表1 酸化ストレスの原因となる生化学的プロセス

グルコース自動酸化とglycoxidation（糖酸化反応）[52]
フリーラジカルスカベンジャーと抗酸化物質の減少[53,54]
ポリオール経路依存性のレドックス（酸化還元）状態の不均衡[34]
ミトコンドリア電子伝達系によるスーパーオキシドの過剰産生[55]
ミトコンドリアの分裂[56]
ミトコンドリアの分極変化[57]
キサンチン酸化酵素の活性化[58]
PKC依存性のNAD（P）H酸化酵素の活性化[36]
初期糖化生成物およびAGEsの過剰産生[59,60]
AGEsとRAGEの相互作用[1]

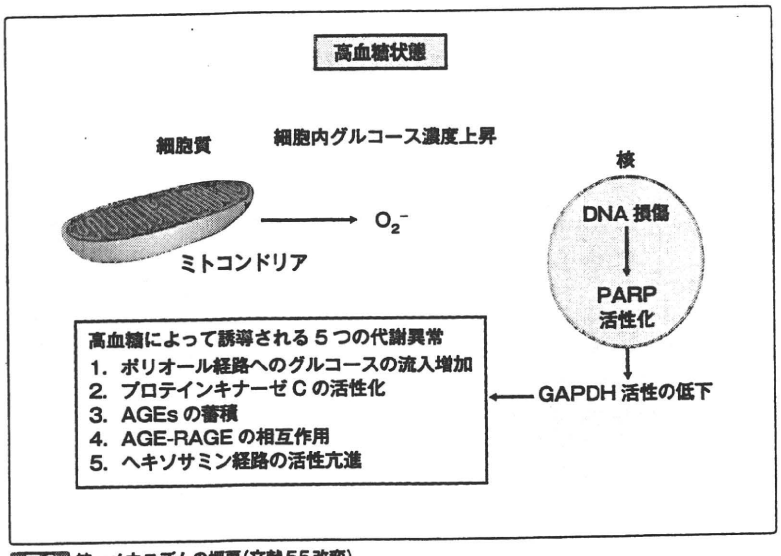

図6 統一メカニズムの概要（文献55改変）
高血糖によってミトコンドリア電子伝達系でのスーパーオキシドの産生が過剰になることで，フリーラジカルがDNA損傷を引き起こす．この際，DNA修復に関与するポリ（ADPリボース）ポリメラーゼ（PARP）が活性化され，活性化したPARPが，解糖系の重要な酵素であるGAPDHをポリ（ADPリボース）で修飾し，この酵素の活性を特異的に抑制する．これにより，GAPDHより上流の解糖系中間生成物の細胞内濃度は上昇し，高血糖由来の５つの代謝異常を引き起こす[61]．

子の発現増加やPAI-1活性化を阻止する[47-49]．血管内皮細胞では，eNOS蛋白のAkt活性化部位のUDP-GlcNAcによる修飾によって，eNOS活性の低下を引き起こす[50]．さらには，血管平滑筋において，高血糖がGFATを活性化させ，いくつかの蛋白のUDP-GlcNAcによる修飾を増加させる[51]．これら血管組織における，高血糖によるヘキソサミン経路の活性を介した負の影響が数多く示されている一方で，末梢神経において，どの神経細胞内蛋白がUDP-GlcNAcによる修飾を受けうるのかは解明されていない．しかし，高血糖下でのUDP-GlcNAcによる蛋白の過剰な修飾は，神経機能異常の要因になりうることが推定されている．

酸化ストレス

高血糖によって引き起こされる酸化ストレスには，表1に示すいくつかの生化学的プロセスを介したものが推定されている．

表1で示したプロセスのなかで，Brownleeは，“unifying mechanism（統一メカニズム）”を提唱し，高血糖によって引き起こされるAGEsの蓄積，AGE-RAGEの相互作用，ポリオール経路へのグルコースの流入増加，プロテインキナーゼC（PKC）の活性化，そしてヘキソサミン経路の活動亢進といった5つの代謝経路の異常が，単一のプロセス，すなわちミトコンドリア電子伝達系によるスーパーオキシドの過剰産生に端を発するものとした[61]（図6）．

