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SERUM FRUCTOSAMINE AS A GLYCEMIC MARKER

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ABSTRACT

Background: Diabetes mellitus is characterized by a syndrome of chronic metabolic disorder with hyperglycemia as a common denominator. One of the less frequently used glycemic markers in the diagnosis of diabetes is serum fructosamine. Fructosamine is formed when glucose reacts with the amino groups of plasma proteins in an irreversible reaction. Its concentration is primarily determined by blood glucose concentration and plasma protein lifespan.

Main body:

Glycosylated Hemoglobin (HbA1c) have been used for decades for diagnosis of diabetes. However, it is altered in many situations including red blood cell wall defects, hemoglobinopathies, chronic renal failure, and chronic liver disease, and various other situations. Therefore, the utility of short-term glycemic markers like Serum Fructosamine is gaining popularity. Glycated serum proteins, of which albumin is the most abundant, are referred to as fructosamine. Fructosamine is made in the same way as HbA1c is made, by nonenzymatic glycation of protein amino groups. Since albumin has a much shorter half-life of about 20 days than HbA1c, it reflects more short-term (2–3 weeks) shifts in glucose regulation

than HbA1c. Fructosamine measures total serum protein-bound to glucose and represents blood sugar levels for a period of two to three weeks, therefore, it could be very useful for tracking early treatment response.

Conclusion:

The measurement of Fructosamine is simple and precise in terms of technology. It may be used where more frequent and tight glycemic control is targeted and in situations where HbA1c as a glycemic marker is inappropriate. Its measurement is very effective in gestational diabetes where there is a need to monitor blood sugar levels more frequently and more closely. Because of its application to diabetes and ageing pathologies, fructosamine has seen a surge in biomedical research.

Keywords: Diabetes; Glycemic markers; Serum Fructosamine; Glycosylated Hemoglobin (HbA1c); Gestational diabetes

INTRODUCTION

Diabetes is one of the most common endocrine diseases, affecting nearly 6% of the global population. It is defined by a chronic metabolic disorder syndrome with hyperglycemia as the common denominator. This hyperglycaemia represents only the tip of the iceberg of larger metabolic derangements.

In 2025, there will be 300 million diabetic patients (International Diabetes Federation, 2001) (Ernest Adeghate) **[1]**. The projected increase in the number of diabetic patients will strain the capabilities of healthcare providers the world over. As a result, it's critical to reconsider the causes and epidemiology (Federation, 2013) **[2]**.

Over the last few decades, researchers have focused on defining the disease and its glycemic parameters. These glycemic parameters have been defined based on the occurrence of various complications in a larger population. The most accepted are the guidelines by the American Diabetic Association which takes into account the threshold of blood sugar levels under different situations (Association, 2014) **[3]**.

Main Text:

Glycemic markers: The glycemic parameters can be classified as short term and long term glycemic markers.

Long term glycemic markers:

One of the long term parameters that have been used for decades is Glycosylated hemoglobin which is used with self-monitoring of blood glucose (SMBG). It takes into account Advanced Glycation End Products (AGEs) and represents mean blood sugar levels in the previous two and a half to three months based on the half-life of red blood cells.

The American Diabetes Association (ADA) recommends an A1c of 6.5 percent for diabetes diagnosis and 5.7-6.4 percent for those who are at the highest risk of developing diabetes.HbA1c testing is a highly standardized test with the least intra-individual variation (Cowie CC, 2010) **[4]**. It is not affected by short-term lifestyle changes. However, the red blood cell turnover is altered in many situations including red blood cell wall defects, hemoglobinopathies, chronic renal failure, chronic liver disease, in infants, and various other situations (MS, 2013) **[5]**. Also, in gestational diabetes, there is a need to monitor blood sugar levels more frequently and more closely (Agarwal MM, 2001) **[6]**. Moreover, In the case of genetic variants such as haemoglobin S and C characteristics or high foetal haemoglobin, as well as chemically modified haemoglobin derivatives, the accuracy of HbA1c measurements is decreased (eg, carbamylated haemoglobin in patients with impaired renal function) (Lippi G, 2011) **[7]**.

