表 1. JDCS 対象者と海外の糖尿病患者とのエネルギー摂取および BMI の比較（文献 6)を改変）

調査年	国/人種	エネルギー摂取量	炭水化物エネルギー比率	脂質エネルギー比率 (%)*	BMI
1996	日本(JDCS)	1737	53.6	27.6	22.9
1997-1999	American Indians	1422-1595	48.7	35.3-35.9	30.6-32.8
2005-2006	アメリカ	1778	36.7	44.6	<25: 5% 25-30: 17.5% ≥30: 77.5%
1993-1994	スペイン	1453-1788	38.0-39.0	36.0-38.5	25.8-28.5
n.d.	ヨーロッパ	604-2202	38.2-41.5	39.5-41.0	25.5-28.1
1990	イギリス	1650	42.7	36.7	27.9
n.d	ヨーロッパ	2390	42.5	37.9	23.5

* 欧米での推奨量は、炭水化物エネルギー比率：45 - 65%、脂質エネルギー比率：35%以下

表 2. JDCS 対象者における塩分摂取量と心血管疾患発症リスク（文献 8)を改変）

	Q1	Q2		Q3		Q4		P for	Interaction
	HR	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	trend	p
食塩摂取量(g)	7.1	9.7		11.4		15.0			
Events/N	23/354	36/350		32/351		41/359			
	ref	1.7	(1.0 to 3.0)	1.6	(0.9 to 2.8)	2.2	(1.2 to 3.9)	0.02	
HbA1C <9.0% の時									
	ref	1.4	(0.8 to 2.6) 0.3	1.2	(0.6 to 2.4) 0.6	1.2	(0.6 to 2.4)	0.70	
HbA1C ≥9.0% の時									
	ref	3.5	(1.0 to 13.1) 0.06	3.8	(1.0 to 14.8) 0.06	9.9	(2.7 to 36.9)	<0.01	<0.01

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ARTICLE

Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study)

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Abstract
Aims/hypothesis The aim of the study was to clarify whether a therapeutic intervention focused on lifestyle modification affected the incidence of vascular complications in patients with established diabetes.
Methods A total of 2,033 eligible Japanese men and women aged 40–70 years with type 2 diabetes from 59 institutes were randomised to a conventional treatment group (CON), which continued to receive the usual care, and a lifestyle intervention group (INT), which received education on lifestyle modification regarding dietary habits, physical activities and adherence to treatment by telephone counselling and at each outpatient clinic visit, in addition to the usual care. Randomisation and open-label allocation were done by a central computer system. Primary analysis regarding measurements of control status and occurrence of macro- and microvascular complications was based on 1,304 participants followed for an 8 year period.
Results Although status of control of most classic cardiovascular risk factors, including body weight, glycaemia, serum lipids and BP, did not differ between groups during

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the study period, the incidence of stroke in the INT group (5.48/1,000 patient-years) was significantly lower than in the CON group (9.52/1,000 patient-years) by Kaplan–Meier analysis (p=0.02 by logrank test) and by multivariate Cox analysis (HR 0.62, 95% CI 0.39–0.98, p=0.04). The incidence of CHD, retinopathy and nephropathy did not differ significantly between groups. Lipoprotein(a) was another significant independent risk factor for stroke.
Conclusions/interpretation These findings suggest that lifestyle modification had limited effects on most typical control variables, but did have a significant effect on stroke incidence in patients with established type 2 diabetes.

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Keywords Complications · Lifestyle intervention · Patient education · Stroke

Abbreviations

CON	Conventional treatment group
CVD	Cardiovascular disease
IGT	Impaired glucose tolerance
INT	Lifestyle intervention group
JDCS	The Japan Diabetes Complications Study

Introduction

Lifestyle management through patient education plays a crucial role in prevention and care of diabetes. It is well established that lifestyle interventions, including diet and/or exercise, can prevent type 2 diabetes [1–6] as well as ameliorate glycaemia and other risk factors for complications [7–12] in patients with established diabetes. Recent reports of two studies that examined the effect of a lifestyle intervention on individuals with impaired glucose tolerance (IGT) over a long-term follow-up period (the China Da Qing Diabetes Prevention Study [13] and the Finnish Diabetes Prevention Study [14]), failed to show significant effects on cardiovascular disease (CVD) events or mortality. However, it is not known whether an intervention mainly focusing on lifestyle modification through patient education could prevent the occurrence of complications in patients with established diabetes, although there have been a few studies [15, 16] on lifestyle modification in combination with pharmacotherapy for hyperglycaemia, hypertension and dyslipidaemia in patients with type 2 diabetes.

The Japan Diabetes Complications Study (JDCS), a nationwide randomised controlled study of Japanese patients with type 2 diabetes, was designed to clarify whether a long-term therapeutic intervention mainly focused on lifestyle education has an effect on the incidence of diabetic macro- and microvascular complication events in patients with established type 2 diabetes (see Electronic supplementary material for members of JDCS). Another aim of this study was to clarify pathophysiological characteristics in East Asian patients with type 2 diabetes [17–20]. We previously published a 3 year interim report [21] showing significant but only limited improvement in glycaemia and no improvement in body weight, BP and serum lipids as a result of lifestyle modifications in patients with type 2 diabetes. This result was quite consistent with other subsequent studies with similar observation periods [8, 11, 22, 23]. The present report shows results after 8 years of an investigation that focused on the incidence of macro- and microvascular complications of diabetes.

Methods

Recruitment of patients Participants in the study were previously diagnosed patients with type 2 diabetes aged 40–70 years whose HbA_{1c} levels were ≥6.5%. From outpatient clinics in 59 university and general hospitals nationwide that specialise in diabetes care, a total of 2,205 patients (mean age 58.6 years; 47% women) were initially registered from January 1995 to March 1996. Excluded were patients with a history of angina pectoris, myocardial infarction, stroke, peripheral arterial disease, familial hypercholesterolaemia, type III hyperlipidaemia, non-diabetic nephropathy, nephrotic syndrome, pre-proliferative and proliferative retinopathy, intra-ocular surgeries, serum creatinine levels >120 μmol/l, and mean values of two spot urine examinations for an albumin excretion rate of <150 mg/g creatinine. Diabetes mellitus and IGT were diagnosed according to the Report of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus, which is almost identical in terms of cut-off values for glucose levels to those of the WHO. The protocol for the study, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health, Labour and Welfare, received ethical

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approval from the institutional review boards of all of the participating institutes (RCT registration number was C000000222 in www.umin.ac.jp). Written informed consent was obtained from all patients enrolled.

Allocation of patients Before April 1996, when the intervention began, patients who did not meet the eligibility criteria were excluded. Finally, a total of 2,033 patients aged 58.5±6.9 years and who had diabetes for a duration of 10.9±7.2 years (both mean ± SD) were included from the present analysis. Figure 1 is a flow diagram of the JDCS. Patients were allocated randomly into either a lifestyle intervention (INT) group or a conventional treatment (CON) group. Randomisation and all analyses were done by a central computer at our database centre. This study was open-labelled and the interventions for the INT group were continued until March 2003.

Lifestyle intervention As basal therapeutic management of all patients in both the CON and INT groups, regular specialists' care was provided throughout the study period and patients were treated as they were before the study started. This included dietary advice by an administrative dietitian, using the 'Food Exchange Lists Dietary Guidance for Persons with Diabetes' [24].

