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ASSOCIATION OF SERUM FRUCTOSAMINE WITH SERUM ALBUMIN AND AVERAGE PLASMA GLUCOSE CONCENTRATION AMONG DIABETES MELLITUS PATIENTS

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Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia; monitoring glycemic status is crucial for effective diabetes management, with fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), and glycated hemoglobin (HbA1c) being commonly used biomarkers. Fructosamine, which is a glycated protein (GP), is an alternative marker that can overcome the limitations of HbA1c associated with red cell abnormalities that reflect intermediate-term glycemic control over 2–3 weeks. Since albumin accounts for 60%to 70% of all extracellular plasma proteins, fructosamine levels primarily reflect glycated albumin (GA) levels. However, the Fructosamine test is not routinely used in developing countries due to its high cost and a lack of awareness of well-established reference ranges. Therefore, this study aims to investigate the correlation between GP and average glucose and total serum albumin concentrations. Patients over 18 years old diagnosed with DM, who met the inclusion criteria were selected for the study (n=202). The laboratory results, including FPG, PPPG, serum albumin, and serum fructosamine, were obtained from Colorimetric assays. Mainly, descriptive statistics and bivariate correlation analysis were conducted to establish associations between serum albumin, FPG, PPPG, and fructosamine. Fructosamine exhibited a strong positive correlation with the average FPG and PPPG ($r = 0.825$, $p < 0.01$) and a moderate correlation with serum albumin ($r = 0.258$, $p < 0.01$). Also, a higher association was observed with lower albumin levels [<3.5 mg/dl], while a weak correlation was found at normal albumin levels [>3.5 mg/dl], indicating that glucose exposure time and albumin half-life are directly influencing glycated protein levels. This study establishes a strong association between Average plasma glucose levels and albumin, emerging as the most reliable predictor for fructosamine. Even though, due to the bromocresol purple assay limitations, the study couldn't obtain the non-glycated albumin portion separately, the study found that glycation of proteins is primarily influenced by the duration of glycemic exposure and the half-life of albumin.

Keywords: diabetes mellitus, average plasma glucose, total serum albumin, fructosamine, glycated albumin, advanced glycation end products

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia (elevated blood glucose levels). It is primarily caused by impaired insulin secretion or insulin resistance in varying degrees (Schleicher *et al.*, 2022). Type 2 DM (T2DM) is the most common form of diabetes, accounting for approximately 90% of all diabetes cases. Crude Prevalence of Diabetes in Sri Lanka, among adults, was 23% in 2018/2019 (Rannan-Eliya *et al*., 2023), which indicates that Sri Lanka has a very high DM prevalence. As prolonged diabetes can cause severe health effects, early diagnosis of Diabetes is crucial to prevent serious health complications. Chronic hyperglycemia is associated with growth impairment and increased vulnerability to specific illnesses (Balaji, Duraisamy, and Kumar, 2019). Along with these, the clinician will request one or more physical characteristics, as well as laboratory investigations such as fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), and HbA1c, to monitor the patient's blood glucose level (American Diabetes Association, 2010). FPG is the most common and widely used method for diagnosing DM. Glycated hemoglobin (HbA1c) is the gold standard method of long-term monitoring of DM (Landgraf, 2006). However, it cannot be used for patients with anemia, hematological disorders, hemoglobinopathies, chronic kidney diseases, liver diseases, or any other condition affecting the life span of red cells (Bergman *et al.,* 2020). Since HbA1C cannot be used in some clinical conditions, the fructosamine test is used as an alternative method for monitoring diabetes control over a short period, like two to three weeks (Danese *et al.*, 2015).

Albumin, the most abundant plasma protein, accounting for 60%–70% of all extracellular plasma proteins, is the primary contributor to fructosamine levels. Therefore, fructosamine predominantly measures glycated albumin (GA), the major form of glycated protein (GP) in plasma, formed through the "glycation" process, also known as the Maillard reaction (Danese *et al.*, 2015).

Albumin, being the most abundant plasma protein, is highly susceptible to glycation with many glycation sites. Based on this, our study aimed to do a correlation analysis using average plasma glucose concentration and total serum albumin to see the association of these with glycated protein concentration. This study seeks to estimate

glycemic control over a specific period by correlating the glucose exposure of albumin with albumin glycation. Also, the fructosamine test is not currently done by Sri Lankan government hospitals due to cost considerations, lack of awareness, and lack of proper clinical justification from the WHO or ADA for standardised reference ranges for fructosamine, unlike the well-established guidelines available for HbA1c. So, it would be beneficial to have an alternative method to estimate fructosamine levels without directly measuring them. Therefore, it would be beneficial to see how fructosamine correlates with average glucose concentration and serum albumin levels in everyone, to understand how albumin concentrations affect glycated albumin values. This study assesses the association between FPG, PPPG, total serum albumin (S.ALB), and fructosamine (glycated protein) levels in diabetes mellitus patients.

