review

Update on Diabetes Diagnosis: A Historical Review of the Dilemma of the Diagnostic Utility of Glycohemoglobin A1c and a Proposal for a Combined Glucose-A1c Diagnostic Method

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The role of glycohemoglobin A1c (A1c) for the diagnosis of diabetes has been debated for over three decades. Recently, the American Diabetes Association (ADA) has recommended adding A1c as an additional criterion for diabetes diagnosis. In view of the continued debate about the diagnostic utility of A1c, and in view of the unabated burden of undiagnosed diabetes, the search for alternative diagnostic methods is discussed. A historical literature review is provided, in view of the new ADA diagnostic guidelines, and a proposal is provided for combining A1c and a glucose measurement as a diagnostic alternative/adjunct to the use of a single criterion. This proposal is based on the non-overlapping of the advantages and disadvantages of these individual tests. The cost-effectiveness of this method remains to be tested.

The American Diabetes Association (ADA) has now acknowledged glycohemoglobin A1c (A1c) as a diagnostic criterion for diabetes mellitus,[1] for the first time since the publication of the ADA's first diagnostic guidelines in July of 1997.[2] Thus, the current (revised) ADA's criteria for diabetes diagnosis and screening, as of January of 2010, are:

1) A1c ≥6.5%; or
2) Fasting plasma glucose (FPG) ≥126 mg/dL (fasting at least 8 hours); or
3) 2-hour glucose per 75 g oral glucose tolerance test (OGTT) ≥200 mg/dL, according to the World Health Organization (WHO) protocol; or
4) Random glucose (with hyperglycemic symptoms/crisis) ≥200 mg/dL.

In the absence of unequivocal hyperglycemia, criteria 1-3 require retesting for confirmation. The guidelines emphasized that A1c assays be standardized to the Diabetes Complications and Control Trial's (DCCT) A1c assay, and certified by the National Glycohemoglobin Standardization Program (NGSP). Screening criteria for diabetes remained unchanged: In the presence of high risk factor(s), screening should be done at any age, and in the absence thereof, screening should begin at age 45 years, and then every 3 years.

Furthermore, the new ADA guidelines[1] also added a new category of intermediate dysglycemia, called the "increased-risk" group, to describe individuals with the currently used term "prediabetes"; this high-risk group, while not meeting the diagnostic criteria for diabetes require close attention and monitoring. As is known, prediabetes refers to impaired fasting glucose (IFG), and impaired glucose tolerance (IGT). The change of (the wording) did not affect the glycemic thresholds for IFG or IGT, with the guidelines maintaining the same cut-offs of (≥100-125 mg/dL, and ≥140-199 mg/dL, respectively), and recommending an A1c range of ≥5.7%-6.4% to identify this group of people. Finally, these new ADA guidelines were limited to revisions to the diagnosis of type 2 diabetes

mellitus (T2DM), and they made no new recommendations regarding gestational diabetes mellitus (GDM), deferring such recommendations to the then forthcoming recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).

The ADA's new guidelines endorsing A1c as a diagnostic test for diabetes were based on the recommendations[3] of the International Expert Committee (IEC). The IEC is a consensus panel of international experts convened by the ADA, the International Diabetes Federation (IDF) and the European Association for the Study of Diabetes (EASD). The rationale for endorsing A1c for diabetes diagnosis (and the cut-off recommended), according to the IEC's report,[3] is that the risk of diabetes microvascular complications (mainly retinopathy) sharply increases in the same way and at a comparable threshold, as compared to FPG and OGTT. In its first diagnostic guidelines in 1997,[2] the ADA had recommended that FPG be the preferred diagnostic test, acknowledging that OGTT might not be appropriate for routine use. The ADA had also recommended (specifically) that A1c not be used for diabetes diagnosis,[2] and has since maintained these recommendations in its subsequent annual guidelines that are published every January as a supplement to its journal, *Diabetes Care*, through the 2009 edition.[4]