この仮説によれば，糖尿病においては，細胞内グルコース濃度の上昇により，グルコース由来のピルビン酸がより多くTCA回路で酸化され，電子供与体のNADHおよび$FADH_2$の電子伝達系への流入が増加する．その結果，ミトコンドリア内膜において電子伝達系を介した供与電子の流れが，プロトンイオンをミトコンドリア膜間腔内へ汲みだし，ミトコンドリア膜を横断する電位勾配が臨界閾値に達することにより，より多くのスーパーオキシドが産生されるという．この際に汲みだされたプロトンイオンは，熱として，プロトン勾配のエネルギーを散逸させる脱共役蛋白質，あるいはATP合成酵素を介して濃度勾配性にミトコンドリア内膜へ再流入する．したがって，脱共役蛋白質の働きによってミトコンドリア膜を横断する電位勾配が解消されたり，ミトコンドリア電子伝達系自体が抑制されたりする場合には，高血糖下でも活性酸素種の増加は引き起こされない．あるいは，MnSODによってスーパーオキシドが分解される場

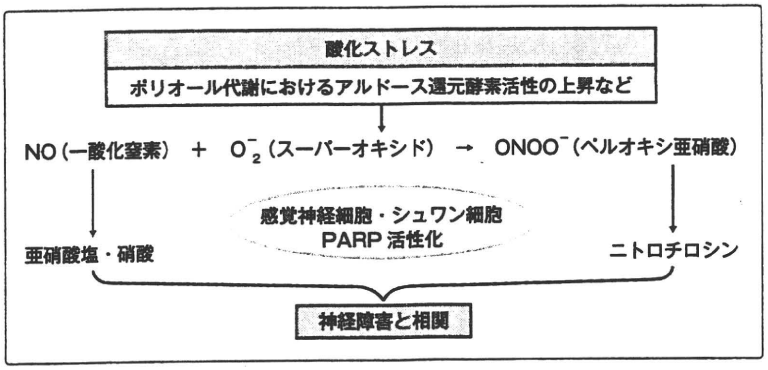

図7 ニトロソ化ストレスと神経障害
高血糖では，一酸化窒素の産生および酸化ストレスの増加を介したニトロソ化ストレスによる神経障害が引き起こされている可能性がある．糖尿病ラットでは，アルドース還元酵素阻害薬が酸化ストレスの減少を介して神経内ニトロソ化ストレスを減少させ，神経機能を改善しうることが示されている[64]．

合も，同様に活性酸素種は増加しないとされる．

さらに，ミトコンドリア電子伝達系によるスーパーオキシドの過剰産生によってDNAが損傷を受けると，DNA修復に関与するポリ(ADPリボース)ポリメラーゼ(PARP)が活性化される．活性化したPARPは，解糖系の重要な酵素であるグリセルアルデヒド-3-リン酸脱水素酵素(GAPDH)のポリ(ADPリボース)による修飾を促し，この酵素の活性を特異的に抑制する．これにより，GAPDHより上流の解糖系中間生成物の細胞内濃度は上昇することになり，このことが先に挙げた高血糖由来の5つの代謝経路の異常を引き起こす．

Obrosovaらは，糖尿病動物モデルにおいて，PARP阻害あるいはPARP遺伝子のノックアウトが，このモデルに認められる神経伝導速度の低下や神経内血流異常をほぼ正常化しうることを報告している[62,63]．

ニトロソ化ストレス(図7)

活性窒素種は，一酸化窒素とスーパーオキシドに由来する分子ファミリーであり，細胞障害性に作用するニトロソ化ストレスの原因となる．とくに，糖尿病ラットでは，高血糖が一酸化窒素の産生を刺激し，スーパーオキシドとの反応を介してペルオキシ亜硝酸を増加させ，神経周膜や神経周膜外細動脈を障害する可能性が指摘されている[65,66]．逆に，ペルオキシ亜硝酸の分解触媒化合物は，糖尿病マウスの神経伝導速度の低下や痛覚異常を正常化させることが報告されている[67]．一酸化窒素およびペルオキシ亜硝酸は，不安定で直接測定することが困難なため，一酸化窒素の代謝産物である亜硝酸塩や硝酸およびペルオキシ亜硝酸によって誘導される蛋白ニトロ化の指標であるニトロチロシンを，ニトロソ化ストレスの生化学マーカーとして測定している．1型および2型糖尿病動物モデルでは，ニトロチロシン免疫反応性が末梢神経，後根神経節，神経栄養血管，脊髄において高まっている[67-74]．また，1型糖尿病患者では，ニトロソ化ストレスの血中生化学マーカーレベルの上昇と，神経伝導速度の遅延および発汗低下との関連性が報告されている[75]．さらに，糖尿病ラットにアルドース還元酵素阻害薬を投与することで，神経内ニトロソ化ストレスおよびシュワン細胞でのPARP活性化のマーカーであるポリ(ADPリボース)の蓄積を正常化させうることが示されている[64]．一方，糖尿病の末梢神経における一酸化窒素の供給源については，誘導型一酸化窒素合成酵素の活性化が推定されている[76]．

