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2型糖尿病患者のQOL、血管合併症及び長期予後改善のための前向き研究
（Japan Diabetes Complications Study; JDCS）
平成21年度　分担研究報告書

大血管合併症

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研究要旨

Japan Diabetes Complications Study（JDCS）コホートの８年次データにおいて、患者教育による生活習慣改善を中心とした介入の、冠動脈疾患（狭心症と心筋梗塞）と脳卒中（脳出血、一過性脳虚血発作と脳梗塞）の発症率に対する効果について解析した。その結果、介入群において非介入群と比較して、脳卒中発症リスクが有意に低下していたことが明らかになり、生活習慣介入を主体とした患者教育が、大血管合併症を抑制した世界最初のエビデンスとして欧州糖尿病学会誌に発表された。

A．研究目的

糖尿病患者に発症する脳卒中・冠動脈疾患・末梢動脈疾患、すなわち大血管合併症は、糖尿病患者の生命予後に直結する重大な合併症である。これらの動脈硬化疾患は、糖尿病特有の合併症ではないものの、糖尿病患者はそうでない者と比較して心血管疾患の発症率が２－４倍高く、さらに重症度も高く発症後の予後も不良である。

近年欧米において、糖尿病大血管症イベントの予防に関する多くの大規模臨床介入試験やメタアナリシスが行われ、特に欧米人患者における臨床エビデンスや、高血糖、高血圧や脂質異常症に対する薬物療法が、糖尿病大血管合併症を抑制するというエビデンスはかなり充実してきた。しかし、生活習慣介入を主体とした患者教育が大血管合併症を抑制しうるか否かという点に関するエビデンスはなく、その意味で、本研究の結果発表が待たれていた。

一方、東アジア人患者の大規模研究は限られており、特に日本人２型糖尿病患者における大血管症の発症率やリスクファクターなどのデータも十分ではない。日本の糖尿病患者の生命予後を改善するためにも、日本人糖尿病患者の大血管合併症に関

する臨床エビデンスを確立する必要がある。

B．研究方法

開始時から平成19年3月31日までに大血管症エンドポイント（冠動脈疾患と脳卒中）に至った患者について、3名（山崎義光、笈田耕治、山田信博）の判定委員が独立して、エンドポイント基準（詳細は平成7年度報告書参照）を満たしているかどうか認定を行った。さらにそれらの患者の登録時データを用いて、既知の危険因子に関して多変量解析を含む統計的解析を実施した。本研究のフローチャートを図１に示す。

C．研究結果と考察

生活習慣指導介入の血糖コントロール改善効果について、欧米のメタアナリシスではHbA1C平均低下度が0.76％で、介入中止後は0.26％まで減少したとされている。ＪＤＣＳでは、開始2年目から5年目までの間だけ介入群が非介入群より有意に低いHbA1Cが値を示し、しかもその差はやはり0.2%に過ぎなかった（図２）。

体重、血圧、血清脂質、喫煙率などについても両群間に有意差はなく（図３）、その理由としては、ＪＤＣＳが糖尿病専門施設において行われ、非介入群患者に対する従来治療に含まれる教育指導内容がもともと高水準であったため、追加の生活習慣指導介入の効果が現れにくかったためと推測された。

一方、糖尿病患者に対する生活習慣介入の合併症に対する効果はこれまで報告されていなかったが、本研究の結果では、網膜症、腎症、冠動脈疾患の発症率については有意差がみられなかった。しかし、脳卒中に関しては、従来治療群の発症率 9.52/1000人年に対して、生活習慣介入群の発症率は 5.48/1000人年と有意に低く（ログランク検定でp=0.02）、生活習慣介入群の従来治療群に対する脳卒中発症ハザード比は0.62（95%信頼区間0.39-0.98, p=0.04）と低下していた（図４、５）。脳卒中の８割以上が脳梗塞であった。

主要な心血管リスクファクターである血清脂質、血圧、喫煙率などについては、両群間で有意差がみられなかったにも関わらず、脳卒中の発症率が有意に抑制された理由については今のところ明らかではない。

