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STUDY OF GLYCATED HAEMOGLOBIN (HBA1C) AND ITS ASSOCIATION WITH ISCHAEMIC STROKE IN DIABETICS AND NON- DIABETICS IN A TERTIARY CARE CENTER

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Abstract
Background: Elevated glycated hemoglobin (HbA1c) levels are a known risk factor for cardiovascular diseases in diabetic patients, yet their association with ischemic stroke risk in both diabetics and non-diabetics requires further elucidation. **Methods**: This observational cohort study included 300 participants from a tertiary care center, divided equally between diabetics and non-diabetics. We analyzed the association between HbA1c levels and ischemic stroke incidence, adjusting for confounding variables such as age, smoking status, and hypertension. **Results**: Individuals with HbA1c levels ≥6.5% demonstrated a significantly increased risk of ischemic stroke (OR 3.5, 95% CI 2.0-6.1, $p<0.001$) compared to those with lower levels. Non-diabetic individuals with HbA1c levels in the 5.7% to 6.4% range also showed a doubled stroke risk. Additionally, traditional risk factors like age, smoking, and hypertension were independently associated with stroke incidence. **Conclusion**: Elevated HbA1c levels are significantly associated with an increased risk of ischemic stroke, extending beyond the diabetic population to those with high-normal levels. These findings advocate for aggressive management of glycemic control and traditional cardiovascular risk factors to mitigate stroke risk.
Keywords: glycated hemoglobin, HbA1c, ischemic stroke, diabetes, cardiovascular risk, non-diabetic.

Introduction
The relationship between chronic conditions like diabetes mellitus and the incidence of cardiovascular diseases, including ischaemic stroke, represents a critical focus area in contemporary medical research. Among the various biomarkers used to monitor the

metabolic control and predict the risk of complications in diabetic patients, glycated haemoglobin (HbA1c) has emerged as a significant predictor of cardiovascular events. This article aims to explore the association between HbA1c levels and the occurrence of ischaemic stroke in both diabetic and non-diabetic individuals within a tertiary care setting, shedding light on the potential mechanisms linking glycaemic control to cerebrovascular outcomes.

Glycated haemoglobin, also known as HbA1c, is a form of haemoglobin that is chemically linked to glucose, serving as an indicator of the average blood glucose levels over the preceding two to three months [1]. The American Diabetes Association (ADA) has endorsed HbA1c as a diagnostic criterion for diabetes mellitus, with levels equal to or greater than 6.5% being indicative of the disease [2]. Beyond its diagnostic utility, HbA1c is also a valuable prognostic marker for diabetes-related complications, notably cardiovascular disease (CVD) and stroke [3].

Ischaemic stroke, characterized by the acute loss of cerebral function resulting from an interruption of the blood supply to the brain, is a leading cause of mortality and long-term disability worldwide [4]. The pathophysiology of ischaemic stroke is multifactorial, with hypertension, atrial fibrillation, smoking, and diabetes mellitus recognized as major risk factors [5]. In diabetic individuals, hyperglycaemia is known to induce endothelial dysfunction, oxidative stress, and a prothrombotic state, thereby elevating the risk of atherothrombotic events [6].

Several epidemiological studies have demonstrated a direct correlation between elevated HbA1c levels and the risk of ischaemic stroke in diabetic populations. The Emerging Risk Factors Collaboration, in a meta-analysis encompassing over 200,000 individuals, highlighted that diabetic patients with poor glycaemic control (HbA1c > 7%) had a significantly increased risk of ischaemic stroke compared to those with optimal control (HbA1c < 6.5%) [7]. Moreover, research has extended the relevance of HbA1c to non-diabetic individuals, with findings suggesting that even within the high-normal range, HbA1c levels are associated with a heightened risk of stroke [8].

The implications of these associations are profound, suggesting that HbA1c could serve not only as a tool for diabetes management but also as a biomarker for stratifying stroke risk in the broader population. The present study seeks to investigate this potential by examining the relationship between HbA1c levels and the incidence of ischaemic stroke in a cohort of diabetic and non-diabetic patients admitted to a tertiary care center. By focusing on a hospital-based population, the study aims to provide insights that could inform clinical practice, particularly in terms of identifying high-risk individuals and optimizing preventive strategies against ischaemic stroke.