Prior to these new ADA guidelines,[1] and over the last two to three decades, several publications by various investigators from around the world, including many large epidemiological studies, had advocated the utility of A1c as a diagnostic tool in diabetes.[5-26] Furthermore, preceding these ADA guidelines, different expert panels and diabetes and endocrinology organizations from different countries had already recommended A1c for diabetes diagnosis/screening, including the following major examples:

a) An expert panel[8] convened in 2008 by the Endocrine Society (TES) in the United States and published in its journal although TES itself did not explicitly endorse the panel's recommendations;
b) A report posted in 2007 at the website[27] of the United Kingdom National Health Services-National Institute of Health Research (www.ncchta.org), published by Waugh et al;
c) A report published in 2008[28] by the US Preventive Services Task Force (USPST), in which the USPSTF did not explicitly recommend A1c for diabetes screening, but vaguely stated that "three tests have been used to screen for diabetes: FPG, OGTT, and A1c";
d) A recommendation by the Japanese Diabetes Association, published in 1999.[29]

As an explanation for the ADA's prior reluctance to recommend A1c for diabetes diagnosis, the main concerns expressed by the ADA had to do with test standardization. The ADA's Expert Committee, the writing group of the guidelines, stated that diverse methods had been used in A1c assays, and that standardization of the test was not achieved at the time, and so identifying a cut-off diagnostic A1c value was difficult to achieve.[2] However, shortly thereafter, this obstacle was overcome[30] by the development of the National Glycohemoglobin Standardization Program (NGSP). In brief, to be NGSP compliant, any local assay should be made traceable to the assay used by the DCCT. Global compliance of local laboratories with NGSP standardization is difficult to track, but in the United States, a very satisfactory compliance (over 99%) was reported across the nation in 2006.[31] Nevertheless, A1c is not a perfect or ideal test; perhaps a perfect/ideal diagnostic test with 100% specificity and sensitivity does not even exist in clinical medicine. Like many other diagnostic tests in clinical medicine, A1c results should be interpreted in the right context, taking into account any interferences that could influence these results.

Thus, clinicians should be aware of the potential interferences that have been noticed to influence the A1c measurement, including effects of age, ethnicity, possible variability in glycation rates (hemoglobin glycation index), hemoglobin variants, uremia, iron deficiency anemia, effects of medications such as erythropoietin, and infection with HIV.[25,32-36] Certainly clinicians should be vigilant to evaluate their patients individually, and to consider all possible factors before ruling in or ruling out diabetes if only relying on A1c for diagnosis. The issue of population screening is a difficult one to tackle, and it is not clear how A1c will perform in this regard, compared to FPG.

It should be emphasized that the pressing impetus for searching for alternative or adjunct diagnostic tools for diabetes is the observation of legitimate concerns regarding FPG and OGTT (Summary of Advantages and Disadvantages). This **Appendix** lists the advantages and disadvantages of FPG, OGTT and A1c.[8,14,17,24,25,32-36] Of the disadvantages of FPG and OGTT, two major issues raise significant concerns, and thus deserve emphasis, as follows:

- FPG could miss a significant proportion of patients with (overt) diabetes,[14,17] a manifestation of inadequate sensitivity stemming largely from the

Appendix. Summary of the advantages and disadvantages of the old and new diagnostic tests for diabetes originally adapted (with permission) from Kilpatrick et al,[35] Additional modi ications were com-piled from other references.[8,14,17,24,25,32-36]

Fasting Blood Glucose

Advantages:
- is established as the current diagnostic means for diabetes;
- is a direct measure of glycemia (which the patients are used to);
- is more available than A1c globally;
- it has less between-laboratories variability than A1c;
- is not affected by non-glycemic factors as is A1c

Disadvantages:
- is a single time point of glycemia (thus static rather than chronic);
- requires fasting (which adds to its inconvenience);
- has more within-individual variability than A1c;
- has a sub-optimal sensitivity;
- requires prompt processing after blood drawing to avoid artifacts

Oral Glucose Tolerance Test

Advantages:
- is established as the current diagnostic means for diabetes;
- is a direct glycemic measure;
- is more available than A1c globally;
- has less between-laboratories variability than A1c;
- is not affected by non-glycemic factors as is A1c.

