Interpretation of HbA_{1c}: analytical and clinical problems

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* references
* pre-analytical phase
* analytical phase
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* future

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*agenda

Clinical Chemistry 57:6
e1–e47 (2011)

Special Report

Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

David B. Sacks,[1*] Mark Arnold,[2] George L. Bakris,[3] David E. Bruns,[4] Andrea Rita Horvath,[5] M. Sue Kirkman,[6] Ake Lernmark,[7] Boyd E. Metzger,[8] and David M. Nathan[9]

*agenda

* references
* pre-analytical phase
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* post-analytical phase
* future

*Advantages of HbA_{1c} for diagnosis of diabetes

*1. Indicates long-term blood glucose concentration
*2. Fasting not necessary
*3. Sample may be obtained any time of day
*4. Sample stable
*5. Low intra-individual variability
*6. Not altered by acute factors eg, stress, exercise
*7. Assay standardised across instruments
*8. Concentration predicts the development of microvascular complications

*Disadvantages of HbA_{1c} for diagnosis of diabetes

*1. Cost (?)
*2. May not be available in some areas of world
*3. May be altered by factors other than glucose (e.g., change in RBC lifespan, ethnicity)
*4. Some conditions may interfere with measurement
  * Carbamylated Hb
  * Labile A1c
  * Fetal Hb
  * Hb variants

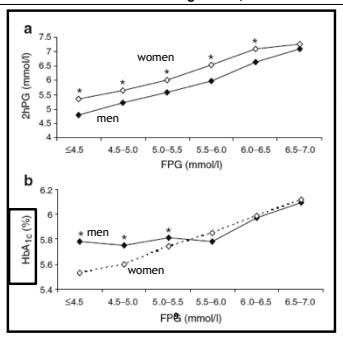
* When HbA_{1c} should not be used for diagnosis

- Children and adolescents
- Women until 2 months postpartum
- People with suspicion of type 1 diabetes (all ages)
- People with acute diabetes symptoms
- Prediabetes with acute stress hyperglycemia (f.e. stroke, MI, organ donor)
- People with drugs (<2 months), which are leading to an acute increase of plasma glucose (glucocorticoids, psychopharmacological drugs)
- Shortly after pancreas surgery, acute pancreatitis
- People with HIV infection
- Endstage renal disease

R. Landgraf (by courtesy)

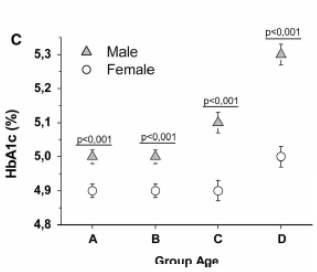
Differences man/woman (Inter99 study)

Faerch K et al. Diabetologia 2010;53:858-65



Reference intervals for HbA1c partitioned for gender and age: a multicenter study

M. Pieri[1] · S. Pignalosa[1] · R. Zenobi[1] · C. Calla[2] · F. G. Martino[3] · G. Menichella[4] · F. Mancina[4] · U. Moscato[4] · G. Nocca[2] · H. Khashoggi[1] · S. Bernardini[1] · M. Dessi[1] · N. Di Daniele[3]



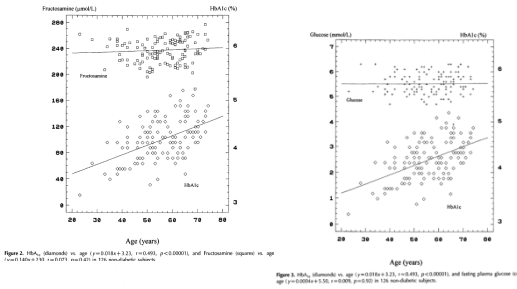
Acta Diabetol
DOI 10.1007/s00592-016-0932-3

*HbA_{1c} and age

From 30 y to >70y:

- **HbA_{1c} increase of 0.5 %**

•Davidson MB, Schriger DL. Diabetes Res Clin Pract.2010; 87:415–421
•Pani et al.: Diabetes Care 2008; 31:1991–1996
•RaviKumar P et al. Diabetic Med 2011;28:590-594



Kilpatrick et al, QJMed 1996;89:307

*Races and HbA_{1c}

HbA_{1c} is higher, respect to Caucasian:

- **Afro-Americans ~ 8 mmol/mol**
- **Latinos ~ 5**
- **Punjabi Sikhs ~ 4**
- **Asian ~ 3**

•KIRK et al. Diabetes Care 2006; 29:2130–2136
•Likhari T, Gama R. Diabetic Med 2009; 26:1068–1069
•Herman et al. J Clin Endocrinol Metab 2009;94 :1689–1694
•Kamps et al. Diabetes Care 2010;33:1025-1027
•Wolfenbuttel et al. Diabetes Care 2013;36:2931–2936

