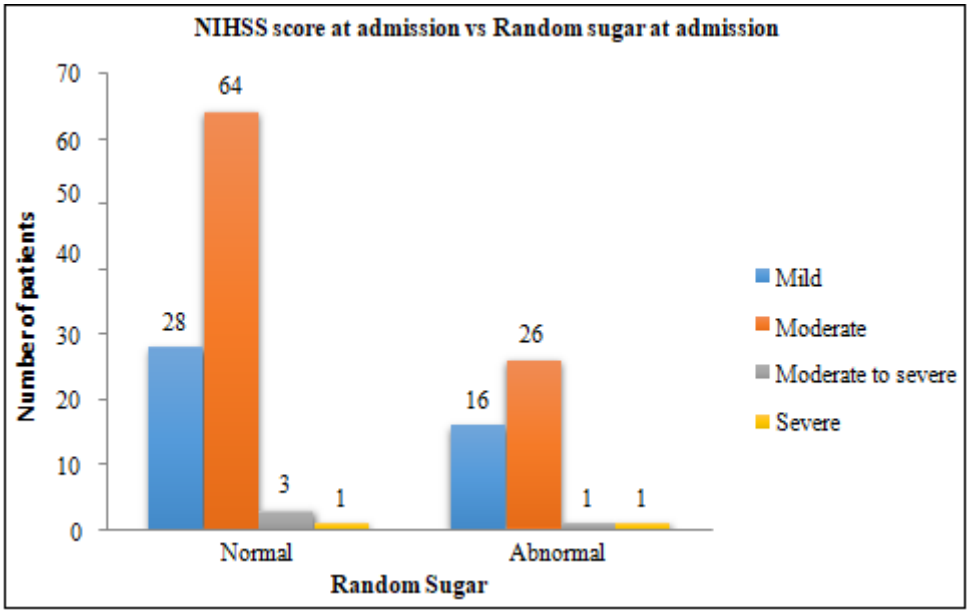

Figure 16

This is the bar chart representation of the above tabular data.

Table 21: Random blood sugar at one month and functional outcome (mean MRS at one month)

Random sugar (mg/dl)	Number of patients	MRS at after one month (follow up)		p-value
		Mean	SD	
Normal<200	96	1.96	1.48	
Abnormal >200	44	1.43	1.70	0.97

The above table represent MRS at the end of one month did not show any statistical significance with random blood sugar (p>0.05 not significant Unpaired t-test used)

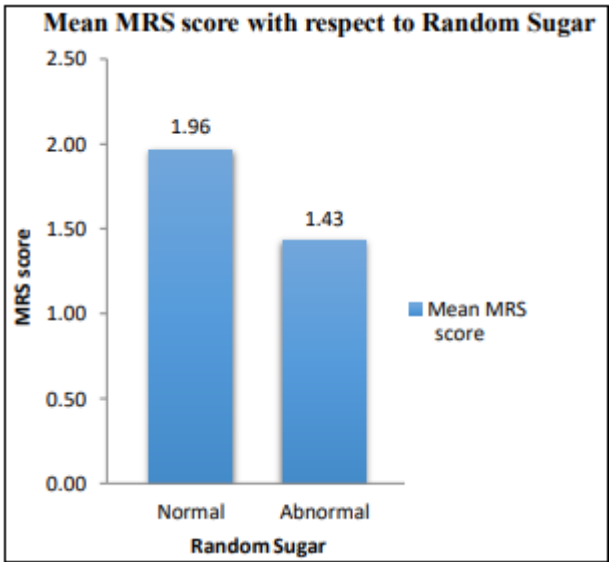

Figure 17

This is the bar chart representation of the above tabular data**.**

Table 22: Correlation of comorbidities and severity of stroke at admission

Comorbidities	NIHSS at admission				Total	p-value
	Mild	Moderate	Moderate to Severe	Severe		
Normal(no comorbidities)	21	48	0	1	70	0.073
DM + HTN + IHD	4	16	1	0	21	
DM + HTN	14	14	1	0	29	
DM + IHD	0	1	0	0	1	
Only DM	5	11	2	1	19	
Total	44	90	4	2	140	

The above table represents multiple comorbidities do not have statistical significance with stroke severity at admission (P-value > 0.05 not significant Fisher's exact test used).

