SCIREA Journal of Clinical Medicine

http://www.scirea.org/journal/CM

October 6, 2019

Volume 4, Issue 6, December 2019

Hemoglobin A1c units, diagnostic limits and quality aspects updated.

Penttilä Ilkka[1], Penttilä Karri[2], Ranta Päivi[3], Törrönen Jukka[1], Savonen Kai[1]

[1]Kuopio Research Institute of Exercise Medicine, 70100 Kuopio, Finland

[2]Finnish Medicines Agency FIMEA, 70210 Kuopio, Finland

[3]Labquality Ltd., 00530 Helsinki, Finland

Corresponding Author:

Ilkka Penttilä, MD, PhD, Professor, Kuopio Research Institute of Exercise Medicine, 70100 Kuopio, Finland, ilkka.penttila@uef.fi

Short Title: Units and diagnostic limits of HbA1c in diabetes

Keywords: diabetes, HbA1c, IFCC recommendation, quality aspects, target limits

Words: Text 2338, abstract 195, references 28, title page, conflict of interest, abbreviations, acknowledgements, figures 1, tables 3

Abstract

In this report the use of the units, diagnostic limits and the quality aspects of hemoglobin A1c (HbA1c) were studied in worldwide clinical laboratory practice. In addition, the quality aspects were calculated for the target values from the surveys of Labquality Ltd. The use of HbA1c units and the diagnostic limits for diabetes were examined using e-mail and mail inquiries to 37 or 51 societies of laboratory medicine (mainly clinical chemistry) from 2009 to 2019. The parametric statistical programs of Labquality Ltd. and commercial programs of SPSS® 13.0 and MS Excel 2013 (Microsoft® Co., Cambridge, MA, USA) were used.

The IFCC system for HbA1c as mmol/mol unit slowly but constantly gaining acceptance in Europe, but remains quite rare outside Europe whereas the DCCT/NGSP system as a per cent unit was reduced. The mean round values of Labquality Ltd. and the corresponding values of the European Reference Laboratory for Glycohemoglobin (ERLGH) were calculated for the target values with ±6% intervals for the per cent results and ±8% intervals for the mmol/mol results. To avoid confusion, the overall use of mmol/mol unit only for HbA1c by the IFCC system could be the best one in the future.

Introduction

In the 1960s, measurement of the hemoglobin A1c fraction (HbA1c) by qualitative or quantitative assays began [1,2,3]. In the seventies Trivelli & al. [4] published the first genuinely quantitative assay for HbA1c showing that more carbohydrates are bound to the HbA1c fraction in diabetics than in non-diabetics. Since then numerous methods have been developed for HbA1c measurements [1,2,4-7] which caused a markedly high variation between laboratories and countries. This was clearly shown by Weyksmp & al. (5) with their quality control round for HbA1c of 111 laboratories and 21 different methods, that the

originally high variation between the methods and the laboratories was substantially corrected when using a third control sample for a new calculation of the results.

However, in the United States and Canada from the 1970s there it was shown that the results of HbA1c analyses varied extensively between methods and laboratories. As a result, working groups (WG) of the Diabetes Control and Complications Trial (DCCT) were set up; these were originally incorporated in a multicentre, randomised clinical trial designed to compare treatments of insulin-dependent diabetes mellitus in the National Glycohemoglobin Standardisation Program (NGSP). This DCCT/NGSP program was subsequently expanded to standardise the HbA1c assays using the liquid chromatography as the DCCT/NGSP reference [7].

In the 1990s, the International Federation of Clinical Chemistry (IFCC) organised working groups to achieve standardisation of all types of assays for HbA1c. For these the reference standards [8] and a standardised method [9] were developed for international use. Also, the reference system for the international standardization of HbA1c measurements in the form of a reference laboratory network was organised [10]. These recommendations were developed for the international use proposed by IFCC [11].

In addition, the American Diabetes Association (ADA) announced in 2010 the possibility to select a specific fixed value for the diagnosis of DM, namely an HbA1c value of 6.5% (12). This proposal involved the assumption that when using a fixed limit of HbA1c for diagnostic purposes, the methods used must be highly accurate and precise to ensure proper clinical practice [13].

