

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

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 hemoglobin (HbA_{1c}) 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 HbA_{1c} in diagnosing diabetes mellitus as an alternative to glucose measurements based on the updated evidence showing that HbA_{1c} has several advantages as a marker of chronic hyperglycemia²⁻⁴. The JDS extensively evaluated the usefulness and feasibility of more extended use of HbA_{1c} 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 *Journal of Diabetes Investigation*⁵ and *Diabetology International*⁶. The new diagnostic criterion in Japan came into effect on 1 July 2010. According to the new version of the criteria, HbA_{1c} (JDS) $\geq 6.1\%$ 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: (i) FPG ≥ 126 mg/dL (7.0 mmol/L); (ii) 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test; or (iii) casual PG ≥ 200 mg/dL (11.1 mmol/L). If both PG criteria and HbA_{1c} in patients have met the diabetic type, those patients are immediately diagnosed to have diabetes mellitus^{5,6}.

In the report, the HbA_{1c} 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 HbA_{1c} 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^{5,6}, the new cut-point of HbA_{1c} (JDS) for diagnosis of diabetes mellitus is 6.1%, which is equivalent to the internationally-used HbA_{1c} (National Glycohemoglobin Standardization Program [NGSP]) 6.5%, as HbA_{1c} (NGSP)(%) is reported to be equivalent to $1.019 \times \text{HbA}_{1c} \text{ (JDS)\%} +$

Table 1 | Differences in glycated hemoglobin values between Japan Diabetes Society and National Glycohemoglobin Standardization Program for assessments of diagnosis and treatment of diabetes mellitus

(a) Diagnostic reference values of HbA_{1c} (NGSP) and HbA_{1c} (JDS)

Diagnostic reference values	HbA _{1c} (NGSP)	HbA _{1c} (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

(b) Assessments of the glycemic control using HbA_{1c}

Assessment of control state	HbA _{1c} (NGSP)	HbA _{1c} (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

HbA_{1c}, glycated hemoglobin; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program.

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In 2007, the Japan Diabetes Society established The Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing, which published an announcement including international clinical harmonization of glycated hemoglobin in Japan in *Jpn Diabetes Soc* 2012; 54: Issue 12 (in Japanese). An abridged version of this commentary was published on the website of Japan Diabetes Society¹.

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0.3%, which is reasonably estimated by the equation of HbA_{1c} (JDS)% + 0.4%, as the difference between the two equations is within error of HbA_{1c} measurements (2~3%).

However, on 1 October 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 HbA_{1c} unit is now traceable to the Diabetes Control and Complications Trial (DCCT) reference method. The comparison was carried out with the Central Primary Reference Laboratory (CPRL) in the University of Missouri School of Medicine. The conversion equation from HbA_{1c} (JDS) to HbA_{1c} (NGSP) units is officially certified as follows: $\text{NGSP} (\%) = 1.02 \times \text{JDS} (\%) + 0.25\%$; conversely, $\text{JDS} (\%) = 0.980 \times \text{NGSP} (\%) - 0.245\%$. Based on this equation, in the range of JDS values $\leq 4.9\%$, $\text{NGSP} (\%) = \text{JDS} (\%) + 0.3\%$; in the range of JDS 5.0~9.9%, $\text{NGSP} (\%) = \text{JDS} (\%) + 0.4\%$; and in the range of JDS 10~14.9%, $\text{NGSP} (\%) = \text{JDS} (\%) + 0.5\%$. These results show that the previous equation of $\text{NGSP} (\%) = \text{JDS} (\%) + 0.4\%$ is also confirmed in the present equation, considering a 2~3% error of HbA_{1c} measurements. The council meeting of the JDS finally decided to use HbA_{1c} (NGSP) values in clinical practice from 1 April 2012, although HbA_{1c} (JDS) values will be included until people become familiar with the new expression. Finally, it is also important to emphasize that the new HbA_{1c} (NGSP) values can be directly measured and printed out from 1 April 2012. However, both new diagnostic reference values and target values of glycemic control have been adjusted to those equivalent values of HbA_{1c} (JDS), as shown in the Table 1.

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