厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
日本人2型糖尿病患者における生活習慣介入の長期予後効果
並びに死亡率とその危険因子に関する前向き研究
(Japan Diabetes Complications Study; JDCS)

平成２３年度　分担研究報告書

JDCStudy の問題点とその解決

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研究要旨
糖尿病における血管合併症の予防、進展抑制を目的とした介入効果についての研究を遂行する上で、問題点を把握、その要因について検討した。

A．研究目的

本研究は、我が国における糖尿病患者における糖尿病合併症特に血管合併症を把握、その予防、進展抑制をはかるための手段、特にライフスタイルへの介入効果を検討し、我が国独自の大規模臨床として成果を上げつつある。そこでさらに効果的な介入をはかるための、問題点とその対策について検討した。

B．研究方法

本研究を実施するにあたり、現状と当施設における遂行上の問題点を把握し、その対策についての検討を行った。

C．研究結果と考察

1）　非血管合併症に関するデータの必要性

糖尿病患者には血管合併症、感染症、膵がんや肝臓がんのような一部の悪性腫瘍の合併頻度が高いことはよく知られた事実である。最近、高血糖に伴って増加するその他の悪性腫瘍や精神疾患、消化器疾患、呼吸器疾患、

自傷行為などによる死亡も注目が集まっている[1]。JDCSにおいても、これらのイベントについても集計することに意義があるかもしれない。

2）　遺産効果の検証

これまでに海外から報告のあった糖尿病患者での心血管イベント抑制試験では、スタチンによる脂質低下治療、血圧低下治療、血糖低下治療の有効性が確立されている。その中で血糖低下療法に関しては、介入中止後もイベント抑制効果が持続する遺産効果(legacy effect)に注目が集まっている[2,3]。一方、類似の効果は脂質低下治療や血圧低下治療では報告されていない。後期糖化生成物(AGE)や高血糖の血管構成細胞に及ぼすエピゲノム変化が血糖低下治療の遺産効果を仲介する機序として想定されている。脳血管障害に対して認められた本試験の介入効果にも、同様の遺産効果が認められるのか検証したいところである[4]。

3）　糖尿病の心血管イベント発症リスク

現在のわが国の診療ガイドラインでは、糖尿病はハイリスク群として扱われている。主に海外の疫学調査や本研究の成果に基づいて糖尿病の心血管リスクが推定されてきた[5]。一方、一般住民を対象にした調査では、そこまで高いリスクではないとする報告も複数ある。恐らく、同じ糖尿病であっても、病型・重症度・罹病期間・合併症有無等等の要素の多様性に起因する差異と解釈される。今後、より精度の高いリスク評価法の確立が期待される。

D．結論

JDCSによって得られたデータが上記のエビデンス形成に資することを期待したい。

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(Japan Diabetes Complications Study; JDCS)

平成２３年度　分担研究報告書

JDCStudy の問題点とその解決

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研究要旨　JDCStudy は糖尿病の血管合併症に対する介入効果を検討するため組織された。８年次の研究成果が発表された。これに伴い、より長期の観察研究が必要である。そのための戦略が求められる。

A．研究目的

長期間の観察を可能にするための方法を確立すること。

B．研究方法

今回得られた８年次の研究成果を踏まえ、さらなる観察期間の延長と症例ごとの臨床経過の参加施設の登録患者を経年的に観察し、合併症の発症・進展に関与する因子についてさらに検討することが必要である。このような点を検討する。

C．研究結果

問題解決のためには参加医師の新たな発想のため、８年次の成績について報告することが必要である。また、さらに経過観察を続行することがこの研究の重要性をさらに増し、日本における糖尿病治療の具体的な目標・方法が確立されることを、周知し進めることが必要である。

D．考察

さらなる研究の継続は今後の JDCS の成果をより充実させ、日常診療の具体的な目標を明らかにすることに貢献することが期待される。

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平成２３年度　分担研究報告書

JDCStudy の問題点とその解決

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研究要旨
糖尿病における血管合併症の予防、進展抑制を目的とした介入効果についての研究を遂行する上での３つの課題：①血圧と糖尿病合併症における J-カーブの存在の有無、②non-HDL コレステロールと動脈硬化性疾患との関連、③血糖コントロールと心血管死亡との関連を挙げて、それを解決するための対策や今後の展望について考察を加えた。

