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NEW GLYCAEMIC TARGETS- TIME TO LOOK BEYOND HBA1C: A REVIEW

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ABSTRACT

Diabetes is a condition defined by elevations in glucose. Historically, glucose measured in the fasting state or glucose measured two hours after a carbohydrate challenge (oral glucose tolerance test) have been the standard measures used to diagnose diabetes. Apart from this the researchers also reported various other shortcomings of measurement of blood glycemic value by HbA1c. A1C is a poor indicator of what occurs in the postprandial state. A1C captures only chronic hyperglycemia. Developed societies in which diabetes diagnosis is made with A1C and less developed societies (between and within countries) in which diabetes diagnosis is made with plasma glucose: such a division should be avoided. It would add to the inequities in health and health care. The objective of this article is to elaborate the uses of some nontraditional markers of hyperglycemia like 1. Fructosamine 2. Glycated albumin 3. 1,5-anhydroglucitol 4. Continuous glucose monitoring to be taken into consideration for estimation of blood glucose level as an alternative for HbA1c level determination.

REVIEW ARTICLE

INTRODUCTION

Hyperglycemia and HbA1c

Diabetes is a condition defined by elevations in glucose. Historically, glucose measured in the fasting state or glucose measured two hours after a carbohydrate challenge (oral glucose tolerance test) have been the standard measures used to diagnose diabetes and identify people at risk for diabetes (frequently termed "prediabetes")[1–3]. HbA1c has been used widely since the 1980s and is the standard measure used for monitoring glycemic control in clinical practice[4,5]. In red blood cells, HbA1c is hemoglobin that has glucose attached to the N-terminal valine of the beta chain and is reported as the proportion of total hemoglobin[6,7]. Because the lifespan of red blood cells is approximately 120 days, HbA1c, therefore, reflects average glycemia over the past two to three months.

Limitations of HbA1c:

The blood glycemic value is well affected by alterations in red cell turnover; some methods for measurement can give inaccurate results in the presence of certain hemoglobin variants.[8–10] Apart from this the researchers also reported various other shortcomings of measurement of blood glycemic value by HbA1c.[11]

Diabetes is clinically defined by high blood glucose and not by glycation of proteins

Diabetes is defined as the elevated glucose level into the blood than normal. Higher glycation of protein can be represented

as the higher A1C results. Which might be contributed to various factors and biochemical abnormality. However, the A1C values are not observed only in increased blood but also how long the delay in an elevated level of A1C matters as well. In many clinical and pathological conditions, such delay has negative consequences. [12]

A1C is a poor marker of important pathophysiological abnormalities featuring diabetes

A1C is a poor indicator of what occurs in the postprandial state. A1C captures only chronic hyperglycemia, but it will miss acute hyperglycemia. Normal blood glucose levels 2 h after glucose load indicates a good β-cell capacity, whereas high 2-h OGTT glucose levels document an impairment of β-cell function. This means that only 2-h OGTT PG can provide reliable information on the key pathophysiological defect of diabetes, also providing advice regarding the correct therapy to overcome it.[13–15]

A1C has poor sensitivity in diabetes diagnosis and would change the epidemiology of diabetes

Diabetes diagnosis based on A1C misses a large proportion of asymptomatic early cases of diabetes that can only be identified by the OGTT. According to a recent Chinese study, A1C sensitivity is inferior compared with fasting blood glucose at the population level. Also, people with impaired glucose tolerance (IGT), in whom the efficacy of diabetes prevention has been unequivocally proven, cannot be detected by A1C.[16–18]

Epidemiological studies carried out in the general population showed that A1C and plasma glucose (FPG and/or 2-h OGTT) identify partially different groups of diabetic subjects.[19–21]

2-h Glucose level and IGT are stronger predictors of CVD than A1C When analyzed jointly, only 2-h PG remains a statistically significant predictor of mortality and CVD.[22] The findings regarding associations of FPG, 2-h PG, and A1C with retinopathy from the Pima Indians in the ADA 1997 report describing diagnostic thresholds of each glycemic parameter were derived by univariate analyses, and the multivariate analysis aiming at identifying the best glycemic parameters for diagnosis.[23]

Fasting is not essential to identify perturbation in glucose metabolism

Measuring blood glucose in the fasting state in nondiabetic individuals is probably the least efficient way to identify early signs of perturbations in glucose metabolism.[24] Because excessive postprandial glucose excursions are marking the first signs of abnormal glucose regulation and they also seem to best predict the cardiovascular outcome, fasting is not really the central issue.