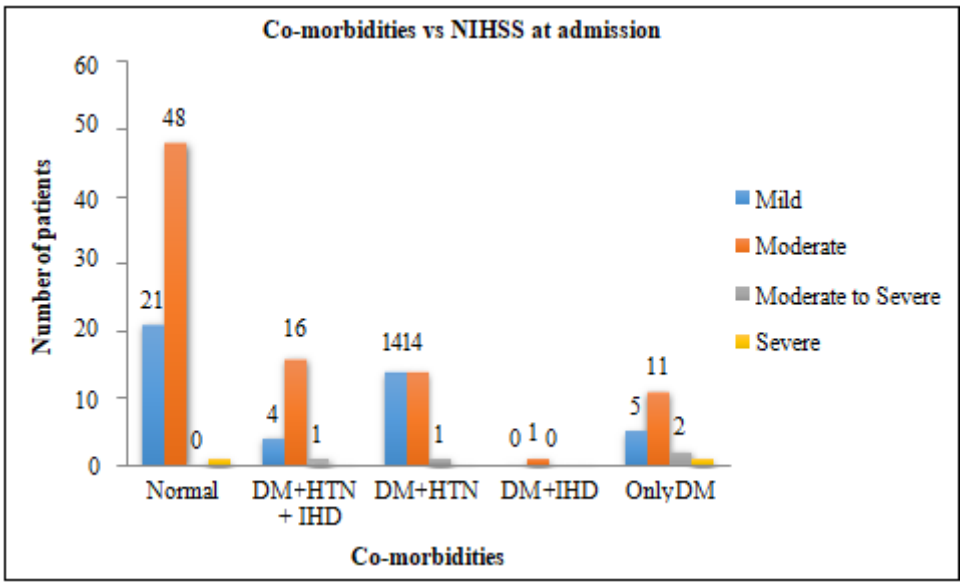

Figure 18

This is the bar chart representation of the above tabular data**.**

7. Discussion

In our study, we enrolled 140 patients above age of 18 years who were diagnosed to have acute ischemic stroke admitted in Deenanath Mangeshkar Hospital during the 12 months period in whom HbA1c, random blood sugar and all other necessary investigations were done.

Statistical analysis of the risk factors was done and observations and results of our study have been discussed here.

Gender, Age distribution and previous history of diabetes (Table no.3- Table no. 6)
In our study out of 140 patients with AIS, 93 were males (66.4%) and 47 were females (33.6%). Similar findings were observed in the study conducted by Sunanda T et al., in which out of 130 stroke patients 94 were males, 36 were females[86].

In our study, there were 7 subjects < 40 years (5%),12 subjects 41-50 Years (8.6%), 26 subjects 51-60 years (18.6%),42 subjects 61-70 years (30%), 36 subjects 71-80 years (25.7%),17 subjects >80 years (12.1). With most common age for acute ischemic stroke is among 61-70 years (30%). Similar findings were noted in study conducted by Lee et.al., out of 2595 patients mean age group of stroke is 55-75 years [87].

After 80 years, incidence of stroke decreased in our study because of two reasons: According to latest WHO data published in 2018, life expectancy in India is :male 67.4 , female 70.3 and total life expectancy is 68.8[83] and Social factors such as decision of not seeking medical advice or non aggressive care in this age group by family members . Majority of these patients were being taken to nearby nursing care instead of tertiary care centre.

Before 40 years incidence is very less because of two reasons: Atherosclerosis is a chronic process, it takes many years before ultimately developing to ischemic stroke and Usually for patients with less than 40 years associated risk factors will be relatively less.

In our study out of 140 stroke patients, 70 were diabetics and 70 were non diabetics. In Sunanda et.al., study out of 130 stroke patients 100 were diabetics and 30 were non diabetics.

Other comorbidities (Table no.7)
Associated comorbidities with stroke includes hypertension in 88 subjects (62.86%), Ischemic heart disease in 32 subjects (22.86%), Peripheral vascular disease in only one (0.71%). In a study conducted by C. Stollberger et.al., out of 992 patients with stroke, 679 patients had hypertension (68%) and 273 patients had ischemic heart disease (27%)[88].

