Table 2—Clinical events and outcomes in patients with severe hypoglycemia*

Event	T1DM	T2DM	*P*
n	88	326	
Severe hypertension†	17 (19.8)/86	125 (38.8)/322	0.001
Preexisting hypertension (+)‡	9 (34.6)/26	92 (41.3)/223	0.51
Preexisting hypertension (−)	8 (13.3)/60	33 (33.3)/99	0.005
Hypokalemia (mEq/L)§			
Serum potassium <3.5	36 (42.4)/85	111 (36.3)/306	0.30
Serum potassium <3.0	9 (10.6)/85	31 (10.1)/306	0.90
QT prolongation (s)			
QTc ≥0.44¶	16 (50.0)/32	100 (59.9)/167	0.29
QTcF ≥0.44‖	9 (28.1)/32	72 (43.1)/167	0.11
QTc ≥0.50	0 (0)/32	24 (14.4)/167	0.02
QTcF ≥0.50	0 (0)/32	12 (7.2)/167	0.11
Newly diagnosed complications			
Cardiovascular disease**	0 (0)/88	5 (1.5)/326	0.58
Atrial fibrillation	0 (0)/88	14 (4.3)/326	0.04
Trauma	5 (5.8)/88	19 (5.8)/326	0.95
Subarachnoid hemorrhage	0 (0)/88	2 (0.6)/326	1.00
Fracture	0 (0)/88	2 (0.6)/326	1.00
Death	0 (0)/88	6 (1.8)/326	0.34

Data are *n* (%)/total *N*. †Severe hypertension was defined as systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥120 mmHg. ‡Preexisting hypertension was confirmed when the patient was being treated with antihypertensive medication or had been previously diagnosed as having hypertension. §Serum potassium levels were measured upon arrival. ¶QTc was calculated using the Bazett formula: QTc = QT interval ÷ square root of the R-R interval. ‖QTcF was calculated using the Fridericia formula: QTcF = QT interval ÷ cube root of the R-R interval. **Cardiovascular disease was defined as coronary heart disease requiring revascularization treatment or radiologically confirmed stroke.

before and after treatment. This result might be partly attributable to the fact that T1DM patients typically experience frequent episodes of hypoglycemia and their counterregulatory response to hypoglycemia becomes blunted as a result of hypoglycemia-associated autonomic failure (22,24). For similar reasons, severe hypertension during an episode of severe hypoglycemia might not be observed as frequently in T1DM patients as in T2DM patients.

Profound hypoglycemia causes neuroglycopenic symptoms, including cognitive impairment, seizure, and coma (1), and this study suggested that the GCS scores were significantly lower in patients with lower blood glucose levels than in patients with higher blood glucose levels, even in patients with severe hypoglycemia. Although the association between hypothermia and hypoglycemia due to intracellular glycopenia has long been known (25), the body temperature of patients with severe hypoglycemia has rarely been examined in clinical settings (26). In the current study, hypothermia was often observed, particularly in patients with relatively low blood glucose levels. Hypothermia can lead to lethal outcomes and arrhythmias such as ventricular tachycardia and atrial fibrillation, which was frequently observed in the current study (16,18,27,28). Conversely, hypothermia may prevent hypoglycemia-induced neuronal death (29), and further research is needed.

The potassium levels in patients with severe hypoglycemia have not been fully investigated. This study demonstrated that many patients with severe hypoglycemia also had hypokalemia. Hyperinsulinemia, hypothermia, and the increased secretion of catecholamines might drive potassium into the cell during hypoglycemia (30,31). Because hypokalemia increases the risk of lethal arrhythmias, this condition presents another threat associated with severe hypoglycemia.

Recently, several studies have reported an association between hypoglycemia and QT prolongation (11–13), which reflects abnormal cardiac repolarization and may be a marker of increased mortality in T1DM patients (32). The results of the current study demonstrated that not only T1DM patients but also many T2DM patients exhibited an abnormal QT prolongation during severe hypoglycemia. In particular, T2DM patients frequently exhibited a highly abnormal QT prolongation during severe hypoglycemia. In addition, the association between QT prolongation and new-onset atrial fibrillation in patients with severe hypoglycemia may be supported by a recent study that revealed an association between prolonged QT interval and onset of atrial fibrillation (33). However, the causation in this study was not clear; therefore, further studies are needed. Although cardiac arrest as a result of torsade de pointes in acquired long QT syndrome is rare, such an event is potentially catastrophic (18,34).