*Nutrition and HbA_{1c}

- **Alcohol from abstinence to heavy drinker: HbA_{1c} drop of ~0.4%**
  The Kaiser Permanente Northern California Diabetes Registry
  Ahmed et al. J Gen Intern Med 2008; 23:275–82
- **The lower the fat consumption and the higher the percentage of unsaturated free fatty acids the lower HbA_{1c}: ~0.2% - 0.3%**
  Harding et al.: Diabetes Care 2001;24:1911-1916

R. Landgraf ***(by courtesy)***

Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c

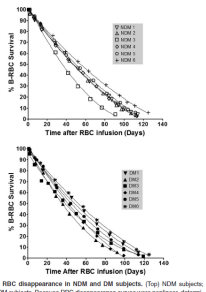


Figure 3. RBC disappearance in NDM and DM subjects. (Top) NDM subjects; (bottom) DM subjects. Because RBC disappearance curves were nonlinear, determination of RBC life span as the x-intercept is not the most meaningful approach to summarizing the exposure of the RBCs to plasma glucose. Mean cell age was therefore used, computed from the survival curves, fitted to cubic equations ("Analysis of RBC life span").

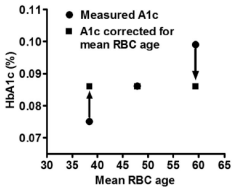


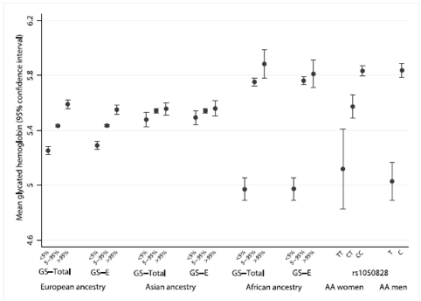
Figure 6. Impact of differences in mean RBC age on measured HbA1c. Three hypothetical patients with identical glycation rates would be expected to have similar HbA1c values (in this case 0.086, the average of the 6 DM subjects in our study). However, variable mean RBC age results in a measured HbA1c that ranges from lower to higher than expected. This could lead to inappropriate clinical management.

CV ~ 12 %

Cohen, Blood 2009;112:4284-91

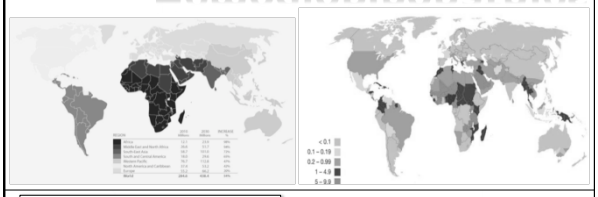
RESEARCH ARTICLE

Impact of common genetic determinants of Hem… diagr… trans…



PLOS | MEDICINE

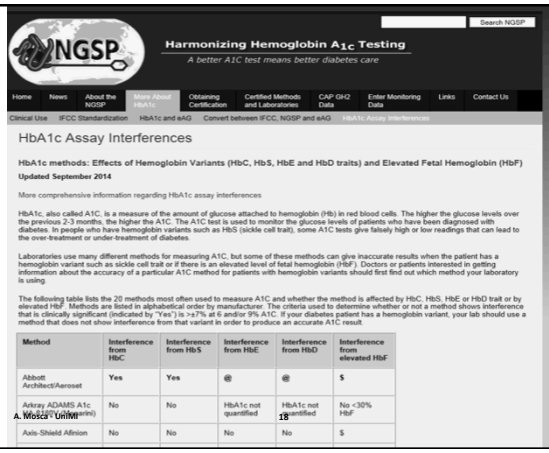
*Diabetes epidemics and Hemoglobinopathies

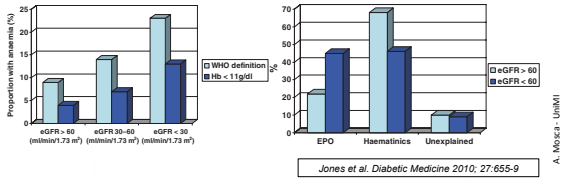


Diabetes growth 2000 – 2030

Hemoglobin disorders incidence
(per 1000 new births)

Hossain et al, NEJM 2007;356;213-5
Modell et al, Bulletin of the World Health Organization 2008;86:480-7