Addictions (Table no.8)
Only few patients have addictions among all 140 patients, alcohol in 4(2.9%), Tobacco in any form either smoking or chewing 3 (2.1%), No addictions in 133 (95%). In contrary to study conducted by Sunanda T et al., Out of 130 patients 78 were smokers and 89 were alcoholics.

Glycemic status based on HbA1c Level (Table no .9)
Our study showed that out of 70 patients, 56 patients have poorly controlled DM (80%), 14 patients have good controlled DM (20%). In study by Sunanda T et.al., out of 100 patients ,60 were good controlled and 40 were poorly controlled [86].

The above classification of Diabetic status is based on HbA1c level as per ADA guidelines.

We had divided acute ischemic stroke patients into groups - Diabetics and non Diabetics , study population are half in each set and further Diabetics are divided into poorly controlled and good controlled .Among Diabetics in our study poorly controlled group predominates over good controlled group in number .

There are 4 patients with increased random blood sugar (>200mg/dl) with normal HbA1c (stress hyperglycemia - increased random blood sugar but normal Hba1c).

Stroke severity based on NIHSS (At admission & Discharge)-(Table no.10)
In our study we found that majority of the patients who present with stroke, 90 patients presented with stroke of moderate intensity at admission (NIHSS 5-15) and 59 patients had stroke of moderate intensity at discharge (NIHSS 5-15). 2 Patients presented with severe stroke (NIHSS 21-42) at admission and no one had stroke with severe intensity at discharge.

In four patients with stress hyperglycemia (Increased BSL at admission and normal HbA1c), 2 patients had stroke of mild intensity and two patients had stroke of moderate intensity.

Functional Outcome based on MRS (At the end of one month)-(Table no.11)

- In our study we found 7 patients had poor functional outcome (MRS 5- 6), 26 patients had moderate functional outcome (MRS 3-4) and 107 patients had good functional outcome (MRS 0-2).Out of 7 patients with poor functional outcome 6 died .
- Gender and age predisposition to Diabetes mellitus - (Table no.12 and table no.13)

There is statistical significance regarding gender predisposition to Diabetes mellitus by using chi-square test ($P<0.05$).

Out of 93 males, 41 had poorly controlled DM, 12 had good controlled DM, 53 in total (56%). Out of 47 females ,15 had poorly controlled DM ,2 had good controlled DM ,17 in total (34%). In study conducted by Sunanda

T. et al., Out of 100 patients 72 were males (72%) and 28 were females (28%)[86].

Most of the diabetic patients presenting with stroke were in between 61-70 years of age. In non diabetics stroke is more common in age group between 71-80 years .In both groups the incidence becomes very less as we compare patients with age <40 years and > 80 years.

Correlation of NIHSS at admission with DM status - (Table no.14) Upto 90 patients in our study who presented with stroke of moderate severity 48 patients (53%) were non diabetics ,42 patients were diabetics in total (47%) , further with good controlled DM 9 patients (21%), poorly controlled DM 33 patients (79%).There were only two patients who presented with severe stroke (high NIHSS) in which there is equal distribution with diabetic and non DM one each . In the study conducted by Sunanda T et al., 97.5% of patients of poor glycemic control group had moderate to severe stroke at admission where as 53.3% of good glycemic control group had stroke of mild severity[86].

The differences in both studies are because in our study poor glycemic control subjects predominates over good control , we had equal number of diabetic and non diabetic patients . Addictions showed no statistical association with stroke in our study.

Correlation of NIHSS at discharge with DM status - (Table no.16) There are 79 patients with mild severity of stroke at discharge (NIHSS 1- 4), among those 29 were poorly controlled, 11 good controlled and 39 were non diabetics .Among 59 patients with moderate severity of stroke at discharge (NIHSS 5-15) 26 were poorly controlled , 3 were good controlled and 30 patients were non diabetics .only 2 patients had moderate to severe intensity of stroke at discharge (NIHSS 16-20) which includes one DM and non diabetic.