The short term glycemic markers are:

Fructosamine: Glycation, a nonenzymatic mechanism involving a labile Schiff base intermediate and the Amadori rearrangement, joins glucose molecules to protein molecules to form stable ketoamines, or fructosamines. Because of the abnormally high sugar concentration in the blood, the amount of fructosamine in the blood is increased in diabetes mellitus. As a result, the level of fructosamine in the blood is reflected (Armbruster, 1987) **[8]**. Fructosamine, is defined as all ketamine linkages resulting from the glycation of serum proteins. Fructosamine represents blood sugar control for a period of two to three weeks. The plasma levels of Fructosamine and Glycated Albumin increase in diabetes, when blood glucose levels are raised. The measurement is quick, simple and inexpensive, and unaffected by red blood cell disorders. Albumin has a 9- to 10-fold higher rate of nonenzymatic glycation than human haemoglobin **[9-12]**. Serum Fructosamine has been found suitable to screen for diabetes during pregnancy (Furusyo N, 2011) **[13]**, in developing countries (Islam N, 1993) **[14]**, and sickle cell disease. (Organization, April 2006; Aliyu ZY, 2008) **[15, 16]**.

Glycated Albumin (GA) Albumin with lysine residues bound to glucose is referred to as glycated albumin (GA) (Shimizu, 2019) **[17]**. The amount of GA in the body determines the glucose concentration and albumin half-life. In diabetes-related complications such as CKD, GA is a very useful diagnostic marker. (Chen HS, 2010)

[18]. Since it reflects the levels of blood glucose more rapidly than HbA1c, and it is useful in patients with fluctuating blood glucose (Ting Gan, 2018) **[19]**.

1,5-anhydroglucitol: 1,5-AG is a 6-carbon monosaccharide derived from food that represents average glycemia over the preceding 2–14 days (Parrinello, 2014) **[20]**. When blood glucose levels are very high (160–180 mg/dl), glucose competes with 1,5-AG for reabsorption in the renal tubule, and 1,5-AG is excreted, resulting in a drop in blood 1,5-AG levels. 1,5-AG levels denote hyperglycemia over the past 2 weeks. It can be used in persons with diabetes and HbA1c <8% (Lorena Alarcon-Casas Wright, 2012) **[21]**. However 1,5-AG levels fluctuate in patients with impaired renal and liver function, during gestational diabetes, and in – maturity-onset diabetes of the young. Hence, we need to focus our attention on the short-term glycemic parameters. In this regard, Fructosamine has an important role to play.

History and development of Fructosamine: Methods for determining Fructosamine and Glycated Albumin have undergone significant development and improvement over the years. There was a lack of analytical standardisation and issues with the specificity of the assay at first. (Agarwal MM, 2001) **[6]**. Glycated Albumin was measured using affinity chromatography (Silver AC, 1991) **[22]**, ion-exchange chromatography (Day JF, 1979) **[23]**, and high-performance liquid affinity chromatography (Yasukawa K, 1992) **[24]** in recent studies. The "gold standard" method was established as liquid chromatography-tandem mass spectrometry (LC-MS/MS). (Brede C, 2016) **[25]**. These strategies are both complex and costly, despite the fact that they are both highly efficient. (Testa R, 2016) **[26]**.