両群間にみられたわずかな運動量の違いや、過去にみられた血糖コントロールの“Legacy effect（遺産効果）”、または精神的ストレスや不安感の低減など、生活習慣指導に伴う未知の因子などが関与している可能性はある。しかし、冠動脈疾患には有意差がみられなかったにも関わらず、脳卒中の発症のみが有意に抑制されていたことと共に、今後の検討課題と考えられる。

D．結論

患者教育による生活習慣改善を中心とした介入が、脳卒中発症リスクを有意に低下させていたことが明らかになった。生活習慣介入を主体とした患者教育が大血管合併症を抑制した世界最初のエビデンスとして、２型糖尿病診療に寄与するものと思われる。

F．健康危険情報

該当事項なし

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図１　JDCS のフローチャート

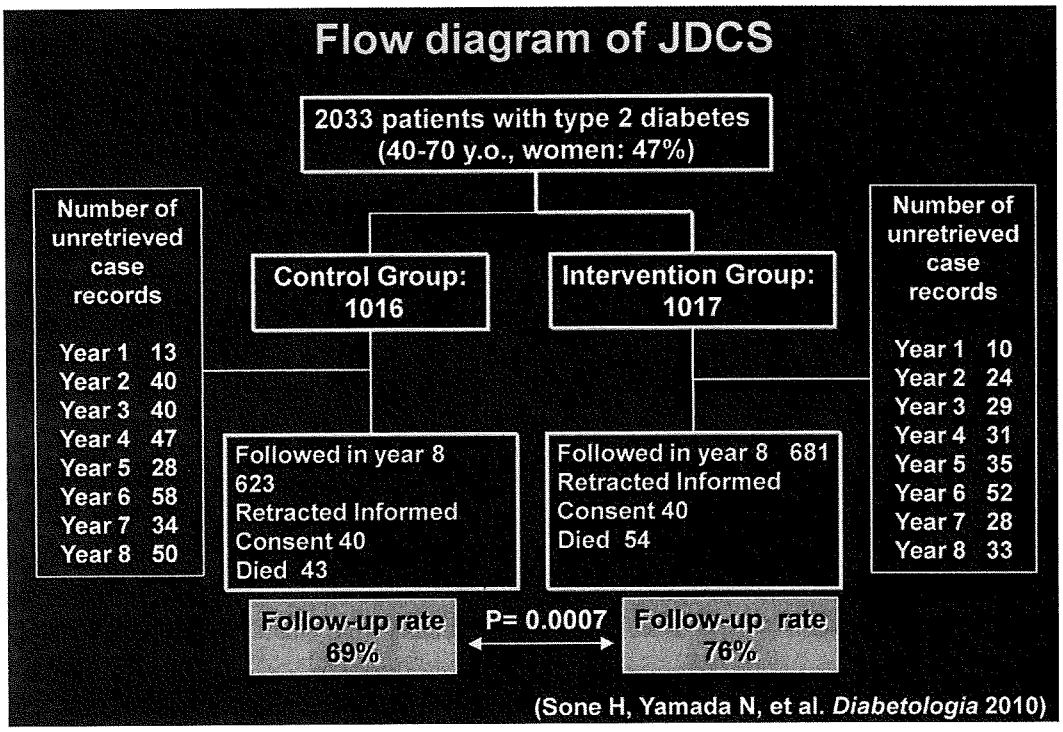

図２　JDCS における HbA1C の推移