Standardization of A1C assay is very poor and standardization of glucose assay is easier to implement[25,26]

Inaccuracies in measurement and poor standardization of A1C assays are still a common problem, even in Western countries. Although a less than perfect standardization also exists for plasma glucose, this assay might be more easily aligned to a standard than A1C.

A1C assay is unreliable and cannot be used in many subjects

Abnormal hemoglobin traits are not uncommon in many regions of the world, and they significantly interfere with A1C assay, leading to spurious results. Also, there are several clinical conditions that influence erythrocyte turnover (e.g., malaria, chronic anemia, major blood loss, hemolysis, uremia, pregnancy, smoking, and various infections) that are responsible for misleading A1C data.

Within-day biological variability of plasma glucose might unveil disturbance of glucose metabolism

In this regard, A1C, which does not have any substantial biological variability, provides little information on pathophysiological processes leading to type 2 diabetes. The variability in A1C is entirely due to other phenomena, not pathophysiological disturbances.[27,28]

Individual susceptibility to glycation of hemoglobin is not relevant to the diabetes diagnosis

The HGI was calculated in patients with type 1 diabetes from the DCCT. This parameter is not relevant to the diagnosis of

diabetes in the general population, in which 99% of subjects have A1C levels definitely lower than patients with type 1 diabetes.[29,30]

Using the same biomarker for diagnosing and monitoring diabetes might not have positive effects only

This approach may be useful, but it also may lead to problems in two ways. First, people who have diabetes (based on their glucose values) will remain undiagnosed and untreated, since they are considered "nondiabetic" according to their A1C. Also, if the intermediate level of A1C (6.00–6.49 or 5.70–6.49%) was used to predict diabetes, it performed less well than impaired fasting glucose and/or IGT.[31–33]

Cost of the assay: glucose is unquestionably cheaper than A1C

Whichever way we calculate the assay costs, A1C assay is more expensive than glucose assay, and it will thus remain so despite the speculative claim that the cost of A1C assay will become less expensive when used more extensively.[34]

In a large part of the world, A1C is not available, and its cost is so high that it is meaningless to even discuss whether it should be given a priority over simple and inexpensive glucose measurements. This step would divide the world into two categories[35]:

Developed societies in which diabetes diagnosis is made with A1C and less developed societies (between and within countries) in which diabetes diagnosis is made with plasma glucose: such a division should be avoided. It would add to the inequities in health and health care.[36,37]

NONTRADITIONAL MARKERS OF HYPERGLYCEMIA

1. Fructosamine

Fructosamine is ketamine formed from the binding of fructose to total serum protein, mostly albumin, through glycosylation). The term fructosamine includes all glycated proteins. Fructosamine assays are cheaper and easier to perform than HbA1c assays. Serum fructosamine values reflect mean blood glucose concentrations over the previous two to three weeks, which can be used clinically as markers of recent changes in glycemic control. When used in combination with other measures, it may play a role in identifying fluctuating glucose levels in DM patients with stable HbA1c. There is a good correlation between HbA1c values and serum fructosamine)[38–40]

This assay is also associated with limitations like Serum fructosamine values must be adjusted if the serum albumin concentration is abnormal). Falsely low levels in relation to mean blood glucose levels will occur with rapid albumin turnovers, such as in nephrotic syndrome, severe liver disease, or protein-losing enteropathy. The level of fructosamine in young children is lower than that in adults, which is also partly due to their lower serum protein concentration)[41,42]

2. Glycated albumin

GA is the proportion of the serum GA to the total albumin. GA is similar to serum fructosamine, except that is not affected by serum albumin levels. The level of GA is approximately three times higher than that of HbA1c. Since the half-life of albumin is shorter than that of RBC, GA reflects a shorter duration, two to three weeks, of glycemic control, than that of HbA1c. GA and fructosamine are strongly associated with HbA1c and fasting glucose.

GA has several advantages for monitoring for glucose control. The first is that it is not influenced by abnormal RBC lifespan or variant hemoglobin. GA is a particularly useful indicator of glycemic control in hematologic disorders, such as in anemia, hemorrhage, renal anemia, pregnancy, liver cirrhosis, and neonatal DM.