METHODOLOGY

This is a Laboratory-based, prospective, cross-sectional study. The study was conducted at the outpatient department and the Biochemistry department at the National Hospital of Sri Lanka (NHSL), Colombo 10. The study group was composed of patients attending the diabetes and endocrine clinic and newly diagnosed diabetic patients at the National Hospital of Sri Lanka. Diabetic patients were selected using inclusion and exclusion criteria. The study population comprised 202 participants of both sexes aged above 18 years. The majority of participants were diagnosed with Type 2 Diabetes Mellitus, while a smaller proportion had Type 1 Diabetes Mellitus or were classified as prediabetic. No participants with gestational diabetes were included in the study. Permission for the study was obtained from the KDU Ethical Review Committee. Additionally, approval to conduct this study was obtained from the NHSL ethics review committee.

The sample size of the study was identified using the following equation

$$N = \frac{[z^2\ p\ (1-p)]}{2}$$

N – sample size

Z – Standard normal deviation of chosen confidence level, which is 95%; 1.96

P – expected proportion in population is 0.143 (prevalence = 14.3%) (Rannan-Eliya et al., 2023)

D – precision

N=188

Therefore, the sample size of the study was calculated as 188. Thus, data from 202 patients were collected

In our study, participants are a majority between 45 and 70 years of age (83.19%). This distribution aligns with the epidemiology of type 2 diabetes, where prevalence rises sharply after age 40 and peaks in middle-aged to early elderly adults (Zhou et al., 2016; IDF Diabetes Atlas, 2021). Their glycemic control varied; some maintained

good control and likely represented earlier stages of the disease, while others had higher glucose levels with more advanced progression.

Previous studies have shown that HbA_1c levels tend to increase modestly with age, even in non-diabetic individuals (from 3.8% at age 20 to 4.4% at age 70), whereas serum fructosamine concentrations remain largely unaffected by age (Yudkin et al., 1996). Although the stage of diabetes can influence the risk of chronic complications, fructosamine primarily reflects short-term glycemic control (~2–3 weeks) (Armbruster, 1987) and is less affected by disease duration. But it can be indirectly affected by age, malnutrition, or severe age-related complications.

FBS test is done in the early morning after 12 12-hour overnight fasting period, and PPBS test is done 2 hours after the patient has a meal (2.00 pm), at the same time, a blood sample was taken for albumin and other liver or kidney profile tests. At NHSL, they performed FBS, PPPG, and albumin testing, also using Abbott Architect C8000. Glucose was analyzed by the hexokinase assay method, and Albumin was measured by the bromocresol purple assay method.

From the residual sample taken for the albumin measurement, we performed the fructosamine test on the Abbott Architect C8000 analyzer by the nitro blue tetrazolium assay method after quality control. Then we recorded all the data collected and conducted the statistical analysis with IBM SPSS version 26.

RESULTS AND DISCUSSION

In this study involving 202 diabetic patients, the relationship between fructosamine and glycemic parameters (fasting plasma glucose [FPG], postprandial plasma glucose [PPPG], and their average) as well as total serum albumin, was comprehensively analyzed using correlation and techniques. Descriptive statistics, histograms, and the Kolmogorov-Smirnov test ($p < 0.05$) indicated non-normal distribution across all variables.

Spearman correlation, Bivariate analysis revealed strong positive associations between fructosamine and glycemic measures, FPG ($r = 0.759$), PPPG ($r = 0.768$), and their average ($r = 0.825$), all with $p < 0.001$. The strongest correlation was observed with the product of FPG and PPPG ($r = 0.831$), highlighting the combined predictive value of both parameters. A moderate correlation was found between fructosamine and albumin ($r = 0.258$), with a stronger association at low albumin levels ($r = 0.434$, $p = 0.001$), while the association was weak and non-significant at normal albumin levels ($r = 0.117$, $p = 0.268$).

The study conducted by Rosediani, Azidah, and Mafauzy (2006), to determine the glucose monitoring by fasting blood glucose or 2-hour PPPG with fructosamine in T2DM patients, both FPG and PPPG significantly correlated with fructosamine levels in T2DM patients. The correlation between FPG and fructosamine was $r = 0.566$, while the correlation between PPPG and fructosamine was $r=0.551$, showing that both had similar significant correlations with fructosamine.

Table 1 - Spearman correlation analysis of fructosamine with other biochemical parameters

Spearman correlation	Correlation coefficient with fructosamine (r)	Sample Number
Lower albumin(<3.5g/dL)	0.434	60
Normal albumin(>3.5g/dL)	0.09	142

Diabetes does not significantly alter normal albumin levels unless it progresses into severe complications caused by advanced glycation end products (AGEs). In early and moderate stages of diabetes (Zhang et al., 2019). Serum albumin concentrations generally remain stable, as the liver maintains albumin synthesis.