In addition to this routine conventional treatment, education of patients in the INT group was given through individual counselling on dietary habits, physical activities and adherence to treatment, including taking medicine properly. Counselling was provided by physicians, nurses, dietitians and other co-medical staff during each outpatient clinic visit. Patients in the INT group had a typically 5–10 min longer interview than the patients in the CON group at each clinic visit for a discussion on possible causes of any changes in HbA_{1c} levels, weight and other control variables from the previous visit, with emphasis on lifestyle changes. For example, when it was revealed that control of glycaemic and other variables had worsened, that dietary intake, including quantity and content, and alcohol intake had changed, that patterns of physical activity had changed or that patients tended to forget to take their medicine, possible strategies for improving lifestyle and habits were discussed. Furthermore, patients in the INT group also received additional advice regarding one or two particular topic(s) at each visit and were given educational material consisting of 23 brochures that discussed various aspects of diabetes care with an emphasis on the importance of lifestyle and behavioural changes such as 'Why am I obese even if I do not eat so much?', 'Tips for continuing exercise', 'What kinds of stress affect the control of diabetes' or 'Is your triglyceride level OK?'.

Patients in the INT group also received 15 min telephone counselling sessions at least once every 2 weeks by nurses, dietitians and psychotherapists who were trained in diabetes education. These telephone sessions were performed based on a structured and uniform format. Additional counselling sessions were encouraged at any convenient time, depending on the needs of patients in the INT group. A diary to record the progress of laboratory and other data was distributed to the INT patients to provide better feedback on therapeutic results. A pedometer was also distributed to INT patients for objective exercise assessment.

Goals were set for patients in the INT group and their physicians: i.e. HbA_{1c} level <6.5%; BMI <22 kg/m^2; BP <140/85 mmHg; serum cholesterol level <5.72 mmol/l; serum triacylglycerol level <1.65 mmol/l; serum HDL-cholesterol >1.04 mmol/l; WHR <0.9 for men and <0.8 for women; smoking cessation; and abstinence from alcohol. Goals regarding BP and serum cholesterol levels were updated in accord with the revision of guidelines made by the Japan Diabetes Society, which were <130/80 mmHg and <5.17 mmol/l, respectively.

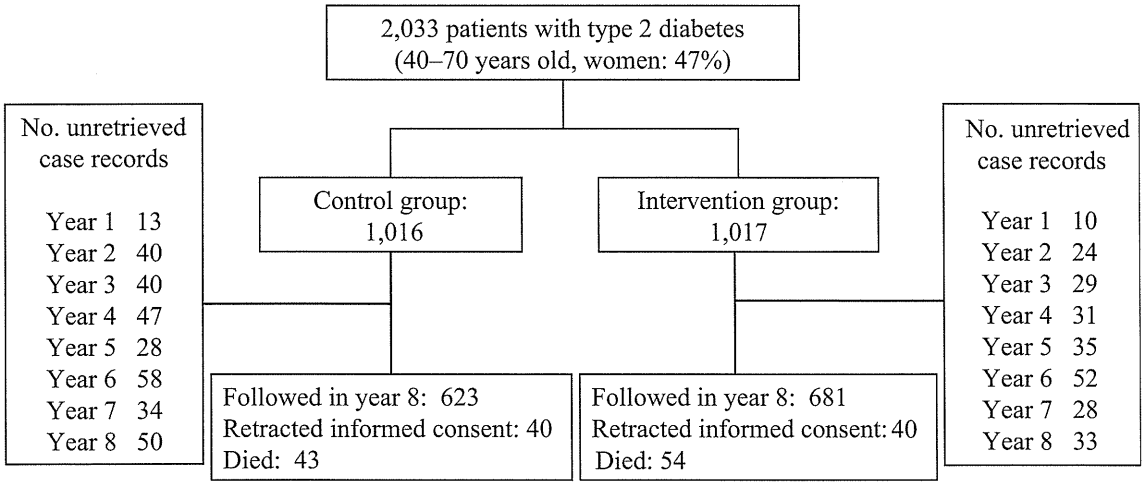

Fig. 1 Flow diagram of the JDCS

During the study period, patients in the INT group with poor control (HbA_{1c} >8.0%, serum total cholesterol level >5.72 mmol/l, serum triacylglycerol level >1.65 mmol/l or BMI >22 kg/m^2) were identified and sent additional educational material. At the same time, their physicians were encouraged to strengthen the intervention through increasing time for education by telephone or at clinic visits or recommending hospital admissions for education. Changes in medication including insulin and oral antihypertension/dyslipidaemia agents were not restricted in either group and were made based on therapeutic necessity.

Assessment of lifestyle Extensive lifestyle surveys were performed at baseline and 5 years after the start of the intervention in both groups. We used detailed questionnaires for patients to determine dietary (including alcohol drinking) content, amount of exercise and smoking rate. The dietary survey comprised food records and a food frequency questionnaire, results of which were analysed by an administrative dietitian using standardised software for population-based surveys and nutrition counselling in Japan (EIYO-KUN v.4.5, manufactured at Shikoku University Nutrition Database) [25] based on the Standard Tables of Food Composition in Japan [26] edited by the Japanese Ministry of Education, Culture, Sports, Science and Technology. Physical activity was determined by a questionnaire that inquired about types of exercise (walking, jogging, tennis, etc) and average time (min) spent exercising per day at baseline and the Baecke's Total Physical Activity Index [27] at the fifth year.

Clinical and laboratory measurements Mean values of at least two measurements each year were obtained for the following variables: HbA_{1c}, fasting plasma glucose/insulin/C-peptide, serum lipids/creatinine/urea nitrogen, and urine analysis. All other measurements including those for body weight, BP and WHR and a neurological/ophthalmological examination were done at least once yearly, with a mean value obtained if measurements were done twice a year. HbA_{1c} assays were standardised by the Laboratory Test Committee of the Japan Diabetes Society, with 5.8% as the upper normal limit. All other laboratory tests were done by standard methods in each clinic. Electrocardiograms and chest x-rays were performed annually. Patients were assessed yearly after the baseline evaluation.

Endpoints of the study Primary outcomes of the study were development and progression of microangiopathy and occurrence of macrovascular complication events. Microangiopathy endpoints consisted of those related to retinopathies and nephropathies. Retinopathy was evaluated by qualified ophthalmologists using the following classification designed for this research: Stage 0, no retinopathy; Stage 1, haemorrhage and hard exudates; Stage 2, soft exudates; Stage 3, intraretinal microvascular abnormalities and venous changes including beading, loop and duplication; Stage 4, new vessels, vitreous haemorrhage, fibrous proliferation and retinal detachment. The retinopathy endpoint was (1) development of retinopathy (from Stage 0 to any other stage confirmed in two continuous years), and (2) progression from Stage 1 to Stage 3 or 4. The nephropathy endpoint was defined as development of overt nephropathy (spot urinary albumin excretion >300 mg/g creatinine in two consecutive samples).

Macroangiopathy endpoints included the occurrence of definite CHD (angina pectoris or myocardial infarction) or stroke. Diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the WHO/MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project and diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour and Welfare of Japan [21]. Information regarding primary outcome and other clinical variables for each patient was collected through an annual report from each physician. Adjudication of endpoints was made by central committees comprising experts in each complication based on additional data such as CT or MRI of the brain or sequential changes in electrocardiograms.

Statistical analysis The sample size required to compare the net change in HbA_{1c} level (level at the third year point minus the baseline level) between the INT and CON groups is based on a consideration of power. It is assumed that the type I error (α) is 0.05 and the type II error (β) is 0.1; therefore, in order to detect a difference of 0.2 in net change in HbA_{1c} level, with an SD of 1.0 among patients, a total sample size of 1,025 is required. In addition, if allowance is made for an up to 20% dropout rate, for 20% of the INT group being unable to complete the intervention and for 10% of the CON group to change treatment method within the follow-up period, the required sample size increases to 2,616. Thus, in terms of the feasibility of the study, it was necessary to recruit more than 2,000 patients. All statistical analyses and data management were conducted at a central data centre. The Wilcoxon's rank sum test, Fisher's exact test and Mantel's test were used for comparison of numerical and categorical variables between groups.