For the present paper the queries were updated to the societies of laboratory medicine about the worldwide use of the units and diagnostic limits for HbA1c (1,14). The queries concerning HbA1c units, the diagnostic cut off limits and the precision and accuracy requirement for the HbA1c assays were calculated and

presented. The results of the quality control rounds from the Finnish quality control organisation Labquality Ltd. [15] and the values of the European Reference Laboratory for Glycohemoglobin (ERLGH) were utilised for the mean values of the rounds [15-17].

Methods

Questionnaires concerning the use of HbA1c units from 2009 to 2019 (1,14,16,17) and later, on the utilisation from 2014 of the fixed diagnostic limit of ADA (12) for diabetes were sent mainly by e-mail but also by mail to 37 or 51 societies of laboratory medicine (mainly clinical chemistry) in Europe as well as some outside of Europe (Table 1). The e-mail and mail addresses for the societies were taken from the latest list of the IFCC on July 2019.

The annual HbA1c rounds of Labquality Ltd. The The annual HbA1c rounds of Labquality Ltd. (15) were started in 1987 by performing from three to six times per year using two native EDTA blood samples from two volunteers [1,15], one close to the level of HbA1c at the diagnostic level recommended by the ADA [12] as 6.5 % (48 mmol/mol). Parallel control samples from 1997 were sent to ERLGH) in the Netherlands (17) for comparison with the values of Labquality Ltd. (15).

From the rounds of Labquality Ltd. only the results from the native EDTA blood samples were used for the calculations. The EDTA samples for control (QC) assays were drawn from two volunteers on the morning of the sample collection, mixed, divided into 0.5 ml portions and sent to the office of Labquality Ltd. by airmail. From the office, the samples were then sent to participants during the same day. The HbA1c reference values of ERLGH were compared to the corresponding values of Labquality Ltd. and informed to the participants. Since

1994, the results only from three surveys were excluded for the calculations due to the sample transfer problems.

In the 1990s, two-thirds of the participants in the HbA1c rounds of Labquality Ltd. were Finnish, but in late 2000s the percentage was down to about one-third. In the same time, liquid chromatography as the principal method (60 %) was reduced to one-third of the methods the most common one now belonging to immunochemistry.

2.1 Statistics

For the calculations of the mean values, standard deviations (SD), and the coefficients of variation (CV%) of the replies the parametric statistical the methods of Labquality Ltd. [15] were used, the SPSS® 13.0 progrem of SPSS (SPSS Inc., Chicago, IL, USA) and the MS Excel 2013 program (Microsoft® Co., Cambridge, MA, USA) and also the Scientific Tables of Documenta Geigy (6th Edition 1962, J.A.Geigy, Basel, Switzerland). The mean ± 2*SD values thus, containing 95.6% of the laboratories participating in every round were used for calculations and the reports.

Results

In Table 1 a summary is pr4sented of the replies to the questionnaires from the societies up to August 15, 2019. Earlier report were presented in 2015 (1), 2017 (14) and 2019 (16). The use of the mmol/mol unit only ($r=0.836$, $p<0.05$) and the parallel units for HbA1c were slowly increased up to 2017 after which no change occurred ($r=0.962$, $p<0.001$). The use of the per cent unit only was correspondingly clearly decreased ($r=0.974$, $p<0.001$). Table 2 contains the detailed a summary of the replies of societies for the groups A to C while eight societies in the group D have not responded all.

During the period of the questionnaires, the units for HbA1c from the rounds of Labquality Ltd. [15] were studied for a comparison to the corresponding ERLGH values (1). As seen in Figure 1, the practice of mmol/mol users was significantly increased during the period from 2009 to 2019 with a corresponding decrease of per cent users (no. 49, $r=0.990$, $p<0.001$). It must be pointed out that in the surveys of Labquality LTD. [15] that most of the participants originate from Europe.

Before the calculation of the target values the quality aspects of the results for the HbA1c methods were studied as the coefficient of variation (CV%) from the replies as per cent and mmol/mol users using the results of Labquality LTD. [15], from 2010 to 2019 while the mmol/mol values for HbA1c cent were available. The mean CV% of the mmol/mol was reduced from 6.03 % in 2010 to 3.17±9.35 % in 2019 (no. 49, $r= 0.771$, $p<0.001$). On the other hand, the CV% of per cent values was decreased from 4.4 % to 2.33±0.06 %. Correlations of the mean HbA1c values of Labquality Ltd. [15] between the per cent values (no. 49, 3.36±0.91) and mmol/mol values (no. 49, 4.40±1.03) the from rounds was highly significant ($r=0.783$, $p<0.001$) corresponding earlier reports [18-20]. Thus, both units may equally be used to follow up on the quality of the methods, while being very close.

