INTRODUCTION

The International Diabetes Federation (IDF) estimates that in 2010, 284.6 million people around the world have diabetes. This total is expected to increase by 54% to 438.4 million, which is 7.7% of the world population, in 2030[2]. In Japan, according to the 2007 Annual Statistical Report of National Health Condition, there were 8.9 million Japanese people with diabetes mellitus and 13.2 million with impaired glucose tolerance (IGT). These represent increases of 29.0% and 94.1%, respectively, over the 6.9 million with diabetes and 6.8 million with IGT in the 1997 survey 10 years earlier[3]. A variety of strategies to address the diabetes problem are under investigation.

In recent years, a number of studies such as the 'Study on the prevention and suppression of the development of vascular complications in diabetics (Japan Diabetes Complications Study: JDCS)[4], have helped to elucidate the clinical features of diabetes in the Japanese population. Longitudinal surveys of the cause of death in Japanese diabetics, and comparisons with that in Caucasian diabetics, have improved our understanding of vascular complications. Surveys of causes of death carried out in Japan have principally included questionnaires, analyses of autopsy statistics, death certificates and prospective surveys in specified institutions or regions. Although information obtained by questionnaire surveys has limitations, the benefits are also considerable, including the ability to cover a large survey population and to obtain information from physicians about the clinical features in addition to the cause of death.

Every 10 years since 1980, the Japan Diabetes Society has set up a 'Committee on Causes of Death in Diabetes Mellitus', which has previously published two reports[5,6]. Periodic surveys of cause of death in diabetic patients and comparisons with the results of prior surveys have yielded a great deal of information concerning changes in the clinical features, influences on the average life expectancy, and the effects of advances in the management and treatment of diabetes. These findings should be extremely advantageous in considering future prospects and initiatives in this field.

In the present study, we collated the results of analyses of the three questionnaire surveys of causes of death in diabetic patients (covering 1971–1980, 1981–1990 and 1991–2000), carried out using the same methods as the 'Committees on Causes of Death in Diabetes Mellitus'. The emphasis will be placed on the third committee report, covering the 10-year period of 1991–2000.

METHODS

The target period for the survey carried out by the third 'Committee on Causes of Death in Diabetes Mellitus' was 1 January 1991 to 31 December 2000. The survey of causes of death in Japanese diabetics contained 10 questions concerning the following: (i) gender; (ii) age at the time of death; (iii) estimated age of onset of diabetes; (iv) duration of treatment for diabetes; (v) type of diabetes; (vi) cause of death; (vii) diabetic complications while alive; (viii) details of treatment for diabetes; (ix) source of diagnosis of the cause of death; and (x) glycemic control status.

We analysed in particular the relationship between vascular complications (diabetic nephropathy, ischemic heart diseases and cerebrovascular diseases) as the cause of death and: (i) glycemic control status; (ii) duration of diabetes; (iii) details of treatment for diabetes; iv) region; and (v) main complications and concomitant diseases.

As for previous surveys, we sent survey forms to 700 institutions that met the criterion, 'institutions that presented papers at an Annual Meeting of the Japan Diabetes Society during the previous 5 years (1996–2000)'. We received responses from 282 institutions (response rate 40.3%), covering 18,639 diabetic patients. Exclusion of survey forms with internal inconsistencies, or missing important data, left an analysis group of 18,385 subjects (11,632 males, 6753 females). Some data were missing in some of these forms, however, so subject numbers will not agree for some parameters. Results are for all the subjects unless specified as pertaining to autopsy cases.

RESULTS

Causes of Death in Japanese Diabetics

Comparison Between All the Subjects and Autopsy Cases

The results of this survey of causes of death in Japanese diabetics are shown for all the cases and autopsy cases in Tables 1 and 2, respectively.

The most frequent cause of death in all the 18,385 cases was malignant neoplasia, accounting for 6275 cases (34.1%), followed by vascular diseases (including diabetic nephropathy, ischemic heart diseases and cerebrovascular diseases) in 4923 (26.8%), and infections in 2638 (14.3%). The most common malignancy was liver cancer in 1575 (8.6%) cases. Of the deaths from vascular diseases, those from ischemic heart diseases and cerebrovascular diseases were similar at 1871 (10.2%) and 1810 (9.8%), with diabetic nephropathy the cause of death in 1242 (6.8%). In the previous two surveys, we grouped together myocardial infarction and angina pectoris under the heading of ischemic heart diseases, but in the present survey we considered them separately. As a result, angina pectoris was the cause of death in merely 0.2% of cases, and almost all the deaths from ischemic heart diseases were as a result of myocardial infarction. Of the deaths from cerebrovascular diseases, cerebral infarction, the cause of death in 1187 patients (6.5%), was 2.2-fold as common as cerebral hemorrhage, the cause in 537 patients (2.9%). Pneumonia as the cause of death in 1768 (9.6%) patients (67% of the deaths from infections), was the most common infectious cause of death. Diabetic coma was the cause of death in 214 (1.2%) cases, and hypoglycemic coma in 74 (0.4%); both were relatively uncommon but emphasise the importance of these conditions in clinical practice.

The autopsy rate was low at 9.5%. The most frequent cause of death in all the 1750 diabetic patients who underwent autopsy was malignant neoplasia, accounting for 685 (39.1%) cases, followed by vascular diseases in 360 (20.6%) cases, and infections in 272 (15.5%) cases. These results were similar to the rates for all the surveyed subjects, with death from malignancy

Table 1 | Causes of death in Japanese diabetics – study of a total number of 18,385 cases during 1991–2000

Causes of death	Male (n = 11,632)	Female (n = 6753)	Total (n = 18,385)
Vascular diseases	2792 (24.0)	2131 (31.6)	4923 (26.8)
Diabetic nephropathy	652 (5.6)	590 (8.7)	1242 (6.8)
Ischemic heart diseases	1064 (9.1)	807 (12.0)	1871 (10.2)
Infarction	1045 (9.0)	787 (11.7)	1832 (10.0)
Angina pectoris	19 (0.2)	20 (0.3)	39 (0.2)
Cerebrovascular diseases	1076 (9.3)	734 (10.9)	1810 (9.8)
Hemorrhage	343 (2.9)	194 (2.9)	537 (2.9)
Infarction	691 (5.9)	496 (7.3)	1187 (6.5)
Others	42 (0.4)	44 (0.7)	86 (0.5)
Diabetic coma	117 (1.0)	97 (1.4)	214 (1.2)
Hypoglycemic coma	47 (0.4)	27 (0.4)	74 (0.4)
Malignant neoplasms	4353 (37.4)	1922 (28.5)	6275 (34.1)
Stomach	494 (4.2)	146 (2.2)	640 (3.5)
Lung	773 (6.6)	207 (3.1)	980 (5.3)
Colon	227 (2.4)	148 (2.2)	425 (2.3)
Liver	1222 (10.5)	353 (5.2)	1575 (8.6)
Pancreas	543 (4.7)	345 (5.1)	888 (4.8)
Uterus	0 (0.0)	70 (1.0)	70 (0.4)
Others	1044 (9.0)	653 (9.7)	1697 (9.2)
Infections	1777 (15.3)	861 (12.7)	2638 (14.3)
Tuberculosis	43 (0.4)	18 (0.3)	61 (0.3)
Pneumonia	1244 (10.7)	524 (7.8)	1768 (9.6)
Others	492 (4.2)	319 (4.7)	811 (4.4)
Liver cirrhosis	579 (5.0)	280 (4.1)	859 (4.7)
Cardiovascular diseases (except ischemic heart diseases)	577 (5.0)	527 (7.8)	1104 (6.0)
Others	1097 (9.4)	706 (10.5)	1803 (9.8)
Unknown causes	293 (2.5)	202 (3.0)	495 (2.7)

Values are given as n (%).

Table 2 | Causes of death in Japanese diabetics – study of 1750 autopsy cases during 1991–2000

Causes of death	Male (n = 1185)	Female (n = 565)	Total (n = 1750)
Vascular diseases	220 (18.6)	140 (24.8)	360 (20.6)
Diabetic nephropathy	58 (4.9)	34 (6.0)	92 (5.3)
Ischemic heart diseases	105 (8.9)	76 (13.5)	181 (10.3)
Infarction	104 (8.8)	73 (12.9)	177 (10.1)
Angina pectoris	1 (0.1)	3 (0.5)	4 (0.2)
Cerebrovascular diseases	57 (4.8)	30 (5.3)	87 (5.0)
Hemorrhage	16 (1.4)	7 (1.2)	23 (1.3)
Infarction	39 (3.3)	21 (3.7)	60 (3.4)
Others	2 (0.2)	2 (0.4)	4 (0.2)
Diabetic coma	12 (1.0)	6 (1.1)	18 (1.0)
Hypoglycemic coma	6 (0.5)	3 (0.5)	9 (0.5)
Malignant neoplasms	496 (41.9)	189 (33.5)	685 (39.1)
Stomach	30 (2.5)	10 (1.8)	40 (2.3)
Lung	86 (7.3)	20 (3.5)	106 (6.1)
Colon	19 (1.6)	7 (1.2)	26 (1.5)
Liver	165 (13.9)	49 (8.7)	214 (12.2)
Pancreas	66 (5.6)	35 (6.2)	101 (5.8)
Uterus	0 (0.0)	5 (0.9)	5 (0.3)
Others	130 (11.0)	63 (11.2)	193 (11.0)
Infections	178 (15.0)	94 (16.6)	272 (15.5)
Tuberculosis	3 (0.3)	2 (0.4)	5 (0.3)
Pneumonia	110 (9.3)	43 (7.6)	153 (8.7)
Others	65 (5.5)	49 (8.7)	114 (6.5)
Liver cirrhosis	73 (6.2)	19 (3.4)	92 (5.3)
Cardiovascular diseases (except ischemic heart diseases)	61 (5.1)	28 (5.0)	89 (5.1)
Others	127 (10.7)	79 (14.0)	206 (11.8)
Unknown causes	12 (1.0)	7 (1.2)	19 (1.1)

Values are given as n (%).

slightly more common, and that from vascular diseases slightly less common. The proportion of deaths from cerebrovascular diseases was also low, reflecting the low autopsy rate for stroke patients.

Analyses of gender differences showed that malignant neoplasia was the most frequent cause of death in all the males and males who underwent autopsy, whereas vascular diseases were the most frequent cause of death in all the females, and malignant neoplasia was the most common cause of death amongst the females who underwent autopsy. Analyses of deaths as a result of vascular diseases showed that cerebrovascular diseases were more common in males than females (males 1076/2792, 38.5%; females 734/2131, 34.4%), whereas diabetic nephropathy was more common in females than in males (males 652/2792, 23.4%; females 590/2131, 27.7%), and ischemic heart diseases were equally common for both genders.