In an alkaline medium, serum glycated proteins reduce nitroblue tetrazolium (NBT) salts (J R Baker, Sep 1985) **[27]**. For Fructosamine determination, this colorimetric method ("second generation of the nitroblue tetrazolium colorimetric procedure") is preferred (Cefalu WT, 1991) **[28]**. This assay is less expensive and simple to perform (Danese E, 2015) **[29]**. The derived fructosamine levels are corrected for total protein concentrations. (Rodríguez-Segade S, 2017) **[30]**. In 430 pregnant women, Agarwal *et al* (Agarwal MM, 2001) **[6]** obtained the value of glycated proteins, as protein corrected Fructosamine (cFRUC) and haemoglobin A1c (HbA1c), individually and in a combined manner for a Gestational Diabetes Mellitus diagnosis. The study concluded with the fact that Fructosamine

levels correlated with HbA1c after being corrected for proteins.

Comparative studies on HbA1c, and Fructosamine in type II diabetic patients:

Glycosylated hemoglobin and serum fructosamine have been compared in their effectiveness as glycemic markers both alone and in combination.Glycemic control and associated morbidity was monitored by Mittman *et al*. (2010) (Mittman N, 2010) **[31]**, by comparing HbA1c levels with Serum Fructosamine (SF) levels in the blood. A significant correlation was found between HbA1c and Serum fructosamine. These parameters also correlated well with mean blood glucose levels.

Non-diabetic first degree relatives of type II diabetic patients and healthy controls were studied for their serum fructosamine and other clinical parameters by Manjrekar *et al*. (2012) (Poornima Ajay Manjrekar, 2012) **[32]**. Elevated serum FA levels (533.62 mg/dl) were seen in the first degree relatives. The first degree relatives are grouped under the high-risk population. This group of people can be treated in advance if markers like serum fructosamine are used.

Apart from serum levels of fructosamine salivary fructosamine values have also been studied Sadhana *et al*. (2017) (Sadhana, 2017) **[33]** studied the relationship between salivary levels of Fructosamine, plasma levels of glycosylated hemoglobin, and plasma Levels of glucose in type II diabetes mellitus. They were compared with the healthy control group. Final results proved that Salivary Fructosamine levels are significantly correlated with fasting blood sugar, Postprandial blood sugar and Glycosylated hemoglobin levels. Moreover diabetic patients had higher values of salivary fructosamine when compared to the control group individuals **[34-37]**.

Clinical applicability:

The average glycaemic levels for a period of over 2–3 weeks, is well predicted by serum fructosamine. In the past Serum Fructosamine was not as frequently used for diabetes mellitus (DM) control monitoring as far as glycated haemoglobin (HbA1c) is concerned. However slowly this glycemic marker is gaining popularity.

With Fructosamine, the potential risk of diabetes can be reliably predicted **[38-40]**. It will be extremely useful in detecting prediabetes early on. Fructosamine is very useful for tracking early response to therapies because it is closely associated with average glucose levels in the previous 10-14 days (Schorr, 2014) (Nagasaka Y, 1988) **[41, 42]**. The clinical studies on Fructosamine can be summarized as:

