HbA1c - overgang til mmol/mol

Noklus fagmøte for sykehus- og private laboratorier
Solstrand, den 15. mars 2018

Jens Petter Berg

Sverre Sandberg

Helsedirektoratets fagråd for diabetes

Resultatenheten for HbA1c endres fra % til mmol/mol den 30. september 2018

- Datoen sammenfaller med 70-årsjubileum for Diabetesforbundet og ble foreslått av Bjørnar Allgot (leder av Diabetesforbundet)

diabetesforbundet 70 år

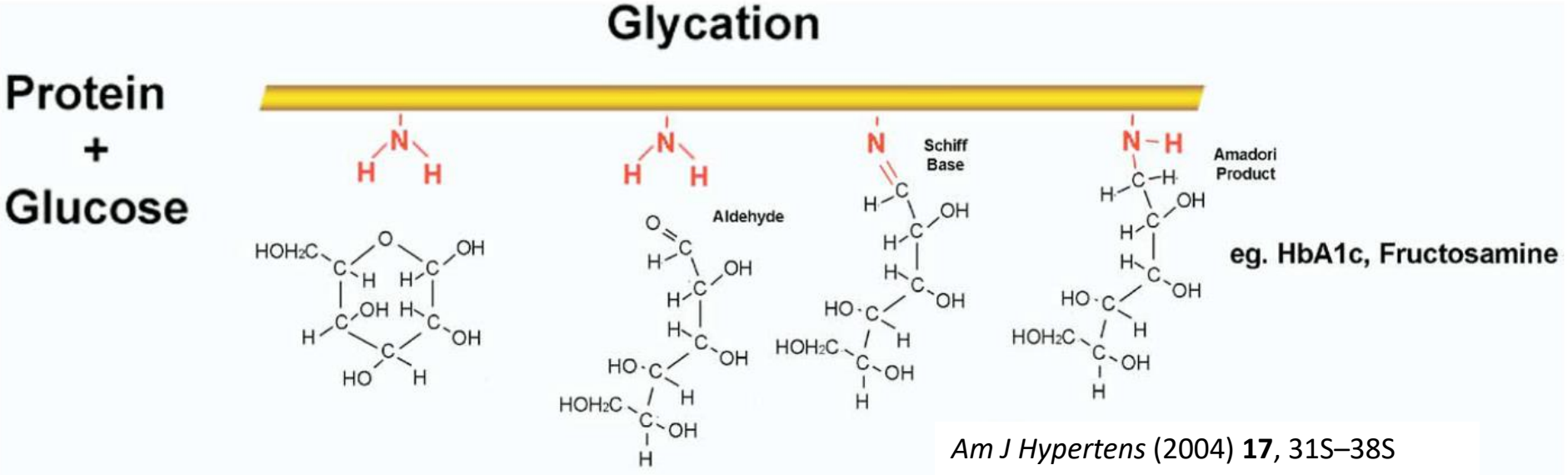
Overgangsfase?

Fagrådet anbefaler at det *ikke* rapporteres svar både som % og mmol/mol i en overgangsfase

Anbefaler at det legges inn en fast kommentar i en overgangsfase for å informere om at resultatenheten er endret og henvisning til mer informasjon

- Helsedirektoratets nettsider med tabell for omregning fra mmol/mol til %
- Diabetesforbundets nettsider
- Informasjon fra NOKLUS