Some previous studies have examined the relationship between hypoglycemia and cardiovascular events (2,3). However, few studies have systematically investigated whether cardiovascular events actually develop during episodes of hypoglycemia. The current study demonstrated that 1.5% of the T2DM patients with severe hypoglycemia actually exhibited new-onset cardiovascular events. Although the causality was not clear, catecholamine hypersecretion as a result of severe hypoglycemia might lead to hazardous cardiovascular stress, aggravating vascular complications

(9,10,35). In addition to the high incidence of new-onset atrial fibrillation, the T2DM patients with newly diagnosed cardiovascular disease had no history of cardiovascular disease, preexisting hypertension, or an estimated GFR of <60 mL/min/1.73 m^2. However, any associations among these diseases remain unclear, and further large-scale investigations are warranted. On the other hand, no cardiovascular events were observed among T1DM patients, consistent with the results reported by a recent study (36). One possible explanation is that, compared with T2DM patients, T1DM patients typically have fewer comorbidities (such as hypertension and dyslipidemia) and a weaker counterregulatory response to hypoglycemia as a result of hypoglycemia-associated autonomic failure.

Previous reports have suggested that severe hypoglycemia is associated with increased mortality (4–6). Although the mortality rates between T1DM and T2DM patients with severe hypoglycemia were not significantly different in this study, none of the T1DM patients with severe hypoglycemia died. In the current study, 1.8% of the T2DM patients with severe hypoglycemia died, and a significant association between the blood glucose levels and death was observed. Although unknown variables might exist, blood glucose levels could reflect the severity of the underlying disease in patients with severe hypoglycemia. Moreover, our study also showed that the death of T2DM patients was significantly associated with infection and cancer, resulting in severe hypoglycemia, as well as preexisting advanced liver disease. Therefore, the etiologic agents and comorbidities in patients with severe hypoglycemia might have influenced the mortality rate.

Our study had several limitations. First, this study was performed at a single national center and was limited to a specific geographical area. Therefore, large-scale studies at multiple centers throughout the world are needed to confirm the results. Second, missing data and limited samples might have influenced the results and the statistical analyses. However, few studies have investigated the detailed conditions of patients with severe hypoglycemia, and we believe that our study provides extremely important information about severe hypoglycemia. Third, coronary heart disease that did not require revascularization and ischemic changes on electrocardiograms obtained upon hospital arrival could not be sufficiently evaluated. Unfortunately, electrocardiograms obtained before the onset of severe hypoglycemia were only available for a few patients. Moreover, stroke that could not be radiologically proven might have occurred. However, the occurrence of coronary heart disease requiring revascularization and radiologically confirmed stroke in T2DM patients with severe hypoglycemia was notable. Finally, patients with prehospital cardiopulmonary arrest could not be examined. Some patients with severe hypoglycemia might have died in prehospital settings. Furthermore, considering the critical conditions of patients with severe hypoglycemia, we believe that dead-in-bed syndrome and sudden cardiac death could possibly occur (37,38).

In conclusion, this study revealed that T1DM and T2DM patients with severe hypoglycemia experienced many critical problems that could lead to cardiovascular disease, fatal arrhythmia, and death. Our results also clarified that each patient with severe hypoglycemia had different risks, depending on his or her underlying disease.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.T. conceived the study, designed the protocol, contributed to data collection and preparation, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. R.Y.-H. contributed to data collection and preparation, analyzed all data, wrote the report, contributed to the interpretation of the results, and approved the final version. H.K. and A.K. contributed to data collection and preparation, contributed to the interpretation of the results, and approved the final version. M.Ki. contributed to data collection and preparation, analyzed all data, contributed to the interpretation of the results, and approved the final version. H.N. analyzed all data, contributed to the interpretation of the results, and approved the final version. R.H. contributed to data collection and preparation, contributed to the interpretation of the results, and approved the final version. M.Ka. designed the protocol, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. M.N. designed the protocol, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. M.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26:1902–1912
2. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010; 340:b4909
3. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
4. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007;35:2262–2267
5. Hermanides J, Bosman RJ, Vriesendorp TM, et al. Hypoglycemia is associated with intensive care unit mortality. Crit Care Med 2010;38:1430–1434
6. Finfer S, Liu B, Chittock DR, et al.; NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108–1118
7. McMurtry RJ. Letter: Propranolol, hypoglycemia, and hypertensive crisis. Ann Intern Med 1974;80:669–670
8. Mann SJ, Krakoff LR. Hypertensive crisis caused by hypoglycemia and propranolol. Arch Intern Med 1984;144:2427–2428
9. Hilsted J, Bonde-Petersen F, Nørgaard MB, et al. Haemodynamic changes in insulin-induced hypoglycaemia in normal man. Diabetologia 1984;26:328–332
10. Fisher BM, Gillen G, Dargie HJ, Inglis GC, Frier BM. The effects of insulin-induced hypoglycaemia on cardiovascular function in normal man: studies using radionuclide ventriculography. Diabetologia 1987;30: 841–845
11. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. Diabetes 2003;52:1469–1474
12. Gruden G, Giunti S, Barutta F, et al. QTc interval prolongation is independently associated with severe hypoglycemic attacks in type 1 diabetes from the