Table 3 shows the calculated target values for per cent and mmol/mol of Labquality Ltd. [15] for HbA1c as well of the corresponding values of ERLFG from the round 5/2018 as an example. The very close agreement and the correlation of the mean values of per cent and mmol/mol results were noted when calculated from the surveys of Labquality LDT. from 2010 to 2019 (no 49, $r=0.995$, $p<0.001$). The new target limits were calculated from the round values of the earlier rounds of Labquality Ltd. [15] and accepted as the mean ±6 % values for per cent and the mean ±8 % for mmol/mol values from January 2016.

The limits correspond well with the CV% values with the ERLGH as ±6% and ±8% from 2016 instead of earlier ±10 % limits for both units.

Discussion

The Finnish Society of Clinical Chemistry (FSCC) and the Finnish Societies for Diabetes Research and Treatment agreed in 2009 that, for the reports of HbA1c of Labquality Ltd. [15] in Finland, the mmol/mol values of HbA1c should also be added corresponding to the recommendation of the IFCC [10] from March 3 2010 [21]. Consequently, the reports for HbA1c were expressed in parallel units in per cent and mmol/mol. After five years of accumulating experience, the FSCC decided that parallel results had been used long enough and from January 1 2016 onwards only the mmol/mol unit for HbA1c was recommended [16].

Since 2009 multiple queries have been sent to European Societies of Laboratory Medicine and some other societies in and outside of Europe concerning the use of the old DCCT/NGSP per cent unit and the new mmol/mol for HbA1c recommended by IFCC (10). In 2011, the use of a fixed diagnostic limit of ADA [12] for HbA1c to diagnose diabetes was added in Finland in 2014 and then to the questionnaires [1,14,16].

The use of the mmol/mol system of IFCC only and the parallel reports in mmol/mol and per cent also are slowly and constantly increasing in Europe, but still

less common outside of Europe as seen in Table 1 [14,16]. Germany [22] was the first country that accepted the mmol/mol unit only for their HbA1c reports Table 2), followed then by other European countries**.** However, the use of the IFCC mmol/mol system has not universally accepted by non-European societies despite the IFCC proposal that the mmol/mol is the only logical unit for use in HbA1c assays [23].

Thus the decrease of CV% for per cent values nearly reached the lowest practical value below 3.0 % and of mmol/mol below 4.0 %, which can be reached in large quality control surveys such as in Labquality Ltd. The CV% results correspond well to the findings of Weykamp & al. (24) that the quality requirements for the HbA1c units are different.

In order to study the QC level of HbA1c analyses, the assay results obtained from the annual rounds of Labquality Ltd. [15] were examined by calculating the variation of the results as the CV% [1]. The mean round CV% of the rounds decreased in the last seven years from 6.1% to 3.17 % in terms of the mmol/mol results ($r = 0.702$, $p < 0.001$) and from 4.0 % to 2.33 % of the per cent results ($r = 0.388$, $p < 0.01$). The mean CV% for the per cent results decreased from 8.1% to 2.33 % from 1994 to 2019 ($r = 0.900$, $p < 0.001$). These findings for HbA1c are highly comparable to earlier publications in terms of the per cent results [18,20] and in terms of the mmol/mol results [2,19,25] for HbA1c corresponding well to the findings of Weykamp & al. [24].

The mean results from the rounds of Labquality Ltd. [15] were very close to the values of ERLGH (Table 3). For the target values, the mean round HbA1c values were selected while the mmol/mol and per cent values were almost identical with the corresponding ERGH values (Table 3). Thus each laboratory participating in surveys can chose the value they will use as their target value.

Correlations between the IFCC methods and the DCCT/NGSP methods were published by Hoelzel & al. [11], and the equations between the IFCC and DCCT methods were: HbA1c (mmol/mol) = 10.93 * HbA1c (%) – 23.50 and HbA1c (%) = 0.0915 * HbA(1c) (mmol/mol) + 2.15. These equations allow the results to be reliably estimated, as shown in the HbA1c rounds of Labquality Ltd. [15] compared to the results measured by ERLGH. This is highly important when considering the fixed HbA1c limit of the ADA [12] in diagnosing DM. The

reported limit of 6.5% corresponds to 48 mmol/mol in the IFCC system. The queries indicated that the most countries/societies recommend the use of either 6.5 % or 48.0 mmol/mol limits in the diagnosis of DM, and this practice is being more widespread over time (Table 2).