Influence of Age and Region

The causes of death in Japanese diabetics according to age group in the 1750 autopsy cases covered by the present survey are shown in Table 3. The male:female ratio in the sixth and seventh decade of life was 3:1, but 2:1 for all subjects. This was thought to influence the gender difference in the average age at the time of death, as described below. The mortality rate as a result of vascular diseases increased with age, although the mortality rates from diabetic nephropathy and cerebrovascular diseases increased little from the fifth decade of life, remaining at approximately 5% each. The mortality rate from ischemic heart diseases increased with age, however, and was higher than that from the other forms of vascular diseases from the sixth decade of life, accounting for 12.3% of all the deaths in the eighth decade, and approximately 50% of all the vascular deaths in the eighth decade. Malignant neoplasia was the most frequent cause of death from the fifth decade of life, and was extremely common in the seventh decade, accounting for 46.3% of all deaths. The mortality rate from infections varied little between age groups from the fifth decade of life, remaining at approximately 15%.

A comparison of causes of death by region is shown in Table 4. As in the previous survey, we divided Japan into three

Table 3 | Causes of death at specified ages in Japanese diabetics – study of 1750 autopsy cases during 1991–2000

Age at death (years)	0–9		10–19		20–29		30–39		40–49		50–59		60–69		70+				
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	Total
No. cases	0	0	3	1	6	3	11	4	47	24	199	61	420	148	499	324	1185 (100)	565 (100)	1750 (100)
Vascular diseases	0	0	0	0	2	0	3	1	7	4	34	12	74	30	100	93	220 (18.6)	140 (24.8)	360 (20.6)
Diabetic nephropathy	0	0	0	0	1	0	1	1	3	1	5	4	23	8	25	20	58 (4.9)	34 (6.0)	92 (5.3)
Ischemic heart diseases	0	0	0	0	1	0	1	0	2	1	18	4	37	16	46	55	105 (8.9)	76 (13.5)	181 (10.3)
Infarction	0	0	0	0	1	0	1	0	2	1	18	4	37	15	45	53	104 (8.8)	73 (12.9)	177 (10.1)
Angina pectoris	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	1 (0.1)	3 (0.5)	4 (0.2)
Cerebrovascular diseases	0	0	0	0	0	0	1	0	2	2	11	4	14	6	29	18	57 (4.8)	30 (5.3)	87 (5.0)
Hemorrhage	0	0	0	0	0	0	1	0	2	1	4	1	6	2	3	3	16 (1.4)	7 (3.7)	23 (1.3)
Infarction	0	0	0	0	0	0	0	0	0	1	7	3	6	3	26	14	39 (3.3)	21 (3.7)	60 (3.4)
Others	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	1	2 (0.2)	2 (0.4)	4 (0.2)
Diabetic coma	0	0	2	0	0	1	1	0	2	0	3	3	2	0	2	2	12 (1.0)	6 (1.1)	18 (1.0)
Hypoglycemic coma	0	0	0	0	0	0	1	0	0	1	2	0	1	0	2	2	6 (0.5)	3 (0.5)	9 (0.5)
Malignant neoplasms	0	0	0	1	0	0	0	0	19	5	77	15	201	62	199	106	496 (41.9)	189 (33.5)	685 (39.1)
Stomach	0	0	0	0	0	0	0	0	1	0	2	1	10	5	17	4	30 (2.5)	10 (1.8)	40 (2.3)
Lung	0	0	0	0	0	0	0	0	1	1	12	2	23	4	50	13	86 (7.3)	20 (3.5)	106 (6.1)
Colon	0	0	0	0	0	0	0	0	1	1	2	2	6	1	10	3	19 (1.6)	7 (1.2)	26 (1.5)
Liver	0	0	0	0	0	0	0	0	6	2	31	2	85	26	43	19	165 (13.9)	49 (8.7)	214 (12.2)
Pancreas	0	0	0	0	0	0	0	0	3	0	11	3	23	7	29	25	66 (5.6)	35 (6.2)	101 (5.8)
Uterus	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	2	0 (0.0)	5 (0.9)	5 (0.3)
Others	0	0	0	1	0	0	0	0	7	1	19	4	54	17	50	40	130 (11.0)	63 (11.2)	193 (11.0)
Infections	0	0	1	0	0	1	0	0	6	5	26	9	48	26	97	53	178 (15.0)	94 (16.6)	272 (15.5)
Tuberculosis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	1	3 (0.3)	2 (0.4)	5 (0.3)
Pneumonia	0	0	0	0	0	0	0	0	3	2	14	3	25	11	68	27	110 (9.3)	43 (7.6)	153 (8.7)
Others	0	0	1	0	0	1	0	0	3	3	12	6	23	14	26	25	65 (5.5)	49 (8.7)	114 (6.5)
Liver cirrhosis	0	0	0	0	0	0	1	0	5	2	22	1	35	6	10	10	73 (6.2)	19 (3.4)	92 (5.3)
Cardiovascular diseases (except ischemic heart diseases)	0	0	0	0	1	1	2	1	2	3	7	4	21	5	28	14	61 (5.1)	28 (5.0)	89 (5.1)
Others	0	0	0	0	2	0	2	2	6	4	27	15	36	17	54	41	127 (10.7)	79 (14.0)	206 (11.8)
Unknown causes	0	0	0	0	1	0	1	0	0	0	1	2	2	2	7	3	12 (1.0)	7 (1.2)	19 (1.1)

F, female; M, male. Values in parentheses are percentage.

Table 4 | Comparison of causes of death by districts in Japanese diabetics – study of a total number of 18,385 cases during 1991–2000

Causes of death	Districts and cases											
	Tohoku and Hokkaido districts			Big city districts*			Other districts			Total districts		
	Male (n = 1088)	Female (n = 640)	Total (n = 728)	Male (n = 3032)	Female (n = 1658)	Total (n = 4690)	Male (n = 7512)	Female (n = 4455)	Total (n = 11,967)	Male (n = 11,632)	Female (n = 6753)	Total (n = 18,385)
Vascular diseases, %	25.3	38.4	30.2	23.3	28.0	25.0	24.1	31.9	27.0	24.0	31.6	26.8
Diabetic nephropathy	6.1	12.0	8.3	4.6	7.2	5.5	5.9	8.8	7.0	5.6	8.7	6.8
Ischemic heart diseases	10.4	12.8	11.3	10.4	12.8	11.3	8.5	11.5	9.6	9.1	12.0	10.2
Infarction	10.4	12.8	11.3	10.4	12.5	11.2	8.2	11.2	9.3	9.0	11.7	10.0
Angina pectoris	0.0	0.0	0.0	0.0	0.2	0.1	0.2	0.4	0.3	0.2	0.3	0.2
Cerebrovascular diseases	8.8	13.6	10.6	8.3	8.1	8.2	9.7	11.5	10.4	9.3	10.9	9.8
Hemorrhage	1.6	2.3	1.9	2.9	2.3	2.7	3.2	3.2	3.2	2.9	2.9	2.9
Infarction	6.9	10.9	8.4	5.1	5.4	5.2	6.1	7.6	6.7	5.9	7.3	6.5
Others	0.4	0.3	0.3	0.2	0.4	0.3	0.4	0.8	0.6	0.4	0.7	0.5
Diabetic coma	0.7	1.4	1.0	0.7	1.7	1.0	1.2	1.3	1.2	1.0	1.4	1.2
Hypoglycemic coma	0.1	0.0	0.1	0.5	0.2	0.4	0.4	0.5	0.4	0.4	0.4	0.4
Malignant neoplasms	39.9	27.7	35.4	37.0	30.7	34.8	37.2	27.7	33.7	37.4	28.5	34.1
Stomach	5.8	3.1	4.8	3.3	2.2	2.9	4.4	2.0	3.5	4.2	2.2	3.5
Lung	6.4	2.5	5.0	6.3	3.6	5.4	6.8	2.9	5.4	6.6	3.1	5.3
Colon	4.0	3.0	3.6	1.9	2.1	2.0	2.3	2.1	2.3	2.4	2.2	2.3
Liver	9.4	4.4	7.5	10.6	5.2	8.7	10.6	5.3	8.7	10.5	5.2	8.6
Pancreas	5.9	6.2	6.0	4.9	5.7	5.2	4.4	4.7	4.5	4.7	5.1	4.8
Uterus	0.0	0.5	0.2	0.0	1.4	0.5	0.0	1.0	0.4	0.0	1.0	0.4
Others	8.4	8.0	8.2	10.0	10.6	10.2	8.7	9.6	9.0	9.0	9.7	9.2
Infections	14.0	11.1	12.9	14.5	12.8	13.9	15.8	13.0	14.7	15.3	12.7	14.3
Tuberculosis	0.0	0.2	0.1	0.2	0.4	0.3	0.5	0.2	0.4	0.4	0.3	0.3
Pneumonia	11.8	7.7	10.2	10.2	7.7	9.3	10.8	7.8	9.7	10.7	7.8	9.6
Others	2.2	3.3	2.6	4.2	4.8	4.4	4.6	4.9	4.7	4.2	4.7	4.4
Liver cirrhosis	4.4	4.4	4.4	4.7	3.6	4.3	5.2	4.3	4.9	5.0	4.1	4.7
Cardiovascular diseases (except ischemic heart diseases)	5.4	7.3	6.1	5.0	7.4	5.8	4.9	8.0	6.0	5.0	7.8	6.0
Others	8.0	6.9	7.6	8.9	9.8	9.2	9.8	11.2	10.4	9.4	10.5	9.8
Unknown causes	2.2	2.8	2.4	5.4	5.7	5.5	1.4	2.0	1.6	2.5	3.0	2.7

*Tokyo, Osaka, Nagoya, Yokohama, Kyoto, Fukuoka.

regions: (i) Tohoku and Hokkaido region; (ii) large municipalities (Tokyo, Osaka, Nagoya, Yokohama, Kyoto and Fukuoka); and (iii) Other region. The proportion of deaths as a result of vascular diseases was higher in the Tohoku and Hokkaido region, but no differences as a result of other causes of death were found.

Cause of Death, Glycemic Control and Duration of Diabetes in Japanese Diabetics

Glycemic Control and Average Age at Time of Death

Table 5 shows the cause of death, level of glycemic control and average age at the time of death in all the subjects. The classification of glycemic control was divided into two groups according to the HbA_{1c} level (good and fair: under 8.0%; and poor: over 8.0%). The average age at the time of death was 69.3 years in all the subjects, and was 2 years shorter in subjects with poor glycemic control than in those with good or fair glycemic control (2.5 years in males and 1.6 years in females). This underlines the importance of maintaining good glycemic control. Lifespans were longer for those with good or fair glycemic control with all the causes of death, and this difference was greater for deaths as a result of infections and vascular diseases, particularly diabetic nephropathy, than for malignant neoplasia. It might be considered natural that lifespans were considerably shorter in subjects with poor glycemic control in whom the cause of death was diabetic coma or hypoglycemic coma.

