

Correlation of HbA_{1c} and Fructosamine in Type II Diabetes Mellitus

Anin G S Queency Stylin¹, Dr. Vasanthi Pallinti^{2*}, Dr.S. Santhi Silambanan³.
Department of Biochemistry, Sri Ramachandra Medical College & Research Institute,
Porur, Chennai – 600 116, Tamilnadu, India.

Abstract

Aim :Fructosamine is a indicator of plasma glucose value showing the short term glycaemic level over 2-3 weeks. Whereas HbA_{1c} is the frequently used method to measure the plasma glucose value over 2-3 months (Long term glycaemic level). The purpose of this study is to point out the correlation between HbA_{1c} and Fructosamine levels in diagnosing Type II diabetes mellitus.

Methods and Results : This study was conducted in 90 Type II diabetic patients between the age group 30-60 years (of both sexes). HbA_{1c} is measured using Bio – Rad VARIANT II TURBO Haemoglobin Testing system (Photometric method) & Fructosamine analysed using Fructosamine (NBT) kit (Biosystems) in Semiauto Analyser..

Conclusion :This study points out the correlation between Fructosamine and HbA_{1c} (r=0.23, p=0.02). Hence this study has proven that Fructosamine can be used in the assessment of glycemic status in a short period (2-3 weeks) when compared to HbA_{1c} (2-3 months).

Keywords : HbA_{1c}, Fructosamine, Type II Diabetes Mellitus, Plasma glucose, , RBC disease, Glycated Protein.

INTRODUCTION

Type II Diabetes Mellitus is one of the most critical and metabolic disease indicating hyperglycemia. Diabetic biomarkers has an important role in monitoring the status of glucose level of an individual [1]

Insulin deficiency is the rootcause for this disease and it can alter the metabolism of carbohydrates, Fats and Proteins [2] . Across the world nearly 382 million persons were affected by this disease as per modern statistics, with a prevalence of 8.3% in 2013. It states nearly 592 million individuals may become the diabetic count in 2035 [3]. The ADA (American Diabetes Association) has published the most recent standards of medical care in diabetes, which highlights the early diagnosis for preventing the onset of symptoms, thereby decreasing the chances of long-term complications of Diabetes [3] Monitoring of glucose level in diabetic patients is very important in maintaining long term changes.

Traditional method for monitoring blood glucose level are Fasting blood glucose, Random blood glucose& Postprandial blood glucose level etc [4] Glycosylation is the process by which glucose units get attached to the protein molecules. Glycated protein level will be high in the case of diabetic patients. HbA_{1c}, Fructosamine & Glycated Albumin are some of the glycated proteins, which helps to screen sugar level of an individual [2]. HbA_{1c} is the most dominant nonenzymatic glycosylated protein and it is measured as a benchmark of glucose level which predicts the sugar level over 2 – 3 months and helps in the management of long-term diabetic control. But this will not apply for hemoglobinopathy or an altered red blood cell lifespan [5]. Frutosamine is another nonenzymatic glycosylated protein which helps in the assessment of hyperglycemia [6]. Fructosamine measurement is rapid, high-tech, economic and unaltered by RBC diseases. Even microsample volume of blood samples can be used for Fructosamine measurement [4]. The aim of this study is to determine the measurement of Fructosamine in the assessment of glycemic status.

MATERIALS AND METHODS

1.Subjects

This is a single centre, Prospective Observational study. A number of 90 Type II diabetic patients were enrolled in this study. Both sexes are included in this study group. Study population is taken between the age group of 30-60 years with their HbA_{1c} values above 6.5%.

2.Methods

Clinical and biochemical parameters of the patient like age, gender, haemoglobin, HbA_{1c}, albumin, globulin level was collected at Sri Ramachandra Institute of Higher Education and Research. HbA_{1c} level is screened using whole blood sample and it is measured in Bio-Rad VARIANT II TURBO Hemoglobin Testing system via High-Pressure Liquid Chromatography (HPLC).

Serum Fructosamine level is measured using Semi-Automated Analyzer, spectrophotometer or photometer with cell holder thermostable at 37°C and able to read at 530±20nm.