ただし，上記報告の大半が一部の限られた研究グループからのものである．ニトロソ化ストレスと神経障害との関連性については，今後より多くの研究者による検証が期待される．

おわりに

本稿では，高血糖によって誘導される種々の代謝異常が神経障害を引き起こしうる機序を解説した．ただし，ここで述べた多くの機序仮説の根拠となるのが，糖尿病動物モデル，とくにストレプトゾトシン誘発糖尿病動物に随伴する神経障害や，その治療効果の知見であることに留意してほしい．この糖尿病動物モデルでは，神経障害患

者に特徴的にみられる神経長依存性の神経線維の脱落を認めない．代わりに認めるのは，神経障害患者ではむしろまれな，軸索萎縮や糖尿病発症直後から生じる神経伝導速度の低下，あるいは痛覚異常である．これら神経障害としては，非典型的な所見から導きだされた「高血糖仮説」において，多くの不確かな点，矛盾点が内在しているのも事実である（とくに，若い研修医のみなさんには本稿を批判的に読んでほしい）．今後，神経障害で最も重症度と密接な関連を示す病理所見である「末梢神経線維の脱落」をターゲットとして，もう一度「高血糖仮説」を検証しなおす必要があると考える．

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Profile

杉本一博（すぎもと　かずひろ）

1990年	弘前大学 医学部 卒業
1994年	弘前大学大学院 医学研究科 修了
1995～7年	弘前大学医学部附属病院 第3内科 医員
1998～2000年	Wayne State大学 医学部 病理学講座 ポスドク研究員
2001～2年	弘前大学医学部附属病院 第3内科 助手
2002年	弘前大学医学部附属病院 検査部 講師
2008年	弘前大学大学院 医学研究科 臨床検査医学講座 准教授，現在に至る

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

Nigishi Hotta[1]*, Jiro Nakamura[2], Yasuhiko Iwamoto[3], Yoshiyuki Ohno[4], Masato Kasuga[5], Ryuichi Kikkawa[6], Takayoshi Toyota[7]

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

[1]Japan Labour Health and Welfare Organization, Chubu Rosai Hospital, Nagoya, [2]Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, [3]Diabetes Center, Tokyo Women's Medical University, Tokyo, [4]Japan Labour Health and Welfare Organization, Asahi Rosai Hospital, Owariasahi, [5]Division of Diabetes, Digestive and Kidney Diseases, Kobe University Graduate School of Medicine, Kobe, [6]Shiga University of Medical Science, Otsu, and [7]Japan Labour Health and Welfare Organization, Tohoku Rosai Hospital, Sendai, Japan

*Corresponding author. Nigishi Hotta Tel.: +81-52-652-5511 Fax: +81-52-652-5623 E-mail address: hotta@chubuh.rofuku.go.jp

[In 2001, the Japan Diabetes Society established a 'Committee on Causes of Death in Diabetes Mellitus', which published its final committee report in 2006[1]. 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 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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A survey of this type could not be successfully carried out without the cooperation of many kind people in providing information, filling in questionnaires and collating the responses. We would like to apologise for putting everyone through so much trouble and offer our deepest appreciation for your efforts. It was entirely due to the assistance of the members of the Japan Diabetes Society, and many non-members as well, that we were able to complete this survey with some degree of success. Once again, our sincere thanks to all who cooperated in the conduct of this survey.