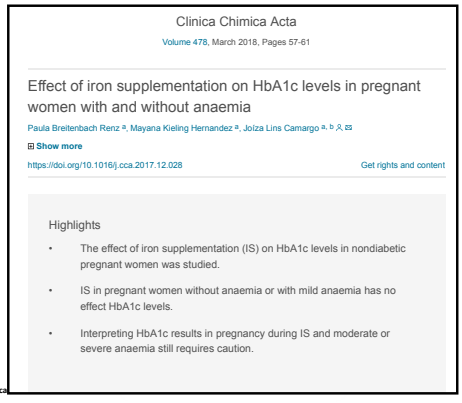


Jones et al. Diabetic Medicine 2010; 27:655-9

n= 7331

* Prevalence of anemia in diabetic patients

UK experiences (Teesside)



Clinica Chimica Acta

Volume 478, March 2018, Pages 57-61

Effect of iron supplementation on HbA1c levels in pregnant women with and without anaemia

Paula Breitenbach Renz [a], Mayana Kieling Hernandez [a], Joíza Lins Camargo [a, b]

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Highlights

- The effect of iron supplementation (IS) on HbA1c levels in nondiabetic pregnant women was studied.
- IS in pregnant women without anaemia or with mild anaemia has no effect HbA1c levels.
- Interpreting HbA1c results in pregnancy during IS and moderate or severe anaemia still requires caution.

Glycated haemoglobin and iron deficiency anaemia: a case-control study

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Abstract
Several studies have suggested an association between iron deficiency anaemia and higher HbA1c levels, but the results are conflicting and the matter is under debate. We conducted a retrospective case-control study to investigate both the effects of iron deficiency and the reduction of haemoglobin level on HbA1c measurement in subjects with iron deficiency anaemia.

Measured haemoglobin concentration range (g/dL)	Percentage decrease of HbA1c (mmol/mol) supposing a normal haemoglobin concentration of 13g/dL (median [5th/95th percentile])*	Lower glycated haemoglobin values in the case of HbA1c 48mmol/mol (median [5th/95th percentile])**
7.0–8.0	-4.2 (-4.6/-3.9)	45.98 (45.79/46.13)
8.1–9.0	-3.3 (-3.7/-3.2)	46.41 (46.22/46.46)
9.1–10.0	-2.6 (-2.9/-2.3)	46.75 (46.61/46.90)
10.1–11.0	-1.9 (-2.2/-1.6)	47.09 (46.94/47.23)
11.1–12.0	-1.2 (-1.5/-0.8)	47.42 (47.28/47.62)
12.1–13.0	-0.3 (-0.7/0.0)	47.86 (47.66/48.00)

*These corrections should be applied to HbA1c levels obtained using ion-exchange HPLC ARKRAY ADAMS A1c series HA (Menarini Diagnostics, Firenze, Italy) haemoglobin analysers.
**Reduction of the cut-off HbA1c 48mmol/mol at different haemoglobin concentrations using estimated percentage differences between measured and estimated HbA1c values.

Table 3. Estimated correction of HbA1c values

* references
* pre-analytical phase
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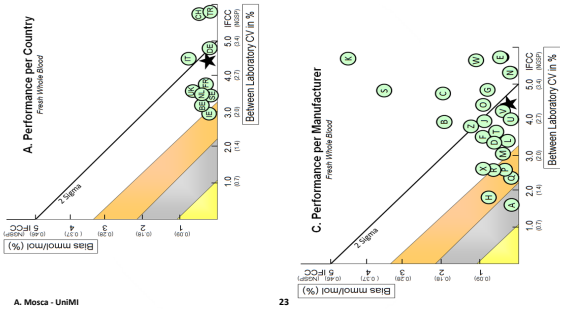
* future

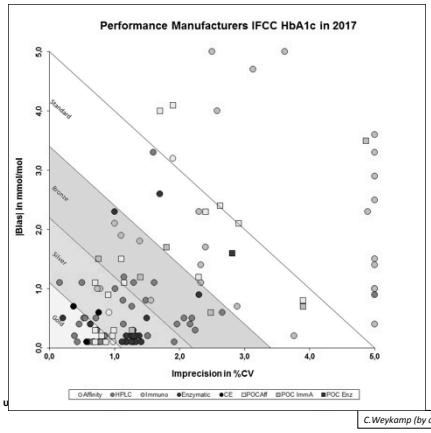
*agenda

EurA1c: the European HbA1c Trial to Investigate the Performance of HbA1c Assays in 2166 Laboratories across 17 Countries and 24 Manufacturers by Use of the IFCC Model for Quality Targets

The EurA1c Trial Group

Clinical Chemistry 64:8
000–000 (2018)





C.Weykamp (by courtesy)

CONCLUSIONS: The state of the art is that 1 of 20 laboratories does not meet the IFCC criterion, but there are substantial differences between country and between manufacturer groups. Efforts to further improve quality should focus on reducing between-laboratory variation.

With some limitations, fresh whole blood and well-defined lyophilized specimens are suitable for purpose.