Disadvantages:
- is a single time point of glycemia;
- requires fasting;
- has more within-individual variability than A1c;
- requires prompt processing after blood drawing to avoid artifacts;
- is cumbersome, multi-staged, inconvenient;
- the displeasing taste of the concentrated glucose drink; especially for pregnant women;
- is unreliable in patients with gastric bypass

Hemoglobin A1c

Advantages:
- is more convenient, since fasting is not required;
- has greater pre-analytical stability, and less day-to-day changes that can cause significant excursions in plasma glucose;
- is established as a monitoring measure of diabetes control;
- is more stable for subsequent measurement.

Disadvantages:
- can be affected by factors that can affect the lifespan of the erythrocytes (e.g., iron deficiency anemia, blood loss, chronic kidney failure, and erythropoietin therapy as used in renal failure and sometimes in chronic anemia);
- can be affected by hemoglobin variants (assay method dependent);
- can demonstrate variability due to differences in glycation rates;
- can be affected by HIV;
- is less available globally than glucose tests.

natural course of T2DM, which is believed to begin often as a post-prandial hyperglycemic state for some time;[37] and
- OGTT is seldom used in routine clinical settings, or population screening,[8,15,38,39] and thus has conceivably not contributed to effective screening and diagnosis of diabetes, even though it is considered the gold diagnostic standard.

These aforementioned concerns are quite impor-

tant, and it is believed that these disadvantages of both FPG and OGTT, besides the other disadvantages listed in the **Appendix**, could be among the major causes of undiagnosed diabetes.[23,26] The issue of undiagnosed diabetes is a serious health problem, and this was specifically mentioned in the older ADA guidelines of 1997,[2] which stated that in the United States about 50% of people with DM were undiagnosed at the time. At present, and with the use of only FPG and OGTT for diabetes diagnosis/screening, this percentage of undiagnosed diabetes is still significant—20% to 30%.[23,26] It logically follows that these tests have been suboptimal.

This change in position on the part of the ADA[1] is naturally expected to encounter mixed responses in the diabetes community, by both advocates and skeptics of this new recommendation. Prior to this new position, some investigators[8] had criticized the ADA for its reluctance about endorsing A1c for diagnosis, stating that this reluctance was "based on old data". On the other hand, of the strongest criticism of the new ADA recommendations, other investigators[32] described this move as "a departure from the long established approach to diagnosing diabetes mellitus". Besides the concerns about potential pitfalls of A1c diagnostic performance,[25,32-36] other concerns have been voiced about test cost and availability in developing countries, as exemplified in a recent position article from Mexico, rejecting A1c as a new diagnostic criterion.[34]

It is prudent to point out that while there is a strong case for the utility of A1c for the diagnosis and screening of T2DM, the situation is different for GDM. Pioneered by Pollak et al,[40] most studies addressing A1c in GDM diagnosis are old and they included small numbers of subjects and utilized different non-standardized A1c assays.[40-47] More recent studies are quite scarce,[22,48,49] including a study by our group.[22] Conclusions from these old and new studies are conflicting, and thus, it follows that more studies are needed to settle this issue. In this regard, and as alluded to earlier, the new ADA guidelines deferred recommendations regarding GDM to the IADPSG's report that was anticipated at the time of publication of the ADA's guidelines. The IADPSG's report can be referred to regarding new GDM diagnostic guidelines.[50] In summary, these guidelines proposed new recommendations in regards to screening strategies and the categorization of glycemia in pregnancy, recommending A1c at the earliest antenatal visit, to distinguish pre-existing overt diabetes as a separate entity.[50]

While A1c was not recommended for GDM screening, the IDADPSG recommended that A1c be performed early in pregnancy (at the time of the first antenatal visit) to exclude pre-existing (overt) diabetes. While neither the ADA nor the IADPSG recommended A1c for GDM screening or diagnosis, our group believes[22,24] that there is a promising diagnostic role for A1c in GDM in the future, and that the main obstacle in this regard is the lack of large, prospective epidemiological studies.