Fructosamine values are not significantly affected by human serum albumin levels unless the albumin concentration falls below 3.0 g/dL (Gounden et al., 2025b). which can vary among individuals. Albumin, a large globular protein (66.5 kDa), contains multiple glycation-prone sites. However, since glucose is a small molecule (180 Da) and glycation is a concentration-dependent reaction, the availability of glucose becomes the rate-limiting factor in the formation of glycated albumin. Additionally, the time of exposure to glucose plays a crucial role, as prolonged exposure allows more glucose molecules to interact with albumin, increasing the likelihood of glycation (Freitas, Ehlert, and Camargo, 2022). This is why in our analysis, glucose correlates more with fructosamine than albumin.

Although albumin possesses numerous glycation sites, steric hindrance and structural changes that occur upon initial glycation reduce its susceptibility to further glycation. After glycation, conformational changes and alterations in local charges limit additional glucose attachment (Kisugi et al., 2007). In this study, free albumin, which is more susceptible to glycation, was not separately measured. The BCP (Bromocresol Purple) method used for albumin quantification measures total albumin, including both glycated and non-glycated forms, further weakening the association between albumin levels and fructosamine in the current study.

According to previous research, glycated albumin (GA) concentration primarily reflects glucose exposure over albumin's lifespan rather than albumin concentration alone. The formation of GA follows,

$$[G\text{-}A] = k[G][A]\ T_{1/2},$$

where k is the glycation rate constant and $T_{1/2}$ is the albumin half-life, highlighting glycation as a rate-limiting reaction influenced by glucose availability and albumin turnover (Schleicher *et al.*, 1993). Lower serum albumin concentrations are often associated with reduced albumin synthesis and catabolism, which prolongs the average circulation time of individual albumin molecules. Because glycation is a time-dependent process, longer-lived albumin molecules have more opportunity to undergo non-enzymatic glycation (Müller et al., 2014). Albumin's numerous

glycation-prone sites (lysine, arginine, Cys-34) provide structural sites for glycation, glycemic exposure, and turnover dynamics, chiefly governing fructosamine and GA formation, making albumin correction alone insufficient to reflect true glycemic status (Sadowska-Bartosz *et al.*, 2015)

The calculated average glucose concentration (FPG + PPPG) demonstrated a very strong correlation with fructosamine ($r = 0.825$, $p < 0.001$). This indicates that fluctuations in short-term glucose exposure are reliably reflected in fructosamine levels. Also, given this strong association, the average glucose value can be effectively used to predict short-term glycemic control over a period of 2 to 3 weeks from routine laboratory parameters. This finding offers a cost-effective approach for hospital laboratories, as it reduces the need for additional specialised assays when estimating intermediate-term glycemic control.

CONCLUSIONS/RECOMMENDATION

This study successfully demonstrated that due to albumin's weak correlation with glycated protein ($r = 0.149$, $p = 0.035$), serum albumin alone cannot reliably predict fructosamine levels, because it has more glycation-prone sites and its half-life changes with the catabolic rate, and in contrast, the calculated average glucose concentration (FPG + PPPG) showed a very strong correlation with fructosamine ($r = 0.825$, $p < 0.001$), indicating that it accurately reflects short-term glycemic exposure. These findings suggest that average glucose can serve as a practical and reliable predictor of short-term glycemic control over 2 to 3 weeks. This approach can reduce the need for frequent costly tests like HbA1c or complex AGE-specific assays, making it especially beneficial in hospital and resource-limited settings to monitor glycemic control from routine analysis results. For future improvements, research should focus on incorporating direct AGE or glycated albumin measurements through ELISA, colorimetric assays, or Raman spectroscopy could enhance precision, reduce reliance on reagents, lower operational costs, and make diabetes monitoring more reliable and sustainable over time.

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ABBREVIATIONS & ACRONYMS

T1DM -Type 1 Diabetes Mellitus
T2DM- Type 2 Diabetes Mellitus
NHSL – National Hospital of Sri Lanka
PPPG- Post Prandial Plasma Glucose
FPG- Fasting Plasma Glucose
ALB- Albumin
T.ALB- Total Albumin
GP- Glycated Protein
GA – Glycated Albumin
G- Glucose
T1/2- Half life
OGTT- Oral Glucose Tolerance Test
BCP – Bromo cresyl purple
NBT – Nitro blue tetrazolium
AGE – Advanced Glycation End products
IQR - interquartile range
AVG – average
S.ALB – Serum Albumin
VIF – Variance Inflation Factor