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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Case Report I

症　例

糖尿病性軀幹神経障害6症例の臨床像

出口 尚寿[*1)]，有村 愛子[*1)]，堂地 ゆかり[*1)]，中村 友紀[*1)]，
宇都 正[*1)]，奥 寛子[*1)]，堀之内 秀治[*1)]，有村 公良[*2)]，
高嶋 博[*1)]

糖尿病性軀幹神経障害6症例を提示する．自験例は49～58歳(男3，女3)，全例2型糖尿病で，推定糖尿病罹病期間1～20年，糖尿病治療内容，細小血管合併症の程度はさまざまであった．いずれも急性～亜急性に一側体幹部の疼痛やアロディニアを自覚し，3例では腹部筋力低下を伴っていた．診断時，2例は血糖コントロール不良であったが，4例は短期間で血糖コントロールが改善した後の発症であり，臨床的に治療後有痛性神経障害の一症状と考えられた．1例は臨床的に糖尿病性筋萎縮症に併発し，IVIg後，臀部・大腿の筋力低下，疼痛の改善のみならず，軀幹の疼痛も速やかに消失した．

糖尿病性軀幹神経障害と糖尿病性筋萎縮症は多巣性糖尿病性神経障害に分類される稀な病型であるが，治療後有痛性神経障害を含め，急性発症し，疼痛と体重減少を特徴とする有痛性糖尿病神経障害の病態機序を考える上で重要であると考え報告する．

Takahisa DEGUCHI, Aiko ARIMURA, Yukari DOUCHI, Tomonori NAKAMURA, Tadashi UTO, Hiroko OKU, Syuji HORINOUCHI, Kimiyoshi ARIMURA, Hiroshi TAKASHIMA：A clinical features of 6 cases of diabetic truncal radiculoneuropathy. Diabetes Journal, 39：16～20, 2011

はじめに

糖尿病性軀幹神経(根)障害(diabetic truncal radiculoneuropathy：DTRN)は，胸腹部神経障害とも呼ばれ，糖尿病神経障害の病型分類[1,2]において，局所性あるいは巣性・多巣性ニューロパチーに分類される稀な病型である．

急性に胸腹部の疼痛や腹筋の筋力低下で発症し，しばしば体重減少を伴い，体幹に分節状に痛み，しびれ，感覚障害をきたす．血糖コントロールと疼痛に対する対症療法により，多くは数ヵ月から1年以内で寛解するが，時に難治例も存在する．

成因として虚血，神経節炎が考えられているが[3]，正確な機序は不明である．一方，DTRNと同様に急性発症し，疼痛と体重減少を伴う糖尿病神経障害である糖尿病性筋萎縮症や治療後有痛性神経障害との類似点も多い[4]．病態機序を考える上で重要と考え，6症例を提示し考察する．

症例 1

58歳女性．眼科にて前増殖糖尿病網膜症を指摘され内科紹介．初めて糖尿病を指摘(HbA1c 11.8%)されインスリン導入．3ヵ月でHbA1cは5.5%まで下降したが，インスリン導入半年後より両足底部のしびれが出現．さらに右大腿部，右側胸腹部にもしびれを自覚するようになり当科紹介受診．両足底の餅を踏んだような違和感，右側腹部(Th9～12皮節)，右大腿内側部にビリビリするしびれを認め，腎症(2期)を合併していた．インスリンによる血糖コントロールを継続しながら，疼痛に対しメキシレチン，イミプラミンにて対症療法を行い，約半年で軽快した．