From the quality assurance results of Labquality LTD.

[15] the precision limits for HbA1c, the mean value ±6 % for per cent results and mean ±8 % for mmol/mol results correspond well to the limits published previously [18,19,22], which also are in line with the findings of Weykamp & al. [24] in that the quality requirements are different for the DCCT/NSGH and the IFCC systems. The decrease of CV% for per cent values reached the lowest possible value below 3.0 % and for the mmol/mol result below 4.0 % (16,25,26).

Recently, Lenters-Westra and English [26] in their article pointed out that the CV% of HbA1c by using NSGH methods should be below 2.0. Their material was based on the results from the reference laboratories (10) which kind of limit cannot be reached from the large quality control reports, such as Labquality Ltd. [15.], which correspond well to other recent findings [27,28].

Conclusions

The mmol/mol system, recommended by the IFCC for HbA1c with the new mmol/mol unit, as well as parallel reporting with both percentage and mmol/mol units are slowly gaining acceptance in Europe, but are rare outside Europe. The use of the diagnostic cut-off limit of the HbA1c value is still not fully established, although it is slowly increasing.

In each round either the mean value of the round of Labquality Ltd. [15] or the corresponding ERLGH value can equally well be utilised as the target value as they correspond significantly with each other.

The authors also hope that the use of mmol/mol unit for HbA1c of IFCC would gain worldwide acceptance to enable the comparison of results from different studies and to lessen confusion, where only one unit would then be used.

Abbreviations

DCCT, DM, EDTA**,** HbA1c, IFCC, NGSP

Acknowledgements

The authors cordially thank Mr. Tero Hongisto for the

collection of the EDTA blood samples for the rounds of Labquality Ltd. We cordially thank Labquality Ltd. [15] for the calculations and for placing the round results of HbA1c at our disposal. We also thank Iiris Rennicke in Apropos lingua for revising the English language.

Legends to the figures and tables

Figure 1.