A．研究目的

JDCStudy 研究は、我が国における糖尿病患者における糖尿病の血管合併症、およびその危険因子を把握し、血管合併症の予防、進展抑制をはかるための手段、特にライフスタイルへの介入効果を検討してきた。JDCStudy 研究は我が国独自の大規模臨床試験として大きな成果を上げつつある。そこで、さらに効果的な研究を遂行する上での課題、その対策、及び今後の展望について考察を加えてみた。

B．研究方法

本研究を実施するに当っての現状の問題点や課題を把握し、他の介入研究との比較より、研究の解析の上で重要と思われる血圧、脂質、血糖における課題を抽出し、今後の対策について検討を加えた。

C．研究結果と考察

１．血圧の問題：

最近の ROADMAP 研究や ORIENT 研究では ARB の投与が致死的心血管イベントを多くするという結果が得られている。例えば、ROADMAP 研究は腎症のない２型糖尿病患者 4,447 名を、オル

メサルタン 40mg/日投与群と非投与の対照群に無作為に割り付け、両群とも130/80mmHg 以下を目標に降圧して、3.2 年間追跡した。オルメサルタン群は微量アルブミン尿の発症を遅らせたが、オルメサルタン群では致死的血管イベントが多くなり、とくに冠動脈疾患既往例でこの傾向が見られた。この結果の解釈は難しいが、オルメサルタン群での頭痛、めまいなどの低血圧症状や低血圧のイベントの増加が見られたことより、血圧を下げすぎることが死亡につながる危険性を示している。

また、日本の高齢糖尿病患者のJ-EDIT 研究におけるランドマーク解析では、血圧と追跡期間中の脳血管障害発症、および糖尿病関連イベントとの間には J-カーブの存在が認められている[1]。即ち、収縮期血圧を 4 分位に分けて検討すると、収縮期血圧が147mmHg 以上の群が最も脳血管障害が多く、収縮期血圧 127–136mmHg の群は最も脳血管障害が少なく、126mmHg 以下では再び脳血管障害が増加した。

海外でも血圧と動脈硬化性疾患の関係においては、J-カーブの存在が再び注目されている。したがって、JDCStudy においても、血圧と糖尿病性合併症や心血管疾患で J-カーブがないかどうか再検討をすることが必要であろう。また、J-カーブは、恐らく血圧が変動しやすく、過度の降圧が悪影響を及ぼす高リスク群において見られると考えられる。従って、JDCStudy の対象で血圧が変動しやすい高リスク群の存在があるかどうかの詳細な検討も必要であろう。

2．脂質の問題：

脂質に関しては、最近、non-HDL コレステロール(non-HDL-C)が注目されている。Non-HDL-C は LDL-C だけでなく、糖尿病で異常が見られる IDL など TG が豊富なリポ蛋白のコレステロールを反映し、酸化 LDL とも関連する。JDCStudy においても non-HDL-C が虚血性心疾患や脳卒中の危険因子であることが明らかになりつつある。

J-EDIT 研究でも、non-HDL-C が脳血管障害、糖尿病関連死、糖尿病関連イベントとの関連していた[1]。J-EDIT 研究は JDCStudy 同時期に行われた研究であり、両者の集団を合わせ、同じ解析手法で検討すれば、non-HDL-C の年齢別の危険因子として重み付けが明らかになることが期待される。

3．血糖の問題：

ACCORD 研究では 5 年後の複合アウトカムは強化治療群と通常治療群とで有意差が認められず、強化治療群の5年間の全死亡の増加が未だ見られた。ADVANCE 試験では強化治療群の全死亡率が通常治療群と比べて1.22倍、心血管死亡が1.35倍増加し、特に罹病期間が長い集団で見られ、死亡が増加した。介入試験では、高齢者や長期罹病期間の患者が含まれているかどうかで介入効果に差が生じる可能性がある。罹病期間の長い高齢者

では低血糖による不整脈、自律神経異常、易血栓性がおこりやすい可能性も考えられる。

したがって、JDCStudy における介入効果や心血管疾患の危険因子も罹病期間、年齢の影響を受ける可能性があり、この観点からの詳細な解析が必要になるであろう。J-EDIT 研究は JDCStudy 同時期に行われた研究であり、評価項目も類似しており、両者の集団を合わせるならば、日本の 2 型糖尿病患者の年齢別の心血管疾患、脳血管疾患、死亡の危険因子が年代別に明らかになるものと期待される。