HbA1c dannes ved glykering av hemoglobinet

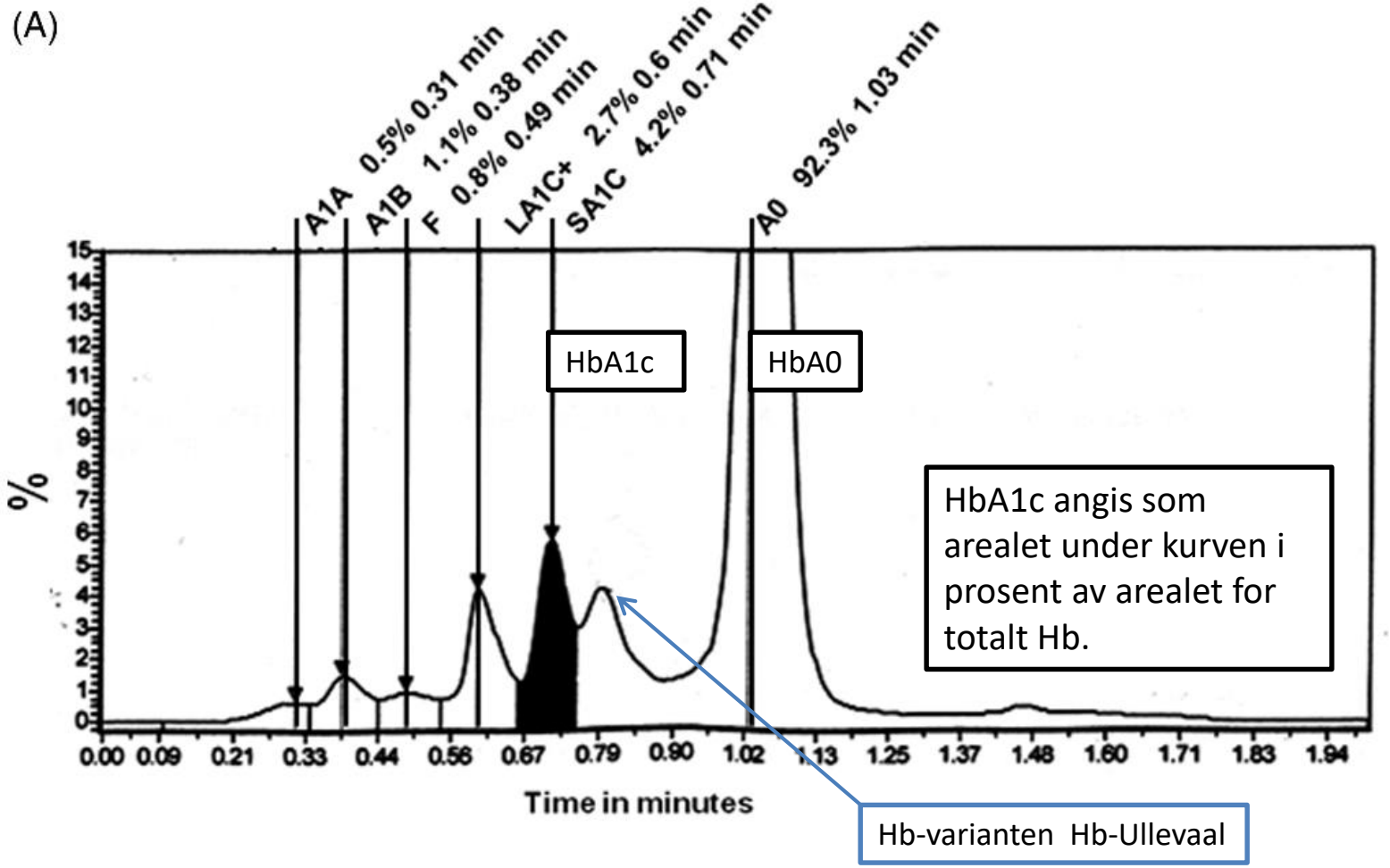


Am J Hypertens (2004) **17**, 31S–38S

Glykering er en ikke-enzymatisk drevet reaksjon hvor glukose binder seg kovalent til aminogrupper i proteiner som Hb. Dette gir en stabil kjemisk binding.

Et protein har mange aminogrupper som kan glykeres. Det dannes en «suppe» av mange forskjellige glykerte former av Hb, men også av andre proteiner som for eksempel albumin.

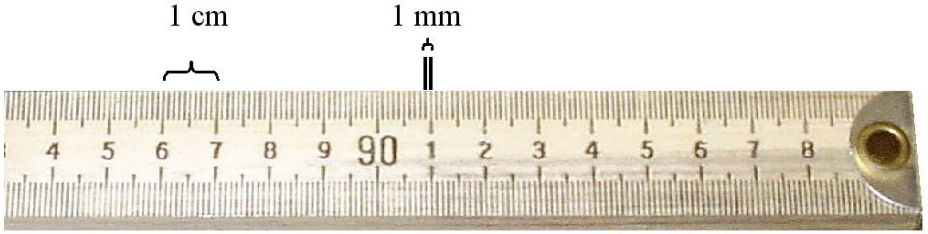
Kromatografisk bestemmelse av HbA1C med Tosoh G7



Grimholt et al. Hemoglobin 2014;38:130-2

Behov for å standardisere HbA1c-resultatene

- Metodeuavhengige aksjonsgrenser ved behandling av diabetes
  - DCCT (diabetes type 1)
  - UKPDS (diabetes type 2)
- Standardisering for å sikre god behandling og forebygging av senkomplikasjoner



IFCC WG for HbA1c

- International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) etablerte en arbeidsgruppe (WG) i 1994
- Standardisering av HbA1c
  - Primære standarder (referansemateriale)
  - Referansemetode(r)

Primært referansemateriale

Clin Chem Lab Med 1998; 36(5):299–308

Preparation of a Candidate Primary Reference Material for the International Standardisation of HbA1c Determinations

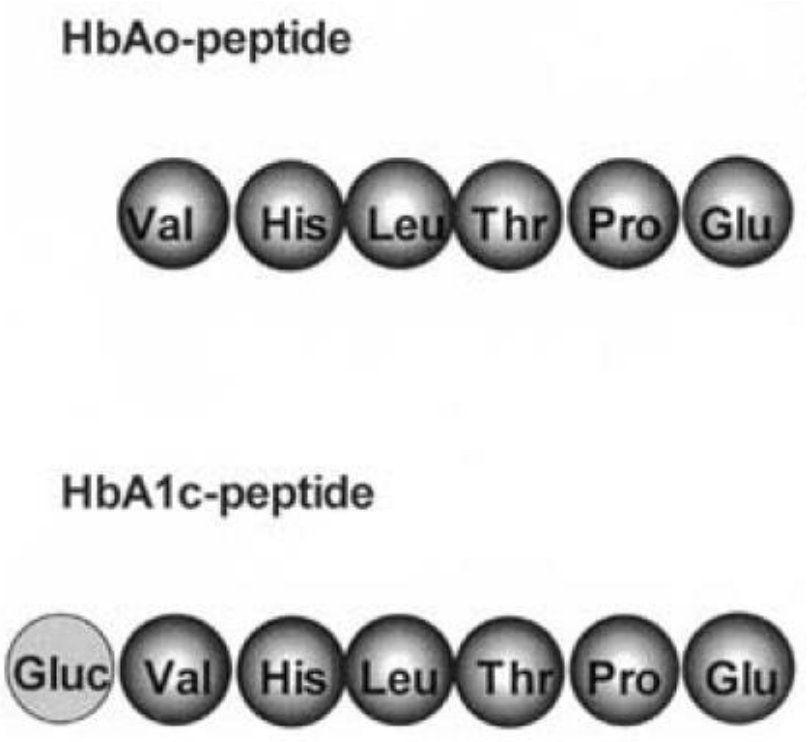
Andreas Finke[1], Uwe Kobold[1], Wieland Hoelzel[1], Cas Weykamp[2], Kor Miedema[3] and Jan-Olof Jeppsson[4]

