



Original Article

Evaluating HbA1c as a Predictive Biomarker for Depression in the Elderly: A Cross-Sectional Analysis

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ABSTRACT

Introduction: Depression in the elderly is a significant public health concern and is linked to elevated HbA1c, a marker of long-term glucose control. Persistent hyperglycemia may impair neurogenesis, disrupt brain networks, and reduce neurotransmitter activity, making HbA1c a potential biomarker for depression.

Purpose: This study aims to explore the potential of HbA1c as a biomarker for predicting depression severity in the elderly.

Methods: This cross-sectional study examined 93 elderly residents at Bina Bhakti Nursing Home, who exhibited varying levels of depression severity. Depression was assessed using the Geriatric Depression Scale (GDS), and HbA1c levels were analyzed using an automated clinical analyzer. To evaluate the predictive ability of HbA1c for depression severity, we used the area under the curve (AUC) from a receiver operating characteristic (ROC) analysis. A GDS score of 4 or higher was used to indicate severe depression.

Results: The AUC for HbA1c was 0.692, with a p-value of 0.049, indicating a statistically significant relationship between HbA1c levels and depression severity.

Conclusion: Elevated HbA1c levels may serve as a potential biomarker for depression risk in the elderly. Routine HbA1c monitoring could support early detection and timely intervention. Further research is needed to clarify its clinical relevance.

INTRODUCTION

Aging is an inevitable and complex process and depression often surfaces as a significant public health concern among older adults that affects their quality of life. This issue has become a global challenge, burdening healthcare systems substantially.^{1,2} Depression is characterized by a range of emotional states, including feelings of sadness, emptiness, and helplessness. Individuals may experience a loss of interest in activities they once enjoyed (known as anhedonia), appetite changes, and sleep

disturbances. Other symptoms can include psychomotor retardation or agitation, fatigue or loss of energy, a sense of helplessness, difficulty concentrating, thoughts of suicide, or specific plans for self-harm and around 20% of individuals will experience depression at some point in their lives.^{3,4}

The prevalence of depression among older adults worldwide is estimated to range from 3% to 30%, and this condition tends to be more common in women than in men.^{5,6} Based on research conducted by Handajani et al., it was found that at least 16.3% of the

4,236 elderly individuals who participated in the study experienced depression in Indonesia.⁷ The high prevalence of elderly people experiencing depression is a critical issue and needs special attention, as the presence and persistence of depressive symptoms can adversely affect quality of life and contribute to increased morbidity and mortality rates.^{8,9}

This issue is compounded by various risk factors, which likely stem from complex interactions between genetic predispositions, cognitive vulnerabilities, age-related neurobiological changes, and stressful life events. Additionally, older adults with diabetes mellitus (DM) are at significantly higher risk for comorbid depression compared to those without DM. Diabetes is a known risk factor for depression, and the prevalence of depression is notably higher in individuals with diabetes than in the general population.¹⁰⁻¹²

Hemoglobin A1c (HbA1c) is a marker of glycosylated hemoglobin and is widely used to monitor long-term glycemic control, reflecting the average blood glucose levels over the past 8-12 weeks. It serves as a key diagnostic tool for diabetes. Notably, diabetes has been linked to a 34% (95% CI: 14-57) increased risk of developing depression, highlighting the significant intersection between hyperglycemia and mental health. Depression has been linked to high HbA1c levels in people with type 2 diabetes (T2DM), suggesting that HbA1c could serve as a marker for depressive symptoms. A study by Dzida et al. found that a 1% (11 mmol/mol) drop in HbA1c can reduce the risk of moderate to severe depression by 40%.¹³⁻¹⁶

Persistent hyperglycemia in diabetes affects brain function by impairing neurogenesis, reducing synaptic plasticity, and causing imbalances in neurotransmitter activity. It also disrupts insulin signaling, the HPA axis, and other regulatory systems linked to mood and behavior. These changes suggest a complex mechanism through which diabetes influences mood, leading to a higher risk of depression, which is related to serotonin (5-HT) regulation.¹⁷

This research aims to further our understanding of the relationship between glycemic control and depression, contributing to more comprehensive healthcare approaches that integrate the management of chronic conditions and mental health in older adults. Ultimately, this study could help improve early detection, prevention, and intervention strategies for depression in elderly individuals, especially those with metabolic comorbidities.