D．参考文献

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E．実用新案登録　なし

別紙　　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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Katayama S, Moriya T, Tanaka S, Tanaka S, Yajima Y, Sone H, Iimuro S, Ohashi Y, Akanuma Y, Yamada N	Low Transition Rate from Normo- and Low Microalbuminuria to Proteinuria in Japanese Type 2 Diabetics: the Japan Diabetes Complications Study (JDCS)	Diabetologia	54	1025-31	2011
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Kodama S, Saito K, Tanaka S, Horikawa C, Fujiwara K, Hirasawa R, Yachi Y, Iida KT, Shimano H, Ohashi Y, Yamada N, Sone H	Effect of Web-based Lifestyle Modification on Weight Control: A Meta-analysis	Int J Obes	in press		2012
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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

Table 1 Baseline clinical characteristics of type 2 diabetes patients in the Japan Diabetes Complications Study

Characteristic	Incidence of diabetic retinopathy (n=1,221)	Progression of diabetic retinopathy (n=410)
Sex (female %)	45.0	49.5
Age (years)	58.2±6.9	59.1±6.9
Diabetes duration (years)	9.8±6.8	12.8±7.1
<5 years (%)	26.2	11.5
5–10 years (%)	33.6	27.6
≥10 years (%)	40.2	60.9
BMI (kg/m^2)	23.1±3.1	23.1±3.0
Systolic blood pressure (mmHg)	130.9±16.1	132.8±16.3
Diastolic blood pressure (mmHg)	77.2±10.0	76.3±9.4
Fasting plasma glucose[a] (mmol/l)	8.4 (7.3–9.9)	8.5 (7.3–9.9)
HbA_{1c} at baseline (%)	7.8±1.3	8.0±1.2
HbA_{1c} at baseline (mmol/mol)	61.7±14.2	63.9±13.1
<7.0% (<53.0 mmol/mol) (%)	27.2	21.5
7.0 to <9.0% (53.0 to <74.9 mmol/mol) (%)	59.4	57.8
≥9.0% (≥74.9 mmol/mol) (%)	13.4	20.7
Total cholesterol (mmol/l)	5.2±0.9	5.1±0.8
LDL-cholesterol (mmol/l)	3.2±0.8	3.1±0.8
Triacylglycerol[a] (mmol/l)	1.2 (0.6–1.7)	1.1 (0.6–1.7)
HDL-cholesterol (mmol/l)	1.4±0.5	1.5±0.4
Exercise (kJ/day)[a]	602.1 (129.3–1,243.1)	498.3 (96.2–1,259.0)
Therapy components		
Diabetes		
Diet only (%)	24.2	10.0
Insulin (%)	14.0	27.1
Sulfonylureas (%)	56.1	64.3
α-Glucosidase inhibitors (%)	16.8	22.0
Biguanides (%)	4.7	6.5
Insulin sensitisers (%)	1.8	1.5
Antihypertensive agents (%)	25.0	26.8
Agents for hyperlipidaemia (%)	24.4	26.1
Smoking status		
Current smoker (%)	29.7	23.9
Past smoker (%)	24.4	22.9
Never smoked (%)	46.0	53.2
Alcohol intake		
0 g/day (%)	61.3	63.3
1–37 g/day (%)	30.9	31.2
≥38 g/day (%)	7.8	5.4

Data are percentages or mean± SD except for: [a] median (IQR)

diabetic retinopathy compared with the control arm: 0.82 [95% CI 0.65–1.02] and 0.76 [95% CI 0.45-1.22], respectively) [21].

Assessment of diabetic retinopathy Presence and severity of diabetic retinopathy was determined annually by local ophthalmologists at each study site and history of ocular surgery was also surveyed. Following the international diabetic retinopathy and diabetic macular oedema disease scales [22], severity of diabetic retinopathy was categorised into five stages of 'no retinopathy', 'mild non-proliferative diabetic retinopathy', 'moderate non-proliferative diabetic retinopathy', 'severe non-proliferative diabetic retinopathy', and 'proliferative diabetic retinopathy'. To validate the consistency of grading between study sites, we cross-examined fundus images and evaluated the agreement in grading between local ophthalmologists and retinal specialists (RK and HY). The estimate of kappa statistics for the

agreement was 0.56 (95% CI 0.52–0.59) and was considered to be above moderate.