[1] Boehringer Mannheim GmbH, Penzberg, Germany
[2] Department of Clinical Chemistry, Queen Beatrix Hospital, Winterswijk, The Netherlands
[3] Department of Clinical Chemistry, De Weezenlanden Ziekenhuis, Zwolle, The Netherlands
[4] Department of Clinical Chemistry, Malmo University Hospital, Malmo, Sweden

the long-term control of the glycemic state of diabetic patients. A wide variety of different analytical methods is currently used by clinical laboratories. These are based on physical, chemical or immunological principles. The methods are standardised either internally or against arbitrarily chosen HPLC comparison methods since there is no internationally accepted reference system available. As a result, HbA1c values differ considerably with different methods. (1-5). On the other

Primært referansemateriale

HbA0-peptid:
Definert som de seks første aminosyrene i beta-kjeden til hemoglobin



HbA1c og HbA0 renses, isoleres og blandes i kjente forhold med hverandre:
mmol/mol

HbA1c-peptid:
Definert som de seks første aminosyrene i beta-kjeden til hemoglobin hvor aminosyre nr 1 (valin) er glykert.

Referansemetode

Clin Chem Lab Med 2002; 40(1):78–89 © 2002 by Walter de Gruyter · Berlin · New York

IFCC 2002/1

Approved IFCC Reference Method for the Measurement of HbA_{1c} in Human Blood

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[1)2)]

Scientific Division
Working Group on HbA_{1c} Standardisation[3)] and
Network of Reference Laboratories for HbA_{1c}[4)]

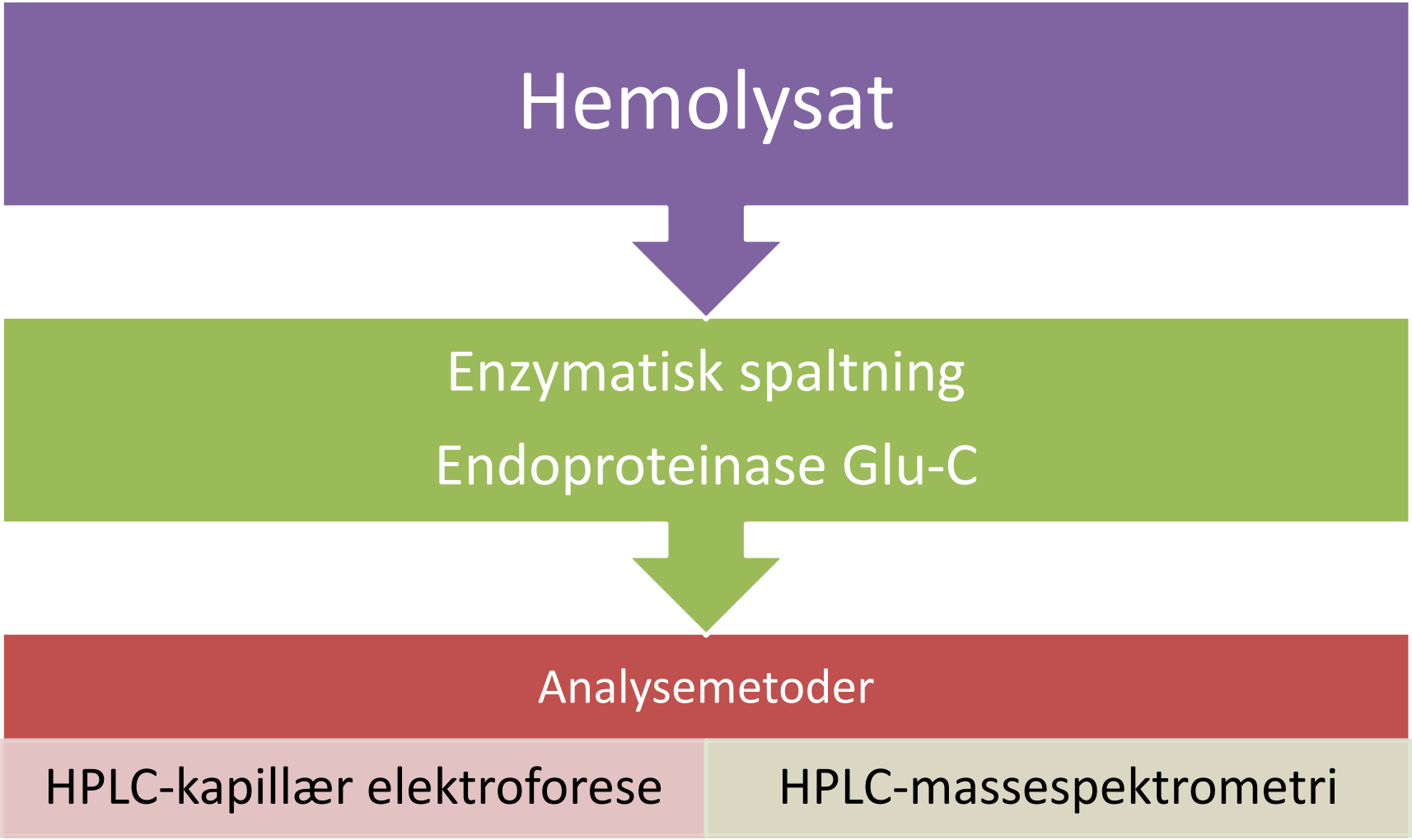
Prepared for publication[5),6)] by

Jan-Olof Jeppsson[1,7)], Uwe Kobold[2], John Barr[3], Andreas Finke[2], Wieland Hoelzel[2], Tadao Hoshino[4], Kor Miedema[5], Andrea Mosca[6], Pierluigi Mauri[7], Rita Paroni[8], Linda Thienpont[9], Masao Umemoto[10] and Cas Weykamp[11]

