14th EFLM* continuing postgraduate Course in Clinical Chemistry and Laboratory Medicine

October 25-26, 2014
Inter University Centre Dubrovnik

New trends in laboratory diagnosis and management of diabetes mellitus: Diabetes mellitus revisited 14 years after the first Dubrovnik course.

* Post-analytical factors – how should HbA_{1c} results be communicated to clinicians

Andrea Mosca
Center for Metrological Traceability in Laboratory Medicine (CIRME)
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Communication (from Latin *commūnicāre*, meaning "to share") is the activity of conveying information through the exchange of ideas, feelings, …..

Thought: First, information exists in the mind of the sender. This can be a concept, idea, information, or feeling.

Encoding: Next, a message is sent to a receiver in words or other symbols.

Decoding: Lastly, the receiver translates the words or symbols into a concept or information that a person can understand.

Wikipedia, accessed Oct 2014

SPECIMEN DATE AND TIME: 20/09/84 09:7 RESULT

S- Sodium	145.0 mmol/L	135.0-148.0
S- Potassium	4.5 mmol/L	3.7-4.6
S- Chloride	105.0 mmol/L	100.0-109.0
S- Calcium	2.3 mmol/L	2.2-2.6
S- Urea	7.4 mmol/L	2.8-7.7
S- Creatinine	105.0 µmol/L	71.0-124.0
S- Protein Total	64.0 g/L	63.0-80.0
S- AST	138.0 U/L	13.0-38.0
S- ALT	69.0 U/L	10.0-41.0
S- LD	1038.0 U/L	227.0-452.0

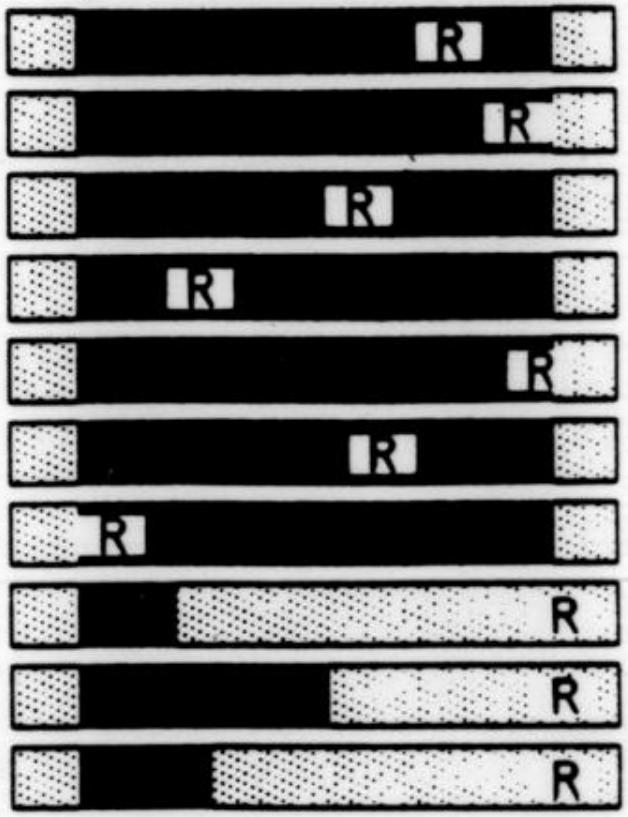


Figure 5-4. Combined numerical and graphical presentation of the observed results of a patient in relation to reference intervals. The figure shows an example from the CLDS computer program (Clinical Laboratory Display System, Department of Clinical Chemistry, Rikshospitalet, Oslo, Norway). The original display on a screen terminal is in color to enhance the interpretation: results are shown in red and reference intervals are displayed in green. The left numeric column contains results. The right numeric column lists the age- and sex-specific reference interval for each value. The graphical display shows both the reference intervals (linear scale, horizontal bars on the screen) and the location of the result (the letter R).

Tietz textbook, 1987

* Turnaround time
* Errors in the keyboard entry
* Missed correction of erroneous findings
* Delayed aknowledgment of laboratory reports
* Failures in interpretation, follow-up and documentation
* Diagnostic errors

*post-analytical errors

Review

Mario Plebani*

The *CCLM* contribution to improvements in quality and patient safety

Clin Chem Lab Med 2013; 51(1): 39–46

contents

* measurement units
* reference intervals
* (interpretation)

Reviews/Commentaries/ADA Statements
CONSENSUS STATEMENT

Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement

The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation

CONSENSUS COMMITTEE*

scientifically correct units, i.e., mmol/mol (13). The impact of both changes proposed by the IFCC would be to signif

DIABETES CARE, VOLUME 30, NUMBER 9, SEPTEMBER 2007

1. A1C test results should be standardized worldwide, including the reference system and results reporting.

2. The new IFCC reference system for A1C represents the only valid anchor to implement standardization of the measurement.