Quantitative enumeration of haemoglobin in whole blood is measured in Beckmann Coulter DXH 800 – automated cell counter by the principle of coulter and photometric method respectively.

3.Statistics

All statistical analyses were performed with the statistical package for the social science, statistical software package for windows, Version (SPSS Inc., Chicago. IL, USA).

4.Ethics Statement

This study was approved by the Institution Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai and was performed in accordance with its recommendations.

RESULT

This study was conducted in 90 Type II Diabetic patients between the age group 30-60 years (of both sexes) at Sri Ramachandra Institute of Higher Education and Research. We have distributed the study population (Type II diabetic patients) according to their various age group (*Fig 1*).

20% of Type II diabetic patients were found in the age group of 30-40. 28% patients were found inbetween the age group of 41-50 and 52% population were found in between 51-60 years. According to this report Type II diabetic population (51%) is higher in between the age group of 51-60.

With this population, we have compared the correlation between HbA_{1c} and Fructosamine for Type II diabetic patients (Table 1)

This study shows a positive weak correlation between HbA_{1c} and Fructosamine value ($r = 0.23$, $p=0.02$), which is statistically significant (Figure 2).

In this study we have also analysed the Albumin and total protein concentration for to refine the correlation by using corrected Fructosamine obtained by the below mentioned formula [7](Table 2)

A positive weak correlation was found between HbA_{1c} and corrected Fructosamine value ($r = 0.26$, $p=0.01$), which is also statistically significant (Where the p value for Fructosamine and HbA_{1c} without albumin correction is 0.02) (Figure 3).

Albumin is the major serum protein, hence Fructosamine is the chief measure of Glycated Albumin. To prove this, we have correlated Fructosamine and albumin level and found a correlation between Fructosamine and Albumin value ($r = 0.21$, $p=0.04$), which is statistically significant (Table 3) (Figure 4)

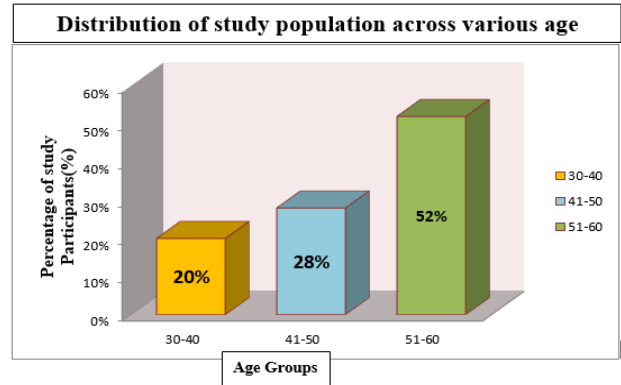


Figure 1 - Study population (Type II diabetic patients) according to their various age group

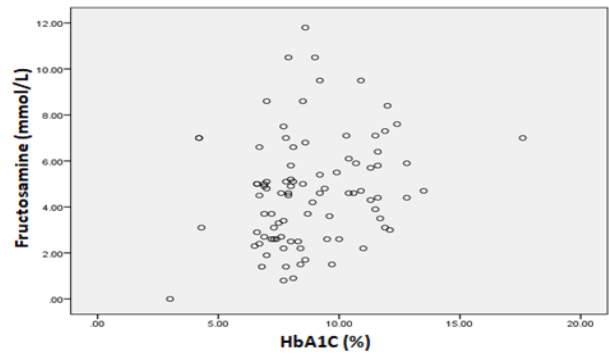


Figure 2 - Correlation between HbA_{1c} and Fructosamine value.