[10] Standard Reference Center, Kawasaki, Japan.
[11] SKZL Queen Beatrix Hospital, Winterswijk, The Netherlands

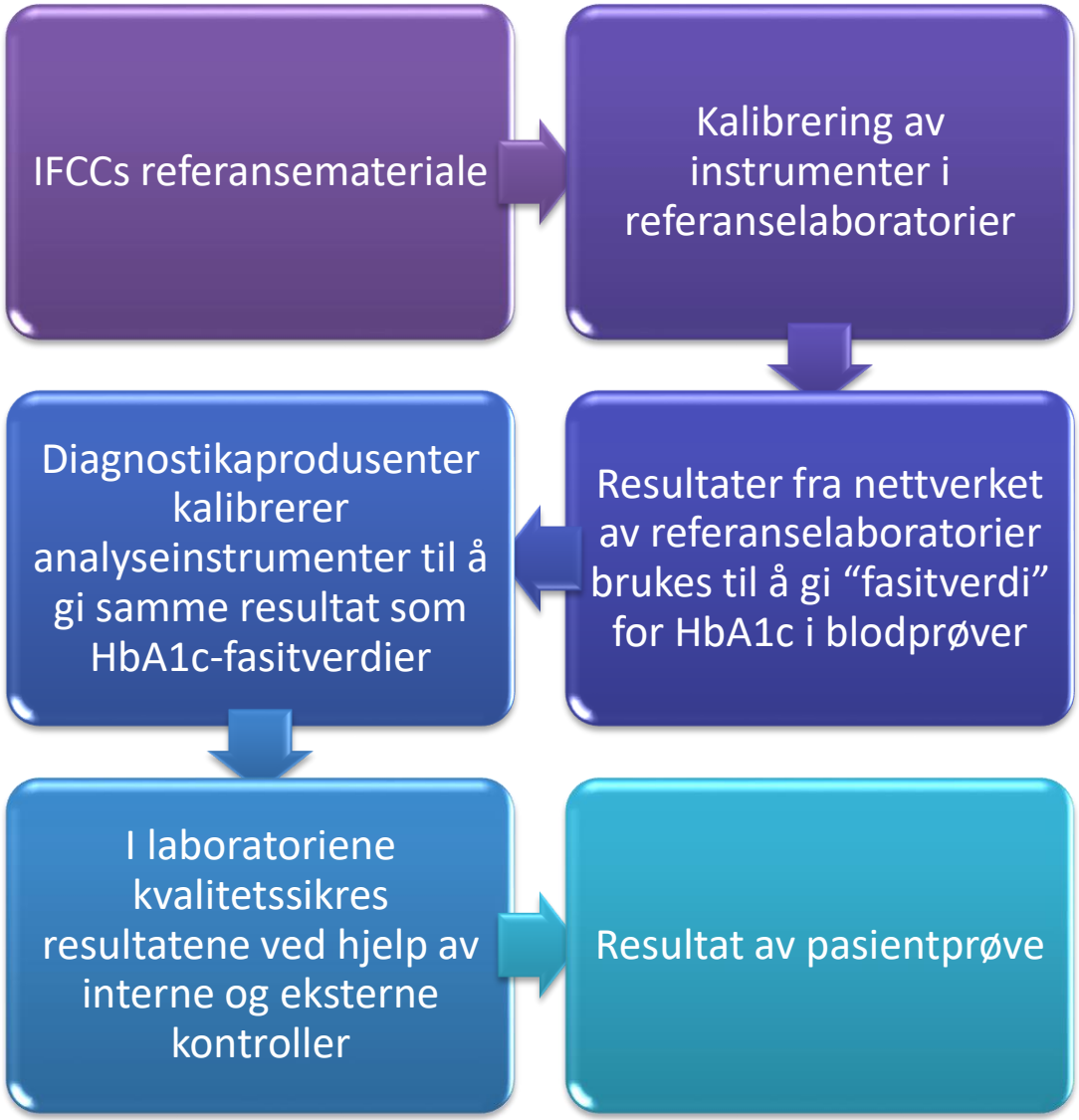
HbA_{1c} is the stable glucose adduct to the N-terminal group of the β-chain of HbA_0. The measurement of HbA_{1c} in human blood is most important for the long-term control of the glycaemic state in diabetic patients. Because there was no internationally agreed reference method the IFCC Working Group on HbA_{1c} Standardization developed a reference method which is here described. In a first step haemoglobin is cleaved into peptides by the enzyme endoproteinase Glu-C,