EURODIAB IDDM complications study. Diabetes Care 2012;35:125–127

13. Christensen TF, Tarnow L, Randløv J, et al. QT interval prolongation during spontaneous episodes of hypoglycaemia in type 1 diabetes: the impact of heart rate correction. Diabetologia 2010;53:2036–2041
14. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl. 1):S11–S63
15. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81–84
16. Brown DJ, Brugger H, Boyd J, Paal P. Accidental hypothermia. N Engl J Med 2012;367:1930–1938
17. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–2572
18. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003;289:2120–2127
19. Drew BJ, Ackerman MJ, Funk M, et al.; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010; 121:1047–1060
20. Matsuo S, Imai E, Horio M, et al.; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53:982–992
21. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988;318: 1487–1492
22. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia 2002;45:937–948
23. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169–3176
24. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004;350:2272–2279
25. Freinkel N, Metzger BE, Harris E, Robinson S, Mager M. The hypothermia of hypoglycemia. Studies with 2-deoxy-D-glucose in normal human subjects and mice. N Engl J Med 1972;287:841–845
26. Tran C, Gariani K, Herrmann FR, et al. Hypothermia is a frequent sign of severe hypoglycaemia in patients with diabetes. Diabetes Metab 2012;38:370–372
27. Vassal T, Benoit-Gonin B, Carrat F, Guidet B, Maury E, Offenstadt G. Severe accidental hypothermia treated in an ICU: prognosis and outcome. Chest 2001;120:1998–2003
28. Collier A, Matthews DM, Young RJ, Clarke BF. Transient atrial fibrillation precipitated by hypoglycaemia: two case reports. Postgrad Med J 1987;63:895–897
29. Shin BS, Won SJ, Yoo BH, Kauppinen TM, Suh SW. Prevention of hypoglycemia-induced neuronal death by hypothermia. J Cereb Blood Flow Metab 2010;30:390–402
30. Christensen TF, Baekgaard M, Dideriksen JL, et al. A physiological model of the effect of hypoglycemia on plasma potassium. J Diabetes Sci Tech 2009;3: 887–894
31. Zydlewski AW, Hasbargen JA. Hypothermia-induced hypokalemia. Mil Med 1998;163: 719–721
32. Rossing P, Breum L, Major-Pedersen A, et al. Prolonged QTc interval predicts mortality in patients with type 1 diabetes mellitus. Diabet Med 2001;18:199–205
33. Nielsen JB, Graff C, Pietersen A, et al. J-Shaped association between QTc interval duration and the risk of atrial fibrillation: results from the Copenhagen ECG study. J Am Coll Cardiol 2013;61: 2557–2564
34. Passman R, Kadish A. Polymorphic ventricular tachycardia, long Q-T syndrome, and torsades de pointes. Med Clin North Am 2001;85:321–341
35. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care 2003;26:1485–1489
36. Gruden G, Barutta F, Chaturvedi N, et al. Severe hypoglycemia and cardiovascular disease incidence in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care 2012;35:1598–1604
37. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. Diabet Med 1991;8:49–58
38. Thordarson H, Søvik O. Dead in bed syndrome in young diabetic patients in Norway. Diabet Med 1995;12:782–787

発表論文

6) **Yamamoto-Honda R, Takahashi Y, Yamashita S, Mori Y, Yanai H, Mishima S, Kajio H, Handa N, Shimokawa K, Yoshida A, Kitazato H, Shimbo T, Kawazu S, Noda M: Constructing the National Center Diabetes Database.**
Diabetology Int **: in press.**

Diabetol Int
DOI 10.1007/s13340-014-0162-2

ORIGINAL ARTICLE

Constructing the National Center Diabetes Database

Ritsuko Yamamoto-Honda · Yoshihiko Takahashi · Shigeo Yamashita · Yasumichi Mori · Hidekatsu Yanai · Shuichi Mishima · Hiroshi Kajio · Nobuhiro Handa · Kotaro Shimokawa · Akiko Yoshida · Hiroji Kitazato · Takuro Shimbo · Shoji Kawazu · Mitsuhiko Noda