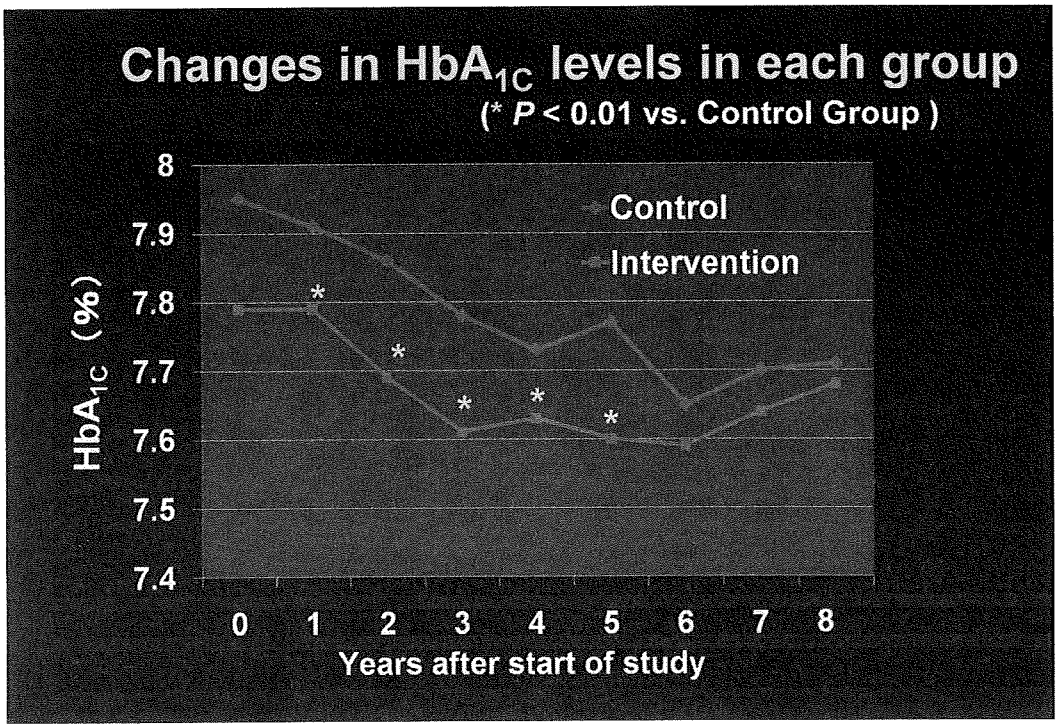

図３　JDCS における肥満度、血圧、脂質指標の推移

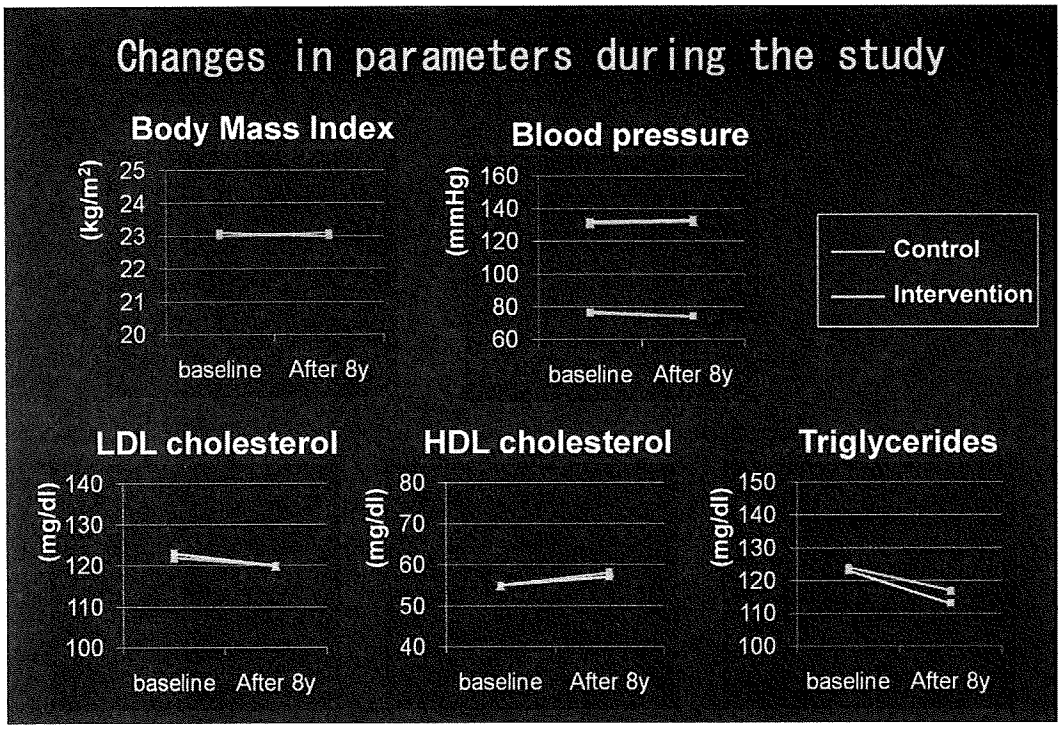

図４　大血管合併症の介入効果

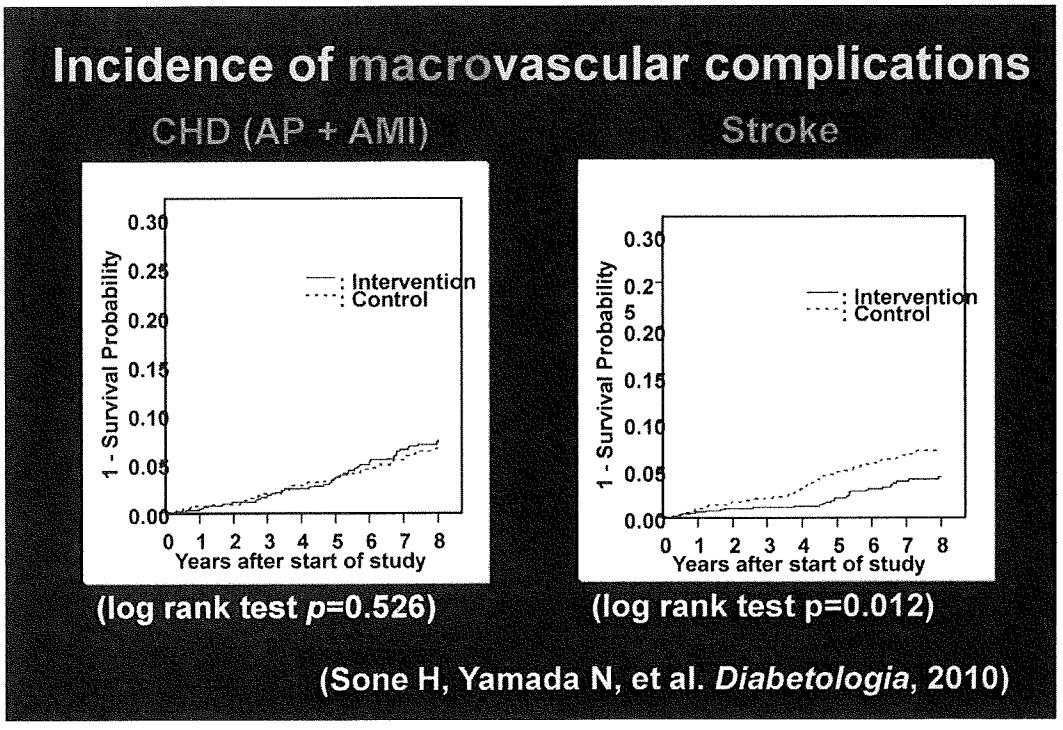

図５　新聞報道（一部）

毎日新聞　第48145号

毎日新聞　MAINICHI

1月9日（土）

毎日新聞東京本社

日航 法的整理へ

関係閣僚一致　19日にも決定

日本航空の再建をめぐり、政府は8日、企業再生支援機構による法的整理を活用した再建案を支持する方向で最終調整に入った。8日午前、菅直人副総理兼財務相、前原誠司国土交通相ら関係閣僚・大臣が首相官邸で会談し、認識が一致した模様だ。機構は19日をめどに日航支援を正式決定する方針を決めており、法的整理に反対する銀行団との調整が焦点になる。

（3面にクローズアップ）

機構や銀行団は、12日に日航の企業年金減額問題に対するOBの意向がまとまる（まえ、法的整理の）是非が可能か

生活習慣改善で　脳卒中が減少

厚労省研究班　糖尿病患者調査

生活習慣の乱れなどが原因となる2型糖尿病患者が積極的な生活習慣改善に取り組むと、従来の治療だけを受けた患者に比べ、脳卒中の発症が少なくなることが、厚生労働省研究班（主任研究者＝山田信博・筑波大学長）の大規模調査で明らかになった。9日、欧州糖尿病学会誌に発表する。生活習慣の改善が、合併症の減少につながることが証明されたのは、初めてという。【永山悦子】

調査は、40〜70歳の2型糖尿病の男女2033人を対象に実施。従来の治療を続ける群と、治療だけでなく生活習慣の改善に積極的に取り組み、主治医の指導回数を増やしたり電話指導を受ける群に分け、96年から8年間追跡した。

その結果、生活習慣改善群の脳卒中発症率が、従来治療群の6割にとどまった。両群の血圧、血中脂肪、体重などに差はなかった。網膜症や心筋梗塞など他の合併症の発症率に差はなかった。