Referansemetoder



Clin Chem Lab Med 2002; 40(1):78–89

Referansemateriale + referansemetode → Standardisering av HbA1c



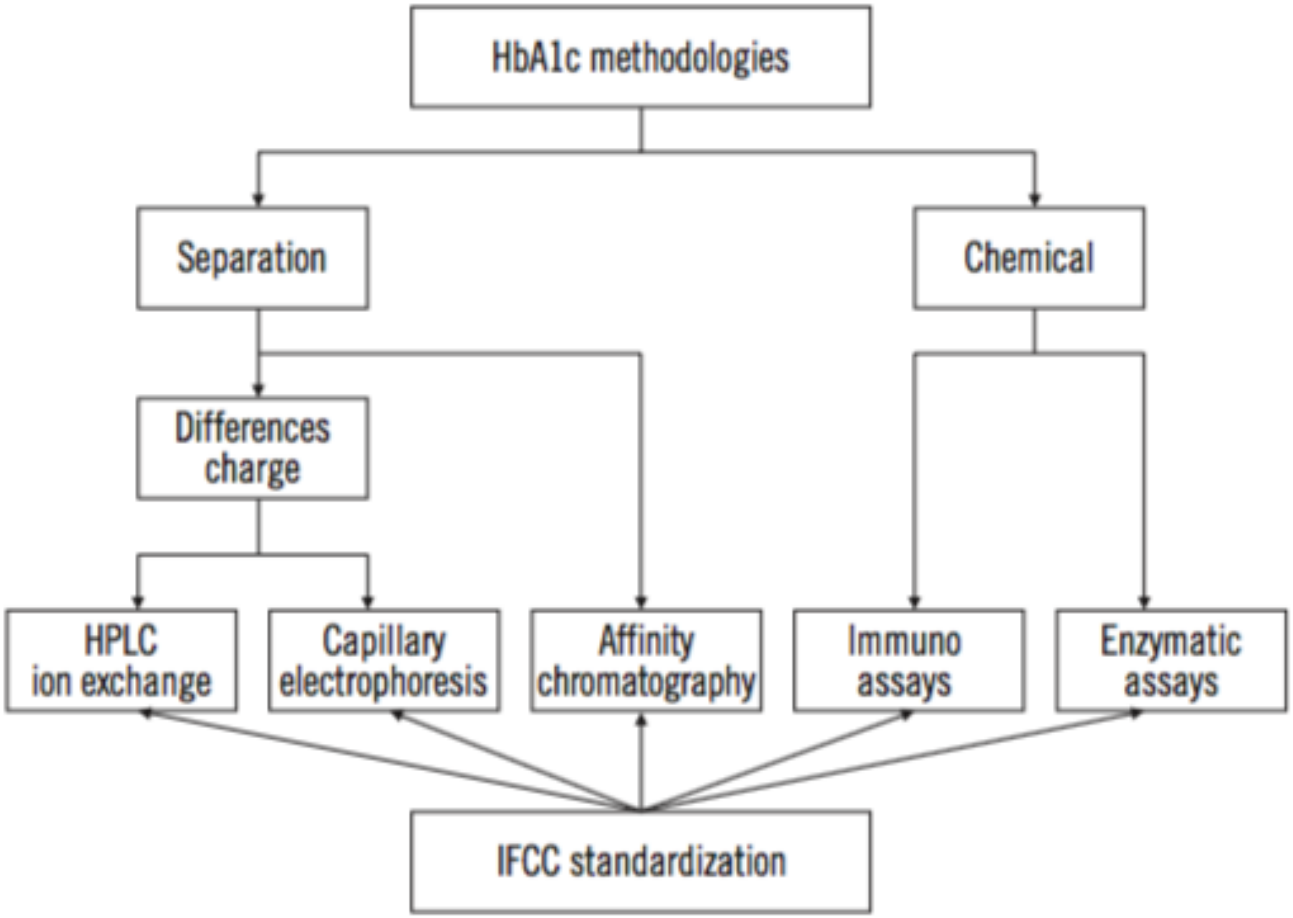


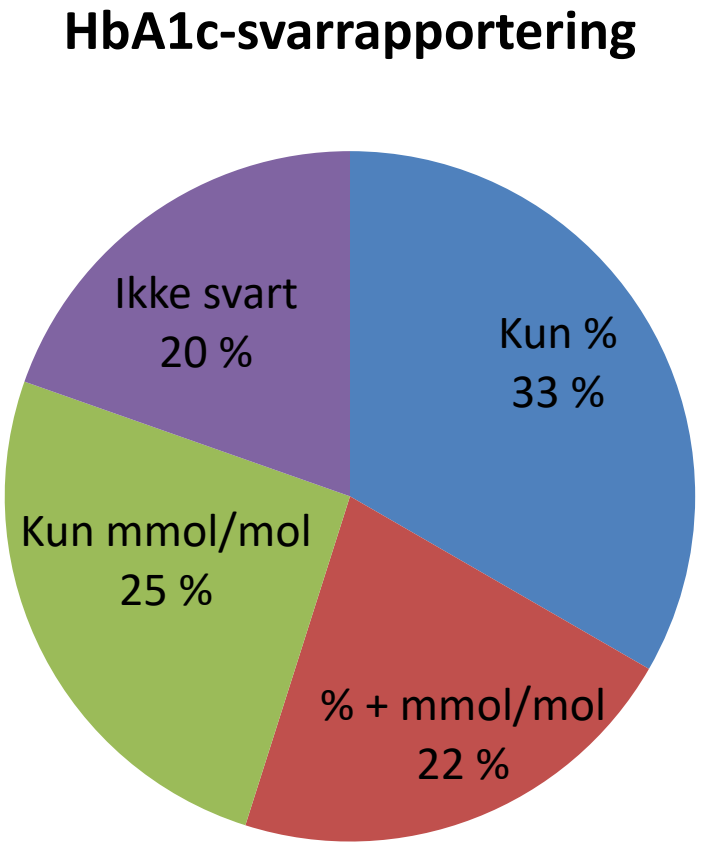
Fig. 1. Analytical concepts of HbA1c measurement methods and their traceability to the IFCC- RMP.
Abbreviations: IFCC, International Federation of Clinical Chemistry; RMP, Reference Measurement Procedure.