Glycemic Control, Duration of Diabetes and Deaths Caused By Vascular Diseases

The level of glycemic control is often implicated in the onset and progression of vascular diseases. In Table 6, we examine the relationship between glycemic control, the duration of diabetes, and deaths caused by vascular diseases. In deaths caused by diabetic nephropathy, glycemic control was good or fair in 536 (51.3%) cases and poor in 508 (48.7%) cases, with no differences

Table 5 | Causes of death, average age at death and glycemic control in Japanese diabetics – study of a total number of 15,312 cases during 1991–2000

Causes of death	Glycemic control								
	Good or fair (n = 8741)			Poor (n = 6571)			Total (n = 15,312)		
	Male	Female	Mean	Male	Female	Mean	Male	Female	Mean
Vascular diseases	69.8	73.4	71.3	67.3	72.0	69.5	68.6	72.7	70.4
Diabetic nephropathy	68.5	72.7	70.5	67.5	69.2	68.2	68.1	70.8	69.4
Ischemic heart diseases	70.6	74.1	72.0	68.0	74.3	70.9	69.4	74.2	71.5
Infarction	70.6	74.0	72.0	67.9	74.4	70.9	69.3	74.2	71.5
Angina pectoris	70.8	75.9	73.4	75.0	71.0	73.5	72.2	74.8	73.4
Cerebrovascular diseases	69.8	73.4	71.2	67.4	72.0	69.4	68.7	72.7	70.3
Hemorrhage	65.2	67.2	65.9	62.5	67.5	64.3	64.0	67.3	65.2
Infarction	72.2	75.5	73.5	69.7	73.4	71.3	71.1	74.4	72.5
Others	66.2	75.6	71.2	66.2	73.0	70.1	66.2	74.8	70.9
Diabetic coma	70.3	69.3	69.8	57.5	65.5	61.1	59.1	66.0	62.2
Hypoglycemic coma	65.9	75.9	68.9	53.8	66.1	59.0	60.0	69.8	63.6
Malignant neoplasms	68.0	71.0	68.9	66.7	70.3	67.8	67.5	70.8	68.5
Stomach	69.4	74.7	70.7	69.2	70.1	69.4	69.4	73.3	70.3
Lung	70.5	72.6	70.9	69.3	72.3	70.0	70.1	72.5	70.6
Colon	68.7	72.4	70.0	68.6	69.3	68.8	68.7	71.4	69.6
Liver	65.1	70.2	66.3	64.1	70.0	65.4	64.7	70.2	66.0
Pancreas	69.0	71.9	70.0	66.0	72.3	68.5	67.6	72.1	69.3
Uterus	0.0	64.0	64.0	0.0	63.2	63.2	66.7	63.7	66.2
Others	68.3	70.1	69.0	66.7	69.2	67.7	68.3	69.8	69.0
Infections	73.1	74.2	73.4	70.0	72.2	70.6	71.6	73.2	72.1
Tuberculosis	72.1	70.3	71.7	68.4	66.9	67.9	70.2	68.2	69.6
Pneumonia	74.5	75.7	74.8	72.3	74.1	72.6	73.5	74.8	73.9
Others	68.9	71.6	70.0	65.3	70.3	67.3	67.0	70.9	68.6
Liver cirrhosis	62.9	67.8	64.5	60.0	66.4	62.1	61.6	67.1	63.4
Cardiovascular diseases (except ischemic heart diseases)	70.5	75.0	72.6	68.3	72.7	70.5	69.6	74.0	71.7
Others	68.9	71.4	69.8	65.2	69.2	66.8	67.5	70.4	68.6
Unknown causes	68.1	70.5	68.7	62.8	64.3	62.8	65.1	67.5	66.1
All the causes	69.1	72.3	70.2	66.6	70.7	68.2	68.0	71.6	69.3

Values are years.

Table 6 | Glycemic control, duration of diabetes and vascular diseases as causes of death in Japanese diabetics during 1991–2000

Glycemic control	Duration of diabetes (years)	Vascular diseases								
		Diabetic nephropathy			Ischemic heart diseases			Cerebrovascular diseases		
		Male (n = 527)	Female (n = 517)	Total (n = 1044) (100%)	Male (n = 719)	Female (n = 661)	Total (n = 1380) (100%)	Male (n = 712)	Female (n = 620)	Total (n = 1332) (100%)
Good or fair	≤4	24	12	36 (3.4)	77	35	112 (8.1)	98	54	152 (11.4)
	5–9	41	37	78 (7.5)	69	49	118 (8.6)	68	56	124 (9.3)
	≥10	218	204	422 (40.4)	262	210	472 (34.2)	277	165	442 (33.2)
	Total	283	253	536 (51.3)	408	294	702 (50.9)	443	275	718 (53.9)
Poor	≤4	18	19	37 (3.5)	39	44	83 (6.0)	35	48	83 (6.2)
	5–10	21	39	60 (5.7)	39	73	112 (8.1)	49	62	111 (8.3)
	≥10	205	206	411 (39.44)	233	250	483 (35.0)	185	235	420 (31.5)
	Total	244	264	508 (48.7)	311	367	678 (49.1)	269	345	614 (46.1)

Values in parentheses are percentage.

between groups. No differences were seen between groups in deaths caused by ischemic heart diseases. In deaths from cerebrovascular diseases, however, glycemic control was good or fair in 718 (53.9%) cases and poor in 614 (46.1%) cases, and in deaths from cerebral hemorrhage control was good or fair in 56.6% and poor in 43.4%, showing a slightly higher proportion with good glycemic control.

The duration of diabetes was 10 years or more in 79.8% of deaths from diabetic nephropathy, whereas the proportions for ischemic heart diseases and cerebrovascular diseases were 69.2% and 64.7%, respectively. In other words, even in diabetics with less than 10 years' duration, the mortality rate from macroangiopathy was higher than that as a result of diabetic nephropathy, a microangiopathy.

Relationship between Deaths Caused by Vascular Diseases, Treatment for Diabetes and Complications and Concomitant Diseases

Treatment for Diabetes and Deaths Caused By Vascular Diseases

As shown in Table 7, treatment of diabetes in all the subjects comprised of diet alone in 21.5%, oral hypoglycemic agents in 29.5% and insulin in 44.2%, (2.1% in combination with oral hypoglycemic agents included) with insulin therapy the most common. In particular, 683/1170 (58.4%) diabetics who died from diabetic nephropathy were on insulin therapy, a higher proportion than the 661/1687 (39.2%) who died from ischemic heart diseases, or the 659/1622 (40.6%) who died from cerebrovascular diseases. Oral hypoglycemic therapy was less common in diabetics who died from diabetic nephropathy (246/1170, 21.0%) than in those who died from ischemic heart diseases (618/1687, 36.6%) or cerebrovascular diseases (496/1622, 30.6%). Diet alone was slightly less common in diabetics who died from diabetic nephropathy (178/1170, 15.2%) than in those who died from ischemic heart diseases (313/1687, 18.6%) or cerebrovascular diseases (335/1622, 20.7%).

Complications and Concomitant Diseases and Death from Vascular Diseases

The relationship between complications and concomitant diseases and deaths from vascular diseases is shown in Table 8 (all the subjects) and 9 (autopsy subjects). The results were similar for both groups.

Diabetic retinopathy and neuropathy were both common in diabetics who died from diabetic nephropathy, and the incidence of ischemic heart diseases in diabetics who eventually died from ischemic heart diseases (almost all from myocardial infarction) was high, which was of course predictable. Hypertension was present in approximately half of the subjects who died from vascular diseases, but the presence of dyslipidemia was relatively low, even in diabetics who died from ischemic heart diseases or cerebrovascular diseases. It is interesting to note that renal dysfunction was present in approximately half of the subjects who died from ischemic heart diseases and cerebrovascular diseases.

Diabetic gangrene (diabetic foot disease) in all the subjects was more common in diabetics who died from diabetic nephropathy (152/1242, 12.2%) than in those who died from ischemic heart diseases (126/1871, 6.7%) or cerebrovascular diseases (87/1810, 4.8%). This confirms once more that microangiopathy plays an important role in the etiology of diabetic gangrene.

DISCUSSION

The present survey of the causes of death of Japanese diabetics (1991–2000) was carried out as a questionnaire survey in the same way as in the previous survey (1981–1990)[6] and the first survey (1971–1980)[5]. The results obtained by such questionnaire surveys have certain advantages and disadvantages. The advantages include: (i) large subject population; (ii) reduced population bias towards specific institutions; (iii) general characteristics can be readily grasped; and (iv) carrying out a nationwide survey makes it possible to identify regional differences. The disadvantages include: (i) filling in the questionnaires requires

Table 7 | Treatment of diabetes and vascular diseases as causes of death in Japanese diabetics during 1991–2000

Treatment	Causes of death													
	Diabetic nephropathy			Ischemic heart diseases			Cerebrovascular diseases			Others			All		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Diet only	87	91	178 (1.08)	181	132	313 (1.90)	217	118	335 (2.03)	1832	891	2723 (16.53)	2317	1232	3549 (21.54)
Oral hypoglycemic agents	131	115	246 (1.49)	335	283	618 (3.75)	274	222	496 (3.01)	2231	1264	3495 (21.21)	2971	1884	4855 (26.47)
Insulin (with/without oral hypoglycemic agents)	356	327	683 (4.15)	381	280	661 (4.01)	395	264	659 (4.00)	3432	1839	5281 (32.05)	4574	2710	7284 (44.21)
Unknown	32	25	57 (0.35)	46	33	79 (0.48)	51	48	99 (0.60)	240	117	357 (2.17)	369	206	575 (3.49)
Untreated	2	4	6 (0.04)	13	3	16 (0.10)	16	17	33 (0.20)	120	37	157 (0.95)	151	61	212 (1.29)
Total	608	562	1170 (7.10)	956	731	1687 (10.24)	953	669	1622 (9.85)	7865	4148	12,012 (72.92)	10,382	6093	16,475 (100)

Values in parentheses are percentage.

much time and effort; (ii) apart from the autopsy cases, the recorded cause of death is not necessarily accurate; (iii) the proportion of inpatient deaths is high; (iv) variability in the assessment criteria; and (v) the possibility of duplication of cases. Although these factors should be considered when interpreting the survey results, for the present survey we collated data for over 18,000 subjects (1.5-fold greater than the previous survey, and twofold greater than the first survey), and the results should more than compensate for the aforementioned possible disadvantages.