糖尿病の合併症には脳卒中、心筋梗塞、腎症、網膜症、神経障害などがある。研究班の曽根博仁・筑波大教授は「脳卒中の大きな原因は高血圧と考えられてきたが、血圧が同程度でも両群に差が表れた点が興味深い」と話している。

NEWSLINE

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Hayashi T, Kawashima S, Itoh H, Yamada N, Sone H, Watanabe H, Hattori Y, OhruiT, Yokote K, Nomura H, Umegaki H, Iguchi A; Japan CDM Group.	Low HDL cholesterol is associated with the risk of stroke in elderly diabetic individuals: changes in the risk for atherosclerotic diseases at various ages.	Diabetes Care	32	1221-1223	2009

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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.

Clinical Trial Registration: UMIN-CTR C000000222
Funding: The Ministry of Health, Labour and Welfare, Japan

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.

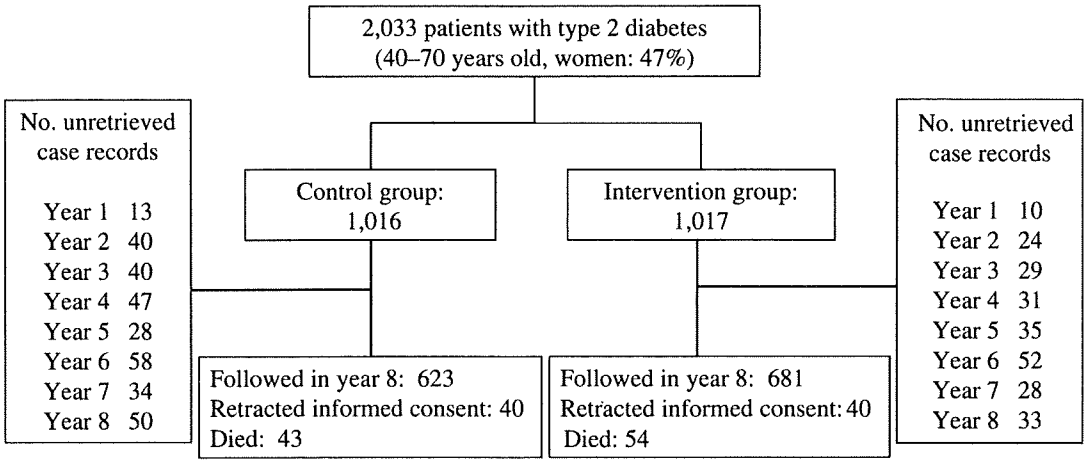

Fig. 1 Flow diagram of the JDCS

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

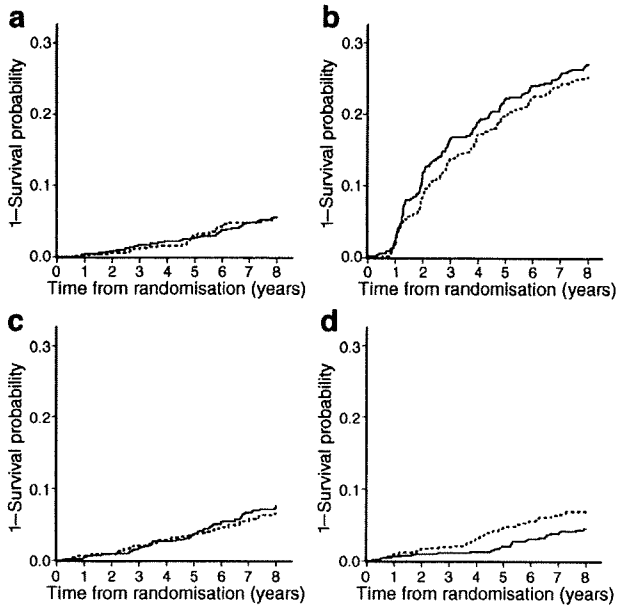

Fig. 2 Kaplan–Meier curves for each complication. **a** Nephropathy, $p=1.00$. **b** Retinopathy, $p=0.43$. **c** CHD, $p=0.40$. **d** Stroke, $p=0.02$. p values by logrank test. Dotted curves, CON; solid curves, INT

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 post-prandial 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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