Received: 16 November 2013 / Accepted: 30 January 2014

Abstract We set up the National Center Diabetes Database with financial support from the National Center for Global Health and Medicine and from the Ministry of Health, Labour and Welfare of Japan. In this report, we describe the structure of this database and present the results of the registry based on the use of this database. Medical records of patients diagnosed as having diabetes and who were visiting either of the two clinics or six hospitals in Japan were registered. In the present report, 8,130 records (5,738 men and 2,392 women) obtained between 2005 and 2010 were analyzed. The demographics of this registry clarified that (1) the population of diabetic patients is becoming older (the average age of diabetic men, 62.1 years old; that of women, 66.7 years old); (2) fewer women patients are diagnosed through health checkups as having diabetes than men patients; (3) ever-smokers are more frequently observed in diabetic patients than in the general population in men aged over 60 and in women aged over 40; (4) 72 % of type 2 diabetic patients become overweight at least once in their life. Men who

R. Yamamoto-Honda and Y. Takahashi contributed equally to this work.

R. Yamamoto-Honda · Y. Takahashi · H. Kajio
Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

R. Yamamoto-Honda · M. Noda (✉)
Department of Diabetes Research and Diabetes and Metabolism Information Center, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
e-mail: mnoda@hosp.ncgm.go.jp

Present Address:
Y. Takahashi
Division of Diabetes and Metabolism, Iwate Medical University, Morioka, Iwate, Japan

S. Yamashita
Department of Diabetes and Endocrinology, JR Tokyo General Hospital, 2-1-3 Yoyogi, Shibuya-ku, Tokyo, Japan

Y. Mori
Division of Endocrinology and Metabolism, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan

H. Yanai · S. Mishima
Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, Ichikawa, Chiba, Japan

N. Handa
Nagara Medical Center, National Hospital Organization, 1300-7 Nagara, Gifu, Gifu 502-8588, Japan

K. Shimokawa
Yutenji Medical Clinic, 1-13-12 Gohongi, Meguro-ku, Tokyo 153-0053, Japan

A. Yoshida
Kanamachi Yoshida Clinic, 1-1-1 Higashikanamachi, Katushika-ku, Tokyo 125-0041, Japan

H. Kitazato · S. Kawazu
Institute for Adult Disease, Asahi Life Foundation, 2-2-6 Nihonbashibakurochou, Chou-ku, Tokyo 103-0002, Japan

Present Address:
H. Kitazato
Omori Red Cross Hospital, Ota-ku, Tokyo, Japan

T. Shimbo
Division of Clinical Epidemiology, Department of Clinical Research and Informatics, National Center for Global Health and Medicine, Toyama 1-21-1, Shinjuku-ku, Tokyo, Japan

Published online: 26 February 2014

smoked and men who drank alcohol more than 4 days per week were more frequently observed in type 2 diabetes patients who had never been obese than in those who had been obese at least once. The data obtained from a large number of patients registered at a combination of hospitals and clinics might provide reports accurately reflecting the present status of diabetes in Japan.

Keywords Diabetes mellitus · Database · Aging of the diabetic population

Introduction

The incidence of diabetes mellitus is rapidly increasing in Asian countries [1]. In Japan, a survey performed by the Ministry of Health, Labour and Welfare in 2007 pointed out that approximately 8.9 million people had diabetes, and another 13.2 million people were at high risk for diabetes [2]. In regard to the status of diabetes treatment, the percentage of those who answered yes to the question "Currently undergoing treatment" is increasing, but of those who answered yes to "Hardly underwent any treatment" still remains at approximately 40 % [2].

Diabetes can lead to many complications and comorbidities, including diabetic retinopathy leading to impaired vision, renal failure leading to hemodialysis and cardiovascular accidents. These conditions contribute significantly to impairing the quality of life of the patients and to being a large financial burden to the health care systems [3].

Accordingly, we set up the National Center Diabetes Database with financial support from the National Center for Global Health and Medicine and from the Ministry of Health, Labour and Welfare of Japan to examine the current status of diabetes management and with the aim of keeping track of diabetic patients and evaluating the risk factors for complications and comorbidities of diabetes.

In this report, we described the structure of this database in detail and presented our patient registration structure using this database system together with the results of the demographic data.

Methods

Constructing the National Center Diabetes Database

First, one of the members (YT) developed a data acquisition system run on personal computers with Microsoft Excel 2007 VBA macro programming, which was later updated to Microsoft Excel 2010 VBA macro programming. The acquired data were stored in a relational database system in which tables were represented by three fixed-format Microsoft Excel 2010 files: (1) an index of subjects with demographics and medical history; (2) data on information on individual patient education, smoking cessation and hypoglycemia; (3) annual data on individual patient review, laboratory data and death records (Tables 1, 2, 3).