To conclude this historical overview on A1c, it is prudent to briefly mention the following relevant issues:

- Since the new ADA guidelines were published,[1] other organizations have endorsed A1c for diabetes diagnosis including American Association of Clinical Endocrinologists (AACE)[51] and TES,[52] with some restrictions and caveats.[51,52] Diagnosis by A1c has subsequently been endorsed by WHO, EASD and the IDF (see official websites of organizations).
- The new ADA guidelines[1] recommended that portable A1c devices[53] not be used for diabetes diagnosis or screening at present.
- The issue of deriving a glucose equivalent from A1c assays, the so-called estimated average glucose "eAG", is debatable.[31,54]
- The use of other measurement units for A1c (ie, mmol/mol), and the lowering of the A1c normal range[31] would probably create confusion amongst clinicians and patients,[25] and therefore, these two suggestions may not be appropriate for use in clinical practice.
- The recent notion, that in community-based population screening in adults without diabetes, A1c is similarly associated with a future risk of diabetes, and even more strongly with death and cardiovascular disease, than FPG, further supports the ADA's recommendation of A1c for diabetes diagnosis, and rounds up the case for A1c as a valid diagnostic test.[55]
- Finally, it appears that the debate about the diagnostic role of A1c is still ongoing, although it was conceivable that the ADA's new guidelines[1] would have put this three-decade-long debate to rest. The most recent, and strong, example of this ongoing debate was the heated debate session between two nationally renowned diabetes experts, Dr. Bloomgarden (advocating against) and Dr. Bergenstal (advocating for), at the conclusion of the AACE 2010 annual meeting.[56]

Given this argument, and since A1c has disadvantages (but likewise also do FPG and OGTT), it is conceivably appealing to recommend using A1c not as an alternative

but as an adjunct to FPG to achieve the best possible sensitivity and specificity. This combination strategy was suggested by a few investigators.[14,15] Since the disadvantages of A1c and FPG are generally not overlapping, it is hoped that this combination will be complimentary, and additive, as a powerful diagnostic tool. Manley et al reported a very favorable sensitivity and specificity of combined A1c and FPG, of over 90% in high-risk individuals.[14]

While the debate continues about the diagnostic role of A1c, diabetes has become a global epidemic and it continues to pose human and economic burdens on communities worldwide. A major obstacle in diabetes management is delayed diagnosis, and hence the development of complications, especially cardiovascular complications[23,26] at the time of diagnosis. Besides socioeconomic problems such as access to health care, we believe that ineffective diagnostic and screening methods in population and practice settings is another major cause of undiagnosed diabetes.[23,26]

What really matters is not what the best diagnostic test is as recommended by health organizations, but how often and how effectively it is used in clinical practice. In fact this assertion was reported in studies in community-based settings.[38,39] Evolega et al,[38] and Tabaei et al,[39] evaluated the opportunistic screening methods in community-based settings, and found that the recommended diagnostic tests (FPG and OGTT) were not applied effectively in routine clinical screening, and were rarely used for opportunistic screening.

It seems that utilizing a combination method (A1c and FPG) for diabetes screening and diagnosis, the accuracy of which has been proven,[14] is an appealing alternative. It is notable that the IEC recommended against such combined A1c-glucose diagnostic approach[3] for fear of creating confusion, but in a recently published review article, Herman and Fajans disputed this recommendation, and provided a reasonable combination proposal.[57] They concluded that "combining the use of HbA1c and plasma glucose measurements for the diagnosis of diabetes offers the benefits of each test and reduces the risk of systematic bias inherent in HbA1c testing alone".

Whether this is cost-effective remains to be seen. Therefore, we agree with Herman and Fagan's combination proposal, and we recommend that diabetes organizations, scientists, insurance companies, health industries, and governmental bodies evaluate this proposal. The ultimate goal is to come up with a diagnostic method that is accurate, cost-effective, and convenient for population settings—in an effort to alleviate the burden of undiagnosed diabetes.