3. A1C results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.

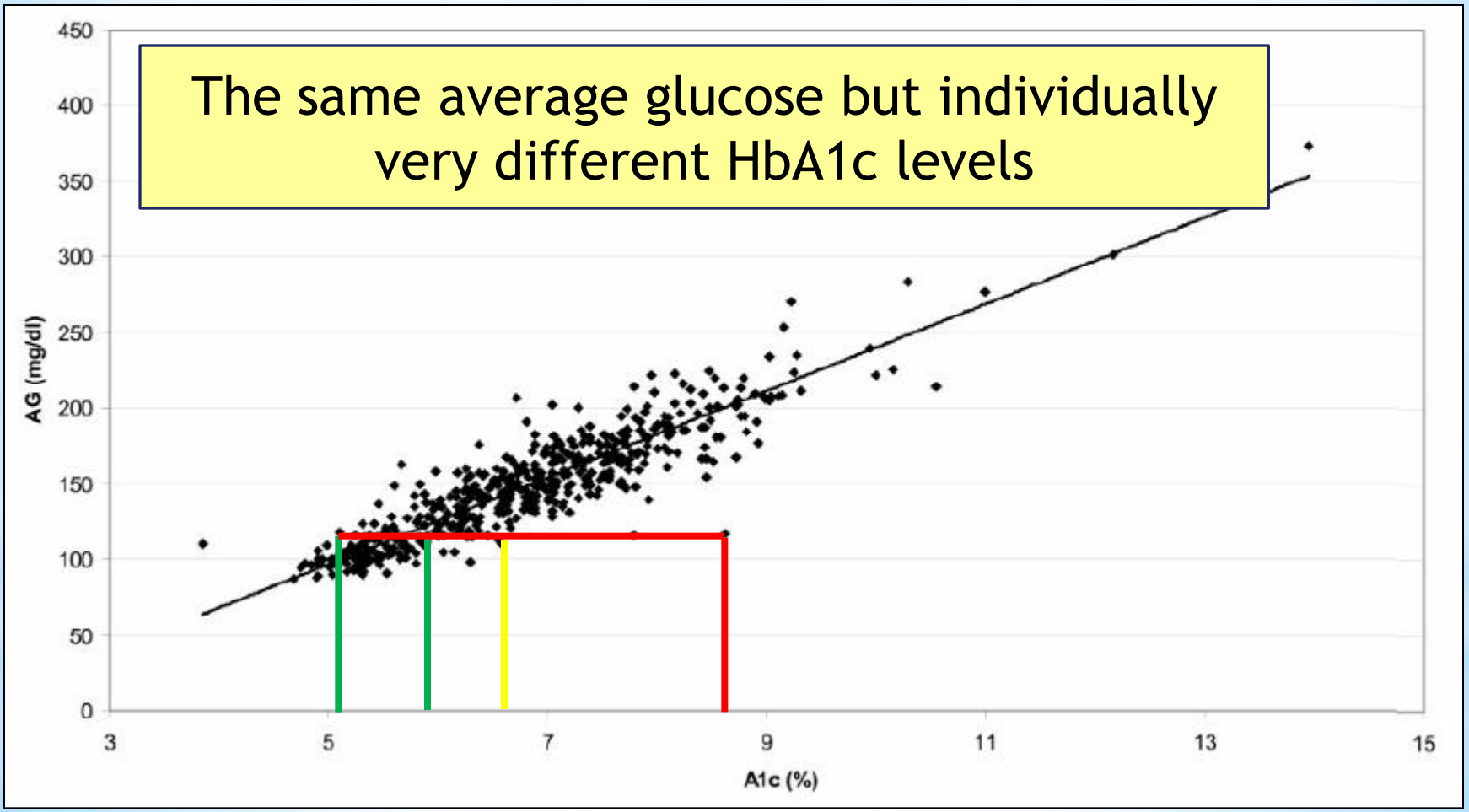
4. If the ongoing “average plasma glucose study” fulfills its a priori–specified criteria, an A1C-derived average glucose (ADAG) value calculated from the A1C result will also be reported as an interpretation of the A1C results.

5. Glycemic goals appearing in clinical guidelines should be expressed expressed in IFCC unitss, derived NGSP units, and as ADAG.

DIABETES CARE, VOLUME 30, NUMBER 9, SEPTEMBER 2007

* Translating the HbA1c assay into estimated average glucose values:eAG

Nathan et al.: Diabetes Care 2008; 31:1473–1478



Mean blood glucose (eAG) mg/dl = 28.7 x A_{1C} - 46.7 (AG mmol = 1.59 x A_{1C} - 2.59) (R^2 = 0.84; p< 0.0001).

*why using IFCC units?

- *Improved reliability and metrological traceability
  - → Abandoning tests with poor performance
- *Measurement units aligned to the S.I. system
- *Avoiding the complications of using two different measurement units (different reference intervals, different decisional limitis, different analytical goals)
  - → Simpler report
- *Expanding the physiopathological range
  - →Greater attention to the result
- *Better relationship to the physiopathological meaning

The Analytical Goals for Hemoglobin A_{1c} Measurement in IFCC Units and National Glycohemoglobin Standardization Program Units Are Different

Weykamp et al, Clin Chem 2011;57:1204-5

Table 1. Biological variation in Hb A_{1c} and estimated analytical goals related to the NGSP and IFCC measurement systems, as expressed in the Hb A_{1c} concentration unit of measure (percentage and millimoles per mole, respectively) and as a percentage of the Hb A_{1c} measured.

