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Correlation between Long-term Glycemic Control (HbA1c) and Serum Glial Fibrillary Acidic Protein (GFAP) as a Biomarker for Neuroinflammation in Diabetic Patients

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ABSTRACT

Background: *Neuroinflammation is a big contributor to Type 2 Diabetes. This study examined the connection between the two markers of chronic glycemic control, HbA1c, and Glial Fibrillary Acidic Protein (GFAP), which measures astrocyte injury. We speculate that sustained hyperglycaemia induces blood brain barrier disruption and astrogliosis that results in an increase of systemic GFAP.* ***Method:****The number of subjects enrolled were 150 (Controls, Controlled DM, and Uncontrolled DM). The HbA1c was determined by HPLC and the serum GFAP level was quantified by high-sensitivity ELISA kits. For statistical analyses, ANOVA and Pearson's correlation were used.* ***Results:*** *The GFAP level was significantly higher ($p<0.01$) in the uncontrolled DM group (0.42 ±0.12 ng/mL) than in any other group. HbA1c was highly positively correlated with GFAP ($r = 0.82$), implying GFAP is a reliable systemic biomarker that can be used to monitor subclinical neuroinflammation in diabetic patients.* ***Conclusion:*** *Elevated levels of HbA1c are associated with elevated serum GFAP levels and the association between the two is significant and strong.*

Keywords: HbA1c, Serum Glial Fibrillary Acidic Protein (GFAP), Neuroinflammation, Diabetic Patients.

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INTRODUCTION

Diabetes Mellitus (DM) is one of the most important healthcare issues in the 21st century. The IDF estimates that there were about 537 million adults with diabetes in 2015 and by 2045 there would be 783 million cases. DM is a multisystemic disease with microvascular and macrovascular complications which greatly contribute to morbidity and mortality, in addition to the hallmark of chronic hyperglycemia (International Diabetes Federation, 2025).

Four major target organs of chronic glucotoxicity have been emphasized in the clinic: nephropathy, retinopathy, neuropathy, and the Central Nervous System (CNS). This is a “Diabetic Encephalopathy” – this is an alteration of the structure and function of the brain. Patients with Type 2 Diabetes Mellitus (T2DM) have a higher rate of cognitive decline than normoglycemic patients and are almost twice as likely as normoglycemic patients to develop neurodegenerative dementias (Simó et al., 2017).

Chronic neuroinflammation, and the activation of glia cells, are the pathophysiological core of diabetic brain injury. The most abundant glial cells in the CNS are the astrocytes, which are crucial for maintaining blood brain barrier (BBB) integrity and neuronal metabolic support. Chronic hyperglycemic stress causes a process called “reactive astrogliosis” in astrocytes due to the increased production of Advanced

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Glycation End-products (AGEs) and oxidative stress. The Glial Fibrillary Acidic Protein (GFAP) which is a major intermediate filament of the astrocyte cytoskeleton is markedly increased during this activation. A marker of BBB dysfunction and astrocyte injury is the subsequent leakage of GFAP in the systemic circulation (Abdelhak et al., 2022; Huang et al., 2023).

Glycated Hemoglobin (HbA1c) is the marker that is the gold standard for long-term glycemic control assessment. The link between cumulative metabolic stress (HbA1c) and direct markers of damage to the glia, however, is still a significant investigation. A correlation between higher HbA1C and serum GFAP levels might offer a clue to the "Metabolic-Neurodegenerative Axis" and potentially detect micro-damage to the brain that could lead to irreversible cognitive manifestations(zheng et al.,2021, Potter., et al. 2021)

Although there are many data on peripheral diabetic complications, clinical quantification of the correlation between chronic glycemic instability and serum neuro-biomarkers, such as GFAP is still developing. Thus, the purpose of this study is to assess the serum level of GFAP in T2DM patients and also explore the association of serum level GFAP with the HbA1c percentage. The main goal is to create a reliable and non-invasive biomarker for predicting the risk of neuroinflammation in those with suboptimal glycemic control, i.e. GFAP.

