Brief Communication
Clinical Chemistry

Ann Lab Med 2015;35:352-355
http://dx.doi.org/10.3343/alm.2015.35.3.352
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Report on HbA_{1c} Proficiency Testing in Asia in 2012

Masao Umemoto, Ph.D.[1], Tadao Hoshino, M.D.[2],Tetsuo Miyashita, Ph.D.[3], Wataru Tani, Ph.D.[4], and Katsuhiko Kuwa, Ph.D.[5]

Reference Material Institute for Clinical Chemistry Standards[1], Kanagawa; Reference Laboratory Institute of Biopathological Medicine[2], Kanagawa; Nihon University Itabashi Hospital[3], Tokyo; Reference Material Institute for Clinical Chemistry Standards[4], Kanagawa; National Metrology Institute of Japan[5], Ibaraki, Japan

In 2010, the Japan Diabetes Society decided to introduce the National Glycohemoglobin Standardization Program (NGSP) values into clinical practice. Accordingly, NGSP Certification of Japanese manufacturers of HbA_{1c}-related diagnostic reagents and instruments was initiated in February, 2012, through an NGSP network laboratory, the Asian Secondary Reference Laboratory (ASRL) #1. Traceability to the NGSP reference system can be endorsed by manufacturer certification, as well as by the College of American Pathologists (CAP) survey. Nevertheless, only a few manufacturers participate in the CAP survey in Japan. Thus, proficiency testing (PT) was proposed and executed by ASRL #1. Single-donor whole-blood samples were used for the PT. The participated measurement systems were NGSP certified. Twenty-two laboratories obtained certification through ASRL #1; 2 through the Secondary Reference Laboratory (SRL) #8; and 9 through the SRL #9. The combination plots of the bias data in this PT and in the NGSP certification performed in March and May in 2012 were consistent with each other: mean NGSP values at each level agreed well with the target value. In conclusion, PT using whole blood is useful in endorsing NGSP certification.

Key Words: HbA_{1c}, National Glycohemoglobin Standardization Program, Proficiency testing, Asian Secondary Reference Laboratory

Received: June 19, 2014
Revision received: October 22, 2014
Accepted: February 7, 2015

Corresponding author: Katsuhiko Kuwa
National Metrology Institute of Japan,
503 Surpass Tsukuba Kenkyugakuen,
5-11-1, Kenkyugakuen,
Tsukuba Ibaraki 305-0817, Japan
Tel: +81-29-852-1654
Fax: +81-29-852-1654
E-mail: kkuwa@gol.com

The Japan Diabetes Society (JDS) decided to use National Glycohemoglobin Standardization Program (NGSP) values, as well as JDS HbA_{1c} values, in clinical practice for international clinical harmonization of HbA_{1c} [1]. Accordingly, NGSP certification of Japanese manufacturers of diagnostic reagents and instruments related to HbA_{1c} was initiated in February, 2012, through NGSP Network Laboratory, the Asian Secondary Reference Laboratory (ASRL) #1 [2]. As a result, 21 routine methods were certified in 2012 and 42 in 2013. Moreover, traceability to the NGSP reference system can now be endorsed by both manufacturer certification and the College of American Pathologists (CAP) survey. The CAP survey is useful for monitoring between-certification proficiency of certified methods. However, only a few manufacturers participate in the CAP survey in Japan. Thus, proficiency testing (PT) similar to the CAP survey targeting NGSP-certified manufacturers and laboratories in Asia has been proposed and executed by ASRL #1 in collaboration with the Japan Reference Measurement Institute (JRMI). The committee for the PT was organized by the Reference Material Institute for Clinical Chemistry Standards (ReCCS) in collaboration with JRMI.

