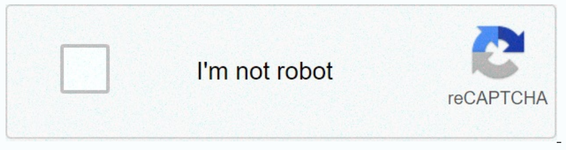

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Fructosamine to a1c conversion formula

Figure 1. Linear regression equation based on Cohen et al “Discordance between HbA1C and Fructosamine: Evidence for a glycosylation gap and its relation to diabetic nephropathy”The Equation is based on a study by Cohen et al titled “Discordance between HbA1C and Fructosamine : Evidence for a glycosylation gap and its relation to diabetic nephropathy”The authors estimated both HbA1C and fructosamine in 153 patients with a mean age of 47 years, of which 46% had type 1 diabetes and 47% type 2 diabetes. A plot of measured HbA1C was compared to measured fructosamine. The regression line for the cohort was HbA1C = 0.017 x Fructosamine + 1.61. The r value was 0.78.Formula Fructosamine to HbA1C conversionHbA1c = 0.017 X fructosamine level (mmol/L) + 1.61Fructosamine to a1c conversion chartGlucose (mg/dl)A1C%Fructosamine (Alarcon et al)Fructosamine (Cohen et al)905212.5199.41206250258.21507287.5317.031808325375.852109362.5434.6724010400493.4927011437.5552.3230012475611.1333013512.567036014550728.7739015587.5787.6Formula for HbA1C to Fructosamine conversionFructosamine (mmol/L) = (HbA1c – 1.61) x 58.82What is fructosamine?Fructosamine is the product of the nonenzymatic glycation of protein (glucose bound to protein). It should be seen as an umbrella term for circulating proteins that have undergone glycation. Albumin, the predominant circulating protein, is measured in the fructosamine assay, although it can also be independently measured as “glycated albumin”In contrast to glycated hemoglobin, which may be valid for assessing glycemic control up to the preceding three months before the test, the glycated albumin (or fructosamine) is only valid for the preceding three weeks. Unfortunately, fructosamine, just like glycated hemoglobin, is also subject to various limitations. The result is unlikely to be reliable in hypoproteinemic states (nephrotic syndrome, severe liver disease, protein-energy malnutrition, protein-losing enteropathy), pregnancy, uremia, or hyperlipidemia.Current Diagnostic Criteria for DiabetesThe current diagnostic criteria involve the utilization of either plasma glucose or glycated hemoglobin in establishing the diagnosis of diabetes mellitus. Although fructosamine is not an accepted tool in diagnosing diabetes mellitus, it can be used for monitoring the disease in clinical scenarios where the clinician expects limited utility of glycated hemoglobin.Glycated hemoglobin (HbA1c) value ≥6.5% (i≥48 mmol/mol)Fasting plasma glucose (FPG) ≥126 mg/dL (≥7.0 mmol/L)2-hour plasma glucose ≥200 mg/dL (≥11.1 mmol/L) after an oral glucose tolerance test (OGTT) using a 75 g anhydrous glucose loadRandom plasma glucose ≥200 mg/dL (≥11.1 mmol/L) in the setting of hyperglycemic symptoms (polyuria, polydipsia, unintentional weight loss).Current diagnostic criteria for prediabetesPrediabetes is a progressive and highly variable clinical entity that leads almost universally to diabetes mellitus if left untreated.HbA1c range of 5.7-6.4% (39-46 mmol/mol)Fasting plasma glucose between 100-126 mg/dL (5.6-6.9 mmol/L)2-hour plasma glucose between 140-199 mg/dL (7.8-11.0 mmol/L) after an oral glucose load (75grams of anhydrous glucose)Monitoring of diabetes mellitusFor nonpregnant adults, the goal of diabetes treatment is to aim for the following glycated hemoglobin and capillary glucose targets.HbA1c value <7.0% (<53 mmol/mol)Preprandial capillary plasma glucose between 70-130 mg/dL (3.9-7.2 mmol/L)Peak postprandial capillary plasma glucose <180 mg/dL (<10.0 mmol/L).Conditions that can affect the clinical utility of glycated hemoglobinA simple rule of thumb for recalling the causes of either falsely high or low glycated A1c is to recognize the conditions that alter the life span of red blood cells.