Parameter	NGSP system		IFCC system	
	Unit of measure, %	Percentage	Unit of measure, mmol/mol	Percentage
Biological variation				
Mean Hb A_{1c}	4.90		30.0	
Intraindividual variation	0.08 (as SD)	1.6%	0.88 (as SD)	2.9%
Interindividual variation	0.20 (as SD)	4.1%	2.20 (as SD)	7.3%
Reference interval (95% central interval)	4.50–5.30	92%–108%	25.6–34.4	85%–115%
Analytical goals (biological variation)[a]				
Imprecision	0.04	0.8%	0.44	1.5%
Bias	0.05	1.1%	0.59	2.0%
Total error	0.12	2.4%	1.32	4.4%
Analytical goals (outcome based)[b]				
Imprecision	0.15	2.0%	1.6	2.8%
Total error	0.50	6.7%	5.0	8.6%

[a] Calculated according to Fraser et al. *(5)*.
[b] Calculated according to Mosca et al. *(4)*.

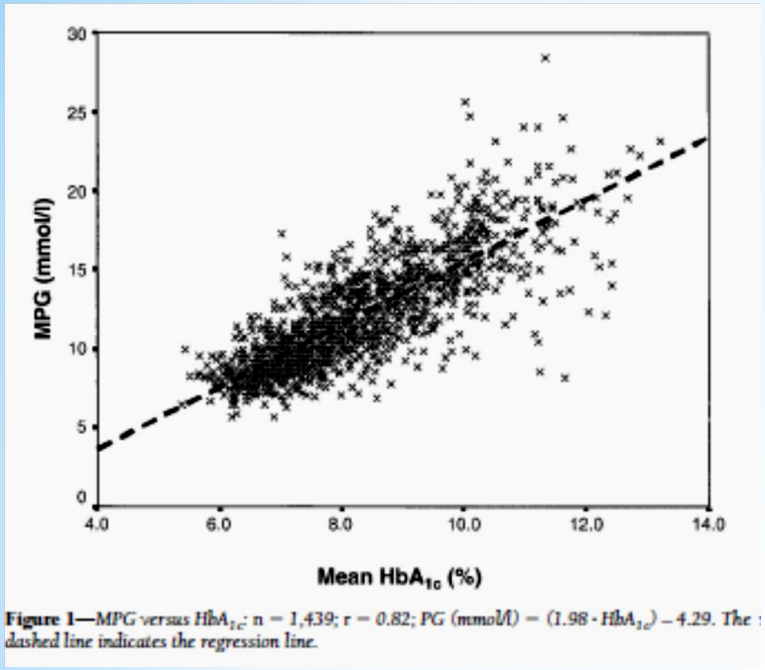
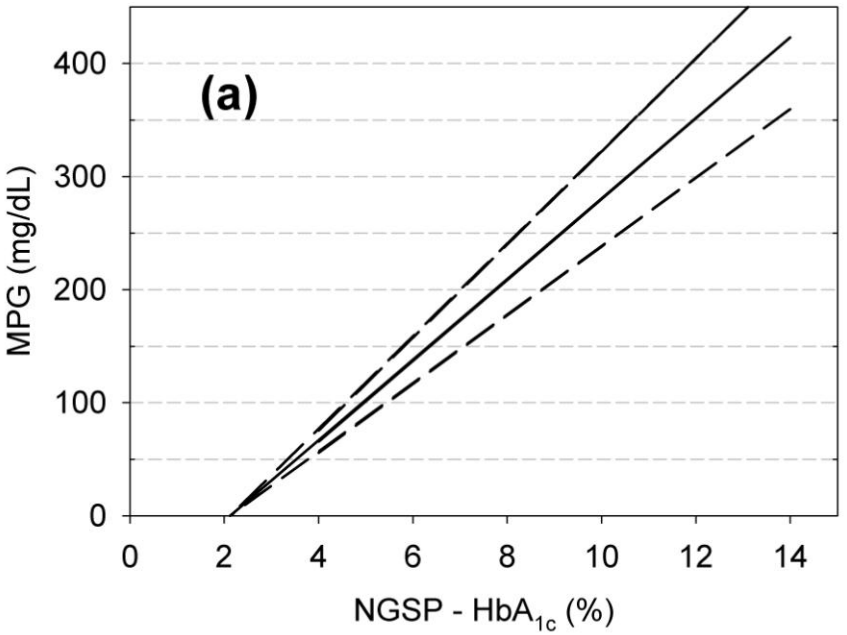
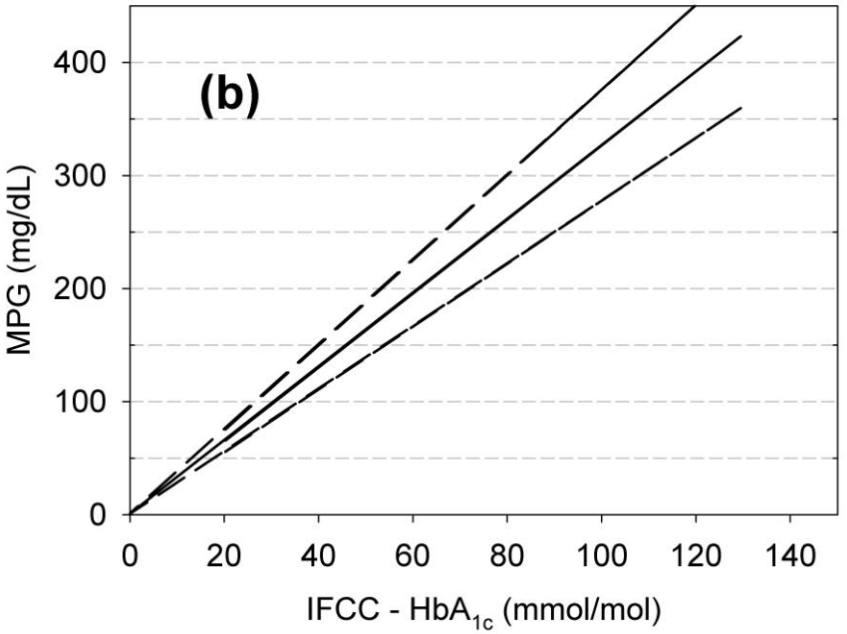