Data collection procedures were standardized in a 3-day training session given by the chief assistant of the National

Table 1 Index of subjects with demographics and medical history (representative data items)

Data item	Description
Linked anonymous code	The unique identifier allocated to a subject by this project
Year of birth	The year and month in which the subject was born
Sex	Classification of the sex of the subject
Date of diabetes diagnosis	The date on which the diagnosis of diabetes was made
	Diabetes was defined according to the criteria of the Japan Diabetic Society
Type of diabetes	Categorized as type 1, type 2, genetic susceptibility to diabetes identified by DNA analysis, diabetes associated with other pathologic conditions or diseases* (diseases of exocrine pancreas, endocrine diseases, liver disease, drug- or chemical-induced, infections and others), gestational diabetes mellitus or unclassifiable, according to "etiological classification of diabetes mellitus and glucose metabolism disorders" of the Japan Diabetic Society [4–6]
Situation of the first diagnosis of diabetes	Categorized as health checkup, diagnosed as comorbid diabetes, appearance of signs and symptoms of diabetes, other situations or not described in the medical records
Comorbidity	Comorbidity of the patients at enrollment
Body weight history	(1) Self-reported body weight at age 20 years
	(2) Self-reported maximal body weight and age at maximal body weight
Drinking habits	Frequency of drinking (including past drinking habits)
Smoking habits	Age at initiation of smoking and the number of cigarettes smoked per day (including past smoking habits)
Family history	To describe family history up to second-degree relatives
History of pregnancy	Number of pregnancies and delivery of babies large for their gestational age, if any

*conditions or diseases that were severe enough to cause diabetes existed before or simultaneous to appearance of hyperglycemia

Center of Global Health and Medicine. Before the data were uploaded, data checks and data correction, if any, were performed to make the data as complete and correct as possible. The data were then received by the central database center to form the National Center Diabetic Database. The feasibility of this database was ascertained by pilot registration of 1,000 diabetic patients with various comorbidities who had been hospitalized in the National Center for Global Health and Medicine Hospital from 2001 to 2010.

Table 2 Data of information on individual patient education, smoking cessation and hypoglycemia (representative data items)

Data item	Formats for presenting the data
Linked anonymous code	The unique identifier allocated to a subject by this project
Event ID	
Date	Year/month/day
Dietary management	Dietary energy consumption, protein consumption, salt intake recommended by dietitians
Smoking status	The date of smoking cessation
Episodes of hypoglycemia	Episodes of hypoglycemia and severe hypoglycemia requiring medical support

Registration

With the use of this database, we established a registry of diabetic patients. Medical records of patients who were diagnosed as having diabetes according to the criteria defined by the Japan Diabetes Society [4–6] and who were visiting either of the two endocrinology/diabetes clinics, diabetologists in five hospitals or cardiologists in one hospital (Nagara Medical Center, National Hospital Organization) in Japan were registered at each institute. The criteria defined by the Japan Diabetes Society were almost

Table 3 Annual data of individual patient review, laboratory data and death records (representative data items)

Data item	Formats for presenting the data
Linked anonymous code	The unique identifier allocated to a subject by this project
Event ID	
Height, body weight, systolic blood pressure and diastolic blood pressure	Numerical data
Blood chemistry test, urinalysis, urine albumin-to-creatinine ratio and urine protein-to-creatinine ratio	Numerical data
Antihyperglycemic drugs, antihyperlipidemic drugs and anticoagulants	Name and dosage of the drug
Antihypertensives	Class of the drug
Diabetic retinopathy	Described as no retinopathy, simple retinopathy, preproliferative retinopathy, proliferative retinopathy or loss of vision
	Pan-retinal laser photocoagulation: performed or not
	Vitrectomy: performed or not
Diabetic neuropathy	Achilles tendon reflex: normal, hypo-reflexive or no response
	Sensation of pain: present or absent
	Sensation measured with the Semmes-Weinstein monofilament 5.07: present or absent
Electrocardiogram (ECG)	ST-T changes: present or absent
	Abnormal Q wave: present or absent
	Atrial fibrillation (Af): present or absent
	Arrhythmia other than Af: present or absent
	Other abnormality on ECG: present or absent
Coronary heart events	Categorized as acute myocardial infarction (MI), coronary heart events other than acute MI or no evidence of coronary heart events
	Acute MI is defined as abnormality in CK-MB or troponin T along with supportive evidence in the form of typical symptoms, suggestive ECG changes or imaging evidence of loss of viable myocardium or abnormality in coronary angiography [42]
	Coronary heart events other than acute MI are defined as unstable angina, recent acute heart failure other than acute right-sided heart failure or subsequent MI treated by cardiovascular intervention (angioplasty or stents) by either catheterization or coronary artery bypass surgery [43, 44]