Unlike HbA1c, GA is inversely influenced by obesity. GA tends to be lower in obese subjects with a high percentage of body fat mass. In addition, GA levels in infants significantly increase with age. The serum glucose levels of infants are lower than that of adults, and higher albumin metabolism is associated with lower GA levels.[43,44]

3. 1,5-anhydroglucitol

The 1-deoxy form of glucose known as 1,5-AG is a naturally occurring dietary polyol. During euglycemia, serum 1,5-AG concentrations are maintained at a constant

steady state due to renal tubular reabsorption of all of the serum 1,5-AG. The normal serum concentration of 1,5-AG has been reported to be 12-40 µg/mL. Serum 1,5-AG competes with very high levels of glucose for reabsorption into the kidney.[45]

4. Continuous glucose monitoring

Although the use of continuous glucose monitoring can accurately evaluate the glycemic variability of within-day and between-day, the current continuous glucose monitoring systems are expensive without national health insurance coverage and are not easily available in clinical practice. Furthermore, they are relatively inaccurate in the lower glucose range and should be used in conjunction with self-monitoring of blood glucose.[46,47]

Correlations of traditional markers of hyperglycemia with fructosamine, glycated albumin, and 1,5-anhydroglucitol. Fructosamine and glycated albumin are strongly associated with HbA1c and fasting glucose, and all four measures have been shown to be similarly correlated with mean glucose from continuous glucose monitoring over about 5 days in persons with diabetes.31 In settings where HbA1c testing is known to be problematic, fructosamine or glycated albumin may be a useful substitute. A difficulty, however, is that there are no established clinical cut-points and these assays are not standardized across instruments. Conversion equations can help estimate the ranges of fructosamine and glycated albumin test results that are similar to HbA1c targets. Various equations have been developed to convert fructosamine and glycated albumin to an "HbA1c equivalent". For example, previous reports demonstrated that glycated albumin values in the range of 16% to 22%, and fructosamine levels around 312 µmol/L as reported by one study, are approximately equivalent to an HbA1c value of 7%. 1,5-AG is strongly inversely associated with HbA1c and fasting glucose in persons with diagnosed diabetes, but appropriate clinical targets are unclear. It should be noted that 1,5-AG is poorly correlated with fasting glucose and HbA1c in persons without diagnosed diabetes--the strongest correlations are observed at the highest glucose concentrations. (additionally, cite Selvin in press) This suggests the utility of 1,5-AG may primarily be limited to persons with overtly elevated glucose.[48]

Since these markers of hyperglycemia are measured on different scales, both clinicians and patients may benefit from being provided with equivalents. However, conversion equations for nontraditional glycemic markers have typically relied on single measurements (which may vary considerably over time, particularly in diabetic patients) and may differ depending on the underlying population from which they are derived, with uncertain generalizability. Furthermore, none of these markers are perfectly correlated, a function of differences in the physiology of each biomarker including the duration of glycemia reflected and other sources of biological and analytical variability. In fact, the discordance across traditional and nontraditional glycemic markers may suggest the complementary nature of these biomarkers. A benefit to the use of multiple measures is that they may each provide a unique insight into different aspects of hyperglycemia and diabetes physiology.[49]

Clinical utility of nontraditional markers of hyperglycemia

For monitoring of short-term glycemic control

Nontraditional markers of hyperglycemia are not formally incorporated into clinical guidelines in the United States. However, various organizations in multiple countries, including the US, India, Australia and the United Kingdom, have suggested fructosamine as a useful alternative to HbA1c for monitoring glycemic control in persons with conditions that may interfere with the interpretation of the HbA1c test. Glycated albumin is used frequently in China, Japan, and South Korea for monitoring intermediate glycemic control. Several assays have been developed to measure glycated albumin but the assays are not standardized, and therefore not necessarily equivalent. Some early studies raised serious concerns regarding the validity and reliability of fructosamine assays, although

second-generation assays had improved technical performance. Modern automated assays for fructosamine have shown high correlations with glucose and HbA1c, strong prognostic value, and very low CVs (approximately 3% in recent studies).[50,51]