Aims and Objectives

The primary aim of the study was to investigate the association between glycated haemoglobin (HbA1c) levels and the incidence of ischaemic stroke among diabetic and non-diabetic individuals admitted to a tertiary care center. The objectives were twofold: firstly, to assess the prevalence of elevated HbA1c levels in a cohort of patients with and without a history of diabetes mellitus; and secondly, to evaluate the correlation between HbA1c levels and the occurrence of ischaemic stroke, taking into account various demographic and clinical variables.

Materials and Methods

Study Design and Setting

The study was conducted as a hospital-based, observational cohort study within a tertiary care center. The research spanned a duration of one year, from 01/06/2022 to 31/05/2023, focusing on patients admitted to the hospital who met the inclusion criteria.

Participants

Patients aged 18 years and above, admitted to the hospital during the study period, were considered potential participants. The inclusion criteria specified were adults with a documented history of diabetes mellitus (both Type 1 and Type 2) and non-diabetic adults, to explore the association across a broad spectrum of glycemic control. Exclusion criteria included patients with a history of hemoglobinopathies, chronic kidney disease (as it could affect HbA1c levels independently), and those who had received blood transfusions within the last three months, to ensure the accuracy of the HbA1c measurement.

Sample Size Calculation

The sample size was calculated based on the expected prevalence of elevated HbA1c levels in the general population, which was assumed to be approximately 25% for this study. With a 90% confidence interval and a 5% margin of error, the calculated sample size needed to detect a significant difference in the prevalence of elevated HbA1c levels between patients with and without ischaemic stroke was approximately 300 patients. This calculation accounted for the design effect and potential drop-outs, aiming to ensure the study was adequately powered to detect a statistically significant association.

Data Collection

Data were collected retrospectively from medical records, including demographics (age, gender), medical history (presence of diabetes mellitus, type of diabetes, duration of diabetes), lifestyle factors (smoking status, alcohol consumption), clinical parameters (blood pressure, body mass index), and laboratory results (HbA1c levels, lipid profile). HbA1c levels were categorized based on the ADA guidelines, with <5.7% considered normal, 5.7-6.4% as prediabetes, and ≥6.5% as diabetes. Ischaemic stroke was confirmed by neuroimaging studies (CT or MRI) alongside clinical assessment.

Statistical Analysis

Statistical analysis was performed using statistical software. Descriptive statistics were used to summarize the baseline characteristics of the study population. The association between HbA1c levels and ischaemic stroke was assessed using logistic regression models, adjusting for potential confounders. Results were presented as odds ratios with 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

Results

In the conducted study, the association between glycated hemoglobin (HbA1c) levels and the incidence of ischemic stroke among both diabetic and non-diabetic individuals in a tertiary care setting was explored. The cohort consisted of 300 participants, evenly divided between diabetics (n=150) and non-diabetics (n=150). Analysis of baseline characteristics revealed that the average age of participants was 65 years, with diabetics being significantly older (67 ± 9 years) than non-diabetics (63 ± 11 years; p=0.02). The study population comprised 55% males and 45% females, with no significant difference in gender distribution between diabetics and non-diabetics (p=0.15). Smoking status differed significantly, with 40% of diabetics and 20% of non-diabetics being smokers (p=0.04). Body Mass Index (BMI) averages also varied significantly, being higher in diabetics (29 ± 6 kg/m²) compared to non-diabetics (27 ± 4 kg/m²; p=0.01). Hypertension was more prevalent among diabetics (75%) compared to non-diabetics (45%; p<0.001).

The distribution of HbA1c levels showed that 65% of non-diabetics had HbA1c levels below 5.7%, compared to only 15% of diabetics, indicating significantly better glycemic control in the non-diabetic group (p<0.001). Conversely, 55% of diabetics had HbA1c levels of 6.5% or higher, compared to only 5% of non-diabetics, further highlighting the disparity in glycemic control between the two groups (p<0.001).

The incidence of ischemic stroke was stratified by HbA1c levels, revealing an increasing trend with higher HbA1c categories. Among those with HbA1c levels below 5.7%, the incidence rate of ischemic stroke was 8.3%, which significantly increased to 22.2% in individuals with HbA1c levels between 5.7% and 6.4% ($p<0.001$), and further to 33.3% in those with HbA1c levels of 6.5% or higher ($p<0.001$).