Since glycated hemoglobin measures how long the red blood cell is exposed to continuing glycation in the setting of significant hyperglycemia, conditions that alter the life span of a red blood cell can impact the final value of this diagnostic test.Patients with blood loss, either acutely or chronically, experience a depletion of red blood cells, which will falsely lower glycated hemoglobin. A similar scenario occurs in patients with hemolytic anemia. Since the spleen is important in the clearing of old (senescent) red blood cells, in patients with a large spleen, a state of “hypersplenism” occurs whereby red cells are removed from circulation at a much faster rate than usual. This also causes a falsely low glycated hemoglobin.Red blood cell transfusion can lead to a falsely high glycated hemoglobin if it is stored in a high dextrose-containing medium or low due to a delusional of circulating red blood cells. To further complicate matters, hemoglobin variants and significant vitamin C ingestion may result in either falsely high or low A1c depending on the assay technique.Falsely high A1cFalsely low A1cDecreased red cell turnover (iron, B12, or folate deficiency)Acute (e.g., hemolysis of variable etiology) or chronic blood loss anemiaSplenectomy (spleen clears senescent erythrocytes)Splenomegaly (storage diseases, infections, etc.)Uremia (false detection of carbamyl-hemoglobin)End-stage renal disease (chronic anemia, decreased red cell survival due to uremic toxicity)Hypertriglyceridemia Hypervitaminosis E (impairs glycation)HyperbilirubinemiaRibavirin (hemolytic anemia)Hyperglycation (physiologic variant)Pregnancy (decreased red cell lifespan, dilutional effect, especially in the second trimester and increased erythropoietin production)Chronic opioid dependence Lead toxicity Alcohol abuse disorder Since glycated hemoglobin A1c is fraught with various limitations, in certain clinical situations the use of an alternative method of monitoring diabetes mellitus may be required.ReferencesRadin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med. 2014 Feb;29(2):388-94.Wendy O. Henderson, MD, Mary H. Parker, PharmD, FASHP, FCCP, BCPS, BCCP and Bryan C. Batch, MD, MHS. Cleveland Clinic Journal of Medicine February 2021, 88 (2) 81-85Robert M. Cohen, Yancey R. Holmes, Thomas C. Chenier, Clinton H. Joiner; Discordance Between HbA1c and Fructosamine: Evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care 1 January 2003; 26 (1): 163–167.Lorena Alarcon-Casas Wright, Irl B. Hirsch; The Challenge of the Use of Glycemic Biomarkers in Diabetes: Reflecting on Hemoglobin A1C, 1,5-Anhydroglucitol, and the Glycated Proteins Fructosamine and Glycated Albumin. Diabetes Spectr 1 August 2012; 25 (3): 141–148. Diabetes mellitus (DM), a global epidemic, is increasing at an alarming rate and is associated with both increased morbidity and mortality. In 2018 the estimated prevalence of diabetes in the USA was 34.2 million people. Globally, the prevalence was 425 million people and this is expected to rise to 629 million by 2045. Currently, only plasma glucose and glycated hemoglobin (HbA1c) are universally accepted as reliable measures of diabetes control. In certain conditions, the HbA1c measurement is not reliable. An example is in patients with red blood cell (RBC) disorders and renal disease. Fructosamine, which is a measure of non-enzymatic glycation of circulating proteins including albumin, globulins, and lipoproteins, has evolved to be a reasonable alternative to HbA1c measurement in situations where HbA1c is not reliable. Because albumin is the most abundant of the serum proteins, fructosamine is predominantly a measure of glycated albumin (GA), which represents the percent of albumin that is glycated. Fructosamine and GA have a potential role in the diagnosis, monitoring, and management of diabetes. [1][2][3]HbA1c is a product of non-enzymatic glycation of hemoglobin. Red blood cells have a lifespan of approximately 90 to 120 days, hence HbA1c indicates the mean blood glucose concentration over the lifespan of the RBC. HbA1c is influenced by conditions affecting RBC survival. Conditions causing low RBC turnover like untreated iron, vitamin B12, or folic acid deficiency anemias, will result in falsely high HbA1c values. On the other hand, conditions causing high RBC turnover like hemolytic anemia, in patients treated for iron, vitamin B12, or folate deficiencies, as well as in patients treated with erythropoietin (like in chronic kidney disease), there will be falsely low HbA1c values.Fructosamine (1-amino-1-deoxy fructose), is a stable ketoamine, formed by the reaction between glucose and the amino group of protein (predominantly albumin, but also including globulins and lipoprotein). The attachment of the aldehyde group of the carbohydrate with the N terminal amino acid of the protein forms the reversible Schiff base product, the aldimine intermediate. The Schiff base product may be converted back to glucose and protein, or undergo the Amadori rearrangement to form stable fructosamine. This process is known as non-enzymatic glycation and is also referred to as the Maillard reaction. The Maillard reaction causes the browning phenomenon that occurs in milk and other food products when heated. Glycated albumin refers to the formation of ketoamine specifically involving the major circulating protein albumin (3.5 g/dl to 5 g/dl). Glycated albumin is an example of a fructosamine (FA). Because albumin is the most abundant of the serum proteins, fructosamine is predominantly a measure of glycated albumin.