METHOD

Study Design and Sampling

This research employs a cross-sectional design and is an analytical observational study conducted in May 2024. This study examined 93 elderly at Bina Bhakti Nursing Home with total sampling, who exhibited varying levels of depression severity and met the predetermined inclusion and exclusion criteria. The inclusion criteria for this study were being at least 60 years old and willing to be interviewed and have their blood drawn. Exclusion criteria included uncooperative individuals, those who had difficulties in two-way communication, or those who were unable to understand the Indonesian language.

Instrumen and Procedure

The research variables comprise two components: HbA1c and depression. HbA1c levels from venous blood were analyzed using an automated clinical analyzer based on the enzymatic assay method. This method involves two primary steps, HbA1c undergoes proteolysis to break it down into glycated amino acids or peptides, so these glycated components react with a specific enzyme, such as oxidase or dehydrogenase, which is designed to target the glycated amino acids or peptides, enabling precise measurement of % HbA1c levels.¹⁸

Depression severity was determined with the Geriatric Depression Scale (GDS) which is a widely used assessment tool to identify symptoms of depression in older adults. The GDS questionnaire is aimed at

assessing key aspects such as mood, activity levels, and engagement in daily activities that consist of 15 “Yes” or “No” questions. Based on the GDS scoring system, depression is classified into four categories: normal (0-4 points), mild depression (5-8 points), moderate depression (9-11 points), and severe depression (12-15 points).¹⁹

Statistical Analysis

Data analysis was conducted using Receiver Operating Characteristic (ROC) analysis to evaluate the predictive ability of HbA1c for depression severity. The ROC curve illustrates sensitivity and specificity at different threshold values of HbA1c, helping to identify the optimal HbA1c level for predicting and potentially preventing depression. The area under the curve (AUC) was used to measure the overall accuracy of HbA1c as a diagnostic tool, with a Geriatric Depression Scale (GDS) score of 4 being used to define severe depression.

Ethical Clearance

This study has been approved by the Tarumanagara University Human Research Ethics Committee, under the Institute of Research and Community Engagement, with the ethics review number 013-UTHREC/UNTAR/VI/2024..

RESULT AND DISCUSSION

This study involved 93 elderly respondents with an average age of 74.19 years ranging from 61 to 97 years. Most respondents were female (82.8%), while the average HbA1c level among respondents was 7.59%. The Geriatric Depression Scale showed that 59.1% of respondents were in normal condition without signs of depression. However, 40.9% of respondents experienced depression, with 20.4% having mild depression, 9.7% moderate depression, and 10.8% severe depression. (Table 1).

Table 1. Characteristics of Research Results

| Parameter | N (%) | Mean (SD) | Med (Min-Max) |
|-----------------------------------|-----------|--------------|------------------|
| Age | 93 (100) | 74.19 (7.95) | 75 (61 – 97) |
| Gender | | | |
| Male | 16 (17.2) | | |
| Female | 77 (82.8) | | |
| HbA1c | | 7.59 (1.41) | 7.5 (4.7 – 12.9) |
| Geriatric Depression Scale | | | |
| Normal | 55 (59.1) | | |
| Mild Depression | 19 (20.4) | | |
| Moderate Depression | 9 (9.7) | | |
| Severe Depression | 10 (10.8) | | |

The ROC analysis demonstrated that HbA1c is a robust predictor of depression severity, with an area under the curve (AUC) of 0.692, indicating a moderate ability to predict severe depression outcomes. The 95% confidence interval (CI) for the AUC, ranging from 0.510 to 0.873, further supports moderate to high predictive capability for

severe depression within the elderly population. With a p-value of 0.049, this result strengthens the evidence for HbA1c as a significant predictor and highlights a statistically significant association between lower HbA1c levels and increased depression severity. (Table 2 and Figure 1).