The study endpoints were analysed as time-to-event variables, i.e. clinical data on patients who were lost during follow-up were used for the period for which they could be followed. Survival curves for the diabetic complications were estimated by the Kaplan–Meier method, and the logrank test was also conducted. Cox regression analysis was used to calculate the unadjusted and adjusted HRs and 95% CIs for group and risk factors. In multivariate Cox analysis, all significant variables selected for the univariate

analysis were used with the criterion of $p<0.1$. All values are presented as means ± SD unless otherwise stated. All p values are two-sided and the significance level is 0.05. All statistical analyses were conducted using SAS packages ver. 9.1 (SAS Institute, Cary, NC, USA).

Results

Clinical variables and their changes Clinical characteristics of the patients at baseline and at the fourth and eighth year after the start of the study are shown in Table 1. There were no differences in most variables between the two groups except for the triacylglycerol level, which was slightly but significantly lower in the INT group at the eighth year. Proportions of patients using agents for hyperglycaemia, including insulin, hypertension and dyslipidaemia and anti-platelet agents did not differ significantly between groups. Frequency of clinic visits also did not differ between groups. Proportions of patients who satisfied all or each of the components of the therapeutic goals did not differ between groups at either the fourth or eighth year. Median follow-up time was 7.8 years.

Of the eligible patients, 73% were followed into the eighth year. The dropout rate, which was defined as the proportion of patients who were lost-to-follow up until the eighth year, in the INT group (24%) was significantly lower than in the CON group (31%). Significant differences in baseline characteristics between patients who completed (i.e. were followed until the end of the observation period) and did not complete (i.e. dropped out during the observation period) follow-up were only found in the proportion of patients on insulin (22% completed vs 18% did not complete, $p=0.03$), in current smokers (20% completed vs 7.5% did not complete, $p=0.01$) and amount of daily exercise (590 kJ/day completed vs 351 kJ/day did not complete, $p<0.0001$).

Effects of lifestyle modification There were no differences in energy or fat intake between groups in either the fifth or the eighth year of the study (Table 1). Physical activity as determined by the Baecke's Total Physical Activity Index [27] after 5 years of intervention was significantly higher in the INT group than in the CON group, with the difference in the total score being derived from the Sports Index (4.1 in the INT group vs 3.7 in the CON group, $p=0.028$), but not Work or Leisure Indices. The proportion of current smokers in both groups decreased from 28% to 23%, with no significance between groups.

Primary endpoint analysis During the study period, 345 retinopathy, 74 nephropathy, 115 CHD and 90 stroke events occurred. Among all CHD events, 60% ($n=69$) were angina pectoris and 40% ($n=46$) were myocardial infarction, and among all stroke events, 83% ($n=75$) were brain infarction, 9% ($n=8$) were brain haemorrhage and 8% ($n=7$) were transient ischaemic attack. Kaplan–Meier curves for macro- and microvascular endpoints are shown in Fig. 2, which demonstrates that the incidence of stroke in the INT group was significantly lower than that in the CON group.

Risk factors for stroke analysed by univariate and multivariate Cox proportional hazard models are shown in Table 2, and belonging to the INT group was associated with an approximately 40% significant risk reduction for stroke by both univariate and multivariate analyses when all significant variables determined by univariate analysis were included. Systolic BP and lipoprotein(a) were also significant factors that remained in multivariate analysis. Despite this, absolute values for BP and lipoprotein(a) did not differ significantly between groups. Even when myocardial infarction (including asymptomatic) or brain infarction was used as an endpoint instead of CHD or stroke, respectively, the above results were not changed (data not shown).

No group differences were found in the occurrence of CHD, development of retinopathy (35.7/1,000 patient-years in the CON group vs 39.0 in the INT group), progression of retinopathy (6.5/1,000 patient-years in the CON group vs 10.0 in the INT group) or development of nephropathy (6.7/1,000 patient-years in the CON group vs 6.7 in the INT group).

Discussion

Although lifestyle interventions in patients with type 2 diabetes have traditionally focused almost exclusively on weight loss, control of glycaemia and other major cardiovascular risk factors should also be considered simultaneously for the prevention of complications [28, 29]. Systematic reviews and meta-analyses have revealed clinically significant but considerably mild effects of lifestyle interventions on glycaemic control, that is about a 0.5% reduction in HbA_{1c} with some variations in HbA_{1c} levels depending on the study and its design [8, 11, 22, 23]. In the Steno-2 study [16], the difference in mean HbA_{1c} levels between the conventional and intensive therapy groups after 7.8 years of follow-up was 1.1%, with a marked reduction in many diabetic complications. This was accomplished through not only behavioural modification but also pharmacological therapy for control of glycaemia, BP and serum lipid levels. HbA_{1c} levels were not reported in previous studies that examined the effects of a lifestyle intervention on cardiovascular events in individuals with IGT [13, 14]. The current study, together with our previous interim report [21], added the information that a lifestyle intervention produced significant but small and temporal

Table 1 Patient characteristics at baseline and 4 and 8 years after start of the intervention in each group

Variable	Baseline		4 years after start of intervention			8 years after start of intervention		
	CON	INT	CON	INT	*p* value[b]	CON	INT	*p* value[b]
No. patients (men/women)	1,016 (538/478)	1,017 (549/468)	850 (437/413)	882 (468/414)		630 (326/304)	689 (369/320)	
Age (years)	58.6±7.0	58.5±6.9	62.8±6.8	62.4±6.9	0.22	66.7±6.8	66.3±6.8	0.28
BMI (kg/m^2)	23.0±2.9	23.1±3.1	23.0±3.0	23.0±3.1	0.96	23.1±3.1	23.0±3.2	0.50
Blood pressure (mmHg)	132±16/77±10	132±16/77±10	132±15/75±9	133±16/76±9	0.23/0.33	132±16/74±10	133±16/74±10	0.17/0.99
Fasting plasma glucose (mmol/l)	9.0±2.4	8.8±2.4	8.9±2.6	8.8±2.5	0.14	8.7±2.6	8.6±2.4	0.90
HbA_{1c} (%)	7.9±1.3	7.8±1.2	7.7±1.2	7.6±1.2	0.10	7.6±1.2	7.7±1.2	0.47
Serum total cholesterol (mmol/l)	5.21±0.92	5.21±0.89	5.20±0.86	5.17±0.86	0.44	5.20±0.80	5.20±0.80	0.32
Serum triacylglycerol (mmol/l)[a]	1.17 (0.85)	1.15 (0.84)	1.14 (0.75)	1.14 (0.78)	0.55	1.19 (0.81)	1.09 (0.76)	0.049
Serum HDL-cholesterol (mmol/l)	1.42±0.46	1.41±0.42	1.50±0.42	1.49±0.44	0.39	1.50±0.40	1.50±0.40	0.88
Serum lipoprotein(a) (mmol/l)[a]	0.82 (1.03)	0.84 (1.10)	0.85 (1.02)	0.83 (1.00)	0.53	0.72 (0.86)	0.75 (1.10)	0.53
Therapeutic measures								
Diabetes								
Diet only (%)	19.1	19.4	7.2	8.5	0.32	3.7	3.5	0.88
Insulin (%)	21.6	20.2	35.2	32.3	0.22	44.3	42.2	0.45
Sulfonylureas (%)	56.7	57.9	62.1	62.7	0.80	56.4	60.5	0.15
α-Glucosidase inhibitors (%)	19.6	20.5	28.9	31.8	0.21	28.2	30.7	0.35
Biguanides (%)	5.4	4.3	15.6	16.6	0.60	31.3	33.6	0.39
Insulin sensitiser (%)	2.0	2.7	8.2	8.6	0.73	8.5	9.3	0.62
Others								
Antihypertensive agents (%)	26.8	27.7	35.5	36.2	0.76	47.8	47.4	0.91
Agents for hyperlipidaemia (%)	26.0	24.5	33.0	32.1	0.72	39.3	37.9	0.64
Diet								
Energy intake (kJ/day)[a]	7,101 (2,258)	7,092 (2,245)	6,891 (2,196)[d]	6,929 (2,062)[d]	0.60[d]	ND	ND	
Fat intake (g/day)[a]	52 (21)	51 (22)	48 (22)[d]	50 (22)[d]	0.30[d]	ND	ND	
Exercise (kJ/day for baseline and Baecke's score for the fourth year)[a]	502 (1,083)	565 (1,142)	9.3 (17.6)[d]	9.9 (17.5)[d]	0.037[d]	ND	ND	
Current/past smoker (%)	29/22	27/25	24/26[d]	21/30[d]	0.21[d]	ND	ND	
Alcohol intake per day: never, one drink or less, more than one drink[c] (%)	64/30/6	62/30/7	65/31/5[d]	60/33/7[d]	0.11[d]	ND	ND	