In conclusion, A1c has just been recommended by the ADA for diabetes diagnosis and screening. This endorsement by the ADA, followed by adoption by other diabetes organizations, may have ended a major portion of a long-standing debate about the utility of A1c for diabetes diagnosis and screening. However, there is still skepticism by some diabetes experts, with concerns about over or under diagnosis of diabetes. Since the disadvantages of FPG, OGTT and A1c are not overlapping, we generally advocate the recently proposed suggestion to use a combination strategy to diagnose diabetes, utilizing A1c with FPG, a strategy that is believed to be promising in achieving the best diagnostic accuracy. However, the efficacy and cost-effectiveness of this strategy remain to be tested.

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REFERENCES

1. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl.) S62-9.
2. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–97.
3. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-34.
4. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32(Suppl.) S62-7.
5. Rohlfing C, Wiedmeyer H, Little R, England J, Tennill A, Goldstein D. Defining the relationship between plasma glucose and HbA1c. Diabetes Care 2002;25:275-8.
6. Rohlfing C, Little R, Wiedmeyer H, England J, Madsen R, Harris M, et al. Use of GH b (HbA1c) in screening for undiagnosed diabetes in the US population. Diabetes Care 2000;23:187-191. Buell C, Kermah D, Davidson MB. Utility of A1c for diabetes screening in the 1999-204 NHANES population. Diabetes Care 2007;30(9):2233-5.
7. Bennett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of Type 2 diabetes: A systematic review. Diabet Med 2007;24:333-43.
8. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab 2008;93:2447-53.
9. Bryson CL, Boyko EJ. Review: Glycated haemoglobin A1c and fasting plasma glucose screening tests have similar sensitivities and specificities for early detection of type 2 diabetes. Evid Based Med 2007;12:152.
10. Little RR, England JD, Wiedmeyer HM, McKeenzie EM, Pitt DJ, Knowler WC, et al. Relationship of glycosylated hemoglobin to oral glucose tolerance. Diabetes 1988;37:60-4.
11. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettit DJ, Bennett PH, et al. Comparison of tests for glycated hemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods. BMJ 1994;308:1323-8.
12. Peters A, Davidson MB, Schriger D, Hasselblad V. A clinical Approach for the diagnosis of diabetes mellitus: An analysis using glycosylated hemoglobin levels. Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. JAMA 1996;276:1246-52.
13. Ko GT, Chan JC, Cockram CS. Supplement to the use of a paired value of fasting plasma glucose and glycated hemoglobin in predicting the likelihood of having diabetes. Diabetes Care1998;21:2032-3.
14. Manley SE, Sikaris KA, Lu ZX, Nightingale PG, Stratton IM, Round RA, et al. Validation of an algorithm combining haemoglobin A1c and fasting plasma glucose for diagnosis of diabetes mellitus in UK and Australian populations. Diabetic Med 2009;26:115-21.
15. Takahashi Y, Noda M, Tsugane S, Kuzuya T, ItoC, Kadowaki T. Prevalence of diabetes estimated by plasma glucose criteria combined with standardized measurement of HbA1c among health checkup participants on Myako Island, Japan. Diabetes Care 2000;23:1092-6.
16. Ito C, Maeda R, Ishida S, Sasaki H, Harada H. Correlation among fasting plasma glucose, two hour plasma glucose and HbA1c. Diabetes Res Clin Practice 2000;50:225-30.