Comparison of the results of the present survey of causes of death in Japanese diabetics with the results of the previous survey[6] and the first survey[5], as well as other Japanese surveys of causes of death, will be of great interest in terms of understanding changes in the clinical features of diabetes in Japan, and should also be useful in formulating future strategies. Table 10 shows a comparison of the causes of death found in the three surveys, including the present survey, with the causes of death in the Japanese general population over the same periods in the 'Annual Statistical Report of National Health Condition' published by the Health and Welfare Statistics Association in 1981, 1991 and 2001[7–9]. In the present survey, the most frequent causes of death were malignant neoplasia, vascular diseases as second in frequency and then infections; with the top two causes exchanging positions from the previous two surveys and the present one. In other words, the proportion of deaths from malignancy in diabetics has risen from 25.3% in the first survey to 29.2% in the second survey and 34.1% in the third survey. Over the same period, the proportion of deaths from malignancy in the general population has risen from 21.6% to 25.9% and then 31.0%, showing that this is not a phenomenon peculiar to diabetics.

It is also worthy to note that the proportion of deaths from vascular diseases declined in the Japanese general population over the past three decades, but in diabetics it has in fact decreased by one-third from 39.3% to 26.8%. Examination of the vascular diseases groupings shows that the proportion of deaths from ischemic heart disease in diabetics rose from 12.3% in the first survey to 14.6% in the second survey, then dropped markedly to 10.2% in the third survey. This is in clear contrast to the upwards trend in the Japanese general population, from 6.4% to 7.3% over the latter period. A decline in the ratio of deaths from ischemic heart diseases to all the deaths from vascular diseases was seen in the present survey, despite marked increases seen in previous surveys of causes of death in Japanese diabetics, for example 6.0% reported in 1967 by Goto *et al.*[10] and 9.7% over the 1968–1970 period reported by Hirata *et al.*[11] Possible reasons for this discrepancy include stricter control of blood lipids through the use of statins and blood pressure through antihypertensive agents, improved glycemic control after the release of the results of the Diabetes Control and Complications Trial and recent advances in interventions for ischemic heart diseases. We must await the next survey to determine whether this trend will be maintained, but the proportion of

Table 8 | Complications in Japanese diabetics with vascular diseases as causes of death – study of a total number of 4923 cases during 1991–2000

Complications	Vascular diseases								
	Diabetic nephropathy			Ischemic heart diseases			Cerebrovascular diseases		
	Male (n = 652)	Female (n = 590)	Total (n = 1242)	Male (n = 1064)	Female (n = 807)	Total (n = 1871)	Male (n = 1076)	Female (n = 734)	Total (n = 1810)
Renal dysfunction (%)	582 (89.3)	542 (91.9)	1124 (90.5)	507 (47.4)	363 (45.0)	870 (46.5)	492 (45.7)	295 (40.2)	787 (43.5)
Retinopathy	421 (64.6)	395 (66.9)	816 (65.7)	387 (36.4)	300 (37.2)	687 (36.7)	369 (34.3)	241 (32.8)	610 (33.7)
Neuropathy	320 (49.1)	272 (46.1)	592 (47.7)	300 (28.2)	215 (26.6)	515 (27.5)	284 (26.4)	189 (25.7)	473 (26.1)
Gangrene (diabetic foot)	92 (14.1)	60 (10.2)	152 (12.2)	83 (7.8)	43 (5.3)	126 (6.7)	57 (5.3)	30 (4.1)	87 (4.8)
Cerebral atherosclerosis	222 (34.0)	189 (32.0)	411 (33.1)	280 (26.3)	196 (24.3)	476 (25.4)	386 (35.9)	254 (34.6)	640 (35.4)
Ischemic heart diseases	162 (24.8)	152 (25.8)	314 (25.3)	508 (47.7)	376 (46.6)	884 (47.2)	184 (17.1)	133 (18.1)	317 (17.5)
Infarction	74 (11.3)	61 (10.3)	135 (10.9)	342 (32.1)	238 (29.5)	580 (31.0)	89 (8.3)	49 (6.7)	138 (7.6)
Angina pectoris	88 (13.5)	91 (15.4)	179 (14.4)	166 (15.6)	138 (17.1)	304 (16.2)	95 (8.8)	84 (11.4)	179 (9.9)
Hypertension	317 (48.6)	306 (51.9)	623 (50.2)	468 (44.0)	381 (47.2)	849 (45.4)	536 (49.8)	409 (55.7)	945 (52.2)
Hyperlipidemia	81 (12.4)	104 (17.6)	185 (14.9)	199 (18.7)	203 (25.2)	402 (21.5)	140 (13.0)	122 (16.6)	262 (14.5)

Values are given as n (%).

Table 9 | Complications in Japanese diabetics with vascular diseases as causes of death – study of 360 autopsy cases during 1991–2000

Complications	Vascular diseases								
	Diabetic nephropathy			Ischemic heart diseases			Cerebrovascular diseases		
	Male (n = 58)	Female (n = 34)	Total (n = 92)	Male (n = 105)	Female (n = 76)	Total (n = 181)	Male (n = 57)	Female (n = 30)	Total (n = 87)
Renal dysfunction (%)	52 (89.7)	34 (100.0)	86 (93.5)	57 (54.3)	47 (61.8)	104 (57.5)	34 (59.6)	13 (43.3)	47 (54.0)
Retinopathy	38 (65.5)	25 (73.5)	63 (68.5)	41 (39.0)	36 (47.4)	77 (42.5)	25 (43.9)	10 (33.3)	35 (40.2)
Neuropathy	33 (56.9)	20 (58.8)	53 (57.6)	32 (30.5)	27 (35.5)	59 (32.6)	19 (33.3)	9 (30.0)	28 (32.2)
Gangrene (diabetic foot)	5 (8.6)	3 (8.8)	8 (8.7)	11 (10.5)	6 (7.9)	17 (9.4)	4 (7.0)	3 (10.0)	7 (8.0)
Cerebral atherosclerosis	19 (32.8)	11 (32.4)	30 (32.6)	32 (30.5)	21 (27.6)	53 (29.3)	24 (42.1)	12 (40.0)	36 (41.4)
Ischemic heart disease	18 (31.0)	8 (23.5)	26 (28.3)	52 (49.5)	43 (56.6)	95 (52.5)	12 (21.1)	6 (20.0)	18 (20.7)
Infarction	8 (13.8)	3 (8.8)	11 (12.0)	37 (35.2)	34 (44.7)	71 (39.2)	7 (12.3)	4 (13.3)	11 (12.6)
Angina pectoris	10 (17.2)	5 (14.7)	15 (16.3)	15 (14.3)	9 (11.8)	24 (13.3)	5 (8.8)	2 (6.7)	7 (8.0)
Hypertension	29 (50.0)	18 (52.9)	47 (51.1)	50 (47.6)	37 (48.7)	87 (48.1)	25 (43.9)	17 (56.7)	42 (48.3)
Hyperlipidemia	7 (12.1)	4 (11.8)	11 (12.0)	19 (18.1)	17 (22.4)	36 (19.9)	10 (17.5)	9 (30.0)	19 (21.8)

Values are given as n (%).

Table 10 | Causes of death of Japanese general population and diabetics – comparisons between 1971–1980, 1981–1990 and 1991–2000

Causes of death	1971–1980		1981–1990		1991–2000	
	General population[7] (n = 695,821)	Diabetics[5] (n = 9737)	General population[8] (n = 793,014)	Diabetics[6] (n = 11,648)	General population[9] (n = 970,331)	Diabetics (n = 18,385)
Vascular diseases, %	31.7	41.5	24.6	39.3	22.7	26.8
Renal failure	1.0	12.8	2.0	11.2	1.8	6.8
Ischemic heart diseases	6.6	12.3	6.4	14.6	7.3	10.2
Cerebrovascular diseases	24.1	16.4	16.2	13.5	13.6	9.8
Malignant neoplasms	21.6	25.3	25.9	29.2	31.0	34.1
Infections	6.2	9.2	8.4	10.2	9.2	14.3
Others	40.5	24.1	41.1	21.3	37.1	24.8

deaths from ischemic heart diseases remains higher in Japanese diabetics than in the general population. It goes without saying that strict management of diabetes is necessary to prevent the onset and progression of ischemic heart diseases. It is of great interest that a number of studies have shown markedly increased levels of ischemic heart diseases in Caucasian Americans and Japanese-Americans[12–17], graphically illustrating the importance of environmental factors in the vascular complications of diabetes.

The proportion of deaths from cerebrovascular diseases in Japanese diabetics declined from 16.4% in the first survey to 13.5% in the second survey and 9.8% in the present survey. A similar trend was also observed in the Japanese general population, however, suggesting that the downward trend in deaths from cerebrovascular diseases can be attributed to improved control of lipids and blood pressure. The proportion of deaths from diabetic nephropathy in diabetics declined from 12.8% in the first survey to 11.2% in the second survey and markedly to 6.8% in the present survey. The proportion of deaths from renal failure in the Japanese general population changed little over the latter period, from 2.0% to 1.8%. Although a comparison of deaths from renal failure in the general population and deaths from diabetic nephropathy in diabetics is at best questionable, the ratio of deaths from diabetic nephropathy to deaths from renal failure in the general population was 12.8-fold greater in the first survey, dropping to 5.6-fold in the second survey, and still high at 3.8-fold in the present survey. If we combine this trend with the increased numbers of new dialysis patients with diabetic nephropathy, the above decrease in the diabetic nephropathy:renal failure ratio can be attributed to advances in dialysis therapy. Dialysis has become possible for diabetics who would previously have been excluded from indications of dialysis therapy as a result of various conditions associated with their diabetes, and increasing numbers of diabetics escape death from nephropathy and eventually from a different cause.

The proportion of deaths from infections, the third ranking cause of death, has risen slightly in both the Japanese general population and diabetics from the first to the second survey, and again from the second to the third survey, with a consistently higher proportion in diabetics. This reinforces the importance of considering the susceptibility of diabetics to infections in the course of clinical practice.

It goes without saying that long-term maintenance of good glycemic control is the lynchpin of treatment of diabetes. The average age at the time of death in the present survey population was 68.2 years for those with poor glycemic control, and 70.2 years in those with good or fair glycemic control. This 2-year difference suggests that the level of glycemic control influences the life expectancy in diabetics. The causes of death that most strongly reflect the level of glycemic control are, predictably, diabetic nephropathy, diabetic coma, hypoglycemic coma and infections; again underlying the importance of maintaining good glycemic control. The average age at the time of death of subjects with poor glycemic control who died from diabetic coma or hypoglycemic coma was extremely young, a fact that should be kept in mind in clinical practice. In contrast, the difference in average ages at the time of death between subjects with good or fair glycemic control and those with poor glycemic control was smallest for deaths from ischemic heart diseases. This might be a result of the role that factors such as postprandial hyperglycemia, that are not completely reflected in HbA_{1c} levels, play in the onset and progression of ischemic heart diseases.