Means ± SD, unless otherwise stated

[a] Median (interquartile range)

[b] *p* values CON vs INT groups (Fisher's exact test for therapeutic measures, Mantel's test for smoking status and alcohol intake and Wilcoxon's rank sum test for other variables)

[c] 'One drink' is equivalent to 12.6 g of ethanol based on the US Department of Agriculture definition

[d] After 5 years

ND, not done

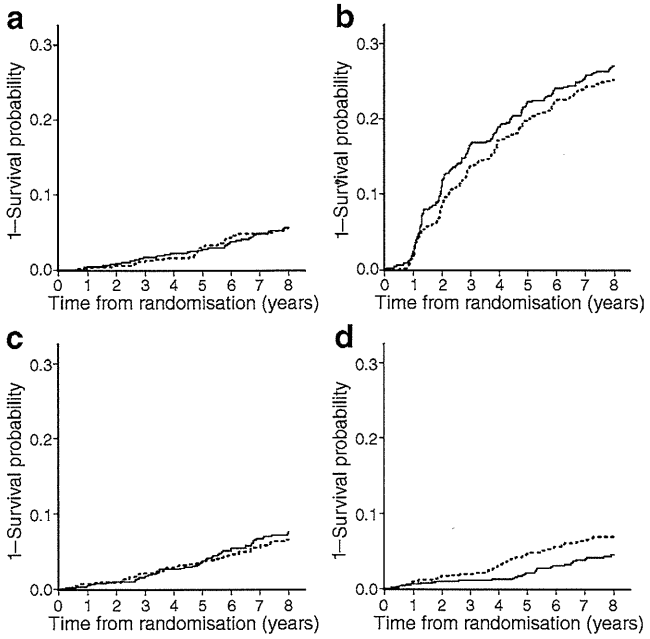

Fig. 2 Kaplan–Meier curves for each complication. **a** Nephropathy, p=1.00. **b** Retinopathy, p=0.43. **c** CHD, p=0.40. **d** Stroke, p=0.02. p values by logrank test. Dotted curves, CON; solid curves, INT

improvement in glycaemic control and only minimal changes in other known risk factors for diabetic complications, indicating the difficulty in changing the lifestyle of patients with long-term diabetes.

One possible reason for these limited effects on lifestyle and risk factors was that the intensity of our lifestyle intervention, which consisted only of education, was considerably lower than that in other studies [3, 15]. The rationale for this strategy was to determine if an intervention that is practicable to apply in the clinical 'real-world' setting with limited resources would be effective. Our results showed only very limited changes in actual lifestyle as well as major risk factors.

Another reason for the limited effects is that, in our study, even patients in the CON group received routine lifestyle education by diabetes specialists, which is an inevitable part of the usual care of persons with diabetes. Consequently, the effects of the lifestyle intervention was somewhat 'diluted'. The sequential increase in mean weight seen in the UK Prospective Diabetes Study (UKPDS) [30] was not observed in this study even in the CON group, indicating some effect of even routine lifestyle education. Also, perhaps if individualised goals with designated per cent changes for each patient in the INT group had been established instead of uniform goals for the entire group, results for the INT group might have been different. Further examination of results might have indicated which subgroups within the INT group would be most likely to benefit from such an intervention, which would be helpful in planning future interventions.

Nevertheless, we found a significant reduced risk for stroke in patients in the INT group compared with those in the CON group regardless of the lack of significant differences in most known cardiovascular risk factors. The mechanism of this apparent contradictory result is yet to be determined but it should be interpreted with care, especially since BP, which is a major risk factor for stroke, did not differ significantly between groups throughout the study period. Multifactorial or combined effects of lifestyle education/behaviours beyond individual factors [31] might have existed but can only be speculated upon. At the same time, the slight but significant differences in HbA_{1c} in the first 3 years, which was reported previously [21], but that disappeared thereafter, could enhance the effects since past interventions to lower HbA_{1c} reportedly have had a very long-term effect (i.e. 'metabolic memory' or 'legacy effect') [32, 33].

Other speculations for the apparent contradictory result include possible improvement in factors that were not determined in this study, such as postprandial glycaemia/lipaemia, BP at home or psychological factors (stress,

Table 2 Risk factors for stroke analysed by Cox univariate and multivariate models

Variable	HR (95% CI)	p value
Univariate analysis		
Sex (women vs men)	0.65 (0.42–1.00)	0.05
Age (per 10 years)	1.53 (1.11–2.13)	0.01
Diabetes duration (per 10 years)	0.95 (0.70–1.28)	0.72
HbA_{1c} (per 1%)	1.12 (0.97–1.30)	0.13
BMI (per 1 kg/m^2)	1.05 (0.98–1.12)	0.18
Waist circumference (per 10 cm)	1.38 (1.09–1.74)	0.01
Systolic BP (per 10 mmHg)	1.22 (1.07–1.38)	<0.01
Diastolic BP (per 10 mmHg)	1.18 (0.96–1.45)	0.12
LDL-cholesterol (per 1 mmol/l)	1.06 (0.82–1.37)	0.66
HDL-cholesterol (per 1 mmol/l)	0.62 (0.37–1.06)	0.08
Triacylglycerol (per 1 mmol/l)	1.16 (0.96–1.41)	0.14
Lipoprotein(a) (per 1 μmol/l)	1.17 (1.04–1.31)	0.01
Current smoker (yes vs no)	1.22 (0.95–1.56)	0.13
Alcohol intake (per 10 g ethanol)	1.06 (0.97–1.16)	0.23
Exercise amount (per 418 kJ)	1.01 (0.93–1.09)	0.80
INT group (vs CON group)	0.61 (0.39–0.93)	0.02
Multivariate analysis		
Sex (women vs men)	0.68 (0.42–1.11)	0.12
Age (per 10 years)	1.42 (0.99–2.04)	0.06
Systolic BP (per 10 mmHg)	1.22 (1.05–1.40)	0.01
Lipoprotein(a) (per 1 μmol/l)	1.16 (1.03–1.31)	0.01
INT group (vs CON group)	0.62 (0.39–0.98)	0.04

All significant variables selected for the univariate analysis with the criterion of a p<0.1 were used in the multivariate analysis

motivation or quality of life) [34], which could be ameliorated in the INT group rather than in the CON group. For example, Roumen et al. [35] recently reported that a lifestyle intervention successfully improved postprandial glucose levels in IGT patients. Changes in diet might also be effective, such as an increase in fruit intake, which is reportedly associated with reduced CVD mortality [36]. The reasons that only stroke, but not CHD or other complications, was found to be responsive to our intervention are speculated to include the following: (1) stroke is more frequent than CHD in Japan compared with other parts of the world, and (2) the independent risk factor for stroke was only systolic BP and lipoprotein(a), and so there would be room for other undetermined risk factors to work.