Whereas HbA1c reflects long-term, 2–3-month glycemic control, fructosamine, and glycated albumin reflect hyperglycemia over the past 2 to 3 weeks. Thus, both have been proposed as useful markers of intermediate glycemic control. In clinical practice, HbA1c is typically measured at minimum every 6 months and more frequently (quarterly) in persons with recent therapy changes who are not meeting treatment goals.[52]

Fructosamine and glycated albumin may be quite useful to evaluate earlier response to changes in treatment. Glycated albumin has been shown to change faster than HbA1c in response to changes in medication or exercise. Compared to HbA1c, glycated albumin is more strongly correlated with continuous glucose measurements over 1 to 2 days, and may more accurately reflect long-term glycemic variability and glucose excursions.[53]

1,5-AG is thought to reflect hyperglycemia over the past 2 weeks and is recommended by the manufacturer for use in persons with diabetes and HbA1c <8% to help identify patients with frequent hyperglycemic excursions. Indeed, 1,5-AG has been shown to be correlated with postprandial hyperglycemia in persons with diabetes and HbA1c <7%;75 and to be more strongly correlated with glucose variability as compared to HbA1c, fructosamine or glycated albumin over 2 to 3 days in persons with moderate glycemic control HbA1c <8%).[54]

For diabetes screening or diagnosis

There is evidence that nontraditional markers of hyperglycemia may help to more accurately identify persons with diabetes. In several studies, fructosamine and glycated albumin had similar performance for the identification of persons with diabetes as compared to either fasting glucose or HbA1c. Furthermore, compared to using either test individually, sensitivity to identify cases of diabetes defined by 2-hour glucose was improved when glycated albumin was used in combination with either fasting glucose or HbA1c.

A large proportion of persons identified as having pre-diabetes do not go onto develop diabetes, highlighting the need for strategies that will accurately identify persons who will progress to overt diabetes. It is possible that fructosamine or glycated albumin may be useful in early identification of high-risk persons. Recent studies have shown that both fructosamine and glycated albumin are associated with future risk of diabetes, independent of fasting glucose and HbA1c. 5-AG has also been associated with future development of diabetes, but observed associations were lower in magnitude as compared to other markers of hyperglycemia and were not present in persons with fasting glucose or HbA1c in the non-diabetic range. Nonetheless, the evidence linking nontraditional biomarkers with future diabetes risk is sparse.

The utility of nontraditional markers in special populations

A focus in the literature has been the potential utility of fructosamine or glycated albumin for monitoring glycemic control in the setting of certain populations where HbA1c is thought to inaccurately reflect glycemia, including severe kidney disease. Recent studies have shown that, compared to HbA1c, glycated albumin is more strongly correlated with glucose in dialysis patients. Fructosamine and glycated albumin may also be useful for the prediction of complications in persons with kidney failure. Indeed, fructosamine and glycated albumin have been both cross-sectionally and prospectively associated with microvascular, macrovascular and all-cause morbidity and mortality in dialysis patients, whereas many studies have reported no association of HbA1c with these outcomes. Nonetheless, despite their associations with clinical outcomes, fructosamine, and glycated albumin may also be limited in this setting, since proteinuria and altered serum protein turnover may affect the interpretation of these tests.

1,5-AG has not been well studied in the setting of chronic kidney disease or dialysis. Because lowered plasma concentrations of 1,5-AG result from accelerated urine excretion due to competitive inhibition of glucose by the renal tubules, 1,5-AG may have a problematic interpretation in the setting of reduced kidney function. 1,5-AG was correlated with fasting glucose and HbA1c in persons with diabetes and mild to moderate CKD, but not in those with end-stage renal disease (ESRD) (stages 4–5 CKD).

There is also evidence to support the use of nontraditional markers of hyperglycemia in persons with other conditions that may decrease the lifespan of red blood cells. Fructosamine and glycated albumin have been shown to better reflect glucose levels in the setting of anemia, autologous blood donations, and HIV, which may all result in artificially low HbA1c. There is also interest in whether fructosamine, glycated albumin, or 1,5-AG testing may play a role in the management of diabetes in patients with liver disease, but evidence for their performance in this setting is inconsistent. Furthermore, during pregnancy, glycated albumin may better reflect average glucose compared to HbA1c, which may be artificially elevated due to iron deficiency. Furthermore, measures of shorter-term glycemia may be especially important in gestational diabetes given the importance of frequent monitoring and strong associations between diabetes control in pregnancy and maternal and fetal outcomes.[55,56]