Statistical Values	Correlation between HbA _{1c} (%) & Fructosamine (mmol/L)
r value	0.23
p value	0.02
N	90
Statistical Significance	Significant

Corrected Fructosamine (mmol/L) = Measured Fructosamine/measured total protein*70g/L
--

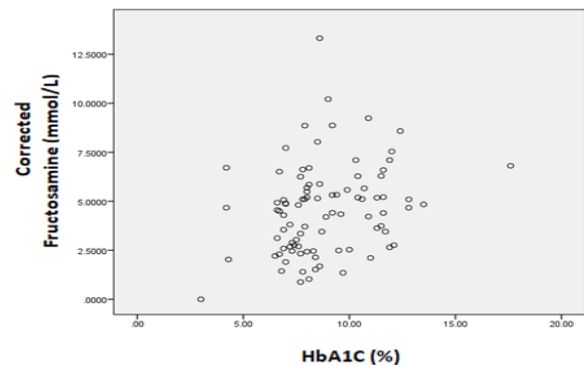


Figure 3 - Correlation between HbA_{1c} and Corrected Fructosamine value.

Table 3 - Correlation between HbA_{1c} & Corrected Fructosamine

Statistical Values	Correlation between HbA _{1c} (%) & Corrected Fructosamine(mmol/L)
r value	0.26
p value	0.01
N	90
Statistical Significance	Significant

Table 4 - Correlation between Fructosamine and Albumin

Statistical Values	Correlation between Fructosamine(mmol/L) & Albumin(g/dl)
r value	0.21
p value	0.04
N	90
Statistical Significance	Significant

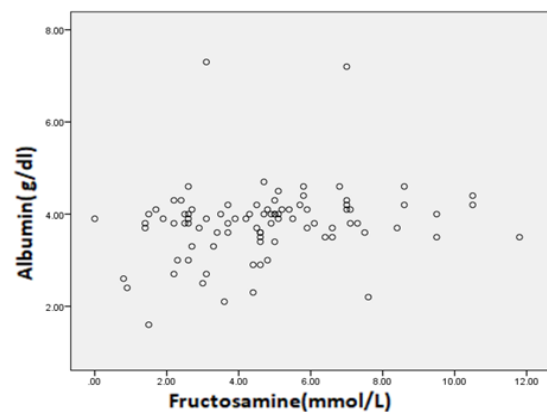


Figure 4 - Correlation between Fructosamine and Albumin.

DISCUSSION

Diabetes Mellitus is a common disorder which damages the organ (eye, kidney etc). Every year more than 1000 patients are affected around the globe. Hence patients need to be diagnosed and monitored properly.

HbA_{1c} (Glycated haemoglobin) is the predominant marker, which reflects the glucose level of a patient over 2-3 months. This marker shows the long-term glucose levels in diabetic patients. The American Diabetes Association (ADA) has referred the use of HbA_{1c} for the diagnosis and follow up of Diabetes Mellitus Patient [2]. As per ADA's report in 2010, value of HbA_{1c} \geq 6.5% is considered to be the diagnostic criteria for Diabetic Mellitus. The ADA has declared that HbA_{1c} is taken into consideration if it is approved by DCCT and the laboratory should be a NGSP [9]

Physiological condition of diabetes patient can affect the results of HbA_{1c}. We thought that the HbA_{1c} assay is insufficient for the diagnosis of diabetes mellitus. Thus, we also measured the serum Fructosamine levels in our patients to verify the diagnosis of diabetes. Serum Fructosamine, which effectively measures the levels of glycated serum proteins, is an indicator of glycemic control over the prior two weeks, which is equal to the lifespan of albumin. It is suggested that the use of serum Fructosamine will significantly improve the follow-up and prevention of diabetic complications.

The Fructosamine and HbA_{1c} level correlate with the each other in the patient whose glucose level is maintained and also in newly diagnosed patient [9]. This study shows a positive weak correlation between HbA_{1c} and Fructosamine value ($r = 0.23$, $p=0.02$), which is statistically significant. Braatvedt et al., (1997) also found similar correlation in between HbA_{1c} and Fructosamine (Van and Zijlstra, 1961 [11]. Selvin et al., (2015) also found that the correlations of HbA_{1c} with Fructosamine and glycated albumin in the overall population were high [6] In a cross-sectional and longitudinal study including 10987 subjects, Malmström and colleagues showed that Fructosamine was effective in discriminating subjects with and without diabetes [12]. Khan et al measured FPG and serum Fructosamine in 165 pregnant women and found that the FPG and Fructosamine could identify high-risk individuals to be screened with the OGTT avoiding unnecessary glucose challenges. Nansseu et al., (found that Fructosamine measurement is quick, technically simple, inexpensive, precise, fairly free of interferences, unaffected by red blood diseases and easily automated for use with microsample volumes [3].

