Evaluation of the new criteria of 2010 for diabetes mellitus: Japan Diabetes Society

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Abstract We investigated the characteristics of the new criteria for diabetes mellitus (DM) issued by the Japan Diabetes Society in 2010, which include HbA_{1C} measurement, and differences between 1999 criteria, in order to indicate clinical caution points. If a person with fasting plasma glucose (FPG) ≥ 126 mg/dl or an oral glucose tolerance test (OGTT) 2-h value ≥ 200 and HbA_{1C} ≥ 6.5 % is determined as having DM, the disease can be detected at a rate of ≥ 70 % in persons < 60 years and at no more than 40–50 % in elderly persons. In longitudinal examination, we observed that individuals with DM with FPG ≥ 126 mg/dl and HbA_{1C} ≥ 6.5 % obtained the same determination over time at a rate of nearly 90 %. The percentage of persons whose result shifted from normal type to DM was 3- to 4-fold lower than that of persons whose result shifted from normal type to diabetic type. Based on these results, measurement of FPG and HbA_{1C} at the same time may be extremely effective in identifying DM, although we should pay attention to a higher likelihood that mild glucose metabolism disorders will be overlooked.

Keywords Diagnostic criteria · Diabetes mellitus · Include HbA_{1C} measurement · Oral glucose tolerance test · Mild glucose metabolism disorders

Introduction

In 2009, the International Expert Committee recommended the use of hemoglobin A_{1C} (HbA_{1C}) in the diagnosis of diabetes mellitus (DM) [1]. It became prevalent across the world, leading to the inclusion of HbA_{1C} in the diagnostic criteria of the American Diabetes Association, European Association for the Study of Diabetes, and World Health Organization [2, 3]. In Japan, a report on classification and diagnostic criteria for DM issued in 1999 was used until the revision [4]. New criteria for DM were proposed in 2010 stating that following a fasting plasma glucose (FPG) level, 2-h oral glucose tolerance test (OGTT) results, or a causal plasma glucose level indicating a diabetic type, and based on HbA_{1C} ≥ 6.5 %, individuals can be diagnosed as having DM [5]. Criteria are evidenced from the association between HbA_{1C} and FPG or OGTT 2-h value, as well as frequency and incidence of retinopathy [6]. Our purpose was to investigate characteristics of the new criteria for DM issued by the Japan Diabetes Society in 2010—which include HbA_{1C} levels—and differences between criteria in 1999, to indicate clinical caution points.

Materials and methods

As shown in Table 1, 11,958 participants comprised men and women with a mean [standard deviation (SD)] of 63.4 ± 9.2 . Men were 61.9 ± 9.3 years old; females were 64.7 ± 8.9 years old.

Study participants were a fixed population of atomic bomb survivors in Hiroshima who were born before May 1946. They had been receiving periodic health examinations based on medical law. Blood pressure was measured in a sitting position using the right arm, and all received

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Table 1 Study participants

Age at initial test (years)	Male	Female	Total
17–39	58	36	94
40–49	489	290	779
50–59	1513	1390	2903
60–69	2451	2564	5015
70–79	1025	1935	2960
80–	90	127	217
Total	5626	6343	11,968

Participants were a fixed population of atomic bomb survivors in Hiroshima born before May 1946. They received 75-g oral glucose tolerance tests (OGTT) from 1984 to 2010. Mean age 63.4 ± 9.2 years (men 61.9 ± 9.3 years; women 64.7 ± 8.9 years)

OGTT from 1984 to 2010. HbA_{1C} was determined by high-performance liquid chromatography (HPLC) (Arkray Inc. and Tosoh Corporation) and calibrated using the whole-blood standard of the Japan Diabetes Society. HbA_{1C} determined at the time of OGTT was converted by the corresponding National Glycohemoglobin Standardization Program (NGSP) [5]. Plasma glucose was determined using the glucose oxidase method and venous blood. Triglycerides were measured using an enzymatic method. Immunoreactive insulin (IRI) was measured with a radioimmunoassay using a double-antibody method. Insulin resistance was evaluated using homeostasis model assessment–estimated insulin resistance (HOMA-IR) and calculated as fasting insulin ($\mu\text{U/ml}$)/(22.5e^{ln_{glucose}}) [7].