Definition of incidence and progression of diabetic retinopathy 'Incidence of diabetic retinopathy' was defined as having no diabetic retinopathy signs in either eye at baseline and having mild to severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy in either of the eyes at two consecutive follow-up years. 'Progression of diabetic retinopathy' was defined as having mild non-proliferative diabetic retinopathy at baseline, and having severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, or laser photocoagulation treatment for diabetic retinopathy at follow-up at two consecutive follow-up years.

Statistical analysis The primary endpoint was 'time-to-incidence' or 'time-to-progression' of diabetic retinopathy. The time from baseline registration was calculated for each participant from the starting point to the date of incidence of diabetic retinopathy, or progression of diabetic retinopathy. In addition to the events of incidence or progression of diabetic retinopathy, cataract surgery and death were considered as censoring. We used the Kaplan–Meier method to plot the cumulative proportion of incidence or progression of diabetic retinopathy. We reported crude and multivariate-adjusted hazards ratios (aHRs) using the Cox proportional hazard models. In the multivariate model, covariates were selected by the backward selection method at $p>0.1$ from the following variables: age, sex, duration of diabetes, age at diagnosis of diabetes, life style intervention, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, HbA_{1c} at baseline, HDL-cholesterol, LDL-cholesterol, triacylglycerol, smoking (current vs non-current smoker), alcohol consumption (≥38 g/day vs 1–37 g/day vs 0 g/day) and intervention (vs control). We also examined associations between diabetic retinopathy and HbA_{1c} using time-dependent Cox regression analysis, which incorporates all measurements of HbA_{1c} during follow up as one time-dependent covariate. To explore whether there is any dynamic change in risk associations, such as a rapid increase in risk of incident diabetic retinopathy, we used multivariate-adjusted generalised additive models with a spline function of three degrees of freedom including diabetes duration, BMI, systolic blood pressure and HbA_{1c} as covariates. All p values are two-sided and $p<0.05$ was considered statistically significant. Statistical analyses were carried out using the SAS software package (version 9.2; SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of people at risk of incidence or progression of diabetic retinopathy are shown in Table 1. The baseline HbA_{1c} level for the entire study sample was 7.8±1.3% (61.7±14.2 mmol/mol) (range 6.0–15.8% [42.1–149.2 mmol/mol]). There were 1,221 patients who had no diabetic retinopathy at baseline and were at risk of incident diabetic retinopathy; there were 325 cumulative incident cases of diabetic retinopathy (risk in 8 year period 26.6%; annual risk 3.3%), and the incidence rate was 38.3/1,000 person-years. There were 410 patients who had mild non-proliferative diabetic retinopathy at baseline and were at risk of progression of diabetic retinopathy; there were 65 cumulative cases with a progression of diabetic retinopathy (risk in 8 year period 15.9%; annual risk 2.0%), and the progression rate was 21.1/1,000 person-years.

Using the stepwise backward variable selection method, duration of diabetes (aHR 1.26 [95% CI 1.17–1.35] per +5 years, $p<0.0001$), higher BMI (aHR 1.05 [95% CI 1.00–1.09] per +1 kg/m^2, $p=0.019$), higher systolic blood pressure (aHR 1.09 [95% CI 1.02–1.17] per +10 mmHg, $p=0.014$) and higher HbA_{1c} (aHR 1.36 [95% CI 1.28–1.45] per +1% [10.9 mmol/mol], $p<0.0001$), were selected as significant characteristics associated with incidence of diabetic retinopathy (Table 2). In contrast, higher HbA_{1c} was the only characteristic selected as significantly associated with progression of diabetic retinopathy (aHR per +1% [10.9 mmol/mol] 1.66 [95% CI 1.41–1.95], $p<0.0001$) (Table 2).