Correlation of Functional outcome at one month with DM status (Table no 17)
Out of 70 DM patients, only 4 had poor functional outcome (MRS 5-6), even in 70 non diabetic patients, only 3 had poor functional outcome .Out of 7 patients who had poor functional outcome 6 died (MRS 6).

Majority of patients presenting with ischemic stroke showed good functional outcome (MRS 0-2) irrespective of glycemic status diabetic vs non diabetic, poor vs good controlled patients.

Relatively few studies have addressed the effect of HbA1c on stroke outcomes.A study involving patients from the Fukuoka stroke registry did not find an association between HbA1c and functional outcomes[84]. Similar findings were noted in study conducted by Lee et.al., out of 2595 patients functional study was not associated with HbA1c level[87]. A study conducted by sung bong et al., in 2014 at dankook university hospital, 65 patients were followed upto 3 months and found that HbA1c is not associated with functional outcome of stroke[89].

A recent study by Chinese investigators showed that newly diagnosed diabetes with isolated elevation of HbA1c which was not accompanied by elevated blood glucose level was not associated with poor outcome after ischemic stroke[85]. In this study Jing Jing et al., studied 1251 patients of ischemic stroke from 2008-2009, among which 539 patients were Non insulin dependent diabetes mellitus (NDDM) and 141 patients of NDDM with single high HbA1c.They were followed upto one year and found that NDDM was associated with poor prognosis at 1 year after ischemic stroke, however, NDDM with single high HbA1c did not predict a poor prognosis
89.

In our study high HbA1c levels could not be correlated with functional outcome at the end of one month, however discrimination of diabetics into NDDM and NDDM with single high HbA1c was not done in our study.
Small population was considered as main limitation in our study and prolonged follow up is necessary.

Correlation of NIHSS at admission (Stroke severity) and random blood sugar -(Table no.20)
We found that out of 140 patients, 96 patients had random blood sugar sugars < 200 mg/dl at presentation, 44 patients had random blood sugar> 200 mg/dl.

Glycemic status based on random blood sugar level has no statistical correlation assessing severity of stroke.

Even in patients with abnormal random blood sugar >

200mg/dl at admission, severity of stroke was mild to moderate which holds same for patients with random blood sugar < 200mg/dl.

Random blood sugar at 1 month and functional Outcome (MRS at 1 month)--(Table no. 21)

MRS (functional outcome) at the end of one month did not show any statistical significance with random blood sugar (p>0.05 not significant).

Out of 96 patients with random blood sugar < 200mg/dl mean MRS was 1.96 , Standard deviation SD was 1.48 while in 44 patients with random blood sugar >200mg /dl mean MRS was 1.43 and SD was 1.70.

The largest trial to date, the Glucose Insulin in Stroke Trial (GIST), did not show benefit in 90 day mortality, which was primary end point, or severe disability, the secondary end point [82].

In our study we followed upto one month, but in above trial they were followed till 3 months.

Correlation of comorbidities and severity of stroke at admission- (Table no.22)
There are 70 individuals (no prior comorbidities) who presented with stroke in whom 21 had mild severity, 48 had moderate severity, one had severe stroke.

In rest 70 ischemic stroke patients, 21 patients had all the three comorbidities, among whom 4 patients had mild stroke, 16 had moderate severity, one had moderate to severe stroke.

29 patients had both diabetes and hypertension, in whom 14 had mild stroke, 14 had moderate stroke and 1 had moderate to severe stroke.

There is only one patient with diabetes and ischemic heart disease, who presented with moderate stroke.

There are only 19 patients with only diabetes, among whom 5 patients had mild stroke, 11 had moderate stroke, 2 had moderate to severe stroke, 1 had severe stroke.

Out of six patients who expired at the end of one month three were non diabetics, two were poorly controlled and one had good controlled DM. Among those six patients, four patients had hypertension and three patients' ischemic heart disease. Two patients had all the three Diabetes mellitus, hypertension and ischemic heart disease.

