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COMMENTARY

International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values

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In 1999, the Japan Diabetes Society (JDS) launched the previous version of the diagnostic criteria of diabetes mellitus, in which JDS took initiative in adopting glycated haemoglobin (HbA1c) as an adjunct to the diagnosis of diabetes. In contrast, in 2009 the International Expert Committee composed of the members of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) manifested the recommendation regarding the use of HbA1c in diagnosing diabetes mellitus as an alternative to glucose measurements based on the update evidences indicating that HbA1c has several advantages as a marker of chronic hyperglycemia [1–3]. The JDS extensively evaluated the usefulness and feasibility of more extended use of HbA1c in the diagnosis of diabetes based on Japanese epidemiological data, and then the "Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus" was published in the *Diabetology International* [4] and *Journal of Diabetes Investigation* [5]. The new diagnostic criterion in Japan came into effect on July 1, 2010. According to the

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new version of the criteria, HbA1c (JDS) ≥6.1% is now considered to indicate a diabetic type, but the previous diagnosis criteria of high plasma glucose (PG) levels to diagnose diabetes mellitus also need to be confirmed. Those are as follows: (1) FPG ≥126 mg/dL (7.0 mmol/L), (2) 2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT, or (3) casual PG ≥200 mg/dL (11.1 mmol/L). If both PG criteria and HbA1c in patients have met the diabetic type, those patients are immediately diagnosed to have diabetes mellitus [4, 5].

In the report, the HbA1c measurements in Japan are well calibrated with Japanese-Clinical-Laboratory-Use Certified Reference Material (JCCRM). The certified values are determined by a high resolution type ion-exchange High Performance Liquid Chromatography (HPLC) (KO 500 method) and certified using the designated comparison method (DCM) of the Japan Society of Clinical Chemistry (JSCC) and the JDS. After incorporating a proportional bias correction to the value anchored to the peptide mapping method of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the DCM actually measures β-*N*-mono-deoxyfructosyl hemoglobin and has an intercept approximately equal to zero against the peptide mapping method of IFCC in measuring fresh raw human blood samples. Furthermore, standardization of HbA1c in Japan was initiated in 1993, and the serial reference materials from JDS Lot 1 to JDS Lot 4 are well certified using the DCM until now. In the new diagnosis criteria [4, 5], the new cut-off point of HbA1c (JDS) for diagnosis of diabetes mellitus is 6.1%, which is equivalent to the internationally used HbA1c (NGSP) 6.5%, as HbA1c (NGSP) (%) is reported to be equivalent to 1.019 × HbA1c (JDS)% + 0.3%, which is reasonably estimated by the equation of HbA1c (JDS)% + 0.4%, as the difference between the two equations is within error of HbA1c measurements (2–3%).

However, on October 1, 2011, the Reference Material Institute for Clinical Chemistry Standards (ReCCS, Kanagawa, Japan) was certified as an Asian Secondary Reference Laboratory (ASRL) using the KO 500 method and the reference materials JCCRM411-2 (JDS Lot 4) after successful completion of NGSP network laboratory certification. Therefore, the HbA1c unit is now traceable to the Diabetes Control and Complications Trial (DCCT) reference method. The comparison was performed with the Central Primary Reference Laboratory (CPRL) in the University of Missouri School of Medicine. Conversion equation from HbA1c (JDS) to HbA1c (NGSP) units is officially certified as follows: NGSP (%) = 1.02 × JDS (%) + 0.25%, conversely, JDS (%) = 0.980 × NGSP (%) − 0.245%. Based on this equation, in the range of JDS values ≤4.9%, NGSP (%) = JDS (%) + 0.3%, in the range of JDS 5.0–9.9%, NGSP (%) = JDS (%) + 0.4%, and in the range of JDS 10–14.9%, NGSP (%) = JDS (%) + 0.5%. These results show that the previous equation of NGSP (%) = JDS (%) + 0.4% is also confirmed in the present equation considering a 2–3% error of HbA1c measurements. The council meeting of the JDS finally decided to use HbA1c (NGSP) values in clinical practice from April 1, 2012, although HbA1c (JDS) values will be included until people become familiar with the new expression. Finally, it is also important

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Table 1 Differences in HbA1c values between JDS and NGSP for assessments of diagnosis and treatment of diabetes mellitus—Diagnostic reference values of HbA1c (NGSP) and HbA1c (JDS)

Diagnostic reference values	HbA1c(NGSP)	HbA1c(JDS)
Standard range	4.6% ~ 6.2%	4.3% ~ 5.8%
Diabetes range	≥6.5%	≥6.1%
Possible diabetes range	6.0% ~ 6.4%	5.6% ~ 6.0%
High risk range for diabetes	5.6% ~ 5.9%	5.2% ~ 5.5%

Table 2 Differences in HbA1c values between JDS and NGSP for assessments of diagnosis and treatment of diabetes mellitus—Assessments of the glycemic control using HbA1c

Assessment of control state		HbA1c(NGSP)	HbA1c(JDS)
Excellent		<6.2%	<5.8%
Good		6.2% ~ 6.8%	5.8% ~ 6.4%
Fair	Inadequate	6.9% ~ 7.3%	6.5% ~ 6.9%
	Not good	7.4% ~ 8.3%	7.0% ~ 7.9%
Poor		≥8.4%	≥8.0%

to emphasize that the new HbA1c (NGSP) values can be directly measured and printed out from April 1, 2012. However, both new diagnostic reference values and target values of glycemic control have been adjusted to those equivalent values of HbA1c (JDS) as shown in the Tables 1 and 2.

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