These associations between HbA_{1c} and incidence or progression of diabetic retinopathy remained consistent

Table 2 Associations between incidence or progression of diabetic retinopathy and risk factors selected by the stepwise backward procedure in multivariate Cox regression models

Variable	Incidence of diabetic retinopathy (n=1,221)			Progression of diabetic retinopathy (n=410)		
	aHR	95% CI	p value	aHR	95% CI	p value
Diabetes duration (per 5 year period)	1.26	(1.17–1.35)	<0.0001	–	–	–
BMI (per 1 kg/m^2)	1.05	(1.00–1.09)	0.019	–	–	–
Systolic blood pressure (per 10 mmHg)	1.09	(1.02–1.17)	0.014	–	–	–
HbA_{1c} (per 1% [10.9 mmol/mol])	1.36	(1.28–1.45)	<0.0001	1.66	(1.41–1.95)	<0.0001

when we used HbA_{1c} level as a time-dependent covariate accounting for change in HbA_{1c} during the follow-up period (aHRs for incidence or progression of diabetic retinopathy per +1% [10.9 mmol/mol] change in HbA_{1c}: 1.36 [95% CI 1.27–1.47], $p<0.0001$ and 1.33 [95% CI 1.11–1.60], $p=0.001$, respectively).

When we replaced duration of diabetes with age at diagnosis of diabetes (≥50 years old vs <50 years old) in the multivariate model, individuals who were diagnosed with diabetes at ≥50 years old were significantly less likely to develop diabetic retinopathy compared with individuals who were diagnosed at <50 years old (aHR 0.72 [95% CI 0.57–0.90], $p=0.004$).

Figure 1a,b show the Kaplan–Meier plot for the incidence and progression of diabetic retinopathy by three levels of HbA_{1c}. Compared with patients with HbA_{1c} <7.0% (53.0 mmol/mol), individuals with 7.0% (53.0 mmol/mol)≤HbA_{1c}<9.0% (74.9 mmol/mol) and individuals with HbA_{1c} ≥9.0% (74.9 mmol/mol) had significantly higher risk of incident diabetic retinopathy (HR 1.98 [95% CI 1.44–2.70], $p<0.0001$, and 4.04 [95% CI 2.83–5.78], $p<0.0001$, respectively). Patients with HbA_{1c} ≥9.0% (74.9 mmol/mol) had an eightfold higher risk of progression of diabetic retinopathy compared with that in the patients with HbA_{1c} <7.0% (53.0 mmol/mol) (HR7.92, 95% CI 3.08–20.36, $p<0.0001$).

Association between risk over an 8 year period of the incidence of diabetic retinopathy and HbA_{1c} (Fig. 2a) or diabetes duration (Fig. 2b) were estimated using generalised additive models. As shown, there was no indication of the presence of a threshold in associations between HbA_{1c} and risk of incidence of diabetic retinopathy. In contrast, as shown in Fig. 2b, there was a dynamic increase in the risk of developing diabetic retinopathy between 5 years and 10 years of duration of diabetes. In general, the risk of incidence of diabetic retinopathy increases with longer duration of diabetes; it increases more rapidly between 5 years (0.185, 95% CI 0.149–0.227) and 10 years (0.313, 95% CI 0.263–0.368). The risk of incidence of diabetic retinopathy is more stable with <5 years or ≥10 years of duration of diabetes.