Figure 1—*MPG versus HbA_{1c}: n = 1,439; r = 0.82; PG (mmol/l) = (1.98 · HbA_{1c}) – 4.29. The dashed line indicates the regression line.*

Rohlfing et al, Diabetes Care 2002;25:275-8





Replies from the societies of laboratory medicine (clinical chemistry) in 2009-2014 concerning the use of the % and mmol/mol units in their daily clinical laboratory service for HbA1c.

Ilkka Penttilä, MD, emeritus professor

Kuopio, Finland, 01. 09. 2014

*FSCC meeting September 2014

Country	answer	% AND mmol/mol	ONLY mmol/mol	HbA1c in diagnosys
Germany	Yes	2009	01/01/10	Yes
Great Britain	Yes	1.6..2009-30.9.2011	01/10/11	Yes
The Nethetlands	Yes	2009-2010	01/01/11	Yes
Sweden	Yes	1.9.-31.12.2010	01/01/11	Yes
Check Rebublic	Yes		01/01/12	Yes
Italy	Yes	From1.1.2011	01/10/12	Yes
Denmark	Yes	From 1.8.2008	01/01/13	Yes
Ireland	Yes	From 1.7.2010	From 16.1.2012	Yes
Hungary	Yes	From 1.4.2011	01/04/13	?
Australia	Yes	From July 2011	July 2013	Partly
New Zealand	Yes	From July 2011	July 2013	Partly
Japan	Yes	In the future	?	Yes
Finland	Yes	From 3.3.2010	1.1.2015 ?	Yes
Belgium	Yes	From 1.6.2011	?	?
Estonia	Yes	From 1.1.2012	?	Yes
France	Yes	From 2009	?	?
Serbia	Yes	From 1.9.2009	?	Yes
Poland	Yes	From 2013	?	Yes
Slovenia	Yes	2011	?	?
Turkey	Yes	From 2012	?	?
Greece	Yes	?	?	?
Israel	Yes	?	?	?
Norway	Yes	?	?	Yes
Iceland	Yes			Yes
Bulgaria	Yes			?
Croatia	Yes			?
Latvia	Yes			?

Country	answer	% AND mmol/mol	ONLY mmol/mol	HbA1c in diagnosys
Lithuania	Yes	From 15.4.2011	Not decided	?
Luxembourgh	Yes			?
Slovakia	Yes	From 13.6.2012	?	Not used
Spain	Yes	Yes (partly)	?	Yes
Switzerland	Yes			?
Albania				
Austria				
Bosnia-Herzeg				
Macedonia				
Portugal				
Romania				
Russia				
USA	Yes	?	?	Yes
Canada	Yes	In the future	?	Yes
Brazil *	Yes			?
Argentina (telefax)				
Chile (telefax)				
Indonesia (telefax)				
China Taipei (telefax)				
South Korea (telefax)				
Egypt (telefax)				
Souft Africa (telefax)				
Kazakzan (telefax)				

Total replies: 23/50 = 46 %

Replies for diabetes limit: 26/50 = 52 %

mmol/mol only: 11/50 = 22 %

Clinical Chemistry 59:10
1457–1460 (2013)

Glycemic Control in the 12 Months following a Change to SI Hemoglobin A_{1c} Reporting Units

Eric S. Kilpatrick,[1*] Alan S. Rigby,[2] Stephen L. Atkin,[3] and Julian H. Barth[4]