REFERENCES:

1. Group NDD. Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance. *Diabetes*. 1979;28(12):1039-1057. doi:10.2337/DIAB.28.12.1039
2. Monnier L, Colette C, Owens DR. Integrating glycaemic variability in the glycaemic disorders of type 2 diabetes: a move towards a unified glucose tetrad concept. *Diabetes Metab Res Rev*. 2009;25(5):393-402. doi:10.1002/dmrr.962
3. Keen H, Ng Tang Fui S. 1 The definition and classification of diabetes mellitus. *Clin Endocrinol Metab*. 1982;11(2):279-305. doi:10.1016/S0300-595X(82)80017-0
4. Clarke SF, Foster JR. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *Br J Biomed Sci*. 2012;69(2):83-93. doi:10.1080/09674845.2012.12002443
5. Yoo E-H, Lee S-Y, Yoo E-H, Lee S-Y. Glucose Biosensors: An Overview of Use in Clinical Practice. *Sensors*. 2010;10(5):4558-4576. doi:10.3390/s100504558
6. Makris K, Spanou L. Is there a relationship between mean blood glucose and glycated hemoglobin? *J Diabetes Sci Technol*. 2011;5(6):1572-1583. doi:10.1177/193229681100500634
7. Gabbay KH, Hasty K, Breslow JL, Ellison RC, Bunn HF, Gallop PM. Glycosylated Hemoglobins and Long-Term Blood Glucose Control in Diabetes Mellitus. *J Clin Endocrinol Metab*. 1977;44(5):859-864. doi:10.1210/jcem-44-5-859
8. Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. *J Gen Intern Med*. 2014;29(2):388-394. doi:10.1007/s11606-013-2595-x
9. Lorenzo-Medina M, De-La-Iglesia S, Ropero P, Nogueira-Salgueiro P, Santana-Benitez J. Effects of hemoglobin variants on hemoglobin a1c values measured using a high-performance liquid chromatography method. *J Diabetes Sci Technol*. 2014;8(6):1168-1176. doi:10.1177/1932296814538774
10. León-Triana O, Calvo GF, Belmonte-Beitia J, et al. Labile hemoglobin as a glycaemic biomarker for patient-specific monitoring of diabetes: a mathematical modeling approach. *J R Soc Interface*. 2018;15(142). doi:10.1098/rsif.2018.0224
11. Sherwani SI, Khan HA, Ekhzaimy A,

Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomark Insights*. 2016;11:95. doi:10.4137/BMI.S38440

12. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. *Diabetes Care*. 2011;34 Suppl 2(Supplement 2):S184-90. doi:10.2337/dc11-s216
13. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. *Diabetes Care*. 2011;34 Suppl 2(Suppl 2):S184-90. doi:10.2337/dc11-s216
14. Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Arch Public Heal*. 2015;73:43. doi:10.1186/S13690-015-0088-6
15. American Diabetes Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2009;32 Suppl 1(Suppl 1):S62-7. doi:10.2337/dc09-S062
16. Hu Y, Liu W, Chen Y, et al. Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance. *Acta Diabetol*. 2010;47(3):231-236. doi:10.1007/s00592-009-0143-2
17. Cohen RM, Haggerty S, Herman WH. HbA1c for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction? *J Clin Endocrinol Metab*. 2010;95(12):5203-5206. doi:10.1210/jc.2010-2352
18. Karakaya J, Akin S, Karagaoglu E, Gurlek A. The performance of hemoglobin A1c against fasting plasma glucose and oral glucose tolerance test in detecting prediabetes and diabetes. *J Res Med Sci*. 2014;19(11):1051-1057. http://www.ncbi.nlm.nih.gov/pubmed/25657750. Accessed May 28, 2019.
19. Kim DL, Kim SD, Kim SK, Park S, Song KH. Is an Oral Glucose Tolerance Test Still Valid for Diagnosing Diabetes Mellitus? *Diabetes Metab J*. 2016;40(2):118-128. doi:10.4093/dmj.2016.40.2.118
20. Maynard JD, Rohrscheib M, Way JF, Nguyen CM, Ediger MN. Noninvasive Type 2 Diabetes Screening: Superior sensitivity to fasting plasma glucose and A1C. *Diabetes Care*. 2007;30(5):1120-1124. doi:10.2337/dc06-2377
21. Nakagami T, Qiao Q, Tuomilehto J, et al. The fasting plasma glucose cut-point predicting a diabetic 2-h OGTT glucose level depends on the phenotype. *Diabetes Res Clin Pract*. 2002;55(1):35-43. http://www.ncbi.nlm.nih.gov/pubmed/11755477. Accessed May 28, 2019.
22. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes*. 2014;5(4):444-470. doi:10.4239/wjd.v5.i4.444
23. Cheng YJ, Gregg EW, Geiss LS, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population: Implications for diabetes diagnostic thresholds. *Diabetes Care*. 2009;32(11):2027-2032. doi:10.2337/dc09-0440
24. American Diabetes Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36 Suppl 1(Suppl 1):S67-74. doi:10.2337/dc13-S067
25. Weykamp C, John WG, Mosca A. A review of the challenge in measuring hemoglobin A1c. *J Diabetes Sci Technol*. 2009;3(3):439-445. doi:10.1177/193229680900300306
26. Little RR, Rohlfing CL. HbA $_{1c}$ Standardization: Background, Progress and Current Issues. *Lab Med*. 2009;40(6):368-373. doi:10.1309/LM3DUSEIBXHTVZ70
27. López-de-Andrés A, Perez-Farinos N, de Miguel-Díez J, et al. Type 2 diabetes and postoperative pneumonia: An observational, population-based study