Ayyappan et al., (found that the serum Fructosamine level correlated significantly with glycated hemoglobin concentrations ($r = 0.97$, $P < 0.001$) in GDM patients compared with healthy control groups [13]. But et al., Bruusgaard et al., Rutle et al., found the Pearson correlation coefficients of HbA_{1c} and Fructosamine at 0.39. (Braatvedt et al., 1997) [11]. Some studies have shown a negative correlation between Fructosamine and HbA_{1c}. Joy et al [14] showed that Fructosamine was not significantly associated with long-term glycemic control in diabetic patients receiving hemodialysis ($r = .345$, $P =$

.11). We have corrected the Fructosamine value and we have correlated the same with HbA_{1c} Value ($r = 0.26$, $p=0.01$) Table 2.

Duran et al., (2015) found out the Test of trend for correlations between albumin-corrected Fructosamine values and HbA_{1c} were significant for both albumin ($p = 0.05$) and

hemoglobin ($p = 0.01$) [15] Kennedy Et al., (1998) found that the Correction of the Fructosamine Test Plus results for total protein concentration significantly increased the correlation between Fructosamine Test Plus and MBG concentration (corrected: $r=0.463$, $P<0.001$; uncorrected: $r=0.347$, $P=0.002$) [7]. Mitmann Et al., (2010) [16] HbA_{1c} and albumin-corrected Fructosamine (AlbF) levels were highly correlated and both were significantly associated with serum glucose.

In this study Fructosamine and Albumin ($r = 0.21$, $p=0.04$) shows a correlation which is statistically significant. Danese et al., (2015) in their study they have mentioned that albumin is the most abundant of serum protein, Fructosamine is predominantly a measure of GA [3]. Filipovic et al., (2011) found that the shorter serum protein life span during the transition period has an influence on the decrease in blood Fructosamine concentrations [17]. Johnson et al., (1987) concluded the study by saying that the Fructosamine activity is a convenient measure of glycosyl protein concentration and that the index responds mainly to glycation of albumin. However, routine correction for serum albumin concentration is inappropriate [18]

Thus, the combined measurement of HbA_{1c} and Fructosamine is useful in the management of diabetes Mellitus. Fructosamine is considered as the good marker to diagnose glycemic status.

CONCLUSION

The HbA_{1c} correlated significantly with Fructosamine ($r = 0.23$, $p = 0.02$).

HbA_{1c} remains the standard for diagnosing diabetes mellitus and glycemic monitoring. Fructosamine can be used in assessment of glycemic status, especially in selected patients, in whom the measurement of HbA_{1c} may be biased or unreliable.

It will be more logical in measuring HbA_{1c} together with Fructosamine in the diagnosis and treatment of diabetic patients.

Limitation of this study

This study has been done in a small sample size.

Association with fasting and postprandial glucose level were not done

This study is a cross sectional study.

Follow up study could have been better to show the efficacy of Fructosamine in assessing diabetic status especially in individuals with high Fructosamine levels.

Scope for future studies

- A larger sample size should be included in future studies
- A cohort study has to be included in future to find out the better marker in hyperglycaemic conditions.
- Glycated albumin measurement has to be taken.

- Study should also include the parameters like Vitamin C & E which inhibit the glycation process.

Acknowledgment

Authors acknowledge the Head, Department of Biochemistry, Sri Ramachandra Medical College & Research Institute for providing samples, which helps us in our research.

Conflict of Interest

All authors declare no conflict of interest.

Abbreviations

HbA_{1c} – Glycated hemoglobin, ADA - The American Diabetes Association, DCCT- Diabetes Control and Complications Trial NGSP- National Glycohemoglobin Standardization Program, FPG – Fasting plasma glucose, OGTT – Oral glucose tolerance test.