Telephone counselling in patients with chronic disease was shown to be associated with a 41% significant reduction in the risk of death [37]. However, attempts to use telephone calls in diabetes care have resulted in relatively mild [38, 39] or no additional [40] effects on control variables or improved quality of life [41] or patient satisfaction [39]. However, its effects on complication events have not been determined previously. Current results suggested that the telephone intervention could have contributed to a reduction in complication events. Further investigation is required to clarify whether telephone counselling alone is effective in improving the occurrence of complication events or death.

Lipoprotein(a), primarily a genetically determined risk factor for atherothrombogenesis, was found to be one significant predictor of stroke in our analysis. It has been reported as a predictor of deterioration of renal function [42], peripheral arterial disease [43], CVD [44] including CHD [45], and cardiovascular mortality [46] in patients with type 2 diabetes and a predictor of CVD [47] in patients with type 1 diabetes. It is of interest that the serum level of lipoprotein(a), which is known to be less affected by lifestyle or medication than other cardiovascular risk factors [48], was also a significant factor independent from lifestyle in our cohort.

The strengths of our study are that (1) it is the first intervention study mainly focused on the effects of lifestyle education on diabetic vascular complications, and (2) follow-up was done by diabetes specialists, ensuring that the quality of data was relatively high. Nevertheless, we acknowledge that the study had certain limitations. First, our participants were hospital-based patients with diabetes of a relatively long duration. Therefore, we cannot make inferences beyond a similar group. Second, only Asian diabetic patients were involved and they are different from other ethnic groups in terms of degree of obesity [49]. Third, we had a low follow-up rate, since the study was done mainly in large hospitals in urban areas where patients move quite frequently. However, it is less likely that this could be a cause of an inter-group difference in stroke incidence since significant differences in the incidence of stroke between groups could already be seen 4–5 years after the intervention began, when the follow-up rates of the two groups were not significantly different.

A therapeutic intervention mainly focused on lifestyle changes produced a significantly reduced risk of stroke in Japanese patients with type 2 diabetes independently of known classic risk factors. The detailed mechanisms for this effect should be investigated in the future.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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ARTICLE

Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS)

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Abstract
Aims/hypothesis The aim of the study was to determine the transition rate and factors associated with the progression of normo- and low microalbuminuria to diabetic nephropathy (overt proteinuria).
Methods For 8 years we prospectively observed 1,558 Japanese patients with type 2 diabetes mellitus whose basal urinary albumin:creatinine ratio (UACR) had been measured as <17.0 mg/mmol at entry. The incidence of nephropathy (UACR >33.9 mg/mmol) was determined by measuring UACR twice a year.
Results Progression to nephropathy occurred in 74 patients. The annual transition rate was 0.67%, and was substantially higher for the low-microalbuminuric group than for the normoalbuminuric group (1.85% and 0.23%, respectively; hazard ratio for the low-microalbuminuric group 8.45, $p<0.01$). The hazard ratio for an HbA_{1c} of 7–9% or ≥9% was 2.72 ($p<0.01$) or 5.81 ($p<0.01$) relative to HbA_{1c} <7.0%, respectively. In comparison with individuals with a systolic blood pressure (SBP) of <120 mmHg, the hazard ratios for patients with an SBP of 120–140 mmHg or ≥140 mmHg were 2.31 ($p=0.06$) and 3.54 ($p<0.01$), respectively. Smoking also affected progression to proteinuria (hazard ratio 1.99, $p<0.01$). In contrast, 30.3% of the low-microalbuminuric group returned to normoalbuminuria (i.e. were in remission).
Conclusions/interpretation These results suggest that if patients with type 2 diabetes mellitus are receiving

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treatment from diabetologists for hyperglycaemia and hypertension when they are in the early stages of nephropathy (i.e. normo- or low microalbuminuria), their rate of transition to proteinuria is considerably lowered, and that differentiating patients with low microalbuminuria from those with high microalbuminuria might be clinically useful.

Trial registration UMIN Clinical Trials Registry C000000222
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Keywords Blood pressure · Diabetic nephropathy · Glycaemic control · Progression · Remission · Smoking

Abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
INNOVATION	Incipient to Overt: Angiotensin II Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy
JDCS	Japan Diabetes Complications Study
SBP	Systolic blood pressure
UACR	Urinary albumin/creatinine ratio
UKPDS	UK Prospective Diabetes Study

Introduction

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in many countries, including Japan [1–3]. In the UK Prospective Diabetes Study (UKPDS), 24.9% of patients developed microalbuminuria within 10 years of diagnosis of type 2 diabetes, but only 0.8% developed ESRD, as assessed by an elevated plasma creatinine level (>250 μmol/l) or the need for renal replacement therapy [4]. Annual rates of transition between successive stages within the classic paradigm of normoalbuminuria to microalbuminuria to macroalbuminuria to ESRD were 2–3% per year [4].

In Japan, the number of patients requiring renal replacement therapy has increased threefold in less than 15 years [3]. Among 36,017 patients who started haemodialysis in 2007, the number of diabetic patients has reached 15,663 (43.5%) [3]. In Hong Kong, the overall number of people receiving renal replacement therapy increased by 50% between 1995 and 1999, and in the diabetic group, a 100% increase was observed [5]. Thus, Asians have a predisposition to diabetic nephropathy and ESRD. In fact, the recent Japanese Incipient to Overt: Angiotensin II Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) trial revealed that about 50% of diabetic individuals with high microalbuminuria (urinary albumin/creatinine ratio [UACR] between 11.3 and 33.9 mg/mmol [100–300 mg/g]) progressed to proteinuria within 2 years [6], indicating that progression is very rapid once high microalbuminuria develops. On the other hand, intervention using angiotensin receptor blockers (ARBs) such as losartan or telmisartan seems to be very effective in Asians in comparison with Europeans [6, 7]. The Japan Diabetes Complications Study (JDCS) is a nationwide randomised controlled study of type 2 diabetic patients focusing on lifestyle modification [8, 9]. Although the status of control of most classic cardiovascular risk factors, including body weight, glycaemia, serum lipids and blood pressure, did not differ between the two groups during the study period, the incidence of stroke in the intensive lifestyle intervention group (0.55/100 patient-years) was significantly lower than in the control group (0.95/100 patient-years) by Kaplan–Meier analysis, while the incidence of nephropathy did not differ significantly between the groups [9]. Here, we report the rate of transition and factors associated with the development and/or progression of normo- and low microalbuminuria to diabetic nephropathy (overt proteinuria) in this JDCS cohort.

Methods

In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels of >6.5% were recruited and registered from 59 hospitals specialising in diabetes care. The protocol for the study, which was in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health, Labour and Welfare, received ethics approval from the institutional review boards of all the participating institutions. Written informed consent was obtained from all the patients enrolled. The inclusion criteria for participating patients have been described previously by Sone et al. [8]. A final total of 2,033 patients aged 58.5±6.9 years (mean ± SD) were included in the study, and their diabetes duration was 10.9±7.2 years.

The recruited patients were randomly allocated to either an intensive lifestyle intervention group or a conventional treatment group. Details of the intervention have been described previously by Sone et al. [8, 9]. We selected a cohort of 1,558 patients in whom the mean value of the two-spot UACR was <17.0 mg/mmol (150 mg/g) without microscopic haematuria or other clinical findings indicating other renal diseases. We followed this cohort for 8 years, and measured their body weight, waist/hip circumference

and blood pressure at least twice a year. Fasting plasma glucose, HbA_{1c}, serum lipids and serum creatinine levels were also determined twice a year. Spot UACR was also determined at least twice a year using the turbidimetric immunoassay to measure the urinary albumin concentration. We defined normoalbuminuria as a UACR of <3.4 mg/mmol (30 mg/g), and low microalbuminuria as a UACR of 3.4 to 17.0 mg/mmol (30 to 150 mg/g). Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine levels according to the modification of diet in renal disease (MDRD) formula modified for Japanese populations [10].