using the Spanish Hospital Discharge Database, 2001-2015. Patman S, ed. *PLoS One*. 2019;14(2):e0211230. doi:10.1371/journal.pone.0211230

28. McCormack S, Grant SFA. Genetics of obesity and type 2 diabetes in African Americans. *J Obes*. 2013;2013:396416. doi:10.1155/2013/396416
29. Davidson MB. Diagnosing diabetes with glucose criteria: worshiping a false God. *Diabetes Care*. 2011;34(2):524-526. doi:10.2337/dc10-1689
30. Glycated haemoglobin (HbA1c) for the diagnosis of diabetes. 2011. https://www.ncbi.nlm.nih.gov/books/NBK304271/. Accessed May 28, 2019.
31. Malik J, Masoodi S, Shoib S. Obstructive sleep apnea in Type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control. *Indian J Endocrinol Metab*. 2017;21(1):106. doi:10.4103/2230-8210.196005
32. Coustan DR. Diagnosis and Management of Diabetes Mellitus in Pregnancy. *Glob Libr Women's Med*. 2009. doi:10.3843/GLOWM.10162
33. Osei K, Rhinesmith S, Gaillard T, Schuster D. Is Glycosylated Hemoglobin A1c a Surrogate for Metabolic Syndrome in Nondiabetic, First-Degree Relatives of African-American Patients with Type 2 Diabetes? *J Clin Endocrinol Metab*. 2003;88(10):4596-4601. doi:10.1210/jc.2003-030686
34. Ghazanfari Z, Haghdoost AA, Alizadeh SM, Atapour J, Zolala F. A Comparison of HbA1c and Fasting Blood Sugar Tests in General Population. *Int J Prev Med*. 2010;1(3):187-194. http://www.ncbi.nlm.nih.gov/pubmed/21566790. Accessed May 28, 2019.
35. McMillin JM. *Blood Glucose*. Butterworths; 1990. http://www.ncbi.nlm.nih.gov/pubmed/21250092. Accessed May 28, 2019.
36. Dagogo-Jack S, ed. *Diabetes Mellitus in Developing Countries and Underserved Communities*. Cham: Springer International Publishing; 2017. doi:10.1007/978-3-319-41559-8
37. Si D, Bailie R, Wang Z, Weeramanthri T. Comparison of diabetes management in five countries for general and indigenous populations: an internet-based review. *BMC Health Serv Res*. 2010;10:169. doi:10.1186/1472-6963-10-169
38. Welsh KJ, Kirkman MS, Sacks DB. Role of Glycated Proteins in the Diagnosis and Management of Diabetes: Research Gaps and Future Directions. *Diabetes Care*. 2016;39(8):1299-1306. doi:10.2337/dc15-2727
39. 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):169-176. doi:10.1177/1932296814567227
40. Lee J-E. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol. *Ann Pediatr Endocrinol Metab*. 2015;20(2):74-78. doi:10.6065/apem.2015.20.2.74
41. Testa R, Guerra E, Bonfigli AR, Di Gaetano N, Santini G, Ceriotti F. Analytical Performances of an Enzymatic Assay for the Measurement of Glycated Albumin. *J Appl Lab Med An AACC Publ*. 2016;1(2):162-171. doi:10.1373/jalm.2016.020446
42. Speeckaert M, Van Biesen W, Delanghe J, et al. Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? *Nephrol Dial Transplant*. 2014;29(12):2167-2177. doi:10.1093/ndt/gfu006
43. Jhk K, Tps S, Kdd D, Eejg A, Baak van M. *Obes Facts 2013;6(Suppl 1):1-246 Abstracts 49 POSTER SESSIONS Adult Body Mass and Common FSNP Variants of BBS Genes Characterizations of the Energy Balance and Circulating Inflammation Makers in a Polygenic Mouse Model of Obesity and Type 2 Diabetes Genet*.;