Five PT samples were prepared: PT samples 1, 2, 4, and 5 were single-donor whole-blood aliquots, and PT sample 3 was a mixture of PT samples 1 and 4, with plasma replaced by physiological saline solution. PT samples were drawn from two Japanese individuals in Japan and two diabetes patients in USA with informed consent and with the approval of the Ethics Committee of ReCCS. PT sample 3 for A_{1c} GEAR in Table 1 shows abnormally high HbA_{1c} values because only whole blood can be applied to A_{1c} GEAR; therefore, in the mean value obtained by immunoassay, the A_{1c} GEAR result of this sample was excluded in Table 2.

ReCCS prepared and shipped the test samples. PT samples were stored in a refrigerator (2-8°C) until shipment, and at each laboratory, they were removed from the container immediately

Table 1. Participating laboratories and supplemental data

HbA1c unit : NGSP%

Method	Participating laboratory	Measurement system	PT sample				
			1	2	3	4	5
Immunoassay	Kyowa Medex Co., Ltd.	Determiner HbA1c/DM-JACK	4.755	5.485	7.895	12.530	12.560
Immunoassay	Kyowa Medex Co., Ltd.	Determiner HbA1c/JCA-BM9130	4.805	5.500	7.940	12.565	12.625
Immunoassay	Kyowa Medex Co., Ltd.	Determiner L HbA1c/DM-JACK	4.795	5.520	8.005	12.540	12.625
Immunoassay	Kyowa Medex Co., Ltd.	Determiner L HbA1/JCA-BM9130	4.795	5.480	7.985	12.485	12.570
Immunoassay	TFB, INC.	Rapidia Auto HbA1c-L/Hitachi 7170s	4.570	5.400	7.660	12.200	12.420
Immunoassay	ROHM Co., Ltd.	Banalyst Ace HbA1c/Banalyst Ace	4.700	5.500	7.900	High*	High*
Immunoassay	ROHM Co., Ltd.	Spotchem Banalyst HbA1c/ Spotchem Banalyst SI-3610	4.800	5.600	8.000	High*	High*
Immunoassay	Wako Pure Chemical Industries, Ltd.	Autokit HbA1c/Hitachi 7170S	4.790	5.440	8.075	12.585	12.535
Immunoassay	SAKAE Corporation	A1c GEAR	4.650	5.300	8.650†	12.050	12.500
Immunoassay	Kotobiken Medical Laboratories, Inc. Biken Central Laboratory Tsukuba	Determiner L HbA1c/JCA-BM9130	4.830	5.360	7.660	12.205	11.965
Immunoassay	Siemens Healthcare Diagnostics	DCA2000+ / DCA Vantage	4.950	5.600	8.150	13.050	13.300
Immunoassay	Siemens Healthcare Diagnostics	Dimension RxL MAX	5.400	6.065	8.440	13.190	13.180
Immunoassay	Ortho Clinical Diagnostics	Vitros d%A1c/Vitros 5,1FS	4.970	5.475	8.125	12.735	12.780
Immunoassay	Ortho Clinical Diagnostics	Vitros d%A1c/Vitros 5600	4.980	5.475	8.110	12.605	12.585
Immunoassay	Roche Diagnostics	TQ HbA1c Gen.3/cobas c501	4.650	5.475	8.275	12.495	12.590
Immunoassay	Roche Diagnostics	TQ HbA1c Gen.2/cobas c501	5.095	5.645	8.135	12.280	12.335
Immunoassay	Boditech Med. Inc	i-ChromaTM	4.450	5.600	8.050	12.150	12.450
Enzymatic assay	Kyowa Medex Co., Ltd.	MetaboLead HbA1c/JCA-BM9130	4.850	5.440	7.910	12.880	13.065
Enzymatic assay	SEKISUI MEDICAL CO., LTD.	Norudia N HbA1c/Hitachi 7170S	4.855	5.715	7.690	12.730	13.420
Enzymatic assay	Hitachi Chemical Co., Ltd.	Seratestum A1C	4.780	5.465	8.085	12.555	12.855
Enzymatic assay	NIHON KOHDEN CORPORATION	BM Test HbA1c/JCA-BM6010	4.870	5.445	8.140	13.205	13.315
Ion-exchange HPLC	Kotobiken Medical Laboratories, Inc. Niigata Laboratory	HLC-723 G8	4.740	5.460	7.920	12.690	12.840
Ion-exchange HPLC	SRL, Inc.	ADAMS A1c HA-8160	4.900	5.650	8.200	12.800	13.100
Ion-exchange HPLC	Bio-Rad Laboratories	Variant II Turbo	4.635	5.535	7.875	12.530	12.675
Ion-exchange HPLC	Bio-Rad Laboratories	D-10	4.800	5.600	7.950	12.500	12.600
Ion-exchange HPLC	Tosoh Corporation	HLC-723 G7	4.710	5.510	7.975	12.735	12.885
Ion-exchange HPLC	Tosoh Corporation	HLC-723 G8	4.680	5.500	7.965	12.805	12.865
Ion-exchange HPLC	Tosoh Corporation	HLC-723 G9	4.700	5.525	7.995	12.855	12.910
Ion-exchange HPLC	Tosoh Corporation	HLC-723 GX	4.695	5.495	7.980	12.835	12.890
Ion-exchange HPLC	Korea Association of Health Promotion	HLC-723 G8	4.740	5.585	8.100	13.035	13.120
Ion-exchange HPLC	Seoul National University Bundang Hospital	Variant II Turbo	4.600	5.600	8.050	13.100	13.400
Ion-exchange HPLC	NEODIN MEDICAL INSTITUTE	HLC-723 G8	4.900	5.750	8.250	13.150	13.250
Ion-exchange HPLC	Chung-Ang University Hospital	Variant II Turbo	4.450	5.300	7.650	12.500	12.600