症例 2

55歳男性．10年来SU薬単剤で加療されるも血糖コントロール不良．2年前より両下肢にジンジン感を自覚．4ヵ月前の某日，臍左側にえぐるよ

[*1)]鹿児島大学大学院神経内科・老年病学講座●〒890-8520 鹿児島県鹿児島市桜ヶ丘8-35-1，[*2)]大勝病院神経内科

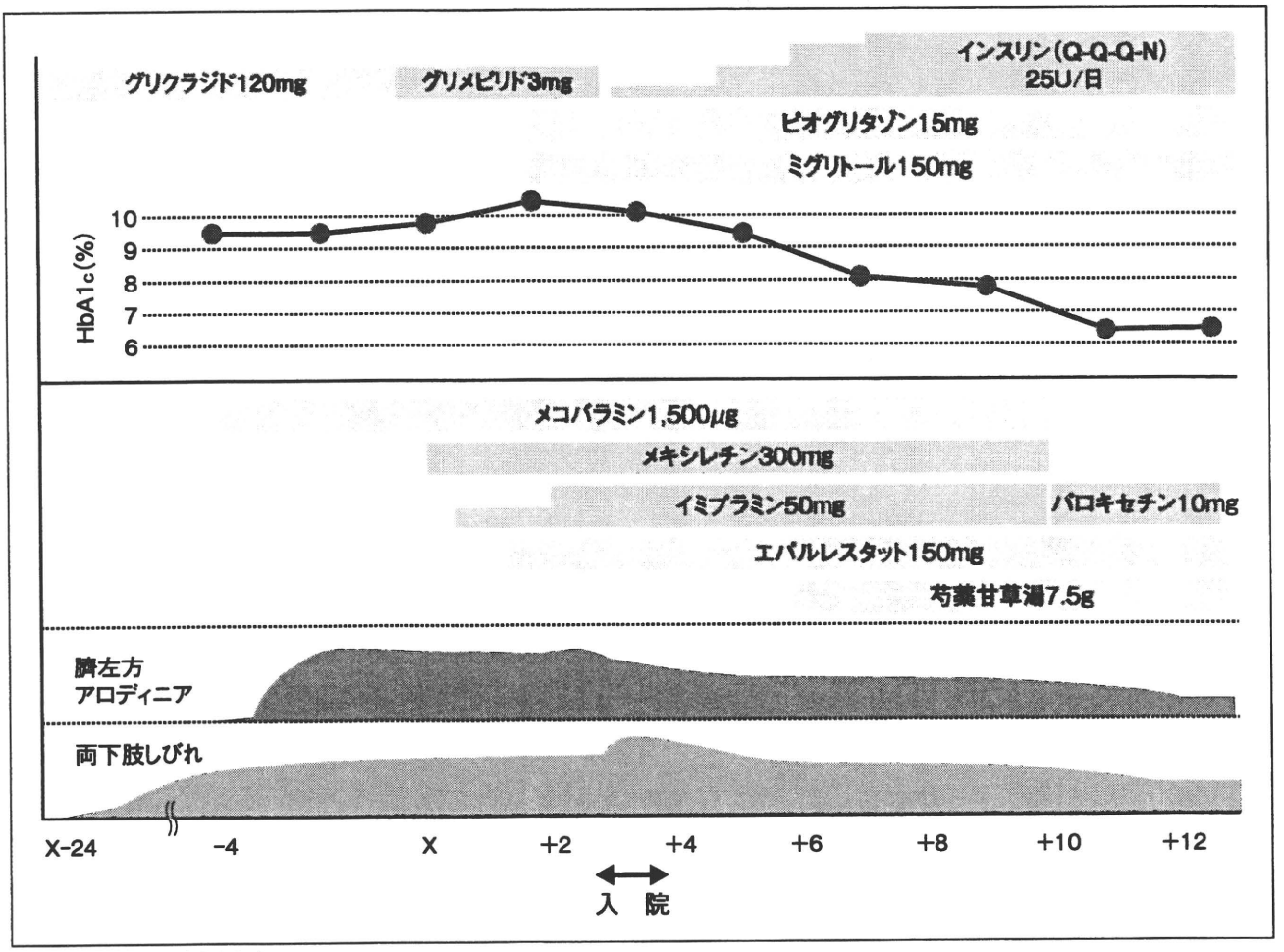

図1 臨床経過(症例2)

うな痛みが出現．複数の病院で消化管内視鏡，腹部CT，胸椎MRI等の精査を行われるも異常なく，当科紹介受診．HbA1c 9.3%と血糖コントロール不良で，単純糖尿病網膜症，腎症(2期)を合併していた．両足のしびれ，両側アキレス腱反射消失，両側内踝振動覚低下を認め，糖尿病多発神経障害(diabetic polyneuropathy：DPN)の簡易診断基準[5]に合致した．臍左方(Th8～11皮節)に強い疼痛とアロディニア(通常では疼痛をもたらさない微小刺激が，すべて強い疼痛として認識される異痛症)を認め，インスリンによる血糖コントロールと疼痛に対する対症療法により，症状は徐々に改善したが，1年以上を経過しても完全には消失しなかった(図1)．

症例 3

57歳男性．初めて糖尿病を指摘(HbA1c 10.2%)され，近医でSU薬内服開始．血糖値は速やかに下降しHbA1c 5.0%となっていたが，治療開始4ヵ月頃，両下肢末梢のしびれ，腹部アロディニアが出現．排便時に下腹に力が入らなくなり，消化器系精査を行われるも異常は指摘されず当科紹介受診．臍周囲～左腰背部(Th8～12皮節)にアロディニアを認め，臍左方の筋弛緩とヘルニアを認めた．両足しびれ，両下肢近位筋力低下，自律神経障害(排尿困難，便秘，勃起障害)，両側アキレス腱反射消失を認めたが，振動覚は保たれ，神経伝導検査は正常範囲であった．血糖コントロール下に疼痛に対する対症療法を行い，約4ヵ月で回復した．