Weycamp, C. HbA1c: a review of analytical and clinical aspects. Ann Clin Biochem 2013;33:393–400.

Alternativene for rapportering av HbA1c-svar

- %
  - Refererer til enheten som ble brukt for de to største diabetesstudiene (DCCT og UKPDS)
  - Overgang til mmol/mol vil ikke i seg selv gi mer eller bedre informasjon til rekvirenten
  - Krever en informasjonskampanje
- mmol/mol
  - Direkte sporbar til referansemetode og materiale
  - Flere land utgir svar i mmol/mol alene eller i kombinasjon med %

Resultatrapportering for HbA1c i 2014 prosentvis fordelt på land



Pentillä et al. Clin Chem Lab Med 2015; 53(9): e215–e217

Anbefalt term og måleenhet for HbA1c

Clin Chem Lab Med 2007;45(8):1081–1082 © 2007 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2007.245

Recommendation for term and measurement unit for "HbA1c"[1),2)]

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)
IFCC Scientific Division

Committee on Nomenclature, Properties and Units (C-NPU)

Gunnar Nordin[1,*] and René Dybkær[2]

[1] External Quality Assurance in Laboratory Medicine in Sweden, Uppsala, Sweden
[2] Department of Standardization in Laboratory Medicine, Region H Frederiksberg Hospital, Copenhagen University Hospital, Frederiksberg, Denmark

calculation of measurement results as "amount-of-substance fraction"[b)] rather than mass fraction. In addition, it provides well-defined metrological traceability to the International System of Units (SI).

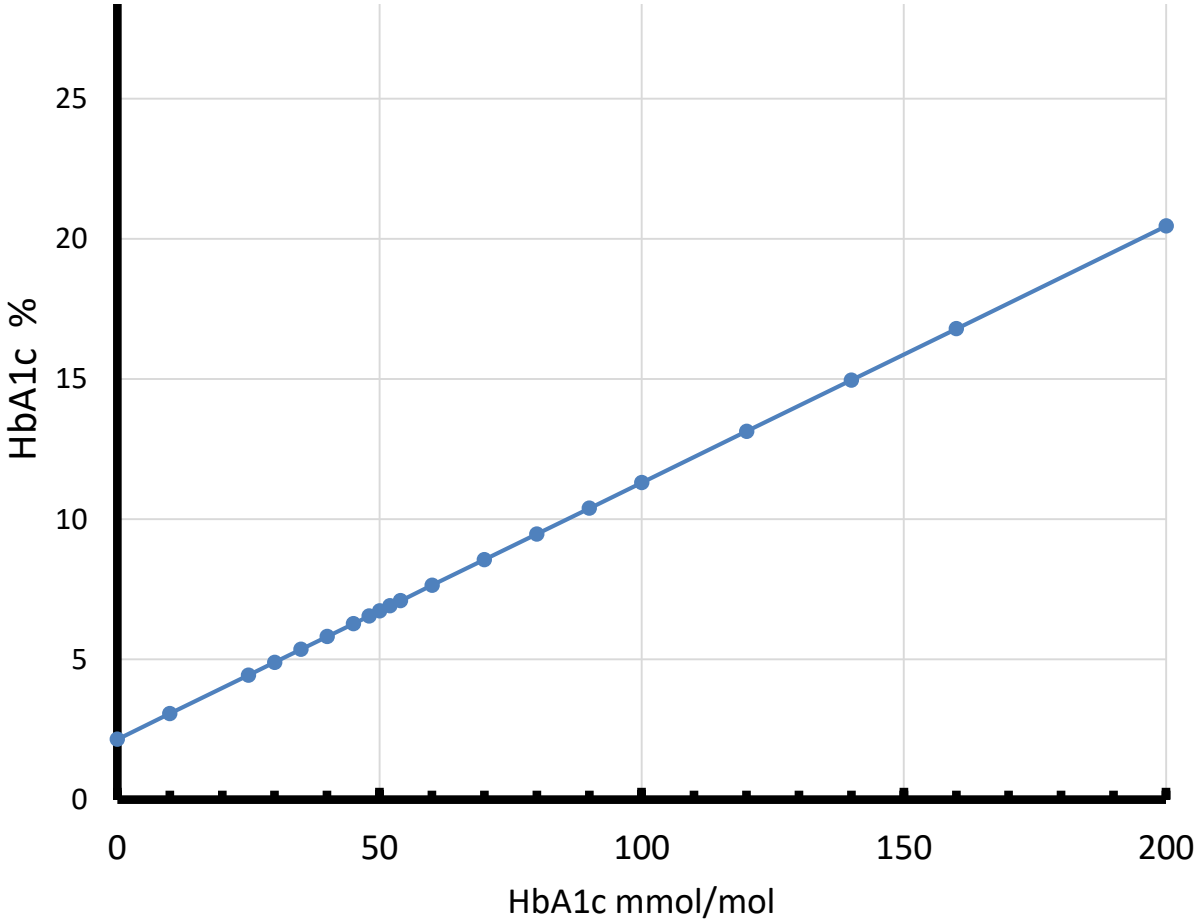
As the numerical values of the measurement results will change with the new measurement procedure, it is timely to reconsider the current terms for the property in terms of system, component, and kind-of-property, as well as the expression of the measurement result.