We used diagnostic criteria for DM issued by the Japan Diabetes Society in 2010 and determined persons with an FPG level ≥ 126 mg/dl or an OGTT 2-h value ≥ 200 mg/dl and HbA_{1C} < 6.5 % as the diabetic type, and persons with an FPG level ≥ 126 mg/dl or an OGTT 2-h value ≥ 200 mg/dl and HbA_{1C} ≥ 6.5 % as having DM.

In longitudinal examination, we observed an OGTT value and HbA_{1C} in persons who had an initial OGTT value indicating DM. In addition, the percentage of persons whose result shifted from normal type to DM or to diabetic type was expressed as 1000 persons per year. We examined hazard ratios (HR) for the diabetic type and DM development using Cox regression model. The average follow-up duration was 9.7 years; average frequency of OGTT was 2.39 times per person. As the identification of individuals was not used, their information was protected. SAS (JMP) was employed in the statistical analysis, and a comparison of differences was made using *t* test or chi-square test. A *p* value < 0.05 was considered to indicate statistical significance.

Results

Rate of HbA_{1C} ≥ 6.5 % in persons with FPG ≥ 126 mg/dl or 2-h value ≥ 200 mg/dl

Table 2 shows the rates of HbA_{1C} ≥ 6.5 in 2032 persons with FPG ≥ 126 mg/dl or 2-h value ≥ 200 mg/dl among those undergoing health examinations. The majority of those showing HbA_{1C} ≥ 6.5 % (822; 43.4 %) met the criterion for FPG ≥ 126 mg/dl and a 2-h value ≥ 200 mg/dl; 138 persons (14.7 %) were detected with the 2-h value alone, and only 65 (6.9 %) were determined with FPG alone. The rate of either FPG ≥ 126 mg/dl or 2-h value ≥ 200 mg/dl and HbA_{1C} ≥ 6.5 % (A + B + C in Table 2) was > 70 % in those < 60 years (A + B + C/D in Table 2). However, this rate decreased with age to 40–50 % in those aged ≥ 60 years.

Meanwhile, the majority of the 947 persons showing HbA_{1C} < 6.5 % had an OGTT 2-h value ≥ 200 [862 persons (91.3 %); A' + B' in Table 2] and were ≥ 60 years. Table 3 shows OGTT follow-up results of 1445 persons whose OGTT values were observed. Overall, 86.0 % of them showed FPG ≥ 126 mg/dl and HbA_{1C} ≥ 6.5 % at the initial visit and at follow-up were determined as showing the same result; according to age group, the percentage of those aged ≥ 80 years was 76.2 %, being slightly lower. Results shifted to the diabetic type in 136 persons (9.4 %) and to normal type in 67 (4.6 %).

Rate and hazard ratio for diabetic type and DM development

Upon longitudinal examination, we compared rates of development between persons with normal type to diabetic type and normal type to DM (Fig. 1). For FPG < 100 mg/dl, the rates of diabetic type and DM were 19.5 and 4.8 per 1000 person per years, respectively, with the latter being only four times smaller than the former. For an FPG level of 100–109 mg/dl, rates were 34.6 and 8.9 per 1000 persons per year, respectively. Furthermore, for an FPG level of 110–125 mg/dl, rates were 68.8 and 21.1 per 1000 persons per year, respectively. The between-group difference was 4.1–3.3 times, indicating a decrease with an increased FPG level.

We examined HRs for the diabetic type and DM development (Table 4). Significant factors were age, FPG, OGTT 2-h value, obesity with body mass index (BMI) ≥ 25 kg/m², and hypertriglyceridemia. Only HOMA-IR was a significant factor for DM.