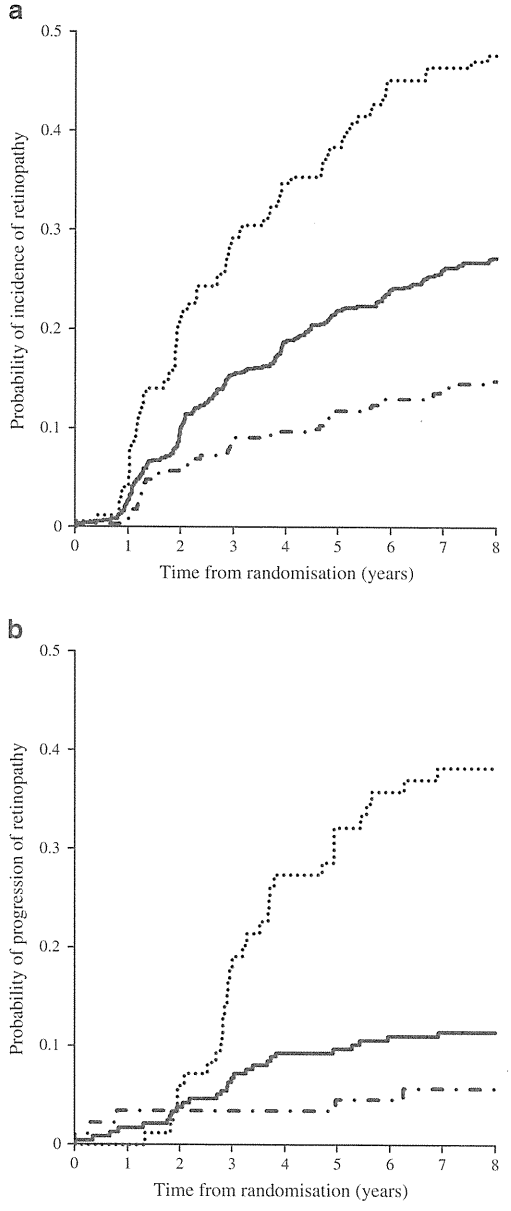

Fig. 1 **a** Kaplan–Meier plot for the incidence of retinopathy by HbA_{1c} level (dotted line, HbA_{1c} ≥9.0%; black line, 9.0%>HbA_{1c}≥ 7.0%; dashed line, HbA_{1c} <7.0%). **b** Kaplan–Meier plot for the progression of retinopathy by HbA_{1c} level (dotted line, HbA_{1c} ≥9.0%; black line, 9.0%>HbA_{1c} ≥7.0%; dashed line, HbA_{1c}<7.0%) (HbA_{1c} 7% is equivalent to 53.0 mmol/mol; 9% is equivalent to 74.9 mmol/mol)

Discussion

Using the JDCS cohort, we reported the incidence rate of diabetic retinopathy in Japanese adult type 2 diabetes patients with a long-term follow up of 8 years. The observed incident rate (38.3/1,000 person-years) was close to the previous reports of incident rate of diabetic retinopathy from Asian populations [13, 14].

Strengths of our study are that it involved a multi-centred study design covering a large geographical area in Japan, and a large sample size of >1,000. Limitations might include the accuracy of diabetic retinopathy grading based on clinical diagnosis, when compared with grading based on seven-field stereo fundus photography. Although we validated the consistency of grading as moderate compared with photographic grading in a sub-sample, subtle diabetic retinopathy change can be overlooked and the outcomes of incidence or progression of diabetic retinopathy can be underestimated. Selection bias by

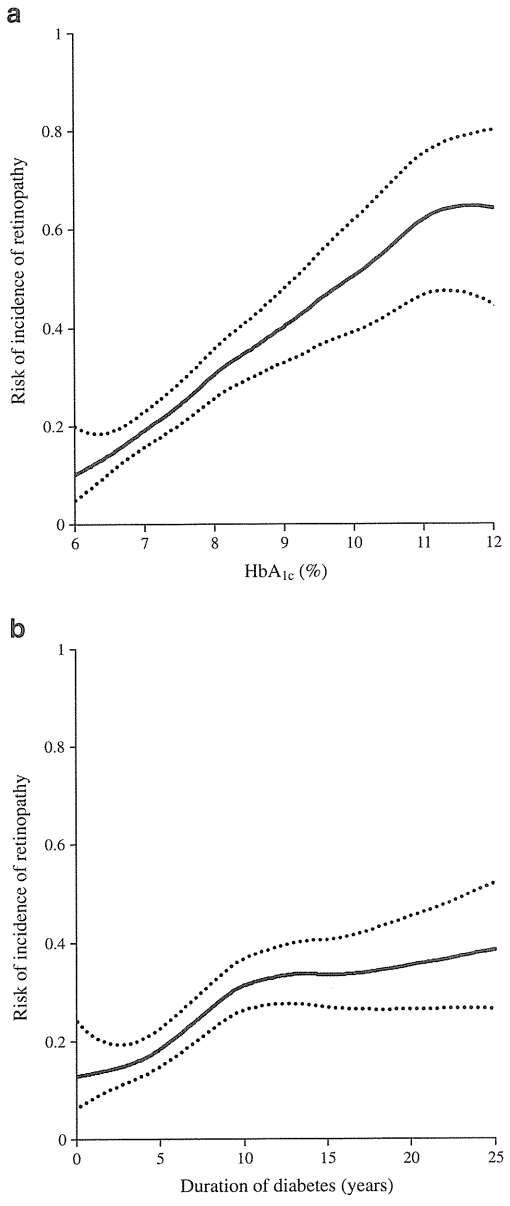

Fig. 2 **a** Risk (black line) and 95% CI (dotted lines) of the incidence of retinopathy in relation to HbA_{1c} estimated by generalised additive models. **b** Risk (black line) and 95% CI (dotted lines) of the incidence of retinopathy in relation to diabetes duration estimated by generalised additive models

including patients for lifestyle intervention might overestimate the incidence and progression of diabetic retinopathy than in the diabetic population in general.