Current terms and measurement unit

The IFCC-IUPAC database on Nomenclature, Properties and Units (NPU) has up to now contained one

Relasjon mmol/mol og %

NGSP/ DCCT (%) = 0.0915 x IFCC (mmol/mol) + 2.15



«%» er på en differanseskala, SD kan kalkuleres,
men CV kan i prinsipp ikke kalkuleres

«mmol/mol» er på en ratio skala og SD og CV kan kalkuleres

Hvis man kalkulerer CV, vil den alltid være lavere ved «%» enheter

Table 1. CVa, CVwp, and CVbp of Hb A_{1c} in healthy individuals.[a]

	Grand mean, %	Total CV, %	CVa, %	CVwp, %	CVbp, %
Ultra[2]					
mmol/mol	34.2 (33.8–34.6)	7.6 (5.9–11.0)	1.3 (1.2–1.5)	0.8 (0.4–1.2)[b]	7.4 (5.6–10.9)
%	5.28 (5.24–5.32)	4.5 (3.5–6.5)	0.8 (0.7–0.9)	0.5 (0.3–0.7)[c]	4.4 (3.3–6.4)
Premier					
mmol/mol	32.5 (32.1–32.9)	7.6 (5.9–11.0)	0.7 (0.6–0.8)	1.3 (1.1–1.6)	7.5 (5.7–10.9)
%	5.13 (5.09–5.16)	4.5 (3.5–6.5)	0.4 (0.4–0.5)	0.8 (0.6–0.9)	4.3 (3.3–6.3)
Tosoh G8					
mmol/mol	33.4 (32.9–33.8)	8.2 (6.3–11.9)	0.7 (0.6–0.8)	1.7 (1.4–2.0)[b]	8.0 (6.1–11.7)
%	5.20 (5.17–5.24)	4.8 (3.7–7.0)	0.4 (0.4–0.5)	1.0 (0.8–1.2)[c]	4.7 (3.6–6.9)
Tina-quant					
mmol/mol	32.6 (32.3–33.0)	7.1 (5.6–10.1)	1.9 (1.7–2.2)	1.4 (0.9–1.8)	6.7 (5.1–9.8)
%	5.14 (5.10–5.17)	4.1 (3.2–5.9)	1.1 (1.0–1.3)	0.8 (0.5–1.1)	3.9 (2.9–5.7)

[a] Data are SI units (mmol/mol) and DCCT units (%) (95% CI).
[b] and [c] are significantly different from each other.

Lenters-Westra E, Røraas T, Schindhelm RK, Slingerland RJ, Sandberg S. Biological variation of hemoglobin a1c: consequences for diagnosing diabetes mellitus. Clin Chem. 2014;60:1570–2.

Omregningstabell fra Hdirs kortversjon av retningslinjene for diagnostikk og behandling av diabetes.

HbA1c mmol/mol	HbA1c %	
40	5,8	
45	6,3	
48	6,5	*diagnostisk grense*
49	6,6	
50	6,7	
51	6,8	
52	6,9	
53	7,0	*behandlingsmål*
54	7,1	
55	7,2	
56	7,3	
57	7,4	
58	7,5	
60	7,6	
61	7,7	
62	7,8	
63	7,9	
64	8,0	
65	8,1	
66	8,2	
67	8,3	
68	8,4	
69	8,5	
70	8,6	
75	9,0	
80	9,5	
85	9,9	
90	10,4	
95	10,8	
100	11,3	
105	11,8	
110	12,2	
115	12,7	
120	13,1	
125	13,6	
130	14,0	
135	14,5	

Omlegging av resultatrapportering av HbA1C

Fra den 30. september 2018 gis svarene ut med enheten mmol/mol

- Det krever informasjon til rekvirenter, laboratorier, legekontorer, diagnostikaleverandører og brukere
  - Helsedirektoratet, NOKLUS, Diabetesforbundet

- Det må brukes en egen NPU-kode for HbA1c rapportert som mmol/mol
  - NPU27300

Noklus gruppe for tema «diabetes» 2018/19

Lutz Schwettmann (leder)

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Gunn Berit Berge Kristensen

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Mathea Kvernhaugen (medisinstudent)

Åslaug Helvig (medisinstudent)

All CVs calculated in DCCT units were much lower compared with CVs calculated in SI units (Ta- ble 1) owing to the lower specificity of the NGSP PRMP. The master equation for converting SI units to DCCT units is: DCCT (0.0915 * IFCC) 2.15, where the positive *y*-intercept value reflects the non-specificity of the NGSP PRMP method. When Hb A1c measured with the IFCC PRMP is zero, the NGSP PRMP method still measures “something” (low specific- ity), and this nonspecificity is added to the results, making the re- sults in DCCT units higher. Because the SD will be the same in the 2 situations, the CV will be lower when calculated in DCCT units. The NGSP PRMP measures Hb A1c on the interval scale because of the positive *y*-intercept, whereas the IFCC PRMP measures on the ratio