Table 11 shows a comparison of the mean ages at death of Japanese diabetics in the three surveys and life expectancy at birth of the Japanese general population over the same periods[18]. The greatest characteristic of diabetics is their short life expectancy in comparison with the Japanese general population. In the present survey, lifespans were approximately 10 years shorter for males and approximately 13 years shorter for females than the average life expectancy for the Japanese general population. Similar results were obtained from the first and second surveys, showing that the remarkable advances in the past 20 years in the management and treatment of diabetes have not led to any improvement in patients' life expectancies. However, treatment for diabetes often continues for long periods of 20, 30 or even 40 years, so any possible improvements in life expectancies brought about by advances in treatment might only be elucidated by further surveys not yet carried out.

As outlined earlier, there are limitations in interpreting the results obtained through questionnaire surveys, such as

Table 11 | Mean ages at death of Japanese diabetics and life expectancy at birth of Japanese general population – comparison between 1971–1980, 1981–1990 and 1991–2000

	(1) 1971–1980		(2) 1981–1990		(3) 1991–2000		Differences between (1) and (2)		Differences between (2) and (3)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
A. General population (life expectancy in years)	73.4*	78.8*	75.9*	81.9*	77.6*	84.6*	+2.5	+3.1	+1.7	+2.7
B. Diabetics (mean ages at death)	63.1**	64.9**	66.5***	68.4***	68.0	71.6	+3.4	+3.5	+1.5	+3.2
Differences between A and B	−10.3	−13.9	−9.4	−13.5	−9.6	−13.0				

*From ref 18; **from ref 5; ***from ref 6.

difficulties in standardising diagnostic criteria and assessment criteria for the cause of death. However, we can say that the results collated from 18,385 subjects received from 282 institutions clarify greatly the clinical features of Japanese diabetics in the decade 1991–2000. In the present study, we tabulated the results of the third questionnaire survey, setting them out in the same manner as the first and second surveys to facilitate comparisons. We fervently hope that the results presented here will be of use in the treatment of diabetes. The next survey will cover the period 2001–2010, and should prove extremely useful in understanding what changes have occurred in the clinical features of Japanese diabetics over that period.

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In the original Japanese version of this report, the names of the doctors who participated in this survey were listed with their affiliations. For this English version, we have omitted this information, for which we ask your understanding.

No potential conflicts of interest to this article were reported.

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REPORT OF THE COMMITTEE

Report of the Committee on the classification and diagnostic criteria of diabetes mellitus

The Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus

Yutaka Seino · Kishio Nanjo · Naoko Tajima · Takashi Kadowaki · Atsunori Kashiwagi · Eiichi Araki · Chikako Ito · Nobuya Inagaki · Yasuhiko Iwamoto · Masato Kasuga · Toshiaki Hanafusa · Masakazu Haneda · Kohjiro Ueki

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Summary

Concept of diabetes mellitus

Diabetes mellitus is a group of diseases associated with various metabolic disorders, the main feature of which is chronic hyperglycemia due to insufficient insulin action. Its pathogenesis involves both genetic and environmental factors. The long-term persistence of metabolic disorders can cause susceptibility to specific complications and also foster arteriosclerosis. Diabetes mellitus is associated with a broad range of clinical presentations, from being asymptomatic to ketoacidosis or coma, depending on the degree of metabolic disorder.

Classification (Tables 1, 2; Fig. 1)

The classification of glucose metabolism disorders is principally derived from etiology, and includes staging of pathophysiology based on the degree of deficiency of insulin action. These disorders are classified into four groups: (i) type 1 diabetes mellitus; (ii) type 2 diabetes mellitus; (iii) diabetes mellitus those due to other specific mechanisms or diseases; and (iv) gestational diabetes mellitus. Type 1 diabetes is characterized by destruction of pancreatic β-cells. Type 2 diabetes is characterized by combinations of decreased insulin secretion and decreased insulin sensitivity (insulin resistance). Glucose metabolism disorders in category (iii) are divided into two subgroups; subgroup A is diabetes in which a genetic abnormality has been identified, and subgroup B is diabetes associated with other pathologic disorders or clinical conditions.

In 2009, the Japan Diabetes Society established The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, which published the final committee report in *J Japan Diab Soc* 2010; 53: 460–467 (in Japanese). This is the English version of that report.
Chair of the committee: Y. Seino
Vice-Chair of the committee: K. Nanjo and N. Tajima
Manager of the committee: K. Ueki

Y. Seino (✉)
Kansai Electric Power Hospital, Osaka, Japan
e-mail: seino.yutaka@e2.kepco.co.jp

K. Nanjo
Wakayama Medical University, Wakayama, Japan

N. Tajima
Jikei University School of Medicine, Tokyo, Japan

T. Kadowaki · K. Ueki
Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

A. Kashiwagi
Shiga University of Medical Science Hospital, Ohtsu, Japan

E. Araki
Department of Metabolic Medicine, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

C. Ito
Grand Tower Medical Court Life Care Clinic, Hiroshima, Japan

The staging of glucose metabolism includes normal, borderline and diabetic stages depending on the degree of hyperglycemia occurring as a result of the lack of insulin action or clinical condition. The diabetic stage is then subdivided into three substages: non-insulin-requiring, insulin-requiring for glycemic control, and insulin-dependent for survival. The two former conditions are called non-insulin-dependent diabetes and the latter is known as insulin-dependent diabetes. In each individual, these stages may vary according to the deterioration or the improvement of the metabolic state, either spontaneously or by treatment.

Diagnosis (Tables 3, 4, 5, 6, 7; Fig. 2): categories of the state of glycemia

Confirmation of chronic hyperglycemia is essential for the diagnosis of diabetes mellitus. When plasma glucose levels are used to determine the categories of glycemia, patients are classified as having a diabetic type if they meet one of the following criteria: (i) fasting plasma glucose level of ≥126 mg/dl (≥7.0 mmol/l); (ii) 2-h value of ≥200 mg/dl (≥11.1 mmol/l) in 75 g oral glucose tolerance test (OGTT); or (iii) casual plasma glucose level of ≥200 mg/dl (≥11.1 mmol/l). Normal type is defined as fasting plasma glucose level of <110 mg/dl (<6.1 mmol/l) and 2-h value of <140 mg/dl (<7.8 mmol/l) in OGTT. Borderline type (neither diabetic nor normal type) is defined as falling between the diabetic and normal values. According to the current revision, in addition to the earlier listed plasma glucose values, hemoglobin A1c (HbA1c) has been given a more prominent position as one of the diagnostic criteria. That is, (iv) HbA1c ≥6.5% is now also considered to indicate diabetic type. The value of HbA1c, which is equivalent to the internationally used HbA1c (%) (HbA1c [NGSP]) defined by the NGSP (National Glycohemoglobin Standardization Program), is expressed by adding 0.4% to the HbA1c (JDS) (%) defined by the Japan Diabetes Society (JDS).

Subjects with borderline type have a high rate of developing diabetes mellitus, and correspond to the combination of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) noted by the American Diabetes Association (ADA) and WHO. Although borderline cases show few of the specific complications of diabetes mellitus, the risk of arteriosclerosis is higher than those of normal type. When HbA1c is 6.0–6.4%, suspected diabetes mellitus cannot be excluded, and when HbA1c of 5.6–5.9% is included, it forms a group with a high risk for developing diabetes mellitus in the future, even if they do not have it currently.

Clinical diagnosis

1. If any of the criteria for diabetic type (i) through to (iv) is observed at the initial examination, the patient is judged to be "diabetic type." Re-examination is conducted on another day, and if "diabetic type" is reconfirmed, diabetes mellitus is diagnosed. However, a diagnosis cannot be made only by the re-examination of HbA1c alone. Moreover, if the plasma glucose values [any of criteria (i), (ii), or (iii)] and the HbA1c [criterion (iv)] in the same blood sample both indicate diabetic type, diabetes mellitus is diagnosed based on the initial examination alone. If HbA1c is used, it is essential that the plasma glucose level [criteria (i), (ii), or (iii)] also indicates diabetic type for a diagnosis of diabetes mellitus. When diabetes mellitus is suspected, HbA1c should be measured at the same time as examination for plasma glucose.
2. If the plasma glucose level indicates diabetic type [any of (i), (ii), or (iii)] and either of the following conditions exists, diabetes mellitus can be diagnosed immediately at the initial examination.
   - The presence of typical symptoms of diabetes mellitus (thirst, polydipsia, polyuria, weight loss).
   - The presence of definite diabetic retinopathy.
3. If it can be confirmed that the above conditions 1 or 2 existed in the past, diabetes mellitus can be diagnosed or suspected regardless of the current test results.
4. If the diagnosis of diabetes cannot be established by these procedures, the patient is followed up and re-examined after an appropriate interval.
5. The physician should assess not only the presence or absence of diabetes, but also its etiology and glycemic stage, and the presence and absence of diabetic complications or associated conditions.

N. Inagaki
Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Y. Iwamoto
Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan

M. Kasuga
Research Institute, National Center for Global Health and Medicine, Tokyo, Japan

T. Hanafusa
Department of Internal Medicine (I), Osaka Medical College, Takatsuki, Japan

M. Haneda
Division of Metabolism and Biosystemic Medicine, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan

Epidemiological study

For the purpose of estimating the frequency of diabetes mellitus, "diabetes mellitus" can be substituted for the determination of "diabetic type" from a single examination. In this case, HbA1c ≥6.5% alone can be defined as "diabetes mellitus."

Health screening

It is important not to misdiagnose diabetes mellitus, and thus clinical information such as family history and obesity should be referred to at the time of screening in addition to an index for plasma glucose level.

Gestational diabetes mellitus

There are two hyperglycemic disorders in pregnancy: (i) gestational diabetes mellitus (GDM); and (ii) diabetes mellitus. GDM is diagnosed if one or more of the following criteria is met in a 75 g OGTT during pregnancy:

1. Fasting plasma glucose level of ≥92 mg/dl (5.1 mmol/l).
2. 1-h value of ≥180 mg/dl (10.0 mmol/l).
3. 2-h value of ≥153 mg/dl (8.5 mmol/l).

However, diabetes mellitus that is diagnosed by the clinical diagnosis of diabetes mellitus defined earlier is excluded from GDM.

Review of the history of diagnostic criteria for diabetes mellitus by the Japan Diabetes Society and international background

The Japan Diabetes Society (JDS) has published reports on the diagnostic criteria for diabetes mellitus three times [2–4]. In 2009, a minor revision was made regarding the normal range of fasting plasma glucose level [5].