Table 3 continued

Data item	Formats for presenting the data
Brain attacks and related conditions [45]	Categorized as follows:
	(1) symptomatic cerebral infarction, including lacunar infarction, atherosclerotic infarction, cardiogenic brain embolism or transient symptom-associated infarction (TSI) confirmed by magnetic resonance imaging (MRI) or computed tomography (CT)
	(2) Symptomatic cerebral hemorrhage, including hypertensive hemorrhage, hemorrhage due to amyloid angiopathy, confirmed by MRI or CT
	(3) Subarachnoid hemorrhage, confirmed by MRI or CT
	(4) Transient cerebral ischemic attack (TIA)
	(5) No evidence of brain attack defined above
	Carotid endarterectomy: performed or not
Peripheral artery disease	Aorto-iliac graft: performed or not
	Leg bypass surgery: performed or not
	Peripheral artery intervention: performed or not
Ulceration and amputation of the lower extremities	The site of ulceration: toe, foot, calf or thigh (if any)
	Amputation: performed or not
	The site of amputation if performed: left or right, toe, foot, below the knee or above the knee
Psychiatric comorbidities	Sleeping disturbances: present or absent
	Cognitive disorders: present or absent
	Major depressive disorder: present or absent
Death or lost to follow-up	The date and cause of death or the date when lost to follow-up

identical to the criteria of the World Health Organization [6, 7]. For identification of patients, the linkable anonymizing method was employed. This research program conformed to the ethical recommendations for epidemiological studies, as declared by the Ministry of Health, Labour and Welfare in Japan, and was approved by the National Center for Global Health and Medicine Research Ethics Committee as well as the Research Ethics Committee of each institute. The data analysis was performed using R [8]. The continuous variables were summarized as mean ± standard deviation or median with 25th–75th percentiles. Differences in the frequency of subjects were examined using a chi-squared test for trends in proportions ('prop. trend. test' [8]) with a Bonferroni correction.

Results and Discussion

Until August 2013, 8,187 medical records of diabetic patients were taken by the registry and stored in the National Center Diabetes Database. In the present report, we analyzed 8,130 records (5,738 men and 2,392 women) obtained between 2005 and 2010. Demographics of the patients are presented in Table 4, and further analyses of the period after the diagnosis of diabetes and cigarette smoking, categorized by age group and sex, are presented in Figs. 1 and 2, respectively. Body mass index (BMI) data at enrollment of type 2 diabetic patients categorized by age group and sex are presented in Fig. 3, and BMIs at the age of 20 and the maximal BMI categorized by sex are presented in Fig. 4. The demographic comparison of type 2 diabetic patients who had never been obese (MAXBMI <25) and those who were obese at least once is presented in Table 5.

Diabetes data surveillance by registry was important for comprehensive recognition of the present situation of diabetic patients. The National Center Diabetes Database system collected data on demographic and laboratory data as well as diabetic patient-centered outcome measures of diabetes-specific conditions such as diabetic retinopathy and diabetes-related conditions such as ischemic heart disease [9].

As the first report, we present demographic data of the patients obtained between 2005 and 2010. Figure 1 shows the population of diabetic patients categorized by age group at registration and by sex. The population of diabetic patients was older in comparison to the previous reports of a cross-sectional survey in 2002 [10]. This trend primarily reflected the aging of the overall population [11, 12] with a small increase in the percentage of "individuals strongly suspected of having diabetes" at the age of 70 or older after 2002 [2]. The management of older adults with diabetes is a major theme that should be considered from various points of view [13]. We are going to analyze the present

Table 4 Demographics of the patients registered in the National Center Diabetes Database