Statistical analyses The primary endpoint for the nephropathy analysis was transition from normo- or low microalbuminuria to proteinuria (>33.9 mg/mmol [300 mg/g]) in two consecutive urine samples. Transition to proteinuria was summarised by the annual rate of transition to proteinuria and the remission proportion was defined as those patients whose mean UACR at the final two visits was <3.4 mg/mmol. Risk factors for proteinuria were explored by the following survival analysis methods. Univariate analyses were performed by the Kaplan–Meier method, logrank test, and univariate Cox regression with a 95% CI. Multivariate Cox regression was also used. The SAS software package (version 9.2, SAS Institute, Cary, NC, USA) was used for all analyses, with the level of significance set at $p<0.05$.

Results

Tables 1 and 2 give the baseline characteristics and glycaemic and blood pressure control at baseline, and at 4 and 8 years after the start of observation. As shown in Table 2, the proportion of patients who were receiving insulin injections increased from 20.7% to 41.9% over 8 years. The use of antihypertensive agents also increased over this period from 28.2% to 42.0%. In particular, usage of renin–angiotensin system inhibitors such as angiotensin-converting enzyme (ACE) inhibitors and/or ARBs increased from 12.3% to 28.4% over 8 years. The use of statins also increased from 20.5% to 31.1%. Over a median follow-up period of 7.98 years, 74 patients developed proteinuria. The annual transition rate was 0.67 per 100 person-years (95% CI 0.53–0.84). For the low-microalbuminuric group, the annual transition rate per 100 person-years was substantially higher than for the normoalbuminuric patients (1.85 [95% CI 1.43–2.41] and 0.23 [95% CI 0.14–0.36]), respectively. On the other hand, remission (i.e. normalisation) occurred in 137 (30.3%) of the 452 individuals with low microalbuminuria (Table 3).

Table 1 Baseline characteristics of 1,558 patients included in the nephropathy analysis

Variable	Mean ± SD[a]
n (men/women)	1,558 (813/745)
Age (years)	58.5±6.9
BMI (kg/m^2)	23.0±2.9
Waist (cm)	79.4±9.2
SBP (mmHg)	132.4±15.8
DBP (mmHg)	76.6±9.5
Fasting plasma glucose (mmol/l)	8.9±2.4
HbA_{1c} (%)	7.8±1.3
Duration of diabetes (years)	10.7±7.1
Serum total cholesterol (mmol/l)	5.19±0.89
Serum triacylglycerols (mmol/l)[b]	1.15±0.82
Serum HDL-cholesterol (mmol/l)	1.41±0.43
UACR (mg/mmol)[b]	1.8±3.0
eGFR (ml min^{-1} 1.73 m^{-2})[b]	81.3±32.1
Current/past/never smoker (%)	27/24/49
Ethanol intake: 0/1–38/≧38 g/day (%)	62/31/7

DBP, diastolic blood pressure

[a] Unless otherwise stated

[b] Median±interquartile range

Figure 1 shows the Kaplan–Meier curves for progression to overt nephropathy on the basis of UACR (Fig. 1a), HbA_{1c} level (Fig. 1b), systolic blood pressure (SBP, Fig. 1c) and smoking status (Fig. 1d). As can be seen, patients with higher UACR, higher HbA_{1c}, higher SBP or current smokers had a higher risk for progression to proteinuria. The hazard ratio for the low-microalbuminuric group was 8.45 ($p<0.01$) relative to the normoalbuminuric group. Stratification of eGFR to >90, 60–90 and <60 ml min^{-1} 1.73 m^{-2} did not predict progression to proteinuria. The hazard ratio of HbA_{1c} for a range of 7–9% or for ≥9% was 2.72 ($p<0.01$) or 5.81 ($p<0.01$) relative to an HbA_{1c} of <7%, respectively. In comparison with individuals with an SBP of <120 mmHg, the hazard ratio for patients with an SBP of 120–140 mmHg or ≥140 mmHg was 2.31 ($p=0.06$) and 3.54 ($p<0.01$), respectively. Smoking also affected progression to proteinuria, with a hazard ratio of 1.99 ($p<0.01$).

Table 4 shows risk factors for the development of proteinuria based on multivariate Cox regression analysis. All the factors shown to be significant by univariate analysis—UACR, HbA_{1c} level, SBP level and smoking status—were significantly associated with the development of proteinuria after adjustment for other clinical factors. Multivariate Cox regression analysis showed that the hazard ratio for use of ACE inhibitors and/or ARBs was 1.49 (95% CI 0.83–2.69, $p=0.19$) and that the hazard ratio for use of statins was 0.73 (95% CI 0.38–1.41, $p=0.35$) in relation to the progression to proteinuria.

Table 2 Measures of glycaemic and blood pressure control at the baseline and at 4 and 8 years after the start of intervention

Variable	Baseline	4 years after start of intervention	8 years after start of intervention
BMI (kg/m^2)	23.0±2.9	23.0±3.0	23.0±3.1
SBP (mmHg)	132.4±15.8	132.5±15.4	132.5±15.9
DBP (mmHg)	76.6±9.5	75.9±9.1	74.0±10.0
Fasting plasma glucose (mmol/l)	8.9±2.4	8.9±2.6	8.6±2.5
HbA_{1c} (%)	7.8±1.3	7.7±1.2	7.7±2.0
Hypoglycaemic agent (%)			
Any use	84.4	89.3	86.6
Insulin	20.7	30.1	41.9
Sulfonylurea	62.3	63.3	59.7
Alpha-glucosidase inhibitor	25.9	29.9	28.8
Biguanide	7.5	16.1	32.8
Insulin sensitiser	1.2	8.0	9.1
Antihypertensive agent (%)			
Any use	28.2	33.3	42.0
ACE inhibitor/ARB	12.3	16.6	28.4
Calcium-channel blocker	20.7	24.4	27.2
Diuretic	1.2	1.1	2.9
Other	6.0	7.1	8.6
Statin (%)	20.5	23.7	31.1

Each value is expressed as mean ± SD or percentage

DBP, diastolic blood pressure

Discussion

Based on the main result of the JDCS study, which was reported previously by Sone et al., the incidence of stroke in the intensive lifestyle intervention group was significantly lower, by 38%, than in the control group, while the incidence of nephropathy did not differ significantly between the groups [9]. Lifestyle intervention resulted in a small but significant temporary improvement of glycaemic control and only minimal changes in other known risk factors for diabetic complications, including blood pressure, indicating the difficulty of changing the lifestyle of patients with long-term diabetes. In this sense, patients who participated in this study could be considered as representative of the general population of patients with type 2 diabetes. This might explain why there was no difference in the incidence of diabetic nephropathy. The main finding of interest in this study was that the annual incidence of proteinuria was as low as 0.67% (0.67/100 person-years), in marked contrast to previous reports. In the UKPDS, the annual rates of transition from normoalbuminuria to microalbuminuria and from microalbuminuria to macroalbuminuria in newly diagnosed patients with type 2 diabetes were 2% and 2.8% per year, respectively [4]. Ravid et al. [11] reported higher progression rates in type 2 diabetic patients in Israel, i.e. 35% from normoalbuminuria to microalbuminuria and 16% from normoalbuminuria to macroalbuminuria during 7.8 years. In Pima Indians with normotensive type 2 diabetes, Nelson et al. [12] also reported that the rates of progression from normoalbuminuria to microalbuminuria and to macroalbuminuria during 4.7 years was 37.8% and 4.3%, respectively. In Japan, a clinic-based observational 6.8 year longitudinal study of 426 patients who developed diabetes before the age of 30 years revealed that the incidence of proteinuria developing from normoalbuminuria or microalbuminuria was 1.41/100 person-years [13]. In another Japanese clinic-based observational longitudinal study conducted for 6 years, 28% of 216 patients enrolled from 1996 to 1998 showed progression from microalbuminuria to proteinuria [14]. It is difficult to compare the annual incidence of proteinuria with that found in other studies because the stages of nephropathy