In 1970, the JDS's first committee proposed reference values for plasma glucose determination in the oral glucose tolerance tests (OGTT) [2]. At that time, glucose tolerance was assessed using the OGTT, and the JDS took the position that the diagnosis of diabetes mellitus should be carried out comprehensively, and should include an evaluation of glucose tolerance. This is the position that diabetes mellitus is not defined by hyperglycemia alone. The classification according to the OGTT includes normal, borderline, and diabetic types. This position is still maintained today.

In 1979, the American National Diabetes Data Group published diagnostic criteria based on the 75 g OGTT and classifications such as insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus [6]. At that time, mild glucose intolerance was categorized as impaired glucose tolerance (IGT). In 1980, the World Health Organization (WHO) Expert Committee issued a report based on this definition [7]. In light of this, the JDS established a second committee and published criteria using the 75 g OGTT [3]. The policy of classifying OGTT by types continued.

In 1997, the American Diabetes Association (ADA) reviewed the plasma glucose reference values for the diagnosis of diabetes mellitus, and a fasting plasma glucose level ≥126 mg/dl (7.0 mmol/l) and an OGTT 2-h value ≥200 mg/dl (11.1 mmol/l) were regarded as diagnostic for diabetes mellitus [8]. The report at that time also recommended making a diagnosis using the fasting plasma glucose level without OGTT in routine clinical practice. Because IGT, which is defined by the 2-h plasma glucose level, cannot be determined without conducting an OGTT, a fasting plasma glucose level between normal and diabetes mellitus values was defined as impaired fasting glucose (IFG) instead. The WHO expert committee issued a similar proposal in 1999, although continuing to recognize the necessity of OGTT in clinical practice [9].

Meanwhile, the JDS had established a third committee on diagnosis and classification in 1995, and had begun updating opinions from an academic panel. They considered the new reports from the ADA and the WHO, and a report on classification and diagnostic criteria for diabetes mellitus was issued in 1999, which has been used until this revision [4]. Etiological classification was emphasized, and diabetes mellitus was divided into type 1, type 2, other types, and gestational diabetes mellitus, together with classification according to pathophysiological stage. The confirmation of chronic hyperglycemia was required for a diagnosis, and diabetic type was defined as a fasting plasma glucose level ≥126 mg/dl (≥7.0 mmol/l), 2-h OGTT value ≥200 mg/dl (≥11.1 mmol/l) or casual plasma glucose level ≥200 mg/dl (≥11.1 mmol/l). Normal type was defined as a fasting plasma glucose <110 mg/dl (<6.1 mmol/l) and 2-h OGTT <140 mg/dl (<7.8 mmol/l), with a diagnosis of borderline type between these two. Clinical diagnosis of diabetes mellitus requires observation of a diabetic type at least twice in tests on different days. However, diabetes mellitus could be diagnosed from a single finding of diabetic type hyperglycemia if (i) there are symptoms of diabetes mellitus; (ii) the hemoglobin A1c (HbA1c) is ≥6.9%; or (iii) there is diabetic retinopathy. However, when conducting an epidemiological survey, researchers may consider a single confirmation of diabetic type hyperglycemia as diabetes mellitus.

In 2003, the ADA lowered the upper limit of normal fasting plasma glucose from 110 mg/dl (6.1 mmol/l) to 100 mg/dl (5.5 mmol/l) [10]. The principal reason for this reduction was that IGT was often overlooked in conventional testing based on fasting plasma glucose level alone. However, the WHO Expert Committee (2006) decided to retain the conventional determination

criterion for fasting plasma glucose level, because a large number of people would be added as having abnormal glycemic control if the fasting plasma glucose level criterion were lowered, and because the population that would be newly determined to have IFG does not have a very high risk of macrovascular disorders [11].

The JDS established a diagnostic criteria exploratory committee on diabetes mellitus and glucose metabolism disorders that examined this question, and found that impaired glucose tolerance is common in the group with fasting plasma glucose levels of 100 mg/dl (5.5 mmol/l) to 109 mg/dl (6.0 mmol/l). In 2008, this segment was called 'high-normal' within the range of normal fasting plasma glucose [5].

Furthermore, the JDS newly established a committee for diagnostic criteria that reviewed the current diagnostic criteria and examined the practical use of HbA1c. The standardization of HbA1c measurement in Japan was examined in the early stage [12], and in the 1999 committee report on the classification and diagnostic criteria for diabetes mellitus, the JDS took global initiative by including HbA1c as an additional tool for diabetes mellitus diagnosis [4]. In Japan, since 1997 the HbA1c has been used to estimate the number of patients with diabetes mellitus in national surveys of diabetes mellitus by the government, and HbA1c is used in national health examinations and health guidance that were initiated in 2008.

Although HbA1c has become widely used as an index for the treatment of diabetes mellitus globally, it hadn't been used as an index for diagnosis. The main reason for this is that HbA1c measurement had not been sufficiently standardized [8]. Thereafter, the standardization of HbA1c measurement was investigated by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and an international expert committee formed by members of the ADA, the European Diabetes Association, and the International Diabetes Federation recommended the use of the HbA1c values of the National Glycohemoglobin Standardization Program (NGSP) for the diagnosis of diabetes mellitus in June 2009 [13]. HbA1c has several advantages in that it is a suitable index of chronic hyperglycemia, a characteristic of diabetes mellitus, blood samples can be taken without concern about the effects of meals, it shows less day-to-day changes than the plasma glucose level, and its relation to the risk of retinopathy is equivalent to that of the plasma glucose level. However, there are also several issues concerning the application of HbA1c for the diagnosis of diabetes mellitus, including that HbA1c is affected by red blood cell turnover in addition to plasma glucose, and that there are differences between the NGSP values that have been used in the USA, Europe, Asia and many other countries for HbA1c (NGSP) and the JDS values used in Japan for HbA1c (JDS).

As described earlier, the fasting plasma glucose level is recommended in the USA for diagnosis of diabetes mellitus because it is simple and easy, while OGTT is recommended in Japan for a more accurate diagnosis. Although HbA1c is widely used as an index for treatment or for epidemiological data, this test alone has not generally been used to diagnose diabetes mellitus. The ADA's expert committee therefore examined the validity of using HbA1c for diagnosis, and in a 1997 report recommended against the use of HbA1c for diagnosing diabetes mellitus. This position was taken mainly because of the lack of progress in standardizing the test [8]. In an additional 2003 report, although HbA1c standardization became possible by applying NGSP, it was still considered that there were disadvantages when using it for diagnosis [10]. However, according to a 2009 report, evaluation of HbA1c as a diagnostic tool was improved, as the accuracy and precision of HbA1c measurement were shown to be similar to those of plasma glucose levels [13]. HbA1c has the further advantage that blood sampling is less burdensome and simpler for the patient, considering that the specimens are comparatively stable after collection and that there has been international progress in standardizing HbA1c measurement.

In addition, HbA1c is a more stable index than the fasting plasma glucose level, and is now considered to be a superior index of chronic hyperglycemia compared to the plasma glucose level, which varies during the day. Based on this, the relationship between HbA1c and diabetic retinopathy specific to diabetes mellitus (moderate non-proliferative diabetic retinopathy or worse) was investigated using a large epidemiological database. Specifically, 48,331 patients aged 20–79 years in nine countries were surveyed, and a diagnosis of diabetes mellitus based on HbA1c was proposed because of the higher frequency of retinopathy with HbA1c (NGSP) $\geq$6.5% [13]. Thus, in January 2010, the American Diabetes Association proposed new diagnostic criteria for diabetes mellitus with HbA1c in parallel with three plasma glucose indices [14].

As described later, HbA1c (JDS) is approximately 0.4% lower than HbA1c (NGSP) [15], and this difference was not considered in the international standardization of plasma glucose control targets. Standardization and precision control of HbA1c measurement has been successfully practiced in Japan, but because most other countries use the NGSP values at present, it is judged appropriate to shift to a new internationally standardized HbA1c by adding 0.4% to the conventional HbA1c (JDS) value.

Concept of diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia due to insufficient

insulin action. The common feature of this group of diseases is a deficiency of insulin action, which leads to abnormalities in almost the entire metabolic system, including carbohydrate, lipid and protein metabolism. The mechanism for a lack of insulin action in this group of diseases includes insufficient insulin secretion (absolute or relative) and decreased insulin sensitivity (insulin resistance) in organs (cells) on which insulin acts.

The causes of diabetes mellitus are various, including both genetic and environmental factors. Insufficient insulin secretion can occur in association with destruction of pancreatic islet β-cells or due to dysfunction within the pancreatic β-cells themselves. Besides the decrease in insulin supply, decreased insulin sensitivity can contribute to relative insufficient insulin action. In either case, the principal mechanism for development of diabetes is decreased functional pancreatic β-cell mass that results in failure to provide adequate insulin action on the organs. The associated metabolic disorders can be improved by various therapeutic means to ameliorate insufficient insulin action.

If the metabolic abnormality is mild, patients may be asymptomatic, and thus may neglect it for a long time. However, in a metabolic state with markedly high plasma glucose levels, thirst, polydipsia, polyuria and weight loss can be seen. In the most extreme cases, ketoacidosis or a marked hyperosmotic, hyperglycemic state occurs, which can lead to disturbance of consciousness, coma and even death if no effective treatment is provided.

With long duration of diabetic metabolism, diabetes-specific complications, chiefly involving small vessels (retinopathy, nephropathy and neuropathy), may ensue and lead to serious outcomes, such as visual disturbance, renal failure and gangrene. Diabetes accelerates and exacerbates the occurrence of arteriosclerosis, increasing the risks for myocardial infarction, stroke and occlusive artery disease of the lower extremities. These complications constitute the major causes of morbidity and mortality in diabetic patients.