2013. https://www.karger.com/Article/Pdf/170983. Accessed May 29, 2019.

44. Vos FE, Schollum JB, Walker RJ. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. *Clin Kidney J*. 2011;4(6):368-375. doi:10.1093/ndtplus/sfr140
45. Kato A, Kunimatsu T, Yamashita Y, Adachi I, Takeshita K, Ishikawa F. Protective Effects of Dietary 1,5-Anhydro- d -glucitol as a Blood Glucose Regulator in Diabetes and Metabolic Syndrome. *J Agric Food Chem*. 2013;61(3):611-617. doi:10.1021/jf304683s
46. Ajjan RA. How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring? *Diabetes Technol Ther*. 2017;19(S2):S27-S36. doi:10.1089/dia.2017.0021
47. Slattery D, Choudhary P. Clinical Use of Continuous Glucose Monitoring in Adults with Type 1 Diabetes. *Diabetes Technol Ther*. 2017;19(S2):S55-S61. doi:10.1089/dia.2017.0051
48. Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. *Curr Diab Rep*. 2014;14(11):548. doi:10.1007/s11892-014-0548-3
49. Krhač M, Lovrenčić MV. Update on biomarkers of glycemic control. *World J Diabetes*. 2019;10(1):1-15. doi:10.4239/wjd.v10.i1.1
50. Parrinello CM, Selvin E. Beyond HbA1c and Glucose: the Role of Nontraditional Glycemic Markers in Diabetes Diagnosis, Prognosis, and Management. *Curr Diab Rep*. 2014;14(11):548. doi:10.1007/s11892-014-0548-3
51. Musenge EM, Michelo C, Mudenda B, Manankov A. Glycaemic Control and Associated Self-Management Behaviours in Diabetic Outpatients: A Hospital Based Observation Study in Lusaka, Zambia. *J Diabetes Res*. 2016;2016:1-9. doi:10.1155/2016/7934654
52. Koga M. 1,5-Anhydroglucitol and glycated albumin in glycemia. *Adv Clin Chem*. 2014;64:269-301. http://www.ncbi.nlm.nih.gov/pubmed/24938022. Accessed May 29, 2019.
53. Vos FE, Schollum JB, Walker RJ. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. *NDT Plus*. 2011;4(6):368-375. doi:10.1093/ndtplus/sfr140
54. Desouza C V, Rosenstock J, Zhou R, Holcomb RG, Fonseca VA. GLYCATED ALBUMIN AT 4 WEEKS CORRELATES WITH A1C LEVELS AT 12 WEEKS AND REFLECTS SHORT-TERM GLUCOSE FLUCTUATIONS. *Endocr Pract*. 2015;21(11):1195-1203. doi:10.4158/EP14570.OR
55. Zheng C-M, Ma W-Y, Wu C-C, Lu K-C. Glycated albumin in diabetic patients with chronic kidney disease. *Clin Chim Acta*. 2012;413(19-20):1555-1561. doi:10.1016/j.cca.2012.04.025
56. Sarkar M, Rajta PN, Khatana J. Anemia in Chronic obstructive pulmonary disease: Prevalence, pathogenesis, and potential impact. *Lung India*. 2015;32(2):142-151. doi:10.4103/0970-2113.152626