Approximate Comparison of Glucose, Fructosamine, & A1C

Glucose (mg/dl)	Fructosamine (umol)	A1C (%)
90	212.5	5.0
120	250	6.0
150	287.5	7.0
180	325	8.0
210	362.5	9.0
240	400	10
270	437.5	11.0
300	475	12.0
330	512.5	13.0
360	550	14.0
390	587.5	15.0

The formation of fructosamine and glycated albumin are post-translational modifications that occur to proteins.Non-immunoglobulin serum proteins have a much lower half-life, approximately 14-21 days.[4] The measurement of fructosamine or GA provides information on glucose control within the previous 2-3 weeks. Another important difference with HbA1c is the rate of nonenzymatic glycation of albumin, which is approximately 9- to 10-fold higher than that of HbA1c.[5][6]Sample type: Serum or plasma are the sample types used for the measurement of fructosamine and glycated albumin. Fasting specimens are not required.

Conversion Table
(in mg/dl and mmol/l)

Hb-A1c	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9
mg/dl	65	69	72	76	79	83	86	90	93	97
mmol/l	3.6	3.8	4.0	4.2	4.4	4.6	4.8	5.0	5.2	5.4
Hb-A1c	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9
mg/dl	101	104	108	111	115	118	122	126	129	133
mmol/l	5.6	5.8	6.0	6.2	6.4	6.6	6.8	7.0	7.2	7.4
Hb-A1c	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9
mg/dl	136	140	143	147	151	154	158	161	165	168
mmol/l	7.6	7.8	8.0	8.2	8.4	8.6	8.8	9.0	9.2	9.4
Hb-A1c	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9
mg/dl	172	176	180	183	186	190	193	197	200	204
mmol/l	9.6	9.8	10.0	10.2	10.4	10.6	10.8	11.0	11.2	11.4
Hb-A1c	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9
mg/dl	207	211	215	218	222	225	229	232	236	240
mmol/l	11.6	11.8	12.0	12.2	12.4	12.6	12.8	13.0	13.2	13.4
Hb-A1c	9.0	9.5	10.0	10.5	11.0	11.5	12.0	12.5	13.0	13.5
mg/dl	243	261	279	297	314	332	350	368	386	403
mmol/l	13.6	14.6	15.6	16.6	17.5	18.5	19.5	20.4	21.4	22.4
Color Key:	Optimal	Good	High	Bad	Terrible	Horrible	Deathly	Suicidal	Suicidal	Suicidal