症例 4

56歳女性．20数年前，妊娠糖尿病を指摘されインスリン療法を行うも出産後放置．十数年前にも高血糖を指摘されたが放置．3ヵ月前，全身倦怠感にて近医受診し，HbA1c 16.1%，足壊疽を指摘されインスリン治療開始．3ヵ月でHbA1cは8.5%下

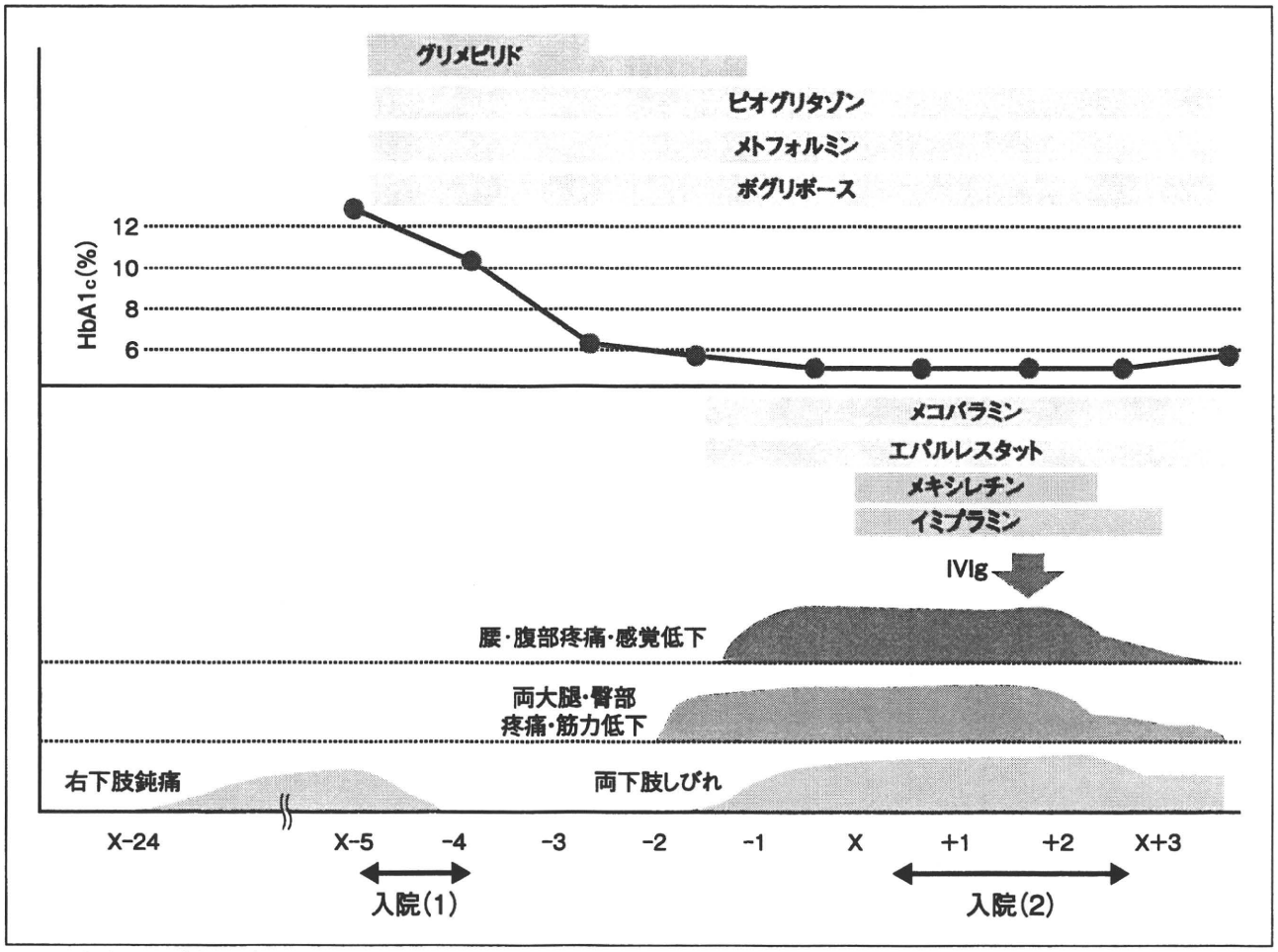

図2　臨床経過(症例5)