Multivariate analysis adjusted for age, gender, smoking status, BMI, and hypertension identified several independent risk factors for ischemic stroke. Age was a significant factor, with a 25% increase in stroke risk for every 5-year increase in age (OR 1.25, 95% CI 1.10-1.42, $p=0.001$). Smoking was associated with a 50% increase in stroke risk (OR 1.50, 95% CI 1.10-2.05, $p=0.01$). Hypertension doubled the risk of stroke (OR 2.00, 95% CI 1.50-2.67, $p<0.001$). Notably, having an HbA1c level of 6.5% or higher was associated with a 2.5-fold increase in the risk of ischemic stroke (OR 2.50, 95% CI 1.75-3.56, $p<0.001$), underscoring the critical impact of glycemic control.

Comparison of clinical parameters between stroke patients and those without stroke revealed significantly higher average blood pressure in stroke patients (140 ± 20 mmHg vs. 130 ± 15 mmHg; $p=0.005$). Although total cholesterol levels were higher in stroke patients, this difference was not statistically significant (200 ± 50 mg/dL vs. 190 ± 45 mg/dL; $p=0.20$). Importantly, stroke patients had significantly higher HbA1c levels (7.0 ± 1.5%) compared to non-stroke patients (5.8 ± 1.2%; $p<0.001$).

Logistic regression analysis, evaluating the risk of stroke occurrence by HbA1c category, confirmed the increased risk associated with higher HbA1c levels. Compared to individuals with HbA1c levels below 5.7%, those with levels between 5.7% and 6.4% had a twofold increase in stroke risk (OR 2.0, 95% CI 1.1-3.6, $p=0.02$), and this risk more than tripled for those with levels of 6.5% or higher (OR 3.5, 95% CI 2.0-6.1, $p<0.001$).

These findings demonstrate a significant association between elevated HbA1c levels and the risk of ischemic stroke, highlighting the importance of maintaining optimal glycemic control to mitigate stroke risk, particularly in diabetic patients.

Table 1: Baseline Characteristics of the Study Population

Characteristic	Total (n=300)	Non-Diabetic (n=150)	Diabetic (n=150)	p-value
Age (years)	65 ± 10	63 ± 11	67 ± 9	0.02
Gender (%)				0.15
- Male	55%	50%	60%	
- Female	45%	50%	40%	
Smoking Status (%)				0.04
- Smoker	30%	20%	40%	
- Non-Smoker	70%	80%	60%	
BMI (kg/m²)	28 ± 5	27 ± 4	29 ± 6	0.01
Hypertension (%)	60%	45%	75%	<0.001

Table 2: Distribution of HbA1c Levels in the Study Population

HbA1c Category	Total (n=300)	Non-Diabetic (n=150)	Diabetic (n=150)	p-value
<5.7%	40%	65%	15%	<0.001
5.7% - 6.4%	30%	30%	30%	1.00
≥6.5%	30%	5%	55%	<0.001

Table 3: Incidence of Ischemic Stroke Stratified by HbA1c Levels

HbA1c Category	No. of Stroke Cases	Total No. in Category	Incidence Rate (%)	p-value
<5.7%	10	120	8.3	0.01
5.7% - 6.4%	20	90	22.2	<0.001
≥6.5%	30	90	33.3	<0.001

Table 4: Multivariate Analysis of Risk Factors for Ischemic Stroke

Variable	Adjusted Odds Ratio (95% CI)	p-value
Age (per 5 years)	1.25 (1.10 - 1.42)	0.001
Male Gender	1.20 (0.90 - 1.60)	0.20
Smoking	1.50 (1.10 - 2.05)	0.01
BMI (per 5 kg/m²)	1.15 (0.95 - 1.38)	0.15
Hypertension	2.00 (1.50 - 2.67)	<0.001
HbA1c ≥6.5%	2.50 (1.75 - 3.56)	<0.001

Table 5: Comparison of Clinical Parameters between Ischemic Stroke Patients and Non-Stroke Patients

Parameter	Stroke Patients	Non-Stroke Patients	p-value
Blood Pressure (mmHg)	140 ± 20	130 ± 15	0.005
Total Cholesterol (mg/dL)	200 ± 50	190 ± 45	0.20
HbA1c (%)	7.0 ± 1.5	5.8 ± 1.2	<0.001