Table 2 Rates of hemoglobin (Hb)A_{1C} ≥ 6.5 in persons with fasting plasma glucose (FPG) ≥ 126 mg/dl or 2-h value ≥ 200 mg/dl

	A	B	C	A + B + C	(A + B + C)/D (%)	A'	B'	C'	A' + B' + C'	(A' + B' + C')/D (%)	D total
FPG	≥ 126	<126	≥ 126			≥ 126	<126	≥ 126			
2-h value	≥ 200	≥ 200	<200			≥ 200	≥ 200	<200			
HbA _{1C}	≥ 6.5	≥ 6.5	≥ 6.5			<6.5	<6.5	<6.5			
Age (years)											
40–49	59	5	4	68	81.9	7	8	0	15	18.1	83
50–59	171	11	7	189	73.8	24	34	9	67	26.2	256
60–69	358	54	21	433	54.7	112	215	32	359	45.3	792
70–79	259	59	28	346	43.4	104	314	33	451	56.6	797
80–	35	9	5	49	47.1	9	35	11	55	52.9	104
Total	882	138	65	1,085	53.4	256	606	85	947	46.6	2,032

Values in parentheses indicate the number of persons or a percentage of the total number

OGTT oral glucose tolerance test, 2-h value OGTT 2-h

Table 3 Oral glucose tolerance test (OGTT) results at follow-up in persons with fasting plasma glucose (FPG) ≥ 126 mg/dl and hemoglobin (Hb)A_{1C} ≥ 6.5 % at initial examination

	Diabetes mellitus	Diabetic type	Normal type	Total
FPG	≥ 126	≥ 126	<126	
OGTT 2-h value			<200	
HbA _{1C}	≥ 6.5	<6.5	<6.5	
40–49	82 (97.6)	2 (2.4)	0 (0.0)	84
50–59	248 (89.6)	17 (6.1)	12 (4.3)	277
60–69	499 (86.2)	54 (9.3)	26 (4.5)	579
70–79	365 (82.6)	57 (12.9)	20 (4.5)	442
80–	48 (76.2)	6 (9.5)	9 (14.3)	63
Total	1242 (86.0)	136 (9.4)	67 (4.6)	1445

Values in parentheses indicate the number of persons observed as a percentage of the age group

OGTT oral glucose tolerance test, FPG fasting plasma glucose, HbA_{1C} hemoglobin A_{1C}, 2-hr value OGTT 2-hr value

Fig. 1 The percentage of persons whose results shifted from normal to diabetic type or diabetes mellitus (DM) according to fasting plasma glucose (FPG) levels. 1000 PY 1000 person-years, HbA_{1C} hemoglobin A_{1C}

Discussion

In this study, we investigated the characteristics of the new criteria for DM issued by the Japan Diabetes Society in 2010, which combine HbA_{1C}, and the differences between 1999 criteria, to indicate clinical caution points. This is the first study employing OGTT in a large population and investigating results based on diagnostic criteria cross-sectionally and longitudinally. Data from Table 2 indicate that if a person with FPG ≥ 126 mg/dl or OGTT 2-h value ≥ 200 and HbA_{1C} ≥ 6.5 % is determined as having DM, the disease can be detected at a rate of ≥ 70 % in persons <60 years and no more than 40–50 % in elderly persons. Among persons with HbA_{1C} <6.5 %, those ≥ 60 years accounted for 91.3 %, and the majority of them showed OGTT 2-h value ≥ 200 .

Table 4 Hazard ratio (HR) for diabetic type and diabetes mellitus (DM) development

	Hazard ratio	
	Diabetic type	Diabetes mellitus
Age (per 10 years)	1.080****	1.088****
FPG	2.024****	5.106****
OGTT 2-h value	1.870****	1.939****
BMI (≥ 25)	1.164****	1.801**
HOMA-IR (≥ 2.5)	1.040	1.591*
Triglycerides (≥ 150)	1.411****	1.494**
Hypertension	1.086	1.267

FPG: <100, 100–109, 110–125 mg/dL. OGTT 2-h value: ~139, 140–159, 160–179, 180–199 mg/dl. Hypertension: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

FPG fasting plasma glucose, BMI body mass index, HOMA-IR homeostasis model assessment-estimated insulin resistance

Significant difference: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

Elderly people reportedly have an increased OGTT 2-h value compared with a FPG level. This seems to involve atrophy and dysfunction of the muscles and liver, which primarily metabolize loaded glucose. This result suggests that we may need to not only measure the FPG level but also conduct an OGTT for elderly people. In addition, in terms of whether the condition involving $\text{HbA}_{1\text{C}} < 6.5\%$ and OGTT 2-h value ≥ 200 mg/dl is meaningful, we should observe the frequency of coronary disease and retinopathy.

