

Causes of death in Japanese diabetics: A questionnaire survey of 18,385 diabetics over a 10-year period

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ABSTRACT

We collated and analysed data from hospital records regarding the cause of death of 18,385 patients with diabetes who died in 282 medical institutions throughout Japan over the 10-year period between 1991 and 2000. Autopsy was carried out in 1750 cases. The most frequent cause of death in all 18,385 cases was malignant neoplasia, accounting for 34.1% of cases, followed by vascular diseases (including diabetic nephropathy, ischemic heart diseases and cerebrovascular diseases) in 26.8%, infections in 14.3%, and then diabetic coma in 1.2%. The most common malignancy was liver cancer, accounting for 8.6% of all the deaths. Of the deaths from vascular diseases, diabetic nephropathy was the cause of death in 6.8% of cases, and the frequency as cause of death for ischemic heart diseases and cerebrovascular diseases were similar at 10.2% and 9.8%, respectively. Myocardial infarction accounted for almost all the deaths from ischemic heart diseases, whereas deaths from cerebral infarction were 2.2-fold as common as those from cerebral hemorrhage. In the analyses of the relationship between age and causes of death in diabetic patients who underwent autopsy, the overall 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. The mortality rate from ischemic heart diseases increased with age, however, and was higher than the other forms of vascular diseases from the sixth decade of life, accounting for approximately 50% of 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 the deaths. The mortality rate from infections varied little between age groups from the fifth decade of life. In the analyses of glycemic control and the age at the time of death, lifespans were 2.5 years shorter in males, and 1.6 years shorter in female diabetics with poor glycemic control than in those with good or fair glycemic control. This difference was greater for deaths as a result of infections and vascular diseases, particularly diabetic nephropathy, than for malignant neoplasia. Analysis of the relationship between glycemic control and the duration of diabetes and deaths as a result of vascular diseases showed no correlation between the level of glycemic control and death from diabetic nephropathy, ischemic heart diseases or cerebrovascular diseases. In diabetics with disease durations of less than 10 years, the mortality rate from macroangiopathy was higher than that as a result of diabetic nephropathy, a form of microangiopathy. Treatment for diabetes comprised of diet alone in 21.5%, oral hypoglycemic agents in 29.5%, and insulin with or without oral hypoglycemic agents in 44.2%, which was 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. The average age at the time of death in the survey population was, 68 years for males and 71.6 years for females. These were 9.6 and 13 years, respectively, short of the average life expectancy for the Japanese general population. In comparison with the previous survey (1981–1990), the average age at the time of death had increased 1.5 years for males, and 3.2 years for females. The average life expectancy for the Japanese general population had also increased 1.7 and 2.7 years, respectively, over that period, showing that advances in the management and treatment of diabetes have not led to any improvement in patients' life expectancies. (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2010.00019.x, 2010)

KEY WORDS: Causes of death in Japanese diabetics, Average age at the time of death, Diabetic nephropathy, Ischemic heart diseases, Cerebrovascular diseases

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[In 2001, the Japan Diabetes Society established a 'Committee on Causes of Death in Diabetes Mellitus', which published its final committee report in 2006¹. This is the English version of that report with some revisions; produced to enhance the understanding for our non-Japanese colleagues and other interested parties.]

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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 2030². 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 earlier³. 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 (%).

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

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 (%).

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+		Total			
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F				
No. cases	0	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	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	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	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	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	0	1	1	2	1 (0.1)	3 (0.5)	4 (0.2)
Cerebrovascular diseases	0	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	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	0	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	0	2	1	0	1	2 (0.2)	2 (0.4)	4 (0.2)
Diabetic coma	0	0	2	0	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	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	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	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	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	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	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	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	0	1	0	0	2	2	0 (0.0)	5 (0.9)	5 (0.3)
Others	0	0	0	1	0	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	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	0	1	3	1	3 (0.3)	2 (0.4)	5 (0.3)
Pneumonia	0	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	0	0	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	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	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	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	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)	Total (n = 3032)	Male (n = 728)	Female (n = 1658)	Total (n = 4690)	Total (n = 7512)	Male (n = 4690)	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) (100%)	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 survey⁶ and the first survey⁵, 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-Americans¹²⁻¹⁷, 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 impor-

ance 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 periods¹⁸. 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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