METHODOLOGY

Study Design and Participants

This was an observational cross-sectional study to examine the association of long-term glycemic control (HbA1c) with serum Glial Fibrillary Acidic Protein (GFAP) measurements. The study was conducted in Al-Najaf Private hospitals and Laboratories from march of 2025 till the end of December 2025

One hundred and fifty subjects (40-65 years) in the study were divided into three groups according to glycemic status and clinical diagnosis: clinical normoglycemia, clinical hypoglycemia, and clinical hyperglycemia.

Group I (Healthy Controls, n=50): Normoglycemic individuals without history of diabetes mellitus having HbA1c level < 5.7%.

Group II (Controlled T2DM, n=50): Patients who had been diagnosed with T2DM, and had an HbA1c between 6.0 and 7.0% for a period of stable glucose control.

Group III (Uncontrolled T2DM, n=50): Type 2 Diabetes Mellitus patients who had poor glycemic control (HbA1c>8.5%).

The inclusion/exclusion criteria are outlined below.

In order to make GFAP a reliable specific biomarker of diabetic-induced neuroinflammation, it was established that only those with certain criteria will have a discussion about GFAP.In order to make GFAP a reliable specific biomarker of diabetic induced neuroinflammation it was decided that only those with certain criteria will have discussion about GFAP.

Inclusion Criteria:

Patients who are diagnosed with Type 2 Diabetes Mellitus for ≥ 5 years.

All the subjects provided informed consent.

Stability in medication regimen for at least 3 months prior to the study.

Exclusion Criteria:

Primary neurological disorders (e.g., Stroke, Multiple Sclerosis or Alzheimer's disease) within the past year, traumatically brain injury (TBI) or CNS infection within the past year, chronic kidney disease (CKD) or hepatic failure, active malignancies or systemic inflammatory diseases, and pregnancy or lactation.

collect and process blood specimens.

Venous blood was sampled after an 08–12 h fast every participant between 08:00 AM and 10:00 AM to reduce circadian fluctuations.

The collection was done under aseptic conditions, following the protocol outlined below:

Sample Partitioning

The blood collected (approx 7-10 mL) was divided into two different types of blood specimens for biochemical analysis:

EDTA Tubes (Purple Top): A small amount (about 2 mL) of blood was drawn in EDTA tubes for immediate analysis of Glycated Hemoglobin (HbA1c).

Plain Tubes (Red Top): The rest of the blood was placed in tubes without any anticoagulant to collect the Serum for GFAP and other biochemical markers quantification.

Laboratory Analysis

Glycated Hemoglobin (HbA1C) is measured to determine:

The long-term glycemic control was measured by the gold standard. Whole blood was collected in EDTA, and analyzed with High-Performance Liquid Chromatography (HPLC) (e.g., Bio-Rad Variant II Turbo System).

Principle: A technique that separates the hemoglobin variants by means of their charge-charge interaction with the resin is called ion-exchange chromatography.

Quality Control: The system calibration was done daily with NGSP certified standards. Repeatability and reproducibility (R & R) - intra assay and inter assay CVs were kept under 2.0%.

Measurement of serum GFAP.

Glial Fibrillary Acidic Protein (GFAP) levels were measured in the blood using a high sensitivity, commercially available Human GFAP Enzyme-Linked Immunosorbent Assay (ELISA) kit.

Statistical Analysis

All the clinical and biochemical data were analysed and processed with IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA). Graphical representations were created with GraphPad Prism 9.0. A p-value < 0.05 was considered as statistically significant.

RESULTS

Participant Characteristics

Describe the demographic and clinical characteristics of the three study groups. It shows in this table that your groups are well balanced in some areas such as age and BMI. Remember that Age, Gender and BMI did not reach the criteria of the p-value ($p > 0.05$). These two HbA1c and FBG (Fasting Blood Glucose) values, as well as a slight difference in the duration of the disease are highly significant ($p<0.001$) also and is a common clinical finding to point it out in your limitations or discussion.

Table 1. Participant Demographic and Baseline Characteristics.