Table 3 Mean UACR measured at the final two visits stratified by the basal value

Basal UACR (mg/mmol)	Final UACR (mg/mmol)			
	<3.4	3.4–17.0	17.0–33.9	≥33.9
<3.4	817 (73.9)	244 (22.1)	27 (2.4)	18 (1.6)
3.4–17.0	137 (30.3)	203 (44.9)	56 (12.4)	56 (12.4)
Total	954 (61.2)	447 (28.7)	83 (5.3)	74 (4.8)

Data shown are *n* (%)

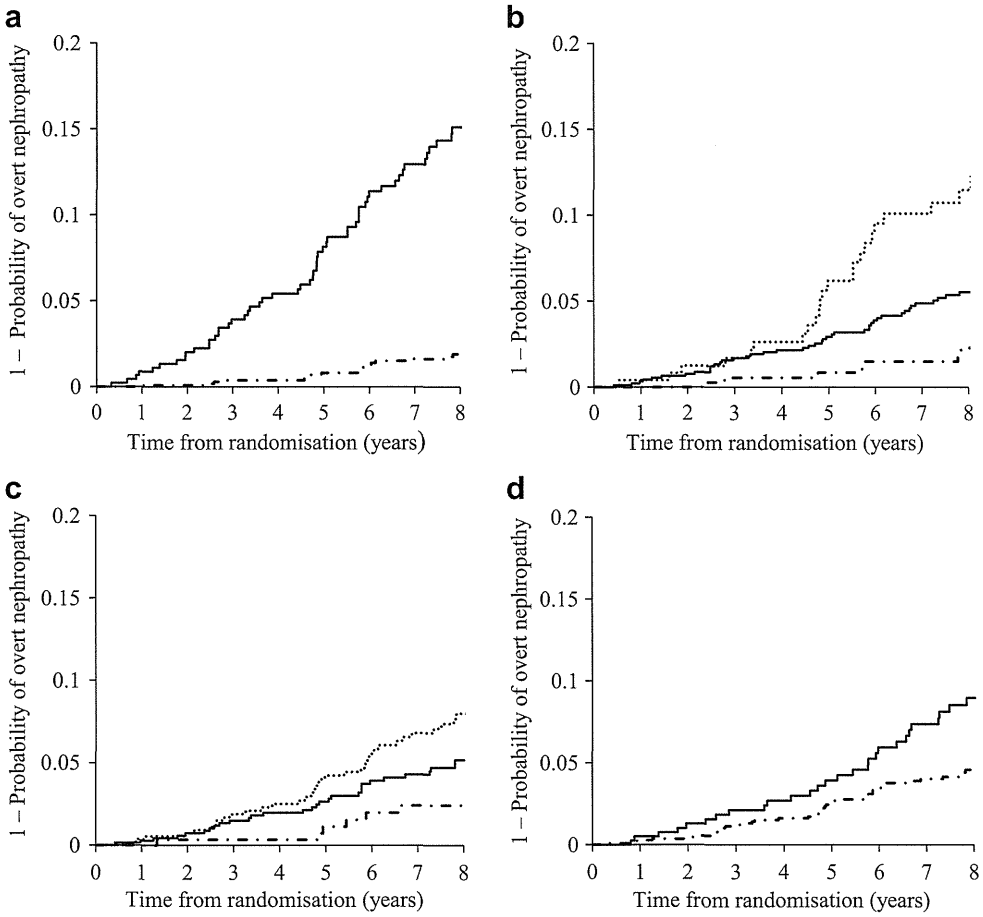

Fig. 1 Kaplan–Meier curves for progression to overt nephropathy according to: UACR (**a**), HbA_{1c} levels (**b**), SBP (**c**) and smoking status (**d**). **a** The hazard ratio for the low-microalbuminuric group (solid line) was 8.45 (95% CI 4.97–14.38, $p<0.01$) relative to the normoalbuminuric group (dashed–dotted line). **b** The hazard ratio of HbA_{1c} for a range of 7–9% (solid line) and for ≥9% (dotted line) was 2.72 (95% CI 1.22–6.03, $p<0.01$) and 5.81 (95% CI 2.49–13.55, $p<0.01$), respectively, relative to an HbA_{1c} of <7% (dashed–dotted line). **c** The hazard ratio for an SBP of 120–140 mmHg (solid line) or ≥140 mmHg (dotted line) was 2.31 (95% CI 0.96–5.54, $p<0.06$) and 3.54 (95% CI 1.50–8.40, $p<0.01$), respectively, relative to an SBP of <120 mmHg (dashed–dotted line). **d** The hazard ratio for current smoking (solid line) was 1.99 (95% CI 1.24–3.18, $p<0.01$) relative to past smoking or never smoked (dashed–dotted line)

differ from one study to another. However, the rate of transition to proteinuria in the JDCS seems to be very low. Of course, one of the reasons for this low incidence might be that two-thirds of the enrolled patients had normoalbuminuria and one-third had low microalbuminuria. In contrast, the placebo group in the INNOVATION trial showed a considerably higher transition rate, amounting to 50%, from high microalbuminuria to proteinuria within 2 years, with a UACR between 11.3 and 33.9 mg/mmol [6], although the UACR was determined using the first-voided

Table 4 Risk factors for progression to proteinuria demonstrated by multivariate Cox regression analysis

Risk factor	Hazard ratio	95% CI	*p* value
Conventional/intervention	1.01	0.63–1.61	0.98
Age, +10 years	1.03	0.71–1.49	0.87
Sex, woman/man	0.74	0.41–1.34	0.32
Duration, +10 years	1.16	0.80–1.68	0.44
BMI, +1 kg/m^2	1.01	0.93–1.10	0.73
SBP, 120–140/<120 mmHg	1.90	0.73–4.95	0.19
SBP, ≥140/<120 mmHg	2.55	0.98–6.63	0.05
HbA_{1c}, 7–9/<7%	2.22	1.00–4.96	0.05
HbA_{1c}, ≥9/<7%	4.16	1.73–10.04	<0.01
LDL-cholesterol, ≥4.0/<4.0 mmol/l	0.85	0.48–1.49	0.57
Triacylglycerol, ≥2.3/<2.3 mmol/l	1.60	0.88–2.89	0.12
HDL-cholesterol, ≥1.0/<1.0 mmol/l	1.43	0.79–2.61	0.24
UACR, ≥3.4/<3.4 mg/mmol	6.98	4.02–12.10	<0.01
Current smoker/past or never smoker	1.87	1.07–3.25	0.03
Ethanol intake, ≥38 g/<38 g/day	0.99	0.98–1.01	0.38

Missing values meant 126 patients were excluded

morning urine. Taken together with these studies, the data suggest that the current treatment by diabetologists along with administration of the usual hypoglycaemic and hypotensive drugs from the stage of normoalbuminuria or low microalbuminuria reduced the annual incidence of proteinuria to a level as low as 0.67/100 person-years. Ideally, however, the inclusion of a control group receiving placebo and matched to the drug-treated diabetic patients would be desirable in order to allow a firm conclusion to be drawn, although admittedly this would be ethically problematic. As the baseline UACR profoundly affected the cumulative incidence of proteinuria, it might be clinically useful to divide patients with microalbuminuria into low- and high-risk groups, i.e. those with low and high microalbuminuria, although the cut-off value remains to be determined.