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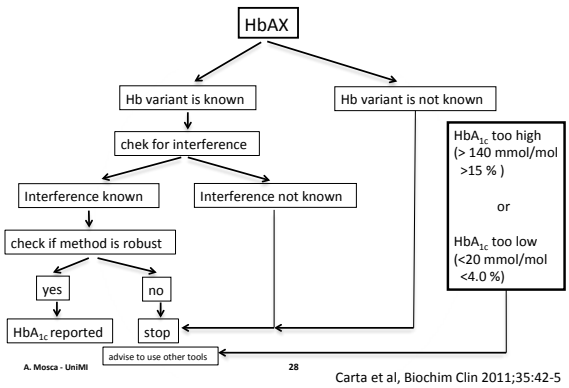
Refertazione dell'emoglobina glicata in presenza di varianti emoglobiniche

Mariarosa Carta[1], Renata Paleari[2], Anna Caldini[3], Alessandro Terreni[3], Andrea Mosca[2] per il Gruppo di Studio Intersocietario SIBioC-SIMeL Diabete Mellito
[1]Laboratorio di Chimica Clinica ed Ematologia, ULSS 6, Vicenza
[2]Dipartimento di Scienze e Tecnologie Biomediche, Università degli Studi di Milano
[3]Laboratorio Generale, Azienda Ospedaliero-Universitaria Careggi, Firenze

ABSTRACT

Glycated hemoglobin reporting in presence of hemoglobin variants. Measurement of glycated hemoglobin

Carta et al, Biochim Clin 2011;35:42-5



Carta et al, Biochim Clin 2011;35:42-5

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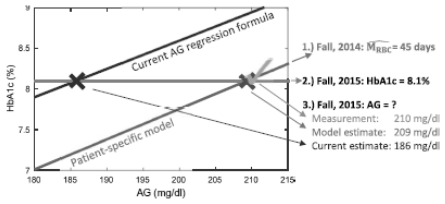

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

DIABETES

Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring

Roy Malka,[1,2] David M. Nathan,[3,4] John M. Higgins[1,2]*

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Ross Molina

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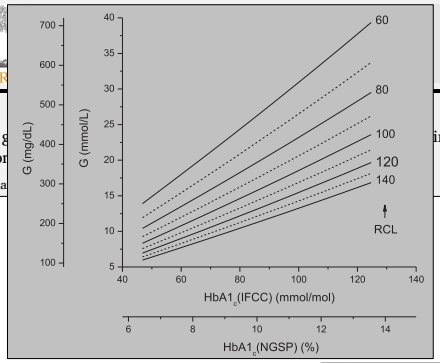

Clinica Chimica Acta 474 (2017) 124–129

Contents lists available at ScienceDirect

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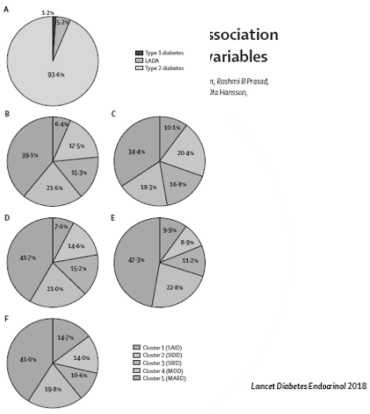
Dougla

Conclusions: Model calculations predict the relationship between changes in estimated average glucose to changes in operative glucose for serial A1c measurements made at intervals <120days. Given that serial measurements of A1c made at short intervals are not uncommon in practice, physicians may find this information to be useful.

Clinical Biochemistry 54 (2018) 73–77

Novel subgroups of ad … ssociation with outcomes: a data … ariables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Dina Mansour Aly, Peter Almgren, Yiva Wessman, Ni… Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, … n, Roshmi B Prasad, … Ha Hansson,



Lancet Diabetes Endocrinol 2018

*Summary

- HbA_{1c} is still the most relevant parameter for monitoring the glycemic control
- The Hb variants causing altered red cell lifespan or glycation rate affect results regardless of assay methodology
- Red cell enzymopathies and red cell membrane disorders may cause also major pre-analytical interference
- Investigate any result that does not match clinical impression or discordant with other parameters for glucose monitoring.

Standardization of HbA_{1c}: are all the pieces in place?

- Top of the chain: YES (IFCC Network)
- Middle: probably YES (information not uniform and difficult to be released)
- Bottom: difficult to draw objective evidences (depending on country and rules); more efforts needed to achieve standardization overall

*What next?

- Always use the best method
- Consensus on interpretation
- Need for more information available to the laboratory (partioned reference ranges)
- More studies on glycation kinetics
- Education and communication (time for personalized medicine?)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