Table 1: Clinical Studies on Serum Fructosamine

S. No.	Author	Title	Findings
1.	(NO., 2020)[43]	"Glycemic Markers in Operative Orthopaedics-Is Fructosamine Better than HbA1c"	Serumfructosamine appears to be a more promising marker for pre-operative glycemic optimisation in orthopaedics because it represents glycemic regulation over 2-3 weeks, and assays are fast, cheap, and values are unaffected by glycated hemoglobin limitations.
2.	(Krhač M, 2019)[44]	"Update on biomarkers of glycemic control"	Glycated proteins like serum fructosamine can provide useful additional information, particularly in cases where HbA1cresults are inaccurate or inadequate.
3.	(Duarte S, 2019)[45]	"Glycated Peptide Levels Are Associated With Cognitive Decline Among Nondiabetic Older Women"	In non-diabetic older adults, serum fructosamine and other glycated peptides significantly predicted cognitive loss
4.	(Km Neelofar, 2017)[46]	"A comparative analysis of fructosamine with other risk factors for kidney dysfunction in diabetic patients with or without chronic kidney disease"	Glycation allows serum proteins to become glycated in a hyperglycaemic state Serum fructosamine is a major contributor to kidney disease. When diabetic patients with CKD were compared to diabetic patients without complications, Serum fructosamine, creatinine levels, cholesterol and LDL and HbA1c, were significantly higher (P 0.001).
5.	(S. Caré, 2018)[47]	"Plasma fructosamine during the transition period and its relationship with energy metabolism and inflammation biomarkers in dairy cows"	During the transition phase, the plasma concentration of Serum fructosamine was used to track retrospective undernutrition in dairy cows. Serum fructosamine was positively linked (P 0.05) to plasma glucose and albumin concentrations during the first month of lactation.
6.	(Neuza Mendes, 2018)[48]	"Beyond self-monitored plasma glucose and HbA1c: the role of non-traditional glycaemic markers in gestational diabetes mellitus"	They addressed the possible importance of non-traditional glycemic regulation metrics in Gestational Diabetes Mellitus patients and found them to be better than the conventional ones.
7.	(Shohat N, 2017) [49]	"Serum Fructosamine: A Simple and Inexpensive Test for Assessing Preoperative Glycemic Control, The Journal of Bone and Joint Surgery".	Patients with serum fructosamine levels of 292 mol/L had a substantially higher risk of deep infection, readmission, and reoperation, according to the researchers.
8.	(Romero, (2016))[50]	"Correlation of Serum Fructosamine and recurrent pregnancy loss: Case–control study"	When compared to controls, serum fructosamine levels were higher in women with recurrent pregnancy loss. As a result, subclinical glucose resistance can be linked to a higher risk of recurrent pregnancy loss.
9.	(Danese, (2015)) [29],	"Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes".	Serum fructosamine and glycated albumin could be appealing alternative, especially in patients who experience rapid changes in glucose homeostasis.
10.	(Li PK, 2015;)[51]	"The Benefit of a Glucose-Sparing PD Therapy on Glycemic Control Measured by Serum Fructosamine in Diabetic Patients in a Randomized, Controlled Trial (IMPENDIA)".	In dialysis patients, Serum fructosamine can be a more accurate indicator of glycemic regulation than HbA1c..
11.	(Wahid, 2002)[52]	"Serum fructosamine as a marker of 5-year risk of developing diabetes mellitus in patients exhibiting stress hyperglycaemia"	A period of five years was taken to assess Patients with stress hyperglycemia. Serum fructosamine and random plasma glucose were measured during this time period. The Random glucose and fructosamine levels at 16.7 ± 7.0 (11.2–55.0) mmol/l and 3.3 ± 0.6 (1.3–4.5) mmol/l were seen in those who developed diabetes later on. The other group who did not become diabetic had similar values of random plasma glucose but a lower value of fructosamine, 2.4 ± 0.4 (1.6–3.8) mmol/l; P < 0.001.

CONCLUSION

The HbA1c test is not sufficient in patients with sudden changes in glucose homeostasis, red blood cell disorders, or renal disease **[5]**. This explains studies focused on other glycemic markers, such as glycated albumin and serum fructosamine. Fructosamine, a short-term glycemic control marker, can provide additional information to glycosylated hemoglobin **[10]**. Long-term prospective studies and additional broad cohort studies are needed to see whether alternative biomarkers can help with early diabetes detection, diabetes control, and diabetic complications prevention.

List of abbreviations:

SMBG: self-monitoring of blood glucose; **AGEs**: Advanced Glycation End Products; **ADA**: The American Diabetes Association; **HbA1c**: Glycosylated hemoglobin; **GA**: Glycated Albumin; 1,5-AG: 1,5-anhydroglucitol; **SF**: Serum Fructosamine.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data and material are available upon request.

Competing interests

The authors declare that they have no competing interests..

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Authors' contributions.

SA came up with the idea for the project and wrote the manuscript. VA, KN, and MT contributed technical expertise to the manuscript's revision. All authors have read and approved the manuscript.

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