In the present study, progression to proteinuria was independently associated with higher baseline HbA_{1c} and SBP levels in addition to an elevated baseline UACR. Furthermore, smoking was also a significant predictor of proteinuria. These results are consistent with previous studies [11, 15]. In the UKPDS, the risk factors most highly associated with proteinuria were reported to be urinary albumin, plasma creatinine, waist circumference, SBP, glycaemic control, LDL-cholesterol, and plasma triacylglycerol [15]. Indian-Asian ethnicity was also an independent risk factor for microalbuminuria and/or proteinuria [12, 15]. Smoking and male sex were reported to be independent predictors of proteinuria in addition to plasma cholesterol, mean blood pressure and HbA_{1c} [11]. Based on these epidemiological studies, tight glycaemic control has been reported to be effective for preventing the onset and/or progression of nephropathy in clinical trials such as the Diabetes Control and Complications Trial (DCCT), the Kumamoto study and the UKPDS [16–18]. Strict blood pressure control, especially with ACE inhibitors or ARBs, has also been demonstrated to be effective for delaying the progression of diabetic nephropathy [6, 7, 19–21]. However, in the present study, the initial usage of an ACE inhibitor and/or ARB, or statin was not significantly associated with the prevention of proteinuria. As this study was designed to clarify the effects of lifestyle intervention on subsequent occurrence of diabetic complications, it might have been difficult to recognise the effects of such drugs on the progression of diabetic nephropathy. In some studies, normalisation of microalbuminuria, i.e. remission/regression, has also been reported [6, 12]. In fact, in our study, 30.3% of 452 individuals with low microalbuminuria demonstrated normalisation.

However, following the advent of modern therapeutics, especially hypoglycaemic and antihypertensive agents, diabetic nephropathy is the most common cause of ESRD, and the number of patients being started on haemodialysis is still increasing dramatically in many countries, particularly in Asia. Our data have major clinical relevance because we have demonstrated that the initiation of hypoglycaemic and antihypertensive treatment from the early stage of nephropathy might lower the rate of transition to proteinuria even in the Japanese, who are highly susceptible to diabetic nephropathy. To reduce the number of patients who require haemodialysis, it is very important to measure UACR, make a diagnosis of diabetic nephropathy, define the stage of nephropathy and initiate strict glycaemic and blood pressure control as early as at the normo- or low-microalbuminuria stage.

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Duality of interest The authors declare that there is no conflict of interest associated with the manuscript.

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ARTICLE

Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS)

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Abstract
Aims/hypothesis The aim of this study was to determine the incidence and progression rates of diabetic retinopathy and their associations in Japanese individuals with type 2 diabetes.
Methods This is a part of the Japan Diabetic Complications Study (JDCS), a multi-centred randomised trial of type 2 diabetes patients aged 40–70 years with an 8 year follow-up. There were 1,221 patients without diabetic retinopathy at baseline; incidence of diabetic retinopathy was defined as the development of any diabetic retinopathy. There were 410 patients with mild non-proliferative diabetic retinopathy at baseline; progression of diabetic retinopathy was defined as the development of severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy. We used multivariate proportional Cox hazard models, and generalised additive models were also applied to identify potential threshold effect.
Results The incidence and progression rate of diabetic retinopathy was 38.3/1,000 person-years and 21.1/1,000 person-years, respectively. Higher HbA_{1c} (adjusted HR [aHR] per 1% [10.9 mmol/mol] 1.36 [95% CI 1.28–1.45]), longer duration of diabetes (aHR per 5 year period 1.26 [95% CI 1.17–1.35]), higher systolic blood pressure (aHR per +10 mmHg 1.01 [95% CI 1.00–1.02]) and higher body mass index (aHR per 1 kg/m^2 1.05 [95% CI 1.00–1.09]) were associated with incident diabetic retinopathy. The association between HbA_{1c} and incident diabetic retinopathy was linear; the association with duration of diabetes increased rapidly between 5 and 10 years. Higher HbA_{1c}

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was also associated with progression of diabetic retinopathy (aHR per 1% [10.9 mmol/mol] 1.66 [95% CI 1.41–1.96]).
Conclusions Observed incidence and progression rates of diabetic retinopathy seemed lower than that in western populations. HbA_{1c} was the only factor associated with both incidence and progression of diabetic retinopathy. The strength of the association between duration of diabetes and incidence of diabetic retinopathy increased rapidly during a period of 5 to 10 years duration of diabetes.
Trial registration: C000000222 (www.umin.ac.jp)
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Keywords Diabetic retinopathy · HbA_{1c} · Incidence · Japan Diabetes Complications Study (JDCS) · Type 2 diabetes

Abbreviations
JDCS Japan Diabetes Complications Study

Introduction

Diabetic retinopathy is one of the leading causes of blindness in the working-age population [1]. Although improved management of risk factors and advances in treatment modalities for diabetic retinopathy have contributed to reducing the risk of blindness from this pathology [2–4], type 2 diabetes per se has been continuously increasing in Asian populations [5, 6]. The report from the International Diabetes Federation estimated that people with diabetes in the Asian Pacific region will increase from 137 million in 2010 to 214 million by 2030 [7]. Because diabetic retinopathy is one of the common microvascular complications in diabetes, the number of people with diabetic retinopathy is also estimated to increase. Therefore, specific incidence and progression rates of diabetic retinopathy in Asian diabetic patients are necessary to estimate the burden and thus to develop strategic preventive interventions for the management of diabetic retinopathy.

While long-term incidence of diabetic retinopathy is well documented in western populations, such as in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [8], the Fyn Study [9] or in a Hispanic population in the US [10], there has been insufficient information from Asian populations. Those studies reported from Asian countries are either based on relatively small sample sizes or single hospital-based samples [11–14].

With regard to the risk associations for diabetic retinopathy, duration of diabetes and HbA_{1c} are two key risk predictors of diabetic retinopathy; diabetic retinopathy develops in nearly 80% of those with type 2 diabetes with duration of diabetes of 15 years [15]. However, detailed association between duration of diabetes or HbA_{1c} and incidence or progression of diabetic retinopathy in Asian samples is also not well documented. Okudaira et al. [16] has reported association between duration of diabetes or HbA_{1c} and progression of diabetic retinopathy in Japanese patients with early-onset type 2 diabetes. Shiraiwa et al. has reported that postprandial hyperglycaemia was more influential than fasting glycaemia or HbA_{1c} in the risk of incidence or progression of diabetic retinopathy in Japanese patients with diabetes who were admitted to their hospital [17, 18].

Recently, the American Diabetes Association recommended using HbA_{1c} levels to diagnose diabetes based on the observation that the prevalence of diabetic retinopathy increases rapidly in individuals with $HbA_{1c} \geq 6.5\%$ (47.5 mmol/mol) [19]. However, whether there is a clear cut-off value in HbA_{1c} associated with rapid increased incidence or progression of diabetic retinopathy is uncertain.

This study aims to determine the incidence and progression rate of diabetic retinopathy in adult Japanese patients with type 2 diabetes, together with their risk associations, with a focus in the duration of diabetes and HbA_{1c}. We used a multi-centred cohort of the Japan Diabetes Complications Study (JDCS) with 8 years of follow up.

Methods

This study is a part of the JDCS, a Japanese nationwide multi-centred randomised trial of 2,033 adults (1,087 men and 946 women) with type 2 diabetes aged between 40 and 70 years. Details of study design have been described elsewhere [20, 21]. Baseline characteristics of the study participants are shown in Table 1. In brief, study participants were invited to participate if they had an HbA_{1c} level of more than 6.5% (47.5 mmol/mol) and were aged 40–70 years; patients with impaired glucose tolerance were excluded. As a result, the HbA_{1c} level of study patients ranged between 6.0% (42.1 mmol/mol) and 15.8% (149.2 mmol/mol). Those who have major ocular disease (e.g. glaucoma, dense cataract or history of cataract surgery) were excluded from the current analysis. Participants were randomly assigned to a lifestyle intervention or conventional treatment and followed up annually from March 1996 until March 2003. We analysed follow-up data until March 2003. The study was approved by the committee of the Ministry of Health, Labour and Welfare, Japan. We obtained written informed consent from all patients. As we reported in our previous paper, there was no significant difference in incidence or progression of diabetic retinopathy between the control group and the intervention group (aHR for incidence or progression of