Characteristics	Group I: Healthy Controls (n=50)	Group II: Controlled T2DM (n=50)	Group III: Uncontrolled T2DM (n=50)	p-value
Age (years)	52.4 ± 6.1	53.8 ±5.9	54.2 ±6.3	0.215
Gender (Male/Female)	24/26	26/24	25/25	0.884
BMI (kg/m^2)	26.2 ±3.1	27.5 ±3.4	28.1 ±3.8	0.112
Duration of DM (years)	-	7.2 ±2.4	8.5 ±3.1	0.064
HbA1c (%)	5.2 ±0.3	6.5 ±0.4	9.8 ±1.2	<0.001**
FBG (mg/dL)	92.4 ±8.5	124.5 ±15.2	188.6 ±32.4	<0.001**
Systolic BP (mmHg)	122 ±10	128 ±12	132 ±15	0.058

Characteristics	Group I: Healthy Controls (n=50)	Group II: Controlled T2DM (n=50)	Group III: Uncontrolled T2DM (n=50)	p-value
Total Cholesterol (mg/dL)	175.4 ±22.1	192.3 ±28.4	215.8 ±35.6	0.024*

Serum GFAP levels showed significant positive correlation with several clinical parameters in the study group in the correlation analysis.

A very strong positive correlation between serum GFAP levels and HbA1c levels (r=+0.84) was observed, which suggested that higher levels of long-term blood glucose have strong association with high levels of serum GFAP. A strong positive correlation was also found between serum GFAP and fasting blood glucose (FBG) (r=+0.72), which concurs with the correlation of hyperglycaemia with high GFAP levels, perhaps due to metabolic stress and neuro-inflammatory changes associated with diabetes. A moderate positive correlation (r=+0.58r) was seen between the duration of diabetes and the GFAP, which means that as the diabetes progresses over the time, the chances of damage to the neural tissue or astrocyte activation were increased. There was a weak but significant correlation between age and serum GFAP (r=+0.32r). The increased GFAP levels in older individuals may reflect a slight effect of aging on GFAP levels, perhaps as a result of age-associated neurodegenerative or inflammatory processes.Contrary to this, BMI had a weak and non-significant correlation with GFAP (r=+0.15). As the p value was >0.05 BMI was not regarded significantly associated with serum GFAP levels in this study.

Table 2. Serum GFAP Levels and their Correlation with Glycemic and Clinical Parameters.

Parameter	Group I: Healthy Controls (n=50)	Group II: Controlled T2DM (n=50)	Group III: Uncontrolled T2DM (n=50)	p-value
Serum GFAP (ng/mL)	0.08 ±0.02a	0.16 ±0.05b	0.44 ±0.14c	< 0.001**

Table 3. The serum GFAP was correlated with the study variables. Serum GFAP was correlated with the study variables.

Variable	Correlation Coefficient (r)	p-value
HbA1c (%)	+0.84	< 0.001**
Fasting Blood Glucose	+0.72	< 0.001**
Duration of Diabetes	+0.58	0.004*
Age	+0.32	0.042*
BMI	+0.15	0.218

Comparative Analysis of Results

The serum GFAP levels differed among groups.Inter-group variance of serum GFAP level.The main result of this study is that the serum level of Glial Fibrillary Acidic Protein (GFAP) was greatly increased between the three cohorts in a stepwise fashion. The diabetic patients with uncontrolled T2DM (Group III) had a 5.5 fold rise in GFAP level (0.44 \pm 0.14 ng/mL) as compared to control

group (0.08 \pm 0.02 ng/mL). There was a significant difference between these groups for the percentage of reactive astrocytes ($p < 0.001$), indicating that high levels of chronic hyperglycemia are likely directly associated with extensive activation of astrocytes. Group II (Controlled) vs. Group III (Uncontrolled): GFAP concentrations were 2.75 times more in the patients with poor glycemic control than in the patients with controlled diabetes (0.16 ±0.05 ng/mL). The importance of this comparison lies in the fact that it demonstrates that there is more going on that just the presence of the disease diabetes; it is the level of hyperglycemia (measured by the HbA1c) that is the key. Bio Marker Sensitivity: In our study, we obtained a higher correlation coefficient of r = +0.84 while Zheng et al. (2021) obtained a correlation coefficient of r = +0.76. This increased sensitivity may be explained by the fact that we have excluded patients with recent head injuries or other inflammatory systemic diseases, leaving just the "diabetic effect" on the brain.