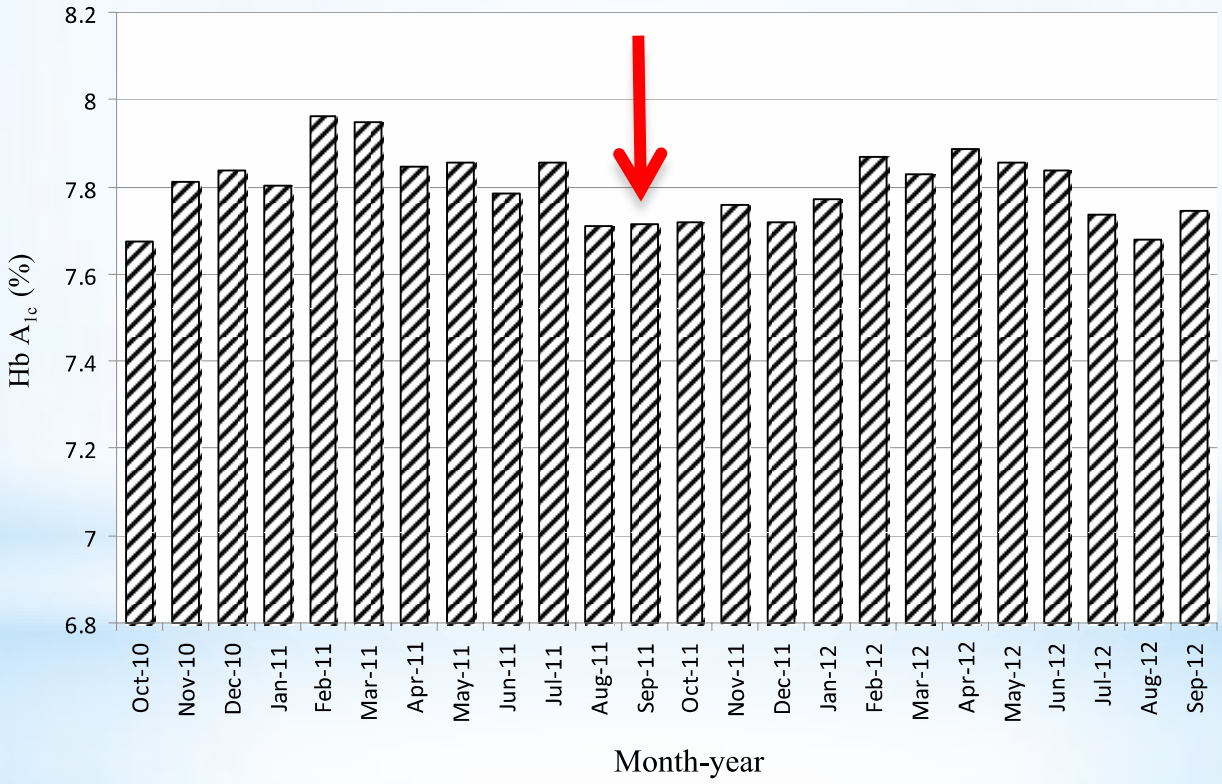


Fig. 1. Monthly mean Hb A_{1c} throughout period of study.

Table 1. Hb A_{1c} before and after change to reporting Hb A_{1c} in SI units alone.[a]

	Year before unit change 2010–2011	Year after unit change 2011–2012	*P*
All samples			
n	21 880	22 841	
Hb A_{1c}			
%	7.5 (6.6, 8.7)	7.5 (6.5, 8.7)	0.34
mmol/mol	58 (49, 72)	58 (48, 72)	
Hb A_{1c} initially >8% (64 mmol/mol)[b]			
n	4316	4396	
Hb A_{1c} change			
%	−0.2 (−0.9, 0.3)	−0.2 (−0.8, 0.3)	0.44
mmol/mol	−2 (10, 3)	−2 (9, 3)	
Days between Hb A_{1c} samples	99 (64, 147)	98 (64, 147)	0.45

[a] All data expressed as median (25th, 75th) centiles.
[b] Change in Hb A_{1c} represents the difference between 2 successive DCCT/SI values (before unit change) and 2 successive SI-only values (after unit change) in samples with initial values >8% (64 mmol/mol).

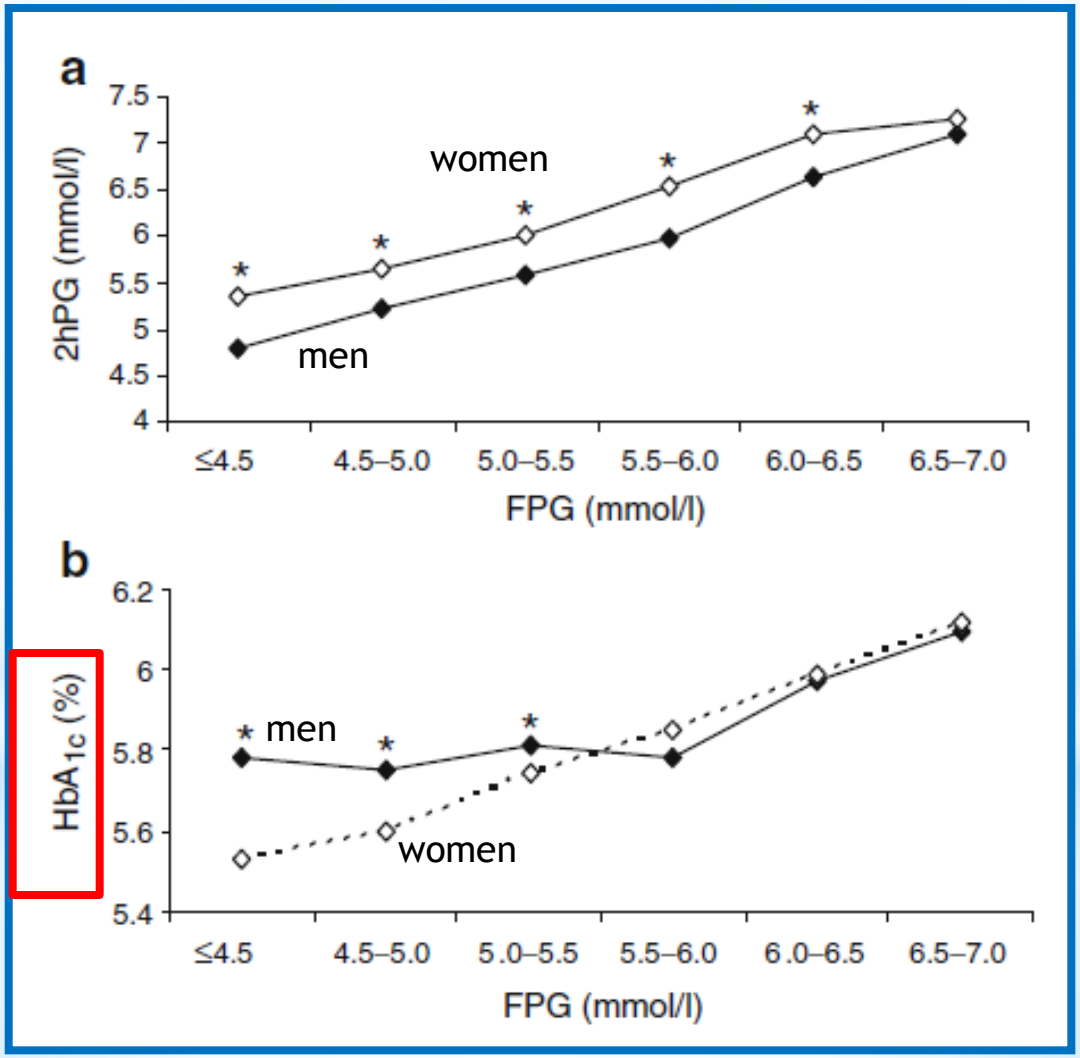
Kilpatrick et al, Clin Chem 2013;59:1457-60