Fructosamine The most common assay available for fructosamine measurement in serum is the colorimetric-based assay. This assay utilizes the reduction of the dye nitroblue tetrazolium (NBT) to formazan. The rate of formazan formation is directly proportional to the fructosamine concentration and is measured with the spectrophotometric technique.[7] These assays are widely available, can be automated, and fairly inexpensive. The reference range for fructosamine in non-diabetic individuals is generally 200 to 285 umol/L. However, unlike HbA1c, there is a serious lack of standardization across the different fructosamine assays. Glycated Albumin There are several different assay methodologies available for the analysis of glycated albumin. These include:Enzymatic assayHigh-performance liquid chromatography (HPLC) and affinity chromatographyImmunoassay, including quantification by radioimmunoassayEnzyme-linked immunosorbent assay (ELISA)Enzyme-linked boronate immunoassay (ELBIA)ColorimetryElectrochemicalThe enzymatic assay (Lucica GA-L kit, Asahi Kasei Pharma, Tokyo, Japan) is easier to use, highly accurate, and automated.[8] First, there is the elimination of endogenous glycated amino acids and peroxide by a ketoamine oxidase, followed by a peroxidase reaction.[9] An albumin-specific proteinase hydrolyzes the GA. The products of this reaction are oxidized by ketoamine oxidase to hydrogen peroxide, which is then measured quantitatively by a colorimetric method. The albumin concentration is also measured concurrently. The final result is expressed as the ratio of glycated to total albumin.[10]The normal value is around 14% and it becomes greater than 17% in diabetes patients. Values in diabetes can go as high as two to five times the upper limit of normal.Fructosamine assays are affected by changes in temperature and by the increased presence of reducing substances in serum, for example, vitamin C and bilirubin. Fructosamine and GA both do not have standardized assays. Additionally, both fructosamine and glycated albumin are affected by the presence of any conditions that influence serum albumin concentrations. However, this is minimized for GA since this is expressed as a percentage of total albumin. Fructosamine will be unreliable when serum albumin is less than 3.0 g/dl.

This will include conditions where there is decreased albumin synthesis, like in liver cirrhosis, or when there is albumin/protein loss such as in nephrotic syndrome and protein-losing enteropathies. Fructosamine levels may also be affected by conditions with raised total protein levels, like in multiple myeloma (due to increased immunoglobulins) and in polyclonal gammopathies.A reference range for fructosamine in non-diabetic individuals is generally 200 to 285 umol/L.While GA assays also suffer from standardization, the newer assay developed by Asahi Kasei appears to be much improved. According to this assay, normal persons have values around 14% and those with diabetes greater than 17%. Values in diabetes can go as high as two to five times the upper limit of normal.The clinical utility of fructosamine and GA includes monitoring of diabetes, diagnosis of pre-diabetes, and prediction of both the microvascular and macrovascular complications. They have the advantage of not requiring a fasting sample. Monitoring of Glucose Control in Diabetes Fructosamine and glycated albumin can be utilized as short-term markers of glucose control.

Both correlate significantly with HBAIc levels. While HbA1c reflects glucose control over a period of the preceding 8 to 12 weeks, fructosamine reflects the average glycemia over the preceding 2 to 3 weeks. This is a result of the inherent shorter half-life of albumin in comparison to hemoglobin in the erythrocyte.Fructosamine has largely been used as an alternative to the use of HbA1c monitoring in the presence of certain conditions that preclude the use of HbA1c, such as hemoglobin variants and alterations in erythrocyte lifespan. Fructosamine and glycated albumin are not affected by hemoglobin level, or red blood cell characteristics to which HbA1c is susceptible. This includes conditions such as hemoglobinopathies, sickle cell anemia, and anemia related to iron, vitamin B12, or folate deficiency.Additionally, fructosamine has clinical utility in conditions where information regarding short-term glucose control is important in the management of the patient such as in pregnancy, or recent medication adjustment. FA and GA can also be useful in monitoring people with diabetes with fluctuating or poorly controlled diabetes. Diagnosis of Diabetes Recent studies have evaluated the use of the alternate glycaemic markers of fructosamine and glycated albumin for the diagnosis of diabetes. It has been reported that in the diagnosis of diabetes, serum GA measurements can be used to ascertain the need for an oral glucose tolerance test (OGTT). There appears to be a negative correlation between GA and body mass index (BMI), and hence it could potentially underestimate glycemia in the obese. Currently, no guidelines support the use of GA or FA for the diagnosis of diabetes or pre-diabetes.[10] Diabetes Outcome Previously there was little evidence of the relationship of fructosamine and glycated albumin with diabetes complications and long-term outcomes. Recent studies, like for example, the Atherosclerosis Risk in Communities Study (ARIC), have demonstrated that fructosamine and glycated albumin were strongly associated with retinopathy as well as significantly associated with the risk of incident chronic kidney disease and incident diabetes.