Table 1. Area Under Curve (AUC) of HbA1c as a Predictor of Depression

| Area | Std. Error | p-value | 95% Confidence Interval | |
|--------------|------------|---------|-------------------------|-------|
| | | | Lower | Upper |
| 0.692 | 0.093 | 0.049 | 0.510 | 0.873 |

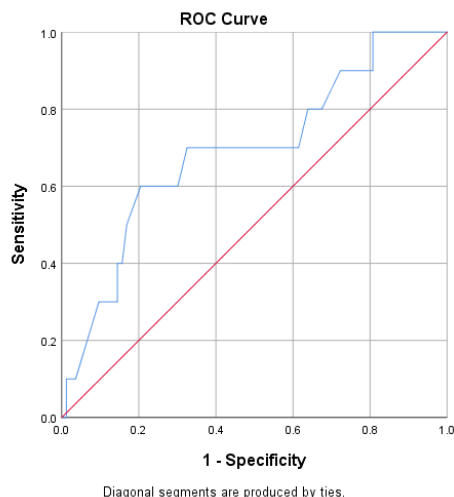


Figure 1. Receiver Operating Characteristic (ROC) Curve of HbA1c as a Predictor of Depression

Chronic hyperglycemia has been shown to diminish the activity of crucial brain neurotransmitters, such as dopamine, epinephrine, and norepinephrine, notably impacting the serotonin (5-hydroxytryptamine or 5-HT) system. This reduction contributes to mood disorders, behavioral challenges and plays a significant role in the neurobiological underpinnings of depression.¹⁷ One possible mechanism linking diabetes and depression involves alterations in brain chemistry. In individuals with diabetes, there is a reduction in the levels of free fraction L-tryptophan (FFT), a crucial precursor for serotonin synthesis. This decrease can inhibit the enzyme that converts FFT into serotonin, ultimately reducing serotonin production. Moreover, diabetes has been found to influence serotonin receptors; in particular, 5-HT_{1A} receptors often show signs of dysregulation, whereas 5-HT_{2A} receptors are typically upregulated in diabetes. These receptor changes may represent the brain's compensatory response to the reduced availability of serotonin. Collectively, these findings underscore a significant relationship between diabetes and depression, highlighting the vital role of serotonin.²⁰⁻²³ Additionally, hyperglycemia has been shown to interfere with normal glutamate function in the brain, which can disrupt emotional and cognitive processing.²⁴

Furthermore, hyperglycemia causes inflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and impairment of the stress reactivity that leads to depression.^{25,26} Neurons were particularly vulnerable to hyperglycemia due to elevated intracellular glucose levels, which can promote the formation of advanced glycation end products (AGEs). This cascade of events is associated with increased oxidative stress, inflammation, and impaired neurogenesis within the hippocampus, especially the dentate gyrus (DG)²⁷⁻³² the activation of the hypothalamic-pituitary-adrenal (HPA) axis and elevated glucocorticoid (GC) levels, such as cortisol. Stress triggers the release of corticotropin-releasing factor (CRF) from the hypothalamus, which leads to the production of glucocorticoids that affect mood and behavior. In diabetes, prolonged high levels of glucocorticoids can damage the hippocampus and disrupt the normal feedback system that controls stress hormones. This damage can lead to chronic high cortisol levels that contribute to depressive symptoms.³³⁻³⁶

Glucocorticoids (GCs) play a key role in regulating postsynaptic serotonin receptors: 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}, resulting in serotonin-driven effects on behavior and neuroendocrine functions. GC receptors are present not only on the cell bodies of ascending serotonergic neurons, suggesting a

direct regulatory influence on presynaptic serotonin activity, but also in areas like the amygdala, prefrontal cortex, and hippocampus. These regions are critical to mood and cognitive processes, hinting that GCs could directly modulate the serotonin system in ways relevant to mood disorders. Chronic exposure to high GC levels, such as during prolonged stress, has been shown to decrease the expression and function of 5-HT_{1A} heteroreceptors in the hippocampus. This reduction, primarily due to transcriptional repression via glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), weakens serotonin neurotransmission and potentially triggers depressive symptoms.³⁷⁻⁴¹