* Gender
* Age
* Ethnicity
* Biological variation

* reference intervals

Sex differences in glucose and HbA1c levels. Inter99 Study

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



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DETERMINATION OF REFERENCE VALUES OF HbA1c: A MULTICENTER STUDY

M. Pieri[1], S. Pignalosa[1], F. Duranti[1], C. Calla[2], F.G. Martino[3], S. Bernardini[1], M. Dessi[1]

We analyzed data from three Hospitals of Rome ("Tor Vergata" University Hospital, “Policlinico Gemelli” University Hospital, S. Filippo Neri Hospital) to evaluate a possible HbA1c differences for gender using the capillary electrophoresis technique (capillarys 2 flex piercing; SEBIA). We collected blood samples (300) from healthy donors. Our data show a significant difference in gender (male 31,5 ± 4,1 mMol/Mol; female 29,9 ± 3,5 mMol/Mol; mean ± SD; $p<0,05$; Anova with Bonferroni test post hoc).

biochimica clinica, 2014, vol. 38, n. 5 535

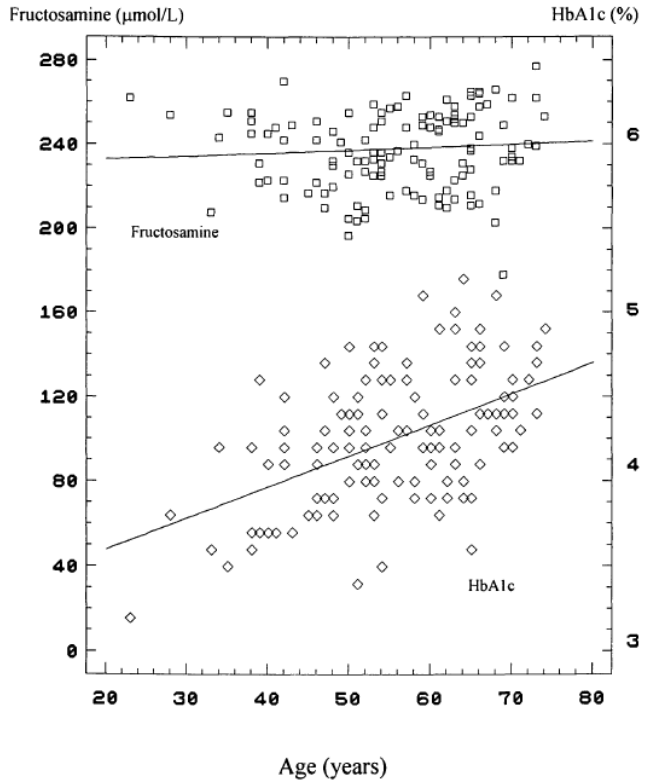


Figure 2. HbA_{1c} (diamonds) vs. age ($y=0.018x+3.23$, $r=0.493$, $p<0.00001$), and Fructosamine (squares) vs. age ($y=0.140x+230$, $r=0.073$, $p=0.42$) in 126 non-diabetic subjects.

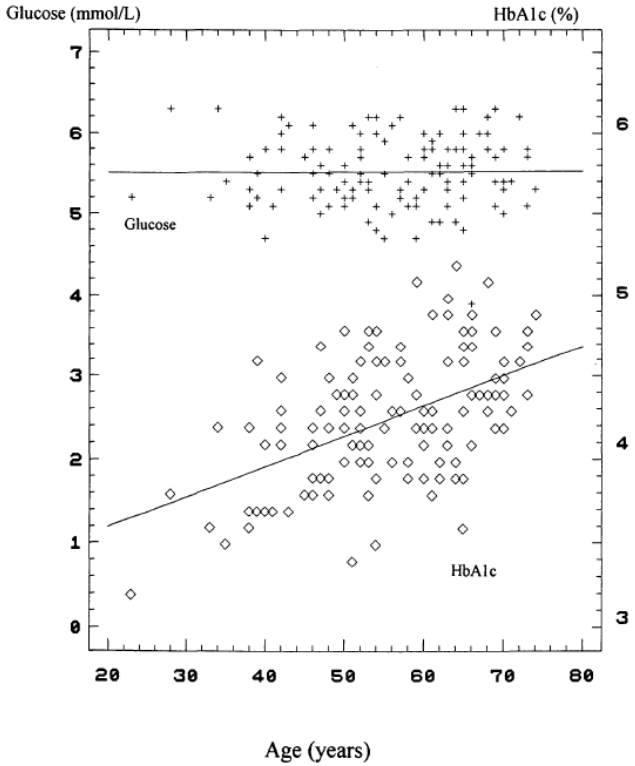
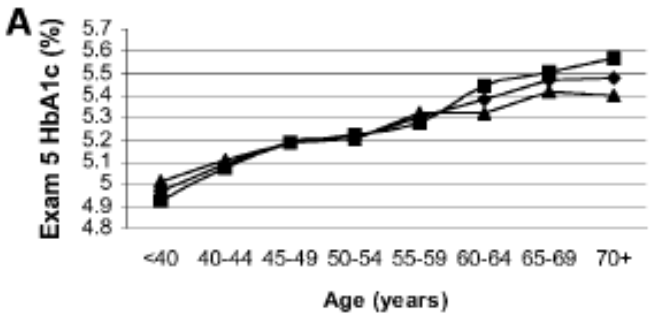