*out of measurement range; †abnormally high values (whole blood only can be applied) for sample 3 (mixture of samples 1 and 4, replacing the plasma with physiological saline solution).
Abbreviations: NGSP, National Glycohemoglobin Standardization Program; PT, proficiency testing; ASRL, Asian Secondary Reference Laboratory; ReCCS, Reference Material Institure for Clinical Chemistry Standards.

Table 2. Comparison of three methods: immunoassay, enzymatic assay, and HPLC

HbA_{1c} unit: NGSP% for target value, Mean and SD

Sample	1	2	3	4	5
Target value	4.863	5.643	7.997	12.678	12.779
Method	Immunoassay (17 measurement systems)				
Mean	4.823	5.525	8.025	12.511	12.601
SD	0.217	0.165	0.199	0.317	0.317
CV (%)	4.51	2.99	2.47	2.53	2.51
Method	Enzymatic assay (4 measurement systems)				
Mean	4.855	5.552	7.997	12.843	13.164
SD	0.051	0.140	0.198	0.239	0.220
CV (%)	1.05	2.53	2.48	1.86	1.67
Method	HPLC (12 measurement systems)				
Mean	4.713	5.543	7.993	12.795	12.928
SD	0.124	0.110	0.155	0.222	0.250
CV (%)	2.63	1.99	1.94	1.73	1.93

Abbreviations: NGSP, National Glycohemoglobin Standardization Program.

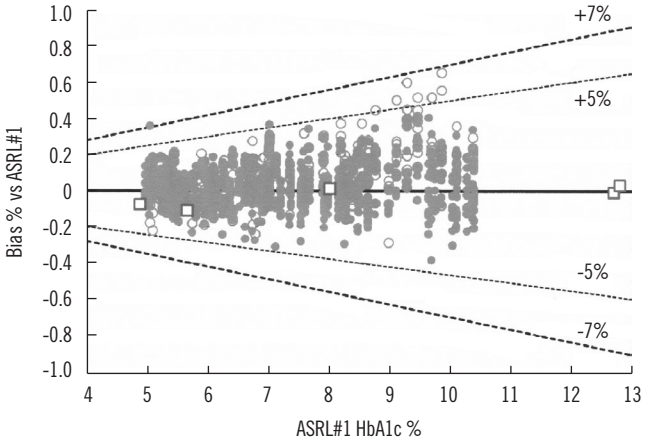

Fig. 1. Observed HbA_{1c} values of each participating laboratory compared to the NGSP/ASRL target (dashed line) in 2012 based on ASRL PT data. Closed circles show within ±5% (dotted line) of relative bias. Open circles show within ±7% (dashed line) of relative bias. Open squares show biases of all manufacturers versus ASRL target PT samples.