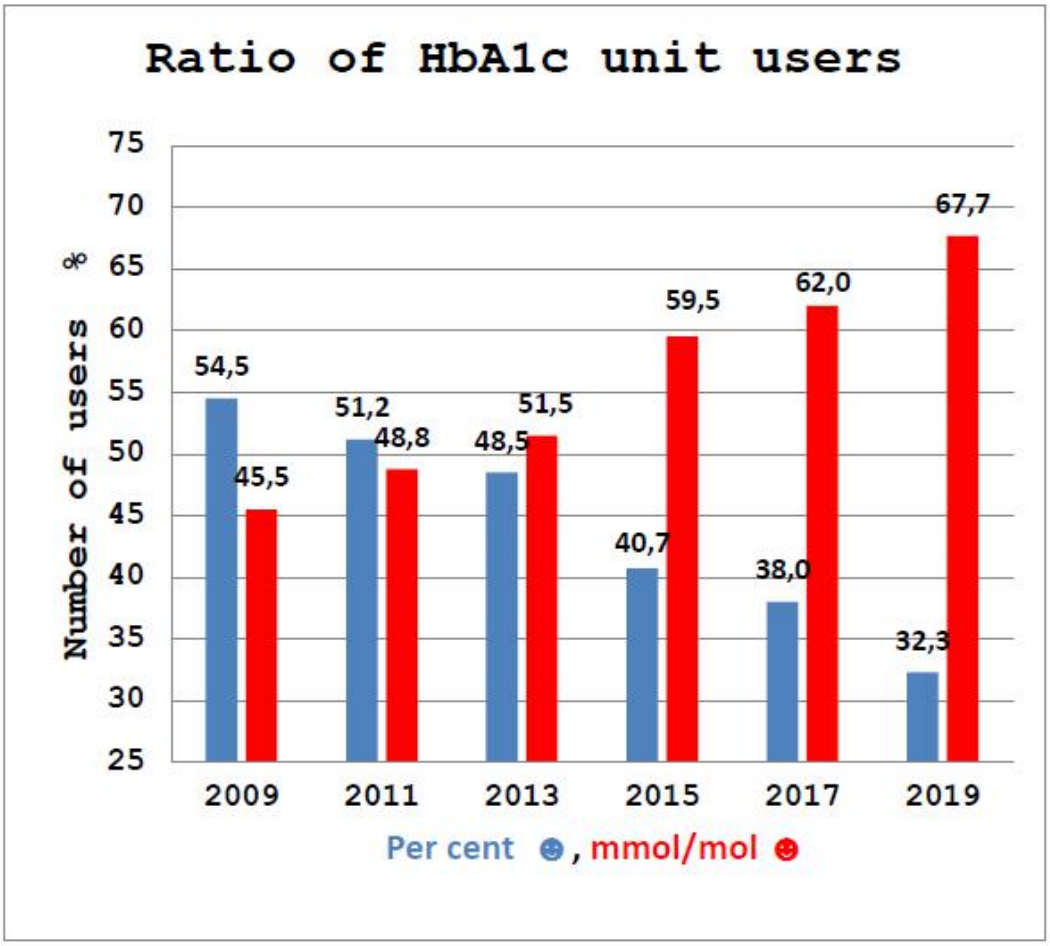

Figure 1. Relationship of the quality control values of the rounds of Labquality Ltd. and the parallel control values of the European Reference Laboratory for Glycohemoglobin as per cent results (mean 6.3%) and as mmol/mol results (mean 46.5 mmol/mol) from 2010 to 2019 ($r = 0.990$, $p < 0.001$).

Table 1.

Results of HbA1c questionnaires to August 15.2019						
Year	2009	2011	2014	2017	2019	2019 %
Questionnaires	37	37	51	51	51	100.0
Total replies	22	29	41	42	43	84.3
Per cent only	16	14	17	13	14	27.5
per cent & mmol/mol	4	9	11	15	15	29.4
mmol/mol only	(*)	6	13	14	14	27.5
No answer at all	15	8	10	9	8	15.7
Positive DM diagnosis			23	26	28	54.9

Table 1. Summary of the enquiries for HbA_{1c} from 2009 to 2019 by e-mail and/or mail. The enquires concerning the use of the units were sent to the societies of laboratory medicine (mainly clinical chemistry) in Europe and other societies outside of Europe. The summary of the replies was collected on August 15 2019.

*The first society that chose the mmol/mol unit was Germany starting the mmol/mol only replies at January 1, 2010.

Table 2.

Replies from 51 societies of laboratory medicine for HbA1c from 2009 to 2019					
Country	Abbr.	Per cent only	Per cent & mmol/mol	mmol/mol only	Dg limit %/mmol/mol
A Germany	HbA1c	Yes	01.01.2009	01.01.2010	Yes
Netherlands	HbA1c	Yes	2009	01.01.2011	Yes
Sweden	HbA1c	Yes	01.09.2010	01.01.2011	Yes
Gr Britain	HbA1c	Yes	01.06.2009	01.10.2011	Yes
Chech Republic	HbA1c	Yes	2010	01.01.2012	Yes
Italy	HbA1c	Yes	01.01.2011	01.10.2012	Yes
Denmark	HbA1c	Yes	01.08.2008	01.01.2013	Yes
Ireland	HbA1c	Yes	1.7.2010	16.01.2012	Yes
Hungary	HbA1c	X	1.4.2011	01.04.2013	Yes
Australia	HbA1c	Yes	July 2011	July 2013	Partly
New Zealand	HbA1c	Yes	July 2011	July 2013	Yes
Turkey	HbA1C	Yes	2012	2016	Yes
Finland	HbA1c	Yes	03.03.2010	01.01.2016	Yes
Norway	HbA1c	Yes	2018	01.09.2018	Yes
B Belgium	HbA1c	Yes	1.6.2011	In future	Yes
Chile	HbA1c	Yes	01.04.2011	No	Yes
Croatia	HbA1c	Yes	2012	No	Yes
Estonia	HbA1c	Yes	1.1.2012	No	Yes
France	HbA1c	Yes	2009	In future	No
Greece	HbA1c	Yes	2012	?	?
Iceland	HbA1c	Yes	01.01.2016	?	Yes
Israel	HbA1c	Yes	2010	?	?
Lithuania	HbA1c	Yes	15.04.2011	In future	?
Poland	HhA1c	Yes	2013	?	Yes
Serbia	HbA1c	Yes	01.09.2009	?	Yes
Slovenia	HbA1c	Yes	2011	?	?
Slovak Republic	HbA1c	Yes	13.6.2012	?	No
Spain	HbA1c	Yes	Yes (partly)	?	Yes
Switzerland	HbA1c	Yes	Yes	No	Yes
C Albania	HbA1c	Yes	No	No	Yes
Austria	HbA1c	Yes	?	?	?
Bosnia-Her.	HbA1c	Yes	?	?	?
Bulgaria	HbA1c	Yes	?	?	?
Latvia	HbA1c	Yes	?	?	?
Luxembourg	HbA1c	Yes	?	?	?
Portugal	HbA1c	Yes	?	?	?
Romania	HbA1c	Yes	?	?	?
Brazil	HbA1c	Yes	?	?	?
Canada	HbA1c	Yes	In future	?	Yes
Indonesia	HbA1c	Yes	No	No	Yes
Japan	HbA1c	Yes	In future	?	Yes
Korea	HbA1c	Yes	?	?	?
USA	HbA1c	Yes	?	?	Partly
D No replies at all from eigth societies in 15.8.2019, four from Europe. Ilkka Penttilä August 15 2019.					