Comparison Pair	Mean Difference (ng/mL)	Significance (p)
Uncontrolled vs. Control	+0.36	< 0.001
Uncontrolled vs. Controlled	+0.28	< 0.001
Controlled vs. Control	+0.08	< 0.01

DISCUSSION

The results of this study offer strong evidence of the effects of chronic hyperglycemia as seen by elevated HbA1c on astrocyte injury and accompanying neuroinflammation in patients with Type 2 Diabetes Mellitus (T2DM). The remarkable increase in serum GFAP in the uncontrolled group (0.44 ±0.14 ng/mL) when compared to the controlled group (0.30 ±0.12 ng/mL) and the healthy group (0.20 ±0.12 ng/mL) has led us to believe in a "metabolic-neurodegenerative axis" whereby poor glycemic control triggers greater activation of the glia.

This stepwise elevation of GFAP observed can be explained by the biochemical effect of Advanced Glycation End-products (AGEs). Chronic hyperglycemia results in glycation of proteins in the absence of enzymes that combine with their receptors (RAGE) on the surface of astrocytes. This interaction is followed by a series of oxidative stress, the release of pro-inflammatory cytokines and a process called "reactive astrogliosis" in the astrocytes. In this state, remodeling of the cytoskeleton of the astrocyte results in an over-expression of GFAP. Huang et al. (2023) proposed that this process of glial activation is a role compensatory measure as a result of changing metabolic conditions in the brain (Ayala-Guerrero, L., et al. (2022).

Our data showed a very high positive correlation coefficient and significance level ($r = +0.84$, $p < 0.001$) between HbA1c and serum GFAP. This discovery is important because it demonstrates that exposure to sugar over a prolonged period of time is much more harmful than drastic surges and dips. Increased HbA1c promotes BBB disruption through the thickening of basement membrane of the cerebral capillaries and loss of pericyte cells. The BBB permeability increases and allows leakage of intracellular proteins, such as GFAP, into the systemic circulation. This is consistent with the work by Simó et al., 2017, who showed that glycemic instability results in the direct leakage of neural proteins into the blood as a non-invasive indicator of the condition of the central nervous system.

In our uncontrolled diabetic group, the level of GFAP was 0.44 ng/mL – a very similar level to what is seen in early-stage neurodegenerative disease. For example,

Abdelhak et al. (2022) have shown that GFAP in serum is a good marker for astrocyte reactivity in different neurological diseases. But our study is the first to demonstrate this increase in elevation in people who have diabetes but not yet had a clinical stroke or dementia. Moreover, we noted a slightly higher correlation coefficient than the one reported by Zheng et al. (2021) with the possibility that this high exclusion criteria for the presence of comorbidities and BMI might have contributed. This evidence shows that although the effect of age has been accounted for, HbA1c is still an independent and strong predictor of glomerular damage.

There is a very close relationship between HbA1c and GFAP and it would seem that in fact maintaining HbA1c below 7.0% is not only important for prevention of retinopathy and nephropathy, but is extremely important for neuroprotection. The results of this study suggest that quantification of GFAP in the serum might be employed in clinic to detect subclinical brain injury in diabetic patients and lead to early pharmacological treatment to prevent cognitive decline (Pereira, J. B., et al. (2021).

CONCLUSIONS

The significant increase in GFAP levels among uncontrolled diabetic patients further validate the neuro-biomarker of diabetic glucotoxicity-induced astrogliosis and neurological tissue damage. HbA1c Impact: In addition to being a vascular risk indicator, a strong positive correlation (r = 0.82) indicates that HbA1c is a good predictor of dysfunction of the blood-brain barrier and inflammation in the brain. Clinical Utility: Quantification of GFAP in serum is a highly sensitive non-invasive diagnostic tool for pre-clinical/early detection of DE even before irreversible cognitive impairment can occur, and thus could be used to provide an opportunity to intervene.

RECOMMENDATIONS

We recommend the use of neuro-biomarker testing as a routine part of the management of diabetic patients (especially those who have elevated HbA1c levels for a longer period).

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