As shown in Table 4, the study revealed a high HR of FPG for DM. This suggests that FPG is closely associated with $\text{HbA}_{1\text{C}}$. There is the evidence that, with poorer day-time postprandial glycemic control, nocturnal PG level deteriorates in a stepwise manner, resulting in aggravated diabetes [8]. DM can refer to a state involving a more advanced glucose intolerance compared with the diabetic type. Also, HOMA-IR was a significant factor for DM but not for the diabetic type. Therefore, DM was associated with insulin resistance, but the association between diabetic type and insulin resistance was not clear.

It may not be surprising that discordance exists between OGTT and $\text{HbA}_{1\text{C}}$, since both have a different meaning: the latter is considered to reflect plasma glucose levels for the prior 1 month at a percentage of 50 %, 1–2 months at 25 %, and 2–4 months at 25 % [9], which is markedly different from OGTT, which reflect the latest glucose tolerance result.

As shown in Fig. 1, the rates of DM development in those whose result shifted from normal type to DM was 3- to 4-fold lower than that of persons whose result shifted from normal type to the diabetic type. According to this

result, it would be difficult to detect persons with mild glucose metabolism disorders. The prevention of DM is desirable from the early stage. Reportedly, when examining screening accuracy for the diabetic type based on $\text{HbA}_{1\text{C}} \geq 6.5\%$ in 36,267 persons undergoing health examinations, sensitivity and specificity were 54.3 and 94.6 %, respectively [6], indicating that, unsurprisingly, all diabetic type persons cannot be detected, including those who have mild glucose metabolism disorders.

In addition, as shown in Table 3, when temporally observing persons who have FPG or OGTT 2-h value and $\text{HbA}_{1\text{C}}$ levels indicating DM, nearly 90 % showed the same result at follow-up. The percentage of persons shifting from DM to normal type was 14.3 % in those 80 years old but 0 % in those 40 years and 4 % in those 50–79 years. According to this finding, measurement of FPG and $\text{HbA}_{1\text{C}}$ at the same time may be extremely effective in identifying persons with DM. As DM does not return to normal type, it can refer to a state involving a more advanced glucose intolerance. Furthermore, diagnostic criteria for DM include apparent retinopathy and subjective symptoms. However, these inclusions will have no marked impact on data, since retinopathy is not observed when first diabetes develops and occurs infrequently.

In this study, we investigated the characteristics of the new criteria for DM issued by the Japan Diabetes Society in 2010—which include $\text{HbA}_{1\text{C}}$ measurement—and differences between criteria in 1999, to indicate clinical caution points. If a person with $\text{FPG} \geq 126$ mg/dl or 2-h value ≥ 200 and $\text{HbA}_{1\text{C}} \geq 6.5\%$ is determined as having DM, this disease can be detected at a rate of 70 % or above in persons younger than 60 years and at no more than 40–50 % in elderly persons. The rates of diabetes development whose result shifted from normal type to DM was 3- to 4-fold lower than that of persons whose result shifted from normal type to the diabetic type. When temporally observing the persons who have FPG or 2-h value and $\text{HbA}_{1\text{C}}$ indicating the DM, nearly 90 % of these persons were determined as showing the same result at follow-up. Thus, given the significantly decreased rate of DM determined when combining $\text{HbA}_{1\text{C}}$ of $\geq 6.5\%$, we should pay attention to a higher likelihood of overlooking mild glucose metabolism disorders.

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Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflict of interest The authors declare no conflict of interest.

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