	Men	Women
Number of patients registered	5,738	2,392
Center Hospital, National Center of Global Medicine[a]	2,025	1,007
Konodai Hospital, National Center of Global Medicine[b]	532	450
Toranomon Hospital[a]	548	202
JR Tokyo General Hospital[a]	1,965	520
Institute for Adult Disease, Asahi Life Foundation[a]	499	93
Nagara Medical Center, National Hospital Organization[c]	54	12
Yutenji Medical Clinic[b]	71	52
Kanamachi Yoshida Clinic[b]	44	56
Age at registration (years, mean ± standard deviation)	62.1 ± 11.9	66.7 ± 12.6
Duration from diagnosis of diabetes to registration (years, median, 25th–75th percentiles)	7 (3–14)	8 (3–16)
Type of diabetes		
Type 1	157 (2.7 %)	119 (5.0 %)
Type 2	5,480 (95.6 %)	2,204 (92.1 %)
Genetic susceptibility to diabetes identified by DNA analysis	3 (0.0 %)	4 (0.2 %)
Diabetes associated with other pathologic conditions or diseases	88 (1.5 %)	45 (1.9 %)
Diabetes diagnosed during pregnancy		8 (0.3 %)
Unclassifiable	10 (0.2 %)	12 (0.5 %)
Situation of the first diagnosis of diabetes		
Health checkup	2,121 (37.0 %)	542 (22.7 %)
Diagnosed as comorbid diabetes	1,051 (18.3 %)	624 (26.1 %)
Appearance of signs, symptoms or complications of diabetes	713 (12.4 %)	331 (13.9 %)
Other situation	55 (1.0 %)	50 (2.1 %)
Not registered	1,798 (31.3 %)	845 (35.2 %)
Family history of diabetes up to second-degree relatives		
Positive	2,240 (39.0 %)	992 (41.5 %)
Negative	1,369 (23.9 %)	470 (19.6 %)
Not registered	2,129 (37.1 %)	930 (38.9 %)
Smoking habits		
Never-smokers	1,341 (23.3 %)	1,432 (59.9 %)
Ex-smokers	1,192 (20.8 %)	136 (5.7 %)
Present smokers	2,300 (40.1 %)	296 (12.4 %)
Not registered	905 (15.8 %)	528 (22.0 %)
Drinking habits at registration		
More than 4 days per week	1,540 (26.9 %)	113 (4.7 %)
One to 3 days per week	931 (16.2 %)	128 (5.4 %)
One to 3 days per month	94 (1.6 %)	40 (1.7 %)
Never or less than once a month	1,428 (24.9 %)	1,109 (46.4 %)
Ex-drinkers	229 (4.0 %)	51 (2.1 %)
Not registered	1,516 (26.4 %)	951 (39.7 %)
Body mass index at enrollment	($n = 4003$)	($n = 1439$)
(Median, 25th–75th percentiles)	24.1 (21.9–26.7)	23.8 (21.0–27.4)
Body mass index at age 20	($n = 2925$)	($n = 929$)
(Median, 25th–75th percentiles)	21.8 (20.2–24.0)	20.7 (19.1–22.8)
Maximal body mass index	($n = 3507$)	($n = 1160$)
(Median, 25th–75th percentiles)	26.9 (24.7–29.7)	27.0 (24.3–30.3)

These hospitals or clinics are located in the central area of Tokyo[a], in suburban Tokyo[b] and in suburban Gifu City[c]

status of older adults with diabetes in more detail. In addition, the age pattern was different by sex; the number of registered men exhibited a peak at 60–64 years old and decreased to 47.4 % at the age of 75–79, while that of registered women increased sharply at the age of 60–64, exhibited a peak at 70–74 years old and decreased only to 81.4 % at the age of 75–79. This age pattern difference by sex was in part reflected by the following three elements: (1) the difference in population distribution by age (a cross-sectional survey in 2009 reported that the number of Japanese men aged 75–79 was 54.9 % of those aged 60–64 and that the number of Japanese women aged 75–79 was 68.3 % of those aged 60–64 [11]); (2) the rate of individuals having been diagnosed as having diabetes was comparable in diabetic men aged over 70 (23.6 %) to those aged between 60 and 69 (23.4 %), while the rate was higher in diabetic women aged over 70 (14.7 %) than those aged between 60 and 69 (13.2 %) [14]; (3) the rate of patients undergoing treatment was comparable in diabetic men aged over 70 (63.6 %) to those aged between 50 and 69 (62.4 %), while the rate was much higher in diabetic women aged over 70 (74.8 %) than in those aged between 50 and 69 (55.5 %) [14]. Other possibilities were that the rate of leaving the hospital might be higher in men than in women aged over 65 years associated with the effect of job