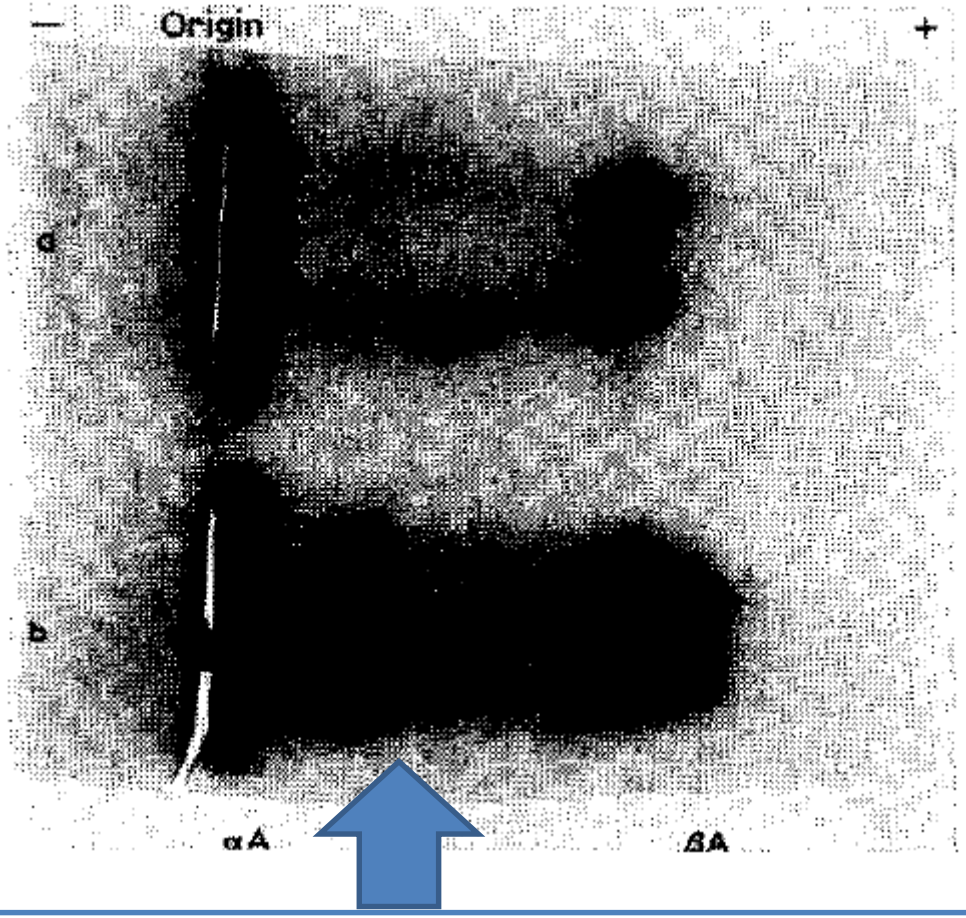
Lenters-Westra E, Røraas T, Schindhelm RK, Slingerland RJ, Sandberg S. Biological variation of hemoglobin a1c: consequences for diagnosing diabetes mellitus. Clin Chem. 2014;60:1570–2.

HISTORIEN
BAK RESULTATENHETENE

Elektroforese hemoglobin

Kontroll

Diabetes



Sammenliknet med kontroller har pasienter med diabetes mer av en Hb-form som fikk betegnelsen HbA1c

SAMUEL RAHBAR*

Clin. Chim. Acta, 22 (1968) 296–298

Clinical Chemistry 50:1
166–174 (2004)

Endocrinology and Metabolism

IFCC Reference System for Measurement of Hemoglobin A_{1c} in Human Blood and the National Standardization Schemes in the United States, Japan, and Sweden: A Method-Comparison Study

Wieland Hoelzel,[1] Cas Weykamp,[2] Jan-Olof Jeppsson,[3] Kor Miedema,[4*] John R. Barr,[5] Ian Goodall,[6] Tadao Hoshino,[7] W. Garry John,[8] Uwe Kobold,[1] Randie Little,[9] Andrea Mosca,[10] Pierluigi Mauri,[11] Rita Paroni,[12] Fransiscus Susanto,[13] Izumu Takei,[14] Linda Thienpont,[15] Masao Umemoto,[16] and Hsiao-Mei Wiedmeyer,[9] on behalf of the IFCC Working Group on HbA_{1c} Standardization

IFCC = international federation of clinical chemistry

Sammenheng mellom ulike analysemetoder: “Master equations”

- IFCC-referansesystem (mmol/mol)
- National Glycohemoglobin Standardization Program (NGSP) (USA)
  - NGSP (%) = 0,09148*IFCC + 2,152
- Mono-S referansesystem (Sverige)
  - Mono-S (%) = 0,09890*IFCC + 1,724
- Japan Diabetes Society Calibrators (JDS)
  - JDS (%) = 0,09274*IFCC + 0,884

http://www.ifcchba1c.net/IFCC_08.asp

Anbefalt term og måleenhet for HbA1c

- "IFCC Committee on Nomenclature, Properties and Units" og "IUPAC Subcommittee on Nomenclature, Properties and Units"
  - Substansfraksjonen av valyl-1-fruktosylerte hemoglobin ß-kjeder blant alle hemoglobin ß-kjeder kan måles spesifikt ved hjelp av IFCCs referansemetoder
  - Substansfraksjonen er metrologisk sporbar til enheten ''millimol per mol''.

Nordin og Dybkær. Clin Chem Lab Med. 2007;45:1081-2

Ulike instrumenter, ulike kalibreringer, ulike HbA1c-svar

- NGSP
  - Standardisert med tanke på DCCT-studien (1993)
    - ”DCCT-enheter”
    - Gir litt høyere verdier enn JDS og Mono S
- JDS
  - Kalibratorer av frosne hemolysater (1995)
- Mono S
  - HPLC-basert kalibrering (Mono S-kolonne) (1998)