8. Summary

- The main purpose of this research was to study the effect of glycemic status in ischemic stroke patients admitted in Deenanath Mangeshkar Hospital Pune on severity and functional outcome.
- All the acute ischemic stroke patients presenting to emergency, neurology and medicine departments are broadly divided into two groups : diabetics and non diabetics based on HbA1c level and random blood sugar .Even diabetics are further divided into good controlled and poorly controlled diabetics .Study was continued till equal number of sample achieved in each group (70 diabetics and 70 non diabetics).This is follow up study . Patients were followed upto one month.
- Glycosylated haemoglobin Hb A1c was done to ascertain whether it was stress hyperglycemia or true diabetes. All the necessary investigations like neuroimaging, blood investigations, electrocardiogram and echocardiography were done in addition to HbA1c and random blood sugar.
- The clinical parameters like age, sex, history of co morbid illnesses, examination findings and details of investigations were recorded.
- Stroke severity was assessed by NIHSS and functional outcome was assessed by MRS.
- We found that, males were more commonly effected with stroke than females .There is statistical significance of gender predisposition to males for diabetes mellitus .Both Diabetes mellitus and acute ischemic stroke are more common among males .Even in diabetes poorly controlled predominates over good control in our study. Henceforth regular screening of diabetes should be done and more awareness should be created among the population.
- In our study we found that age between 61-70 years was the most commonly affected age group for acute ischemic stroke in diabetics while 71-80 years was the most commonly affected age group in non diabetics.
- Hypertension was most commonly found in ischemic stroke accounting to 62.86 % and Ischemic heart disease was next common cause accounting to 22.86% of study population .Combination of diabetes and hypertension would become most common significant risk factor for stroke than diabetes alone.
- There is no significant association between smoking /alcohol with stroke in our study .Because most of the patients are not ready to reveal their addictions due to social issues .Some might have addictions in the past which they thought could not be significant at the time of stroke. Duration of smoking and alcohol also matters which should be studied in depth.
- In our study we found no correlation between glycemic status at admission and good glycemic control in follow up with stroke severity and functional outcome. Although there are many previous studies showing significant correlation between glycemic status at admission with stroke severity and functional outcome. The concept has become questionable debate after this study. Small sample size was considered main limitation of these findings. Prolonged follow up is also necessary.Also there are other confounding factors in addition to diabetes which could be risk factors for stroke.
- In our study stress hyperglycemia is associated with stroke of mild to moderate intensity.
- In our study we found that mortality in stroke was not affected by glycemic status.
- In our study we found better results were obtained in reducing severity of stroke at discharge with multimodality approach irrespective of glycemic status.
- In our study three patients were thrombolysed during window period in which one was poorly controlled

diabetic and two were non diabetics. All the three patients had good outcome after one month .

- Less stringent goal can be used in older individuals who have limited life expectency and others who may not benefit from tighter control to avoid hypoglycemia.
- Majority of patients presenting with ischemic stroke showed good functional outcome at discharge (MRS 0-2) with treatment irrespective of glycemic status diabetic vs non diabetic, poor vs good controlled patients.

9. Conclusions

- In our study we found no statistical association of glycemic status with stroke severity and functional outcome.
- In our study we found that mortality in stroke had no statistical association with glycemic status.
- We found that HbA1c which represents average blood glucose concentration over last three months as well as indicator of glucose control has no prognostic value in stroke severity and functional outcome.
- Irrespective of glycemic status and other comorbidities, majority of the patients presented to us with stroke are of moderate intensity (NIHSS 5-15).

10. Limitations

- Sample size may not be representative of the entire community as the study was conducted in a private tertiary care institute.
- Majority of the sample was representing urban population , results cannot be attributed to rural population which includes major part of India .
- A longer follow up period would have been ideal but was not possible in the present scenario.
- As HbA1c indicates glycemic control over last three months only , there is no tool or indicator available to know glycemic control over long term in diabetic patients with ischemic stroke as atherosclerosis occurs over years .

11. Recommendations

- As per our study tight Glucose control in acute phase of stroke may not be required.
- Stroke occurs as a result of multiple risk factors like smoking, alcohol, hypertension, cardiovascular disease, peripheral vascular disease in addition to diabetes, a detailed approach and targeted studies are required to avoid bias in preventing and treating ischemic stroke.
- Mortality would be higher in patients with recurrent stroke with diabetes mellitus, studies should be undertaken in near future to address this issue.

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