Table 2. Summary of the replies to the questionnaires sent to the societies of laboratory medicine (mainly clinical chemistry) concerning the use of per cent and mmol/mol units in HbA1c analyses in daily reports and the acceptance of

the diagnostic limit of HbA1c as of 2019 in the diagnosis of diabetes. The whole summary of the replies was collected on August 15, 2019.

Table 3

HbA1c from the round 5/2018					
HbA1c in per cent unit					
Source	ERLGH	Labquality Ltd.			ERLGH
Value	Value	Mean±SD	Mean±2SD	Mean±6%	6.81±6%
No. 44	6.81	6.80±0.14	6.52-7.04	6.39-7.21	6.40-7.22
r		0.992			
HbA1c in mmol/mol unit					
Source	ERLGH	Labquality Ltd.			ERLGH
Value	Value	Mean±SD	Mean±2SD	Mean±8%	50.9±8%
No. 72	50.9	50.7±1.36	48.0-53.9	46.6-54.8	47.8-55.0
r		0.989			

Table 3. Calculation results of the target values for HbA1c from the mean values of Labquality Ltd. and the corresponding values of ERLGH from the round 5/2018. The correlation between the mean

valies of Labquality Ltd. and the value of ERLGH

was 0.990 for per cent results ($p<0.001$) and

0.989 for mmol/mol results ($p<0.001$).

References

[1] Penttilä I, Penttilä K, Holm P, Laitinen H, Rauramaa R. Hemoglobin A_{1c} reported in units and cutoffs in relation to international recommendations. Clin Chem Lab Med 2015;53:e277-e279.

[2] Holmquist WR, Schroeder WA. A new N-terminal blocking group involving a Schiff base in hemoglobin A1c. Biochemistry 1966;5:2489-2503.

[3] Rabhar S. An abnormal hemoglobin in red cells of diabetes. Clin Chim Acta. 1968;22:296-298.

[4] Trivelli LA, Ranney HM, Lai H-T. Hemoglobin components in patients with diabetes mellitus. New Engl J Med. 1971;284:353-357.

[5] Weykamp CW, Penders TJ, Muskiet FAJ, van der Silk W. Effect of calibration on dispersion of glycohemoglobin values determined from 111 laboratories using 21 methods. Clin Chem. 1994;40:138-144.

[6] Jensen ON, de Fine Olivarius N, Hyltoft Petersen P, Klitgaard NA, Blaabjerg O, Hørder M. Discrepancy in HbA_{1c} measurements performed at different local laboratories and selected central reference laboratory. Uppsala J Med Sci 1993;98:275-282.

[7] Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE; NGSP Steering Committee. The National Glycohemoglobin Standardization Program: A five-year progress report. Clin Chem. 2001;47:1985-1192.

[8] Finke A, Kobold U, Hoelzel W, Weykamp C, Miedema K, Jeppsson J-O. Preparation of a candidate primary reference material for the international

standardization of HbA_{1c} determinations. Clin Chem Lab Med. 1998;36:299-308.

[9] Jeppsson J-O, Kobold U, Barr J, Finke A, Hoelzel W, Hashino T, Miedema K, Mosca A, Mauri P, Paroni R, Thienpont L, Umemoto M, Weykamp C. Approved IFCC reference method for the measurement of HbA_{1c} in human blood. Clin Chem Lab Med. 2002;40:78-89.