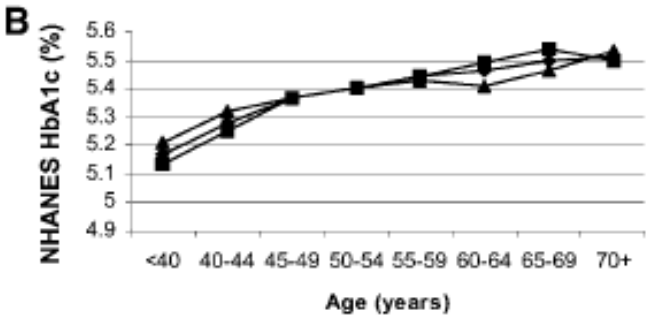
Figure 3. HbA_{1c} (diamonds) vs. age ($y=0.018x+3.23$, $r=0.493$, $p<0.00001$), and fasting plasma glucose (crosses) vs. age ($y=0.0004x+5.50$, $r=0.009$, $p=0.92$) in 126 non-diabetic subjects.

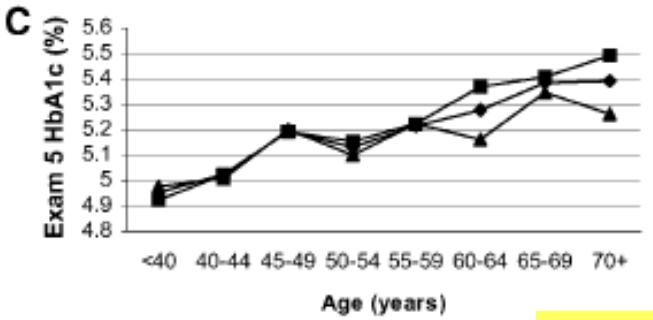
Kilpatrick et al, QJMed 1996;89:307-12

Effect of Aging on A1C Levels in Individuals Without Diabetes

Evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001–2004







Pani et al, Diabetes Care 2008;31:1991-6

*Age and HbA1c

Age between 30 and >70 years old:

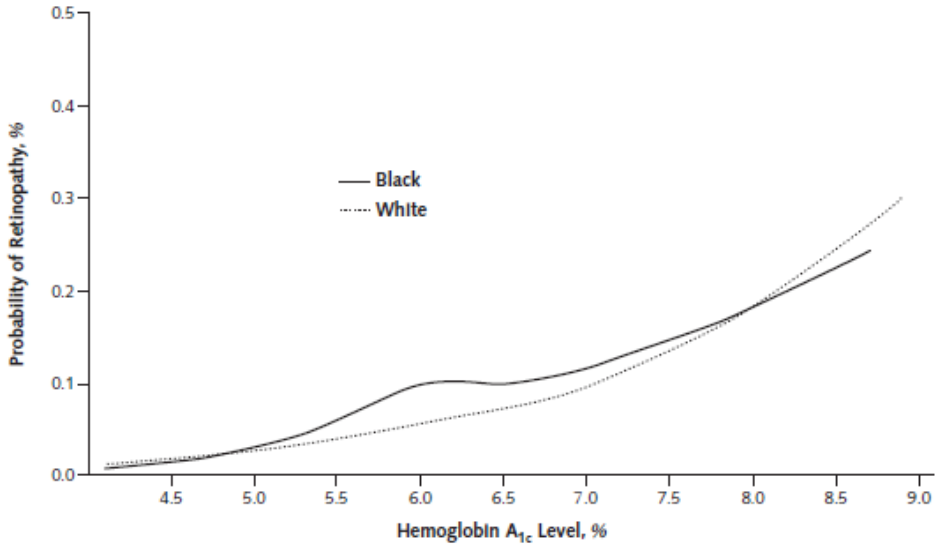
- **Increase of HbA1c of 0,4% to 0,6%**

•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

Table 2. **Adjusted Standardized Risk for the Prevalence of Retinopathy in U.S. Adults Aged 40 Years or Older (Model 1)***