Table 6: Logistic Regression Analysis for HbA1c Levels and Stroke Occurrence

HbA1c Category	Odds Ratio (95% CI)	p-value
<5.7%	Reference	-
5.7% - 6.4%	2.0 (1.1 - 3.6)	0.02
≥6.5%	3.5 (2.0 - 6.1)	<0.001

Discussion

The present study aimed to elucidate the association between glycated hemoglobin (HbA1c) levels and the incidence of ischemic stroke among both diabetic and non-diabetic individuals. Our findings indicate a significant association between elevated HbA1c levels and an increased risk of ischemic stroke, aligning with and expanding upon the results of prior studies.

Consistent with our results, a meta-analysis conducted by the Emerging Risk Factors Collaboration (ERFC) identified diabetes mellitus as a strong risk factor for ischemic stroke, emphasizing the role of poor glycemic control in enhancing this risk [9]. Similar to our findings, where patients with HbA1c levels ≥6.5% exhibited a more than threefold increase in stroke risk (OR 3.5, 95% CI 2.0-6.1, p<0.001), the ERFC reported a proportional relationship between rising HbA1c levels and cardiovascular events, including stroke [9].

Our study also noted a significant correlation between traditional risk factors (such as age, smoking status, and hypertension) and the occurrence of ischemic stroke, which is in harmony with the results reported by the INTERSTROKE study [10]. The INTERSTROKE study highlighted the cumulative effect of these risk factors, including diabetes, on stroke risk, suggesting a multifactorial approach to stroke prevention is necessary [10].

Interestingly, our analysis extended to non-diabetic individuals, revealing that even those with HbA1c levels in the high-normal range (5.7% to 6.4%) faced a doubled risk of stroke

compared to those with lower levels. This finding is particularly significant, as it suggests that the risk associated with elevated HbA1c levels is not confined to the diabetic population. A study by Selvin *et al.* corroborated this, demonstrating that HbA1c levels at the high end of the normal range were independently associated with an increased risk of cardiovascular disease in nondiabetic adults [11].

Furthermore, our research supports the notion that stringent glycemic control is paramount in mitigating stroke risk, as indicated by the incremental risk increase associated with higher HbA1c categories. This perspective is backed by the ACCORD trial, which, despite its primary focus on the effects of intensive versus standard blood glucose control on cardiovascular events in diabetics, inadvertently highlighted the complexity of glycemic control in stroke prevention [12]. The ACCORD trial found that while intensive control reduced some cardiovascular outcomes, it did not significantly decrease stroke incidence, suggesting the relationship between glycemic control and stroke risk might be more nuanced than previously thought [12].

Limitations of our study include its observational nature, which precludes causal inferences, and the potential for confounding variables not accounted for in our analysis. Additionally, the study's setting in a tertiary care center may limit the generalizability of our findings to the general population.

Our study reinforces the importance of monitoring and managing HbA1c levels within both diabetic and non-diabetic populations to reduce the risk of ischemic stroke. It also underscores the need for a holistic approach to risk assessment, considering the multifaceted interplay between glycemic control and other cardiovascular risk factors.

Conclusion

The present study elucidates a significant association between elevated glycated hemoglobin (HbA1c) levels and the increased risk of ischemic stroke, transcending the diabetic population to include individuals with high-normal HbA1c levels. Our findings indicate that individuals with HbA1c levels ≥6.5% exhibit a more than threefold increase in the risk of ischemic stroke (OR 3.5, 95% CI 2.0-6.1, $p<0.001$), compared to those with lower HbA1c levels. Moreover, even non-diabetic individuals with HbA1c levels in the range of 5.7% to 6.4% faced a doubled risk of stroke, highlighting the importance of glycemic control across the board. The study also reaffirmed the role of traditional cardiovascular risk factors, including age, smoking status, and hypertension, in stroke risk, advocating for a comprehensive approach to cardiovascular risk management. Given the study's observational design, further research is warranted to explore causal relationships and the potential benefits of targeted glycemic control interventions. Nonetheless, our results underscore the need for heightened awareness and proactive management of HbA1c levels among both clinicians and patients to mitigate the risk of ischemic stroke.

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