降したが，臍周囲から背部にかけて鉛を抱いているような感じと，ビリビリするしびれが出現し当科紹介入院．Th9～12皮節の感覚低下と腹筋麻痺を認め，針筋電図にて傍脊柱筋に脱神経所見を認めた．血糖コントロール下に，疼痛に対し対症療法を行ったが，軀幹のしびれは難治であった．ガバペンチンが奏効し，1年以上かけて症状は徐々に消失した．

症例 5

54歳女性．5ヵ月前，近医にて糖尿病を初めて指摘(HbA1c 13.3%)され入院．食事療法と経口糖尿病薬で血糖値は約1ヵ月で正常化したが，治療3ヵ月頃，急に臀部・両大腿の疼痛を伴う筋力低下が出現．さらに，臍周囲～腰部(Th9～12皮節)にかけて広範な帯状の疼痛，感覚低下部位が出現したため当科紹介入院．針筋電図にて大腿直筋，腸腰筋，傍脊柱筋(Th8，Th12，L3)に脱神経所見を認め，髄液蛋白は176mg/dlと著明に上昇していた．神経学的に糖尿病性筋萎縮症にDTRNを併発していると考えられた．下肢筋力低下がADLを著しく損ねていたため，免疫グロブリン大量療法(IVIg)を施行したところ，下肢筋力のみならず，下肢，臍周囲～腰部の疼痛も劇的に改善し，杖歩行で退院．現在下肢筋力は正常化し，仕事に復帰している(図2)．

症例 6

50歳男性．罹病期間約10年の2型糖尿病．近医通院するも血糖コントロール不良．半年前，急に臍右方に疼痛，しびれを自覚．症状は徐々に拡大し両側性となり(Th8～12皮節)，両側大腿内側部(右＞左)にも同様の疼痛が出現した．消化管精査施行されるも異常なく当科紹介受診．針筋電図で右腹直筋，傍脊柱筋(Th10)に脱神経所見を認め，多発根神経障害と診断した．血糖コントロール下

表　糖尿病性躯幹神経障害6症例の臨床的背景

症例	年齢	性	BMI	病型，罹病期間	HbA1c(%)	網膜症	腎症	多発神経障害	糖尿病治療
1	58	F	23.4	2型，8年	11.8→5.7	前増殖型	2期	あり	インスリン，BG，α-GI
2	55	M	20.5	2型，10年	9.3	単純型	2期	あり	SU→インスリン，TZD，α-GI
3	57	M	22.2	2型，1年	10.2→5.0	なし	1期	あり	SU
4	56	F	22.8	2型，20年	16.1→7.3	増殖型	3A期	あり	インスリン
5	54	F	21.3	2型，10年	13.3→5.7	単純型	2期	あり	SU，TZD，BG，α-GI
6	49	M	19.8	2型，10年	10.6	単純型	3A期	あり	SU，TZD，α-GI

症例	発症	障害部位	体重減少	腹筋麻痺	自律神経障害	糖尿病性筋萎縮症	PPN	神経障害治療	回復
1	亜急	右側胸部 Th9～12	なし	なし	なし	なし	あり	エパルレスタット，メキシレチン，イミプラミン	6ヵ月
2	急	臍左方部 Th8～11	あり	なし	あり	なし	なし	エパルレスタット，メキシレチン，イミプラミン，メコバラミン，芍薬甘草湯	14ヵ月
3	亜急	左側腹部 Th8～12	あり	あり ヘルニア	あり	あり	あり	メキシレチン，メコバラミン	4ヵ月
4	亜急	両腹～腰背部 Th9～12	あり	あり ヘルニア	あり	なし	あり	カルバマゼピン，ガバペンチン，イミプラミン，メコバラミン	12ヵ月
5	亜急	臍周囲部 Th9～12	あり	なし	あり	あり	あり	IVIg，エパルレスタット メキシレチン，イミプラミン，メコバラミン	2週
6	急	両腹部 Th8～12	あり	あり	あり	なし	なし	エパルレスタット，イミプラミン，メコバラミン	10ヵ月