Classification

Etiological classification and pathophysiological stages

Etiology and pathophysiological stages (or states) should be assessed separately for each patient. Before development of overt diabetes, patients will pass stages at which different degrees of deficiency of insulin action exist. The abnormal glucose metabolism not only progresses, but may regress spontaneously or in response to treatment. For example, islet autoantibodies are occasionally detected before recognition of hyperglycemia, suggesting that the autoimmune process of type 1 diabetes has already begun. Obese diabetic patients may be improved to borderline type

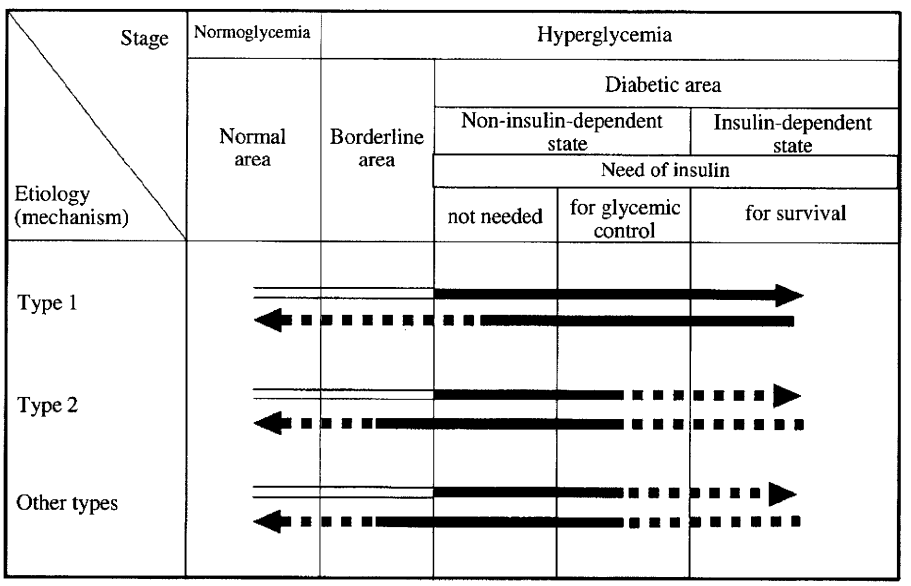

Fig. 1 A scheme of the relationship between etiology (mechanism) and patho-physiological stages (states) of diabetes mellitus. *Arrows* pointing *right* represent worsening of glucose metabolism disorders (including onset of diabetes mellitus). Among the *arrow lines*, ▬ ▪▪▪ indicates the condition classified as "diabetes mellitus". *Arrows* pointing *left* represent improvement in the glucose metabolism disorder. The *broken lines* indicate events of low frequency. For example, in type 2 diabetes mellitus, infection can lead to ketoacidosis and require temporary insulin treatment for survival. Also, once diabetes mellitus has developed, it is treated as diabetes mellitus regardless of improvement in glucose metabolism, therefore, the *arrow lines* pointing *left* are filled in *black*. In such cases, a *broken line* is used, because complete normalization of glucose metabolism is rare

Table 1 Etiological classification of diabetes mellitus and glucose metabolism disorders

I. Type 1 (destruction of pancreatic β-cells, usually leading to absolute insulin deficiency)
A. Autoimmune
B. Idiopathic
II. Type 2 (ranging from predominantly insulin secretory defect, to predominantly insulin resistance with varying degrees of insulin secretory defect)
III. Due to other specific mechanisms or diseases (see Table 2 for details)
A. Those in which specific mutations have been identified as a cause of genetic susceptibility
(1) Genetic abnormalities of pancreatic β-cell function
(2) Genetic abnormalities of insulin action
B. Those associated with other diseases or conditions
(1) Diseases of exocrine pancreas
(2) Endocrine diseases
(3) Liver disease
(4) Drug- or chemical-induced
(5) Infections
(6) Rare forms of immune-mediated diabetes
(7) Various genetic syndromes often associated with diabetes
IV. Gestational diabetes mellitus

The occurrence of diabetes-specific complications has not been confirmed in some of these conditions. Those that cannot at present be classified as any of the above are called unclassifiable

or even to normal glucose tolerance after weight reduction with diet therapy. The horizontal axis in Figure 1 shows the degree of deficiency of insulin action associated with a disorder of glucose metabolism. The patients are judged to have diabetes when hyperglycemia has exceeded a certain level, which is presumed to confer risk for specific complications. The diabetic area is divided into three stages, (i) in which insulin treatment is not needed; (ii) in which insulin injections are required for glycemic control; and (iii) in which insulin treatment is indispensable to prevent ketosis and to sustain life.

The terms type 1 and type 2 are used for classification based on etiology. The terms insulin-dependent and non-insulin-dependent are used for pathophysiological staging of diabetes mellitus regardless of the etiology. In this case, failure to administer insulin in an insulin-dependent condition can lead to ketosis and can be life threatening. Patients whose conditions do not require insulin treatment for prevention of ketosis or for survival, but require insulin for glycemic control are considered to be in a non-insulin-dependent state.

Etiological classification

Etiological classifications of diabetes mellitus and glucose metabolism disorders are shown in Table 1, and use the terms type 1 and type 2. In recent years, various forms of diabetes with genetic abnormalities have been identified, and are treated as a separate category. An individual patient may have diabetes mellitus resulting from multiple etiological causes. Those that cannot be classified at the present time are called unclassifiable.

Type 1 diabetes mellitus

Diabetes mellitus is caused by insulin deficiency due to destruction of pancreatic β-cells principally via an autoimmune reaction, which is itself triggered by different factors. Type 1 diabetes develops in association with certain hereditary factors, such as HLA alleles, plus inducements/environmental factors, such as a virus infection. Diabetes resulting as one of the manifestations of other autoimmune disorders is not rare. As destruction of pancreatic β-cells progresses, an absolute deficiency in insulin often occurs. It is typically regarded as developing rapidly in young people, but it can occur in any age group.

In many cases, autoantibodies against islet antigens (islet-associated antibodies) are verifiable in the early phase of the disease, and because pancreatic β-cell destruction involves autoimmune mechanisms, these are called "autoimmune" type 1 diabetes mellitus. There are also cases that reach an insulin-dependent state without verifiable autoantibodies, and these are called "idiopathic" type 1 diabetes mellitus. However, patients who are dependent on insulin therapy and are autoantibody negative, but due to an identified cause, such as a genetic abnormality, and those with temporary insulin dependence, such as soft drink ketosis, are not included in the idiopathic category. Depending on the manner of onset and progression, it is classified as fulminant, acute or slowly progressive [16–20].

Type 2 diabetes mellitus

Diabetes mellitus develops in association with multiple genetic factors that lead to decreased insulin secretion or

insulin resistance augmented by lifestyle habits, such as overeating (especially high fat diet), lack of exercise and resultant obesity, as environmental factors and results in insufficient insulin action. It is presumed that most cases involve multiple genetic factors, with some of these now elucidated [21, 22]. Decreased insulin secretion and decreased insulin sensitivity are both involved in the onset of type 2 diabetes mellitus, but the proportion of their involvement differs according to the patient. Non-insulin-dependent diabetes mellitus is mostly of this type. Pancreatic β-cell function is retained to a certain degree, and insulin injections are rarely required for survival. However, complications, such as infections, can lead to ketoacidosis temporarily. Insulin secretion is particularly decreased in the early secretory response after a glucose load. Obesity or a history of obesity is common.

Onset is commonly regarded to be in middle age or later, but this type of diabetes mellitus has recently been shown to be increasing in children and young people [23]. The nature of type 2 diabetes mellitus is clearly not uniform, but it might possibly be further divided according to the presence or absence of obesity and differences in the degree of involvement of decreased insulin secretion and decreased insulin sensitivity.

Other types of diabetes mellitus due to specific causes

These are divided into two groups (Table 2)

(A) Diabetes mellitus with identified genetic abnormalities: With the recent progress in genetic technology, several single genetic abnormalities have now been identified as causing diabetes mellitus [24–29]. These are divided into (i) genetic abnormalities related to pancreatic β-cell function; and (ii) genetic abnormalities relevant to mechanisms of insulin action. Each group can be further divided according to the type of genetic abnormality. For example, (i) includes defects in the insulin gene itself and MODY [24, 25]. MODY 1 through to 6 correspond to genetic abnormalities of HNF-4α, glucokinase, HNF-1α, IPF-1 (PDX-1), HNF-1β and NeuroD1/Beta 2 [30], respectively. Mitochondrial genetic abnormalities [26] and amylin genetic abnormalities [27] are also included in (i). Recently, in neonatal diabetes, genetic abnormalities in Kir6.2 and SUR1, which form the K_{ATP} channel in pancreatic β-cells, have been identified [31, 32]. Genetic abnormalities such as those in insulin receptors are included in (ii) [28].

(B) Various types of diabetes associated with other disorders and conditions: Some disorders, syndromes and conditions can be accompanied by a diabetic stage, and these have conventionally been called secondary diabetes. They include diabetes associated with pancreatic disease, endocrine disease, liver disease, drug use, exposure to chemical substances, viral infections, and various genetic syndromes.

Gestational diabetes mellitus

Glucose metabolism disorder that is first discovered or develops during pregnancy, excluding clinically diagnosed diabetes mellitus (details described later). The etiology is presumably based on common pathogenic mechanisms with type 1 and type 2, with pregnancy triggering the manifestation of a glucose metabolism disorder. It is debated whether gestational diabetes mellitus (GDM) should be treated as an independent etiological classification, but due to its clinical importance, the need for special consideration and different features from diabetes in the absence of pregnancy, it is treated as a separate category. This is because pregnancy itself worsens glucose metabolism, and diagnosis and control require special considerations that are different from those in the absence of pregnancy, and even a comparatively mild disorder in glucose metabolism during pregnancy can exert significant influence on the infant and mother. In addition, glucose metabolism disorders during pregnancy often return to normal after delivery, but the risk of developing diabetes in the future is increased in women who have disorders of glucose metabolism during pregnancy.