Abbreviations: NGSP, National Glycohemoglobin Standardization Program; ASRL, Asian Secondary Reference Laboratory; PT, proficiency testing.

on receipt and then stored in a refrigerator (2-8°C) until use. Analyses were completed within two days of receipt when less than 14 days passed after each sample collection.

The participated measurement systems were NGSP certified (according to manufacturer's methods and laboratory certification) by ASRL #1, SRL #8, and SRL #9. Each PT sample was measured in duplicate. Measured HbA_{1c} values were reported to 2 decimal places. Mean values (calculated to 3 decimal places) of the duplicate values for each PT sample were reported as final values, which were compared with target values determined by ASRL #1. The obtained values were consistent with those of SRL #8 and SRL #9. An overall test of coincidence by 2 least squares linear regression lines was performed using Microsoft Office Excel 2007.

A total of 33 laboratories (29 Japanese and four overseas laboratories) participated in the PT. Among these facilities, 22 were certified by NGSP through ASRL #1, two through SRL #8, and nine through SRL #9. Furthermore, 17 participating laboratories used immunoassay, four used enzymatic assay, and 12 used HPLC. PT samples 4 and 5 yielded HbA_{1c} values over 12 NGSP %, which exceeded measurement ranges for some measurement instruments; therefore, these values were excluded for those systems. Target values of PT samples 1, 2, 3, 4, and 5 were determined by ASRL #1 to be 4.86 NGSP%, 5.64 NGSP%, 8.00 NGSP%, 12.68 NGSP%, and 12.78 NGSP%, respectively. The comparison of values as measured by instruments and the NGSP/ASRL target values are shown in Table1.

The regression line comparing the relationship between total mean values and target values was Y (the total mean values) = 1.013×(the target value)+0.141. That is, the total mean values were higher than the target values. Furthermore, the values of CV of PT samples 1 through 5 were 3.72%, 2.54%, 2.23%, 2.41%, and 2.71%, respectively. PT sample 3 (containing red cells and saline) did not show any difference compared with other hemolyzed blood samples. CV values were 2.51-4.51% by immunoassay, 1.05-2.53% by enzymatic assay, and 1.73-2.63% by HPLC (Table 2).

Compatibility with JDS criteria (less than or equal to a relative bias of ±5.0% by mean of duplicate measurement) was checked by comparing the measured values of test samples 1 through 3 for the certification of 5% to10.0% HbA_{1c}. The results indicate that 26 out of 28 methods in test sample 1, 26 out of 28 in test sample 2, and 26 out of 27 in test sample 3 were compatible with JDS criteria [1]. Fig. 1 shows combination plots of bias data in this study and bias data from NGSP certification through ASRL #1 conducted during March and May, 2012. Bias plots of mean values versus target values of PT samples in this report are also shown for comparison, and they are in good agreement with each other.

The determined target values using the Central Primary Reference Laboratory reference panels (100 samples) correspond with measured values obtained by SRL #3 and SRL #9. In con-

http://dx.doi.org/10.3343/alm.2015.35.3.352

clusion, the PT is useful to monitor NGSP-certified methods. Mean values at each level correspond well with the target value, including point-of-care testing.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interests relevant to this article were reported.

Acknowledgments

We are grateful to Dr. R. Little, University of Missouri School of Medicine, for giving us the data of NGSP network Laboratory Monitoring for the measurement of HbA_{1c} PT samples by the NGSP Laboratory Network.

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