SU：スルホニル尿素薬，BG：ビグアナイド薬，TZD：チアゾリジン薬，α-GI：アルファグルコシダーゼ阻害薬

に疼痛に対する対症療法を行い，10ヵ月余で疼痛はほぼ消失した．

6症例のまとめを示す(表)．

考　察

自験6例は49～58歳と中高年発症で男女差はなかった．全例が2型糖尿病で，罹病期間(1～20年)，治療内容(内服2例，インスリン4例)，DPN，糖尿病網膜症，糖尿病腎症の程度や病期は多様であり，DTRNは高血糖の持続や代謝異常の程度と必ずしも相関しないことが示唆された．DTRNの障害皮節は数髄節に及び，障害皮節に境界明瞭な表在感覚低下部がみられ，アロディニアを伴う[6]．自験例も急性～亜急性に，多くは下位胸髄数髄節レベルのアロディニアを伴う疼痛やしびれで発症した．腹部疼痛の強かった症例2，6では，腹部臓器の精査が先行されていた．下位胸髄レベルの障害では腹筋麻痺からヘルニアを生じることもあり[7]，自験例でも2例でヘルニアを認めた．

2例は血糖コントロール不良状態での発症であったが，4例(症例1，3，4，5)は急速な血糖コントロール後に急性発症し，治療後有痛性神経障害(post-treatment painful neuropathy：PPN)の範疇にあった．PPN 86例の検討[8]において，神経症状は膝下の疼痛が最も多く，原則的に左右対称(全例がDPNを合併)であったが，体幹部の疼痛を伴う症例も5～10%程度含まれていた．その後，同施設より，腹部に限局して知覚過敏，異常感覚を呈した症例が非典型的PPNとして報告されており[9]，DTRNには，長期にわたる血糖コントロール不良状態からの急速な血糖コントロールがトリガーとなる病態が存在すると考えられる．

一方，症例5は臨床的にPPNに加え，糖尿病性筋萎縮症に併発していた．糖尿病性筋萎縮症は骨盤大腿筋群，傍脊柱筋の急性神経原性変化を特徴とし，腰仙骨神経叢～神経根を責任病巣とするため，最近は糖尿病性腰仙部神経根叢障害(diabetic lumbosacral radiculoplexus neuropathy：DLSRPN)と呼ばれる[10]．DTRN患者の針筋電図で，神経根の領域で分枝する後枝支配の傍脊柱筋に脱神経所

見がみられることから，DTRNの病変部位も神経根あるいは脊髄内神経根と考えられている[11]．

DLSRPNの機序として，IVIg，ステロイド療法など免疫療法の有効性[12]や，組織学的検討[10, 13]から，免疫介在性の神経内微小血管炎に伴う虚血が想定されている．DLSRPNでは髄液蛋白上昇に象徴される血液神経関門(blood nerve barrier：BNB)の破綻を伴うが，神経症状を伴わない糖尿病患者でもしばしば髄液蛋白が上昇していることから[14]，BNBが脆弱な神経根は免疫異常の影響を受けやすいと考えられる[15]．DTRNはDLSRPNに随伴することもしばしばであり[13]，糖尿病性頸部神経根叢障害(diabetic cervical radiculoneuropathy：DCRN)も含めて，多巣性糖尿病神経障害(multifocal diabetic neuropathy：MDN)として一括分類されるべきかもしれない[3, 13]．

DLSRPNに対しIVIgを施行した症例5では，IVIg後，臀部・大腿の筋力低下，疼痛の改善のみならず，軀幹の疼痛も速やかに消失した．自己免疫機序による神経障害では，主に運動や深部覚に関わる大径有髄線維が主に侵される．他方，DPNに伴う疼痛は，無髄もしくは小径有髄線維障害によるものが主である．今回IVIg後に，運動神経障害のみならず，DTRNによる軀幹の疼痛やしびれも改善したことは，糖尿病による小径線維障害にも何らかの免疫機序が関与している可能性を示唆する重要かつ興味深い知見である．

DTRNは，血糖コントロールと対症療法により予後良好とされるが，血糖コントロール不良例では明らかに治癒が遷延した(症例2, 4, 6)．DTRNの治療として，体重減少の強い重症例や，DLSRPNに併発する症例では，成因に免疫異常が介在している可能性もあり，QOL，予後改善のために早期の免疫療法も考慮すべきかもしれない．しかしながら，糖尿病がどのような機序で免疫異常を惹起するのかは不明であるし，MDNの病態機序に免疫が介在する可能性は高いにしても，それだけで説明できるものではない．DTRNを含むMDNは頻度の低い稀な病型だけに，今後も症例の蓄積と，再発を含めた長期予後のfollowが必須である．

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