Variable	HbA_{1c} Category					
	<5.5%	5.5%–5.9%	6.0%–6.4%	6.5%–6.9%	7.0%–7.4%	≥7.5%
White persons (n = 2804)						
Sample size	1242	1034	276	98	52	102
Risk (95% CI), %	3.9 (2.6 to 5.1)	5.1 (4.0 to 6.3)	8.7 (4.8 to 12.6)	11.7 (5.7 to 17.6)	16.2 (8.9 to 23.6)	23.6 (12.4 to 34.8)
Risk difference (95% CI), %	0	1.3 (−0.3 to 2.8)	4.8 (0.5 to 9.1)†	7.8 (2.1 to 13.5)†	12.4 (4.7 to 20.1)†	19.7 (8.3 to 31.2)†
Black persons (n = 1008)						
Sample size	255	352	184	70	41	106
Risk (95% CI), %	4.5 (1.6 to 7.4)	9.7 (6.1 to 13.3)	10.9 (5.4 to 16.3)	14.8 (7.0 to 22.5)	22.4 (6.9 to 37.9)	42.1 (29.2 to 55.0)
Risk difference (95% CI), %	0	5.3 (1.0 to 9.5)†	6.4 (−0.4 to 13.2)	10.3 (3.7 to 16.9)†	17.9 (2.0 to 33.8)†	37.6 (24.6 to 50.7)†

Figure 1. **Results of restricted cubic spline models showing the association between hemoglobin A_{1c} level and the probability of retinopathy in U.S. adults aged 40 years or older not treated for diabetes.**



The lines represent the probability determined from restricted cubic spline models, with knots specified at hemoglobin A_{1c} levels of 5.5%, 6.0%, 6.5%, and 7.0%.

Tsugawa et al, Ann Int Med 2012;157:153-9

*Ethnicity and HbA1c

HbA1c is higher in comparison to Caucasians:

- **Afro-Americans ~ 0.8%**
- **Hispanics ~ 0.5%**
- **Punjabi Sikhs ~ 0.4%**
- **Asians ~ 0.3%**

•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

Biological variability of HbA_{1c} (1/2)

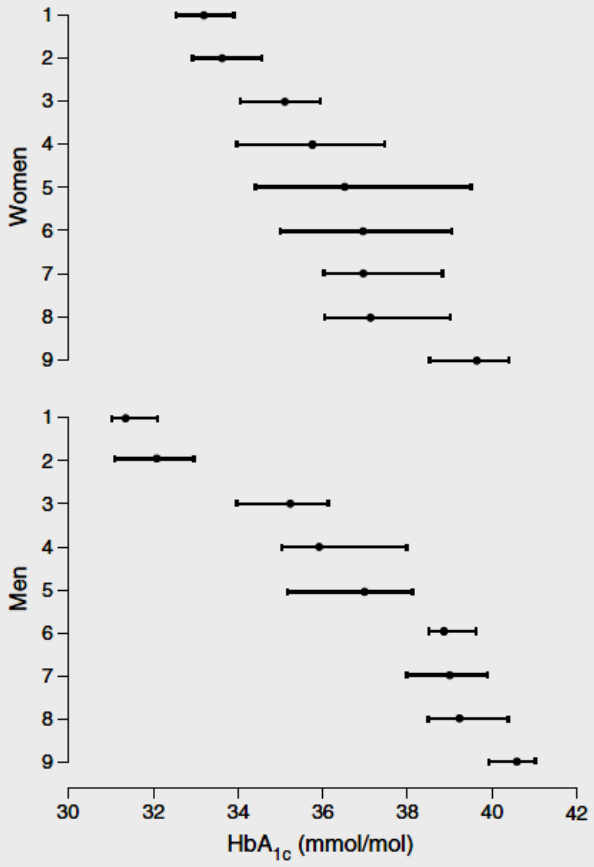


Fig. 1. Individual parametric mean and absolute range of HbA_{1c} values in studied subjects.

Table 2
Mean values, estimated average variance components and indices derived from data on biological variation of HbA_{1c}.

Group	HbA_{1c}, mmol/mol	CV_A, %	CV_I, %	CV_G, %	II	CD, %	*n*
All	36.3	2.4	2.5	7.1	0.35	9.5	2
Men	36.5		1.9	8.9	0.21		
Women	36.1		3.2	5.1	0.62		

CV_A, CV_I, CV_G, II, CD and n as explained in Table 1.

Table 3
Analytical goals for HbA_{1c} measurement derived from data on biological variation.

Quality level	Imprecision, %	Bias, %	Total error, %
Optimal	≤0.6	≤±0.9	≤±2.0
Desirable	≤1.3	≤±1.9	≤±3.9
Minimal	≤1.9	≤±2.8	≤±5.9

Braga et al, Clin Chim Acta 2011;411:1606-10

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EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

European Commission
Joint Research Center
IRMM
Institute for Reference Materials and Measurements

CIRME
Università degli Studi di Milano

1st EFLM Strategic Conference

Defining analytical performance goals 15 years after the Stockholm Conference

8th CIRME International Scientific Meeting

Milan (IT)
24-25 November 2014

conclusions

- world-wide standardization of HbA1c
  - Measurement units?
  - Analytical aspects? (EQAS?) (uncertainties?)
- general population based reference intervals should be abandoned (OR…)
- role of the Scientific Federations (EFLM, IFCC, WHO) for new consensus statements:
  - development
  - implementation

b-glycated hemoglobin (HbA_{1c}): 38 mmol/mol

(desirable value: <39 mmol/mol;
cut-off for the diagnosis of diabetes: >47 mmol/mol;
therapeutic target: <53 mmol/mol)

*reporting, a proposal

* thank you for your attention