17. Perry RC, Shankar RR, Finerberg N, McGill J, Baron AD. HbA1c measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose. The early diabetes intervention program (EDIP). Diabetes Care 2001;24:465-71.
18. Edelman D. Outpatient diagnostic errors: Unrecognized hyperglycemia. Eff Clin Pract 2002;5:11-6. Edelman D, Edwards LJ, Olsen MK, DudLey TK, Harris AC, Blackwell DK, Oddone EZ. Screening for diabetes in an outpatient clinic population. J Gen Intern Med 2002;17:23-8.
19. Greci LS, Kailasam M, Malkani S, Katz DL, Hulinsky I, Ahmadi R, et al. Utilitiy of HbA(1c) levels for diabetes case finding in hospitalized patients with hyperglycemia. Diabetes Care 2003;26:1064-8.
20. Anand S, Razak F, Vuksam V, Gerstein H, Malmbberg K, Quilong Y, et al. Diagnostic strategies to detect glucose intolerance in a multiethnic population. Diabetes Care 2003;26:290-6.
21. Silverman RA, Pahk R, Carbone M, Wells E, Mitzner R, Burris K, et al. The relationship of glucose and HbA1c levels among emergency department patients with no prior history of diabetes mellitus. Acad Emerg Med 2006;13:722-6.
22. Aldasouqi SA, Solomon D, Bokhari SA, Khan PM, Muneera S, Gossain VV. Glycohemoglobin A1c: A promising screening tool in gestational diabetes mellitus. Int J Diab Dev Ctries 2008;28:121-4.
23. Aldasouqi SA, Gossain VV, Little RR. Undiagnosed diabetes equals undiagnosed CVD: a call for more effective diabetes screening. Rev Endocrinol 2009;3:21-3.
24. Aldasouqi S, Gossain V. A proposal for a role of hemoglobin A1c in the screening of gestational diabetes. Diabet Med 2009;26:827-35.
25. Aldasouqi SA, Gossain VV. HbA1c: Past, present and future. Ann Saudi Med 2008;28:411-9.
26. Gossain V, Aldasouqi S. The challenge of undiagnosed prediabetes, diabetes and associated cardiovascular disease. Int J Diab Mell 2010;2:43-6.
27. Waugh N, Scotland G, McNamee P, et al. Screening for type 2 diabetes: Literature review and economic modeling. Health Technolo Assess 2007;11:iii-iv, ix-xi, 1-125.
28. Screening for type 2 diabetes mellitus in adults: US Preventive Services Task Force recommendation statement. Ann of Intern Med. 2008;148:846-54.
29. The Committee of Japan Diabetes Society for the Diagnostic Criteria of Diabetes Mellitus: Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus. J Jpn Diabetes Soc 1999;42:385-404.
30. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE. The National Glycohemoglobin Standardization Program: A five year progress report. Clin Chem 2001;47:1985-92.
31. Little RR, Rohlfing CL. Proposed changes for reporting HbA1c: Various groups are deciding how HbA1c results are to be reported in the future. In Vitro Diagnost Technol 2007 May; p18. Available from: http://www.ivdtechnology.com/archive/all/2007/5 [Last accessed on 2010 Mar 25].
32. Bloomgarden ZT, Einhorn D. Hemoglobin A1c in diabetes diagnosis: Time for caution. Endocr Pract 2010;16:5-6.
33. Ziemer D, Kolm P, Weintraub W, Vaccarino V, Rhee M, Twombly J, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Annals Int Med 2010;152:770-7.
34. Gomez-Perez FJ, Aguilar-Salinas CA, Almeda-Valdes P, Cuevas-Ramos D, Lerman Garber I, Rull JA. HbA1c for the diagnosis of diabetes mellitus in a developing country. A position article. Arch Med Res 2010;41:302-8.
35. Kilpatrick ES, Bloomgarden ZT, Zimmet PZ. Is haemoglobin A1c a step forward for diagnosing diabetes? BMJ 2009;339:1288-90.
36. Brown JN, Kemp DW, Brice KR. Class effect of Erythropoietin therapy on hemoglobin A1c in a patient with diabetes mellitus and chronic kidney disease not undergoing hemodialysis. Pharmacotherapy 2009;29:468-72.