Besides, both Fructosamine and GA, even following adjustment for HBAIc, are significant prognosticators of cardiovascular outcomes and mortality.[11]Commercial assays for fructosamine and glycated albumin have internal quality control materials available for use. Additionally, laboratories measuring these assays would subscribe to a recognized proficiency testing scheme to monitor test performance.Healthcare workers including the nurse practitioner should be familiar with the diagnosis of diabetes. Fructosamine and GA can be utilized as alternate markers in those patients where the HbA1c assay is unreliable. Also, they can identify poor glucose control more rapidly than HbA1c, i.e., short-term hyperglycemia. A major promise of the tests is their ability to predict those pre-diabetic patients who progress to clinical diabetes since this could lead to major lifestyle and pharmacological interventions to prevent the onset of diabetes and its complications. Finally, they may also have a role in the management of diabetes during pregnancy since pregnant patients need frequent glucose monitoring.

Table 1 NGSP and IFCC A1C Values[a] Correlated With Estimated Average Glucose

NGSP A1C (%)	IFCC (mmol/mol)	eAG (mg/dl)
5.0	31	97
6.0	42	126
6.5	48	140
7.0	53	154
7.5	58	169
8.0	64	183
9.0	75	212
10.0	86	240
11.0	97	269
12.0	108	298

[a] Blue area represents acceptable A1C ranges depending on patient factors and clinical guidelines.
eAG: estimated average glucose; IFCC: International Federation of Clinical Chemistry; NGSP: National Glycohemoglobin Standardization Program.
Source: Reference 14.

They can provide a measure of glycemia over 2 to 3 weeks rather than 8 to 12 weeks as is with HbA1c.[12]Glycated albumin has been reported to be a better marker than HbA1c for the assessment of glucose control in people with diabetes with chronic kidney disease and those on hemodialysis and peritoneal dialysis.[13][14]Review Questions1.Neelofar K, Ahmad J. A comparative analysis of fructosamine with other risk factors for kidney dysfunction in diabetic patients with or without chronic kidney disease. Diabetes Metab Syndr. 2019 Jan-Feb;13(1):240-244. [PubMed: 30641705]2.Garrahy A, Mijares Zamuner MB, Byrne MM. An evolving spectrum of diabetes in a woman with GCK-MODY. Endocrinol Diabetes Metab Case Rep. 2019 Jan 03;2019 [PubMed: 30608898]3.Pedrosa W, Sander Diniz MFH, Barreto SM, Vidigal PG. Establishing a blood fructosamine reference range for the Brazilian population based on data from ELSA - Brasil. Pract Lab Med. 2019 Jan;13:e00111. [PMC free article: PMC6295605] [PubMed: 30581949]4.Roohk HV, Zaidi AR. A review of glycated albumin as an intermediate glycation index for controlling diabetes. J Diabetes Sci Technol. 2008 Nov;2(6):1114-21. [PMC free article: PMC2769832] [PubMed: 19885300]5.Muñoz-Prieto A, Escribano D, Cerón JJ, Martínez-Subiela S, Tvarijonaviciute A. Glucose, fructosamine, and insulin measurements in saliva of dogs: variations after an experimental glucose administration. Domest Anim Endocrinol. 2019 Jan;66:64-71. [PubMed: 30472034]6.Gingras V, Rifas-Shiman SL, Switkowski KM, Oken E, Hivert MF. Mid-Pregnancy Fructosamine Measurement-Predictive Value for Gestational Diabetes and Association with Postpartum Glycemic Indices. Nutrients. 2018 Dec 18;10(12) [PMC free article: PMC6315870] [PubMed: 30567328]7.Rivera-Velez SM, Hwang J, Navas J, Villarino NF. Identification of differences in the formation of plasma glycated proteins between dogs and humans under diabetes-like glucose concentration conditions. Int J Biol Macromol. 2019 Feb 15;123:1197-1203. [PubMed: 30465839]8.Kouzuma T, Usami T, Yamakoshi M, Takahashi M, Imamura S. An enzymatic method for the measurement of glycated albumin in biological samples. Clin Chim Acta. 2002 Oct;324(1-2):61-71. [PubMed: 12204426]9.Kouzuma T, Uemastu Y, Usami T, Imamura S. Study of glycated amino acid elimination reaction for an improved enzymatic glycated albumin measurement method. Clin Chim Acta. 2004 Aug 16;346(2):135-43. [PubMed: 15256314]10.Kohzuma T, Koga M. Lucica GA-L glycated albumin assay kit: a new diagnostic test for diabetes mellitus. Mol Diagn Ther. 2010 Feb 01;14(1):49-51. [PubMed: 20121290]11.Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, Coresh J. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol.

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