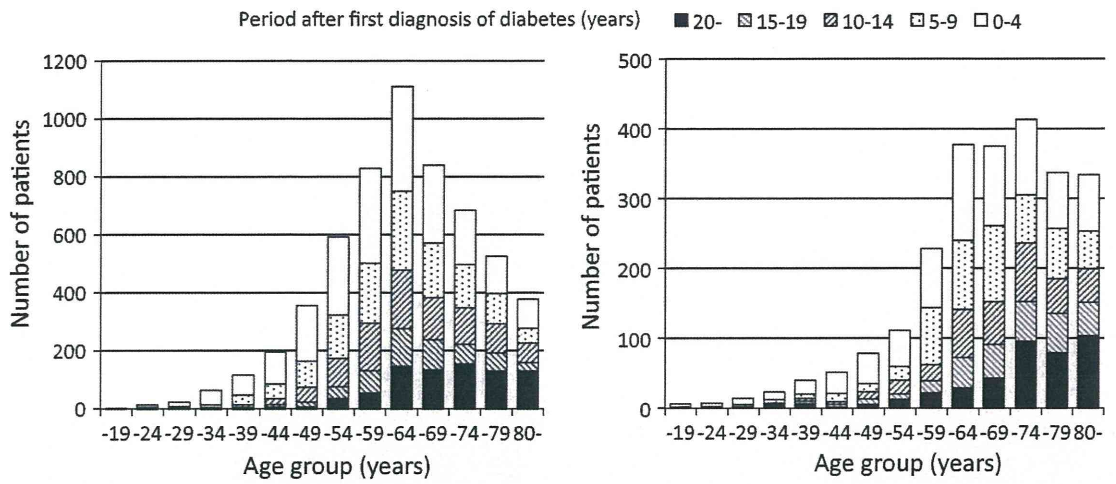

Fig. 1 Age at registration of diabetic patients categorized by age group, sex and period after the first diagnosis of diabetes. *Left* men patients; *right* women patients

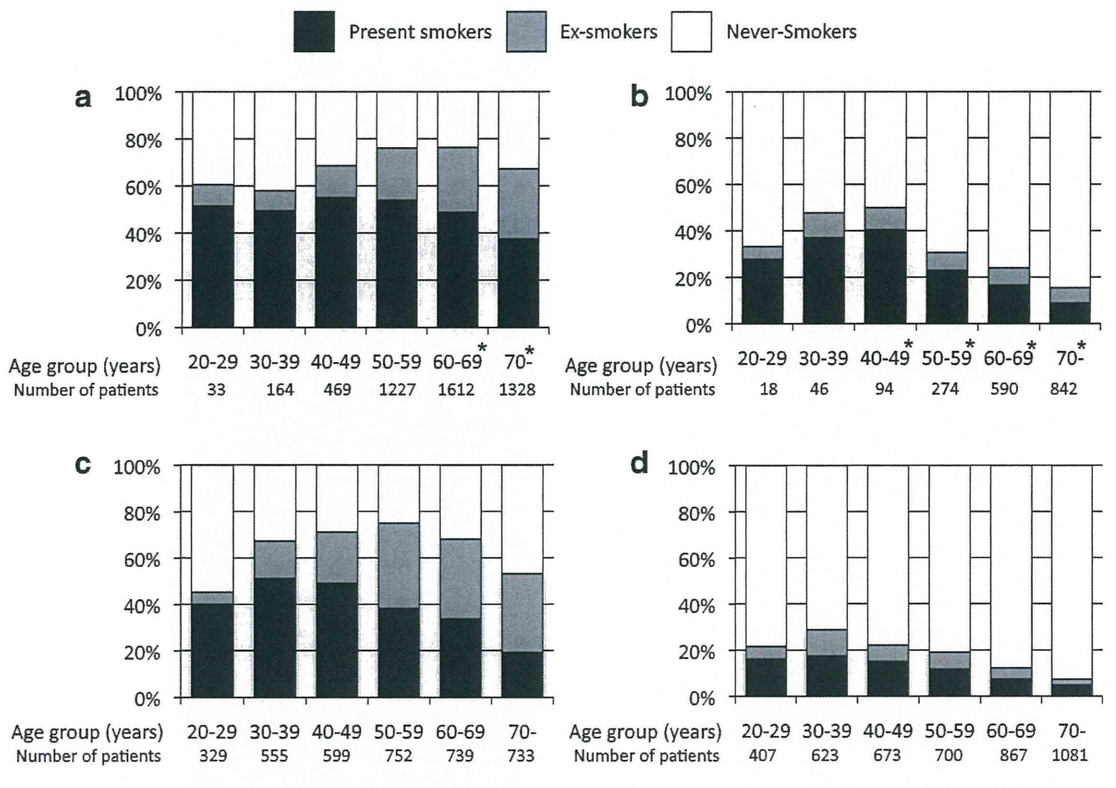

Fig. 2 Status of cigarette smoking of diabetic patients at registration categorized by age group and sex in comparison to the result of "Current situation on the smoking habit" dealing with the general population in the National Health and Nutrition Survey by Ministry of Health, Labour and Welfare of Japan in 2009 (ref. [17]). Data not registered were omitted. **a** Diabetic men; **b** diabetic women; **c** men of the general population (redrawn from ref. [17]); **d** women of the general population (redrawn from ref. [17]). *Rate of ever-smokers of diabetic patients was significantly higher ($p < 0.001$) than that of the general population

retirement and by events that disturb healthy life expectancy. By following up the registered patients, we would like to examine the rate of and reason for leaving our registry.

Early detection and treatment of diabetes are keys to decreasing the risk of developing diabetes-related complications [6, 15], whereas many patients, most of whom had type 2 diabetes, still remained undiagnosed or ignored the