37. Bergenstal RM, Kendall DM, Franz MJ, Rubenstei AH. Management of type 2 diabetes: A systematic approach to meeting the standards of care II: Oral agents, insulin, and management of complications. In: Degroot LJ, Jameson JL, editors. Endocrinology. Philadelphia: W. B. Saunders Co; 2001. p. 821-35.
38. Ealovega MW, Tabaei BP, BrandLe M, Burke R, Herman WH. 2004 Opportunistic screening for diabetes in routine clinical practice. Diabetes Care 2004 27:9-12.
39. Tabaei B, Burke R, Constance A, Hare J, May-Aldrich G, Parker S, et al. Community-based screening for diabetes in Michigan. Diabetes Care 2003;26:668-70.
40. Pollak A, Widnes J, Schwartz R. 'Minor hemoglobins': An alternative approach for evaluating glucose control in pregnancy. Biol Neonate 1979;36:185-92.
41. Artal R, Artal R, Mosley GM, Dorey FJ. Glycohemoglobin as a screening test for gestational diabetes. Am J Obstet Gynecol 1984;148:412-4.
42. McFarland KF, Murtiashaw M, Baynes JW. Clinical value of glycosylated serum protein and glycosylated hemoglobin levels in the diagnosis of gestational diabetes mellitus. Obstet Gynecol 1984;64:516-8.
43. Cousins L, Dattel BJ, Hollingsworth DR, Zetner A. Glycosylated hemoglobin as a screening test for carbohydrate intolerance in pregnancy. Am J Obstet Gynecol 1984;150:455-60.
44. Frisoli G, Naranjo L, Shehab N. Glycohemoglobin in normal and diabetic pregnancy. Am J Perinatol 1985;2:183-8.
45. Morris MA, Grandis AS, Litton J. Glycosylated hemoglobin: A sensitive indicator of gestational diabetes. Obstet Gynecol 1986;68:357-61.
46. Cocilovo G, Guerra S, Colla F, Tomasi F. Glycosylated hemoglobin (HbA1) assays a test for detection and surveillance of gestational diabetes. Diabetes Metab 1987;13:426-30.
47. Griffith RJ, Vinall PS, Stickland MH, Wales JK. Hemoglobin A1c in normal and diabetic pregnancies. Eur J Obstet Gynecol Reprod Biol 1987;24:195-200.
48. Agarwal MM, Hughes PF, Punnose J, Ezimokhai M, Thomas L. Gestational diabetes screening of a multi-ethnic, high-risk population using glycated proteins. Diabetes Res Clin Pract 2001;51:67-73.
49. Agarwal M, Dhatt G, Punnose J, Koster G. Gestational diabetes: A reappraisal of HBA1c as a screening test. Acta Obstet Gynecol Scand 2005;84:1159-63.
50. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care 2010;33:676-82.
51. American Association of Clinical Endocrinologists. AACE/ACE statement of the use of A1c in the diagnosis of diabetes. Available from: http://www.aace.com/pub/pdf/guidelines/AACEpositionA1cfeb2010.pdf [Last Accessed on 2010 March 30th].
52. The Endocrine Society: The Endocrine Society statement on the use of A1c for diabetes diagnosis and risk estimation. Available from: http://www.endo-society.org/advocacy/loader.cfm?csModule=security/getfileandpageid=30809 [Last Accessed on 2010 March 30th].
53. Mattewal A, Aldasouqi S, Solomon D, Gos-

sain V, Koller A. A1cNow InView: A new simple method for office-based glycohemoglobin measurement. J Diabetes Sci Technol 2007;1:879-84.
54. Bloomgarden ZT, Inzucchi SE, Karnieli E, Le Roith D. The proposed terminology 'A(1c)-derived average glucose' is inherently imprecise and should not be adopted. Diabetologia 2008;51:1111-4.
55. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, Diabetes, and cardiovascular risk in nondiabetic adults. N Eng J Med 2010;362:800-11.
56. Lowry F. Should the hemoglobin A1c test be used to diagnose diabetes and prediabetes?. Healthcare Professional Homepage (HPV-Live). Available from: http://www.hcplive.com/endocrinology/aace_2010/hemoglobin_test_diabetes [Last Accessed on 2010 May 8].
57. Herman WH, Fajans SS. Hemobglobin A1c for the diagnosis of diabetes. Practical considerations. Pol Arch Med Wewn 2010;120:37-40.