[10] Hoelzel W, Miedema K. Development of a reference system for the international standardization of HbA1c/glycohemoglobin determinations. J Int Fed Clin Chem. 1996;9:62-67.

[11] Hoelzel W, Weykamp C, Jeppsson J-O, Miedema K, Barr JR**,** Goodali I, Hoshino T, John WG, Kobold U, Little R, Mosca A, Pierluigi M, Paroni R, Susanto F, Takei I, Tienpont L, Umemoto M, Wiedmeyer H-M on behalf of the IFCC Working Group on HbA_{1c} Standardization. IFCC reference system for measurement of HbA_{1c} in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem. 2004;50:166-174.

[12] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33(Suppl 1):S62-S69.

[13] Hanas R, John WG; International HbA1c Consensus Committee. 2013 Update on the worldwide standardization of the hemoglobin A_{1c} measurement. Pediatr Diabetes. 2014;15:e1-e2.

[14] Penttilä I, Penttilä K, Holm P, Laitinen H, Ranta P, Törrönen J, Rauramaa R. Methods, units and quality requirements for the analysis of haemoglobin A_{1c} in diabetes mellitus. World J Methdol. 2016;6:133-142.

[15] Labquality Ltd., Helsinki, Finland; www.labquality.fi.

[16] Penttilä I, Penttilä K, Laitinen H, Ranta P, Törrönen J, Rauramaa R. Hemoglobin A(1c) Reporting Units and Diagnostic Cut-Offs in Relation to International Recommendations. Int J Clin Exper Med Sci 2019; 5: 18-25.

[17] Weykamp C, Lenters-Westra E, van der Vuurst H, Slingerland R, Siebelder C, Visser-Dekkers W. Evaluation of the Menarini/ARKRAY ADAMS A_{1c} HA-8180V analyzer for HbA_{1c}. Clin Chem Lab Med. 2011;49:647-651.

[18] Little RR, Rohlfing CL, Sacks DB for the NGSP Committee. Status of hemoglobin A_{1c} measurement and goals for improvement: from chaos to order for improving diabetes care. Clin Chem. 2011;57:205-214.

[19] Lindblad B, Nordin G. External quality assessment of HbA_{1c} and kits effect on comparison between Swedish pediatric diabetes clinics. Experiences from the Swedish pediatric diabetes quality register (Swediabkids) and Equalis. Clin Chem Lab Med. 2013;51:2045-2052.

[20] Lenters-Westra E, Boraas T, Schindhelm RK, Slingerland RJ, Sandberg S. Biological variation of hemoglobin A_{1c}: consequences for diagnosis of diabetes mellitus. Clin Chem. 2014;60:1570-1572.

[21] Finnish Society of Clinical Chemistry. ww.skky.fi

[22] DGKL (Deutsche Vereinte Gesellschaft für Klinische Chemie und Laboratoriums-medizin). Stellungnahme der Deutschen Diabetes Gesellschaft, diabetes und des Kompetenznetzes Diabetes mellitus zur Verwendung des HbA1c-Wertes als Biomarker zur Diabetesdiagnose; www.diabetesde.org/

[23] Nordin G, Dybkaer R. Recommendation for term and measurement unit for "HbA_{1c}". Clin Chem Lab Med. 2007;45:1081-1082.

[24] Weykamp CW, Mosca A, Gillery P, Panteghini M. The analytical goals for hemoglobin A_{1c} measurement in IFCC units and in National Glycohemoglobin Standardization Program units are different. Clin Chem. 2011;57:1204-1206.

[25] Nielsen AA, Petersen PH, Green A, Christensen C, Christensen H, Brandslund I. Changing from glucose to HbA_{1c} for diabetes diagnosis: predictive values of one test and importance of analytical bias and imprecision. Clin Chem Lab Med. 2014;52:1069-1077.

[26] Lenters-Westra E, English E. Evaluating new HbA1c methods for adoption by the IFCC and NGSP reference networks using international quality targets. Clin Chem Lab Med. 2017;55:1426-1434.

[27] EurA1c Group. 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. Clin Chem 2018;64:1183-1192

[28] Little RR, Rohlfing C, Sacks DB. The National Glycohemoglobin Standardization Program: Over 20 Years of Improving Hemoglobin A_{1c} Measurement. Clin Chem 2019;65:839-848.