Conversely, research conducted by Gilzans et al. indicates that individuals experiencing severe hypoglycemic events also have a 75% increased risk of developing depression. This finding raises the possibility that lower HbA_{1c} levels may result from stringent glycemic control, which often leads to a higher frequency of hypoglycemic episodes. Recurrent hypoglycemia can adversely impact cognitive function, impair mitochondrial respiration in the hippocampus, and subsequently elevate levels of free radicals. Furthermore, these episodes can disrupt the brain's glutamate and GABA neurotransmitter systems, ultimately resulting in increased neuronal death.^{42,43}

While our findings indicate that HbA_{1c} holds potential as a biomarker for identifying depression severity in elderly individuals with diabetes, caution must be exercised before advocating its routine use in clinical screening. The study design presented certain limitations that may have introduced confounding variables affecting both glycemic and psychological outcomes. Notably, participants in the elderly cohort were informed of the forthcoming evaluation four months in advance, which likely influenced their behavior, prompting dietary modifications, improved medication adherence, or lifestyle changes aimed at optimizing test results. Such anticipatory adjustments could have independently impacted depressive

symptoms, thereby masking the natural relationship between chronic glycemic control and mood.

Moreover, HbA_{1c} provides a retrospective view of average blood glucose over the past three months, rather than offering insight into current glucose fluctuations. As a result, it may not fully capture acute changes in metabolic status that could be more closely linked with mood at the time of assessment. In this context, random blood glucose measurements might offer a more immediate and accurate reflection of present glycemic status and its association with emotional well-being. Therefore, while HbA_{1c} shows potential as a predictive biomarker, these limitations indicate that it may not yet be suitable as a standalone screening tool for depression in routine clinical practice. Further research with tighter controls and real-time glucose assessments is needed to validate its utility and accuracy in diverse, real-world settings.

There is also the possibility of overlapping symptoms between hypoglycemia and depression. There's a complex relationship between hypoglycemia and depression, especially in elderly individuals, where overlapping symptoms, such as mood swings and increased irritability, make it challenging to diagnose and manage these conditions separately. Hypoglycemia can often mimic symptoms of depression, showing up as irritability, anxiety, fatigue, confusion, and physical signs like sweating, tremors, and a racing heart as the body releases adrenaline to cope with the low glucose levels. This symptom overlap implies shared neurobiological pathways, involving adrenergic signaling and neurotransmitter systems essential for mood regulation.⁴⁴⁻⁴⁶

Genetic and epigenetic factors are also significant and may predispose elderly individuals to depression, whether associated with metabolic disturbances or even with normal HbA_{1c} levels. Genetic predispositions play a role in depressive symptoms, varying based on individual genetic liability. For instance, brain-derived neurotrophic factor

(BDNF) is crucial for neuronal survival, neurogenesis, neuronal differentiation, and neuroplasticity, all of which influence mood regulation. Additionally, polymorphisms in *SLC6A4*, the gene encoding the serotonin transporter, are also associated with an increased risk of major depressive disorder over a lifetime and with higher severity of depressive episodes.^{47–50}

CONCLUSIONS

This finding highlights the potential utility of HbA1c as a valuable biomarker for the early detection of depression in elderly individuals. We suggest that routine diabetes management for older adults should include screening with the Geriatric Depression Scale (GDS) to detect and address depressive symptoms at an early stage

Study Limitations and Futuristic Research

This study focused exclusively on the elderly population to assess the potential role of HbA1c in predicting depression, without considering other variables that may influence either HbA1c levels or depressive symptoms. Additionally, the lack of longitudinal data

restricts the ability to analyze changes in HbA1c levels and depression over time, limiting our understanding of how fluctuations in glycemic control may affect mental health outcomes. Further research is essential to determine HbA1c limits to prevent depression and confirm HbA1c's therapeutic relevance in depression management among older adults and to understand underlying mechanisms.

Informed Consent Statement

Data in this study were obtained with informed consent from the respondents. Respondents were thoroughly informed about the study's nature, purpose, and potential applications, with documented consent following institutional protocol and ethical standards

Data Availability Statement

The dataset can be requested from the corresponding author and will be released on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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