Useful findings for the classification of diabetes mellitus

For etiological classification of diabetes, the following clinical information is useful:

1. Detailed information about the family history of diabetes and the mode of inheritance.
2. Age of onset and the course of diabetes.
3. Physical characteristics, such as obesity, history of weight changes in the past, hearing disturbance (mitochondrial DNA abnormality) and acanthosis nigricans (severe insulin resistance).
4. For diagnosing type 1 diabetes mellitus, examination of islet-associated antibodies such as GAD antibody, IA-2 antibody, insulin autoantibody (IAA; present before the use of insulin), islet cell antibody (ICA) and ZnT8 antibody. The presence of any of these autoantibodies suggests type 1 diabetes.
5. Examination of HLA antigens. Disease-susceptible HLA related to type 1 diabetes in Japanese patients are DR4 and DR9, while disease-resistant HLA is DR2; as DR4 and DR9 are also frequently present in healthy individuals, a diagnosis of type 1 diabetes cannot be made only if these

Table 2 Diabetes mellitus and glucose metabolism disorders due to other specific mechanisms and diseases

A. Those in which specific mutations have been identified as a cause of genetic susceptibility	B. Those associated with other diseases or conditions
(1) Genetic abnormalities of pancreatic β-cell function. Insulin gene (abnormal insulinemia, abnormal proinsulinemia, neonatal diabetes mellitus)	(1) Diseases of exocrine pancreas
HNF 4α gene (MODY1)	Pancreatitis
Glucokinase gene (MODY2)	Trauma/pancreatectomy
HNF 1α gene (MODY3)	Neoplasm
IPF-1 gene (MODY4)	Hemochromatosis
HNF 1β gene (MODY5)	Others
Mitochondria DNA (MIDD)	
NeuroD1 gene (MODY6)	
Kir6.2 gene (neonatal diabetes mellitus)	
SUR1 gene (neonatal diabetes mellitus)	
Amylin	
Others	
(2) Genetic abnormalities of insulin action	(2) Endocrine diseases
Insulin receptor gene	Cushing's syndrome
(type A insulin resistance, leprechaunism, Rabson–Mendenhall syndrome etc.)	Acromegaly
Others	Pheochromocytoma
	Glucagonoma
	Aldosteronism
	Hyperthyroidism
	Somatostatinoma
	Others
	(3) Liver disease
	Chronic hepatitis
	Liver cirrhosis
	Others
	(4) Drug- or chemical-induced
	Glucocorticoids
	Interferon
	Others
	(5) Infections
	Congenital rubella
	Cytomegalovirus
	Others
	(6) Rare forms of immune-mediated diabetes
	Anti-insulin receptor antibodies
	Stiffman syndrome
	Insulin autoimmune syndrome
	Others
	(7) Various genetic syndromes often associated with diabetes
	Down syndrome
	Prader-Willi syndrome
	Turner syndrome
	Klinefelter syndrome
	Werner syndrome
	Wolfram syndrome
	Ceruloplasmin deficiency
	Lipoatrophic diabetes mellitus
	Myotonic dystrophy
	Friedreich ataxia
	Laurence-Moon-Biedl syndrome
	Others

The occurrence of diabetes-specific complications has not been confirmed in some of these conditions

antigen types are shown; this condition should be considered with an ancillary diagnosis that patients having no DR4 or DR9 and those having DR2 are unlikely to have type 1 diabetes, that major disease-susceptible haplotypes of type 1 diabetes in Japanese patients at the gene level (DNA typing) are DRB1*0405-DQB1*0401 and DRB1*0901-DQB1*0303, and that the manner in which these haplotypes are combined has a bearing on the mode of development of the disease.

6. Tests for insulin secretion and insulin resistance (fasting plasma insulin and C-peptide levels, insulin response to glucose loading, and, in particular cases, hyperinsulinemic euglycemic clamp or minimal model etc.).
7. DNA analysis may give a definite diagnosis in special cases belonging to A(1) and A(2) in Table 2.

However, the etiological classification of diabetes mellitus based on these data is not immediately required for treatment.

To assess the pathophysiological stage of diabetes, clinical information (history of the disease, glycemic level and its stability, ketosis-proneness, and response to diet and drug therapy), plasma insulin assays (fasting and after glucose load, and after intravenous glucagon), and C-peptide assays in plasma and urine will help to evaluate the degree of insulin deficiency.

Diagnosis

The diagnosis of diabetes mellitus is the process of confirming that the subject conforms to the disease concept described earlier. Confirmation of chronic hyperglycemia is essential for a diagnosis of diabetes mellitus. Table 3 shows the criteria for fasting plasma glucose levels, 75 g OGTT 2-h plasma glucose levels, casual plasma glucose level and HbA1c measurements. Fasting plasma glucose is measured before breakfast under fasting conditions, at least 10 h from the night before (water may be consumed). OGTT is described later. Temporal relation of diet to blood sampling time is disregarded in the casual plasma glucose test.

Table 3 Criteria of fasting plasma glucose levels and 75 g oral glucose tolerance test 2-h value

	Normal range	Diabetic range
Fasting value	<110 mg/dl (6.1 mmol/l)	≥126 mg/dl (7.0 mmol/l)
75 g OGTT 2-h value	<140 mg/dl (7.8 mmol/l)	≥200 mg/dl (11.1 mmol/l)
Evaluation of OGTT	Normal type: if both values belong to normal range	Diabetic type[a]: if any of the two values falls into diabetic range
	Borderline type: neither normal nor diabetic types	

Even for normal type, if 1-h value is ≥180 mg/dl (10.0 mmol/l), the risk of progression to diabetes mellitus is greater than for <180 mg/dl (10.0 mmol/l) and should be treated as with borderline type (follow-up observation, etc.). Fasting plasma glucose level of 100–109 mg/dl (5.5–6.0 mmol/l) is called "high-normal": within the range of normal fasting plasma glucose. Plasma glucose level after glucose load in oral glucose tolerance test (OGTT) is not included in casual plasma glucose levels. The value for HbA1c (%) is indicated with 0.4% added to HbA1c (JDS) (%)

[a] Casual plasma glucose ≥200 mg/dl (≥11.1 mmol/l) and HbA1c ≥6.5% are also regarded as to indicate diabetic type

The plasma glucose is often elevated temporarily in cases of severe stress (for example, infections, myocardial infarction, stroke and surgery). Therefore, excepting the situation of a severe metabolic disturbance necessitating immediate treatment, the evaluation of hyperglycemia should be made after resolution of such stressful conditions.

We first describe the procedures for diagnosis in the clinical setting, and then epidemiological study and health screening.

Clinical diagnosis

Clinical diagnosis involves not only the presence or absence of diabetes mellitus, but requires a comprehensive understanding of the etiology, stage, degree of glucose metabolism disorder, and the presence and degree of complications. In the present report, plasma glucose and HbA1c levels are described as "type," as in past reports of the JDS. This is based on the position that determination of test results and diagnosis of the disease (or a group of diseases) are different.

Procedures for the diagnosis of diabetes mellitus (Tables 4, 5; Fig. 2)

1. At initial examination, if any of the following is observed, it is determined to be "diabetic type": (i) fasting plasma glucose level ≥126 mg/dl (≥7.0 mmol/l); (ii) 75 g OGTT 2-h value ≥200 mg/dl (≥11.1 mmol/l); (iii) casual plasma glucose level ≥200 mg/dl (≥11.1 mmol/l); or (iv) HbA1c ≥6.5%. Re-examination is conducted at another date, and diabetes mellitus is diagnosed if "diabetic type" is reconfirmed. However, a diagnosis cannot be made only on the basis of a repeat HbA1c examination. If the same blood sample is confirmed to be a diabetic type both by the plasma glucose level and HbA1c [any of (i)–(iii) plus (iv)], then diabetes mellitus can be diagnosed from the initial examination. When HbA1c is used, it is essential that the plasma glucose level [any of (i)–(iii)] also indicates diabetic type for a diagnosis of diabetes mellitus.
2. If the plasma glucose level indicates diabetic type [any of (i)–(iii)] and either of the following conditions

Table 4 Procedures for diagnosing diabetes mellitus

Clinical diagnosis
1. At initial examination, a "diabetic type" is diagnosed if any of the following criteria are met: (1) fasting plasma glucose level ≥126 mg/dl (7.0 mmol/l), (2) 75 g OGTT 2-h value ≥200 mg/dl (11.1 mmol/l), (3) casual plasma glucose level ≥200 mg/dl (11.1 mmol/l) or (4) HbA1c[a] ≥6.5%. Re-examination is carried out at another date, and diabetes mellitus is diagnosed if "diabetic type" is confirmed again[b]. However, diagnosis cannot be made on the basis of a repeated HbA1c test alone. If the same blood sample is confirmed to be diabetic type by both plasma glucose and HbA1c levels [any of (1) to (3) plus (4)], then diabetes mellitus can be diagnosed from the initial test
2. If plasma glucose level shows diabetic type [any of (1) to (3)] and either of the following conditions exists, diabetes mellitus can be diagnosed immediately at the initial examination
•The presence of typical symptoms of diabetes mellitus (thirst, polydipsia, polyuria, weight loss)
•The presence of definite diabetic retinopathy
3. If it can be confirmed that either of the above conditions 1. or 2. existed in the past, diabetes mellitus must be diagnosed or suspected even if present test values do not meet the above conditions
4. If diabetes mellitus is suspected but the diagnosis cannot be made by the above 1. to 3., the patient should be followed-up
5. The following points should be kept in mind when selecting the method of determination in initial examination and re-examination
• If HbA1c is used at initial examination, another method of determination is required for diagnosis at re-examination. As a rule, both plasma glucose level and HbA1c should be measured
• If casual plasma glucose level is ≥200 mg/dl (11.1 mmol/l) at the initial test, a different test method is desirable for re-examination
• In the case of disorders and conditions in which HbA1c may be inappropriately low, plasma glucose level should be used for diagnosis (Table 5)
Epidemiological study
For the purpose of estimating the frequency of diabetes mellitus, determination of "diabetic type" from a single test can be considered to represent "diabetes mellitus". Whenever possible, the criteria to be used are HbA1c ≥6.5% or OGTT 2-h value ≥200 mg/dl (11.1 mmol/l)
Health screening
It is important to detect diabetes mellitus and identify high risk groups without overlooking anyone. Therefore, besides measuring plasma glucose and HbA1c, clinical information such as family history and obesity should be referred

OGTT oral glucose tolerence test

[a] The value for HbA1c (%) is indicated with 0.4% added to HbA1c (JDS) (%)

[b] Hyperglycemia must be confirmed in a non-stressful condition

Table 5 Disorders and conditions associated with low HbA1c values

Anemia
Liver disease
Dialysis
Major hemorrhage
Blood transfusion
Chronic malaria
Hemoglobinopathy
Others

exists, diabetes mellitus can be diagnosed, even at the initial examination.

- The presence of typical symptoms of diabetes mellitus (thirst, polydipsia, polyuria, weight loss).
- The presence of definite diabetic retinopathy.

3. If it can be confirmed that either of the conditions 1 or 2 existed in the past, diabetes mellitus must be diagnosed or suspected, even if the present test values do not meet these conditions.
4. If diabetes mellitus is suspected, but the diagnosis cannot be made by conditions 1–3, diabetes mellitus should be suspected, and plasma glucose level and HbA1c should be measured again within 3–6 months.
5. Points to keep in mind are that when fasting plasma glucose level is used for determination, it is important to confirm the fasting conditions. If the casual plasma glucose level is ≥200 mg/dl (≥11.1 mmol/l) at the initial examination, an alternative test method is desirable at the second time. As a rule, both plasma glucose level and HbA1c should be measured during examination. In case of the disorders and conditions shown in Table 5, in which HbA1c may be apparently low, the plasma glucose level should be used for diagnosis.

OGTT and the criteria for OGTT

1. Procedure of OGTT
   OGTT evaluates the rate of glucose disposal after an oral glucose challenge, and is the most sensitive test to detect a mild disturbance of glucose metabolism. When the results of the fasting plasma glucose level, casual plasma glucose level or HbA1c measurement are not definite, OGTT results provide solid information for diagnosing diabetes mellitus. In clinical