REFERENCES

1. Lee J-E. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol ©2015 *Annals of Pediatric Endocrinology & Metabolism*. Ann Pediatr Endocrinol Metab. (2015) 20:74–8.
2. KAYALIK H, CANDAR T, ... SD-IJPA, 2016 undefined. Comparison of the Diagnostic Value of HbA_{1c} with Fructosamine in Diabetes Mellitus. *IjpbCom* (2016), 4(2):17–26.
3. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. *J Diabetes Sci Technol*. (2015),9(2):169–76.
4. Nansseu JRN, Fokom-Domgue J, Noubiap JN, Balti E V., Sobngwi E, Kengne AP. Fructosamine measurement for diabetes mellitus diagnosis and monitoring: A systematic review and meta-analysis protocol. *BMJ Open*. (2015),5(5).
5. Kang DS, Park J, Kim JK, Yu J. Clinical usefulness of the measurement of serum fructosamine in childhood diabetes mellitus. *Ann Pediatr Endocrinol Metab* (2015), 20(1):21–6.
6. Selvin E, Rawlings AM, Lutsey PL, Maruthur N, Pankow JS, Steffes M, et al. Fructosamine and glycated albumin and the risk of cardiovascular outcomes and death. *Circulation*. (2015), 132(4):269–77.
7. Kennedy DM, Johnson AB, Hill PG. A comparison of automated fructosamine and HbA_{1c} methods for monitoring diabetes in pregnancy. *Ann Clin Biochem*. (1998), 35(2):283–9.
8. Horvath AR, Bakris GL, Kirkman MS, Arnold M, Metzger BE, Bruns DE, et al. Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. *Clin Chem*. (2011), 57(6):1–47.
9. Stan- NG, Control D, Trial C. Executive Summary: Standards of Medical Care in Diabetes--2014. *Diabetes Care*. (2014), 37
10. Sharma B, Bhandari S. Correlative Study on Fructosamine and HbA_{1c} in Type 2 Diabetes Mellitus. *Int J Basic Appl Med Sci*. (2013), 3(3):162–71.
11. Howey EA, Browning MCK. Assay of Serum Fructosamine That Minimizes Standardization and Matrix Problems: Use to Assess Components of Biological Variation. (1987),33(2):269–72.
12. Gudbjörnsdóttir S, Walldius G, Malmström H, Hammar N, Grill V, Junger I. Fructosamine Is a Useful Indicator of Hyperglycaemia and Glucose Control in Clinical and Epidemiological Studies – Cross-Sectional and Longitudinal Experience from the AMORIS Cohort. *PLoS One*. (2014),9(10)
13. Ayyappan S, Philips S, Kumar Ck, Vaithiyanandane V, Sasikala C. Serum fructosamine a better indicator than glycated hemoglobin for monitoring gestational diabetes mellitus. *J Pharm Bioallied Sci* (2015),7(5):32.
14. Joy MS, Cefalu WT, Hogan SL, Nachman PH. Long-term glycemic control measurements in diabetic patients receiving hemodialysis. *Am J Kidney Dis*. (2002) Feb 1;39(2):297–307.
15. Duran L, Rodriguez C, Drozd D, Nance RM, Delaney JAC, Burkholder G, et al. Fructosamine and hemoglobin a_{1c} correlations in HIV-infected adults in routine clinical care: Impact of anemia and albumin levels. *AIDS Res Treat*. (2015)
16. Mittman N, Desiraju B, Fazil I, Kapupara H, Chattopadhyay J, Jani CM, et al. Serum fructosamine versus glycosylated hemoglobin as an index of glycemic control, hospitalization, and infection in diabetic hemodialysis patients. *Kidney Int* (2010) 78(SUPPL. 117):S41–5.
17. Filipović N, Stojević Z, Mašek T, Mikulec Ž, Prvanović N. Relationship between fructosamine with serum protein, albumin and glucose concentrations in dairy ewes. *Small Rumin Res* (2011), 96(1):46–8.
18. Johnson RN, Metcalf PA, Baker JR. Relationship between albumin and fructosamine concentration in diabetic and non-diabetic sera. *Clin Chim Acta*. (1987), 164(2):151–62.