The incidence rate of diabetic retinopathy in this study was comparable to previous studies from Asian populations. Kim et al. [13] reported the incidence rate of diabetic retinopathy in Korean type 2 diabetic patients as 44.4/1,000 person-years over a follow-up of 5.3 years; Sasaki et al. [14] reported the incidence rate of diabetic retinopathy as 39.8/1,000 person-years in Japanese type 2 diabetes patients (n=976; follow-up of 8.3 years). The observed incident rate in this study was slightly lower than that reported in white or Hispanic populations in western countries (3.3% in this study vs 4.4–8.6%) [10, 23, 24].

With regard to risk associations, HbA_{1c} (either at baseline or change over time) was the most relevant risk factor for both incidence and progression of diabetic retinopathy. Risk of incidence and progression of diabetic retinopathy increased linearly by 36% and 66% for every 1% [10.9 mmol/mol] increase in HbA_{1c} at baseline, respectively. This association was consistently found when we treat HbA_{1c} level as a time-dependent variable accounting for change in HbA_{1c} over follow-up time. We also found that here were no suggestions of a threshold effect in HbA_{1c} level, which would rapidly increase the risk of incidence or progression of diabetic retinopathy; the association between HbA_{1c} level and incidence or progression of diabetic retinopathy seems to be linear (Fig. 2a). One limitation of our study is that individuals involved in this study have an HbA_{1c} range of 6.0% (42.1 mmol/mol) to 15.8% (149.2 mmol/mol), and we cannot confirm whether there is a threshold effect outside this range. This warrants further study to determine the therapeutic target with a cut-off HbA_{1c} value for reducing risk of incidence or progression of diabetic retinopathy. We have also observed that individuals who were diagnosed at ≥50 years old were significantly less likely to develop diabetic retinopathy compared with individuals who were diagnosed at <50 years old; association of HbA_{1c} and incidence or progression of diabetic retinopathy did not change significantly even adjusting for age at onset.

An association between longer duration of diabetes and incidence of diabetic retinopathy was also confirmed in this study. With regard to the duration of diabetes, the risk of incidence of diabetic retinopathy increases rapidly from 5 years to 10 years duration while the change in risk was stable at <5 years or ≥10 years of duration (Fig. 2b). Although the duration of diabetes is not a modifiable risk characteristic, our findings might contribute to better management strategies by suggesting that patients with 5–10 years of duration of diabetes may have greater risk of developing diabetic retinopathy and thus need more intensive follow up compared with those with ≥10 years of duration of diabetes.

We found an association between higher BMI and incidence of diabetic retinopathy. While it is still controversial, obesity has been shown to be associated with increased risk of incident diabetic retinopathy [1]. In our earlier analysis, we have reported a significant difference in BMI in persons with type 2 diabetes between western and Japanese populations [25]; BMI in Japanese patients with type 2 diabetes was significantly lower than that in western populations [25]. In this study, we found that higher BMI is significantly associated with the incidence of diabetic

retinopathy even within the relatively lower BMI range (23.1 ± 3.0 kg/m^2). This finding warrants further research to assess whether Asian individuals who are overweight are also at risk of developing diabetic retinopathy.

In conclusion, we have reported the incidence rate and progression rate of diabetic retinopathy in adult Japanese patients with type 2 diabetes over 8 years. We found that higher HbA_{1c} level was significantly and linearly associated with both incidence and progression of diabetic retinopathy. Higher BMI and higher systolic blood pressure were also associated with higher risk of developing diabetic retinopathy. Duration of diabetes was also associated with increasing risk of incidence of diabetic retinopathy; the risk of incidence of diabetic retinopathy increases rapidly between 5 and 10 years. This study emphasises the importance of glycaemic control in the management of diabetic retinopathy in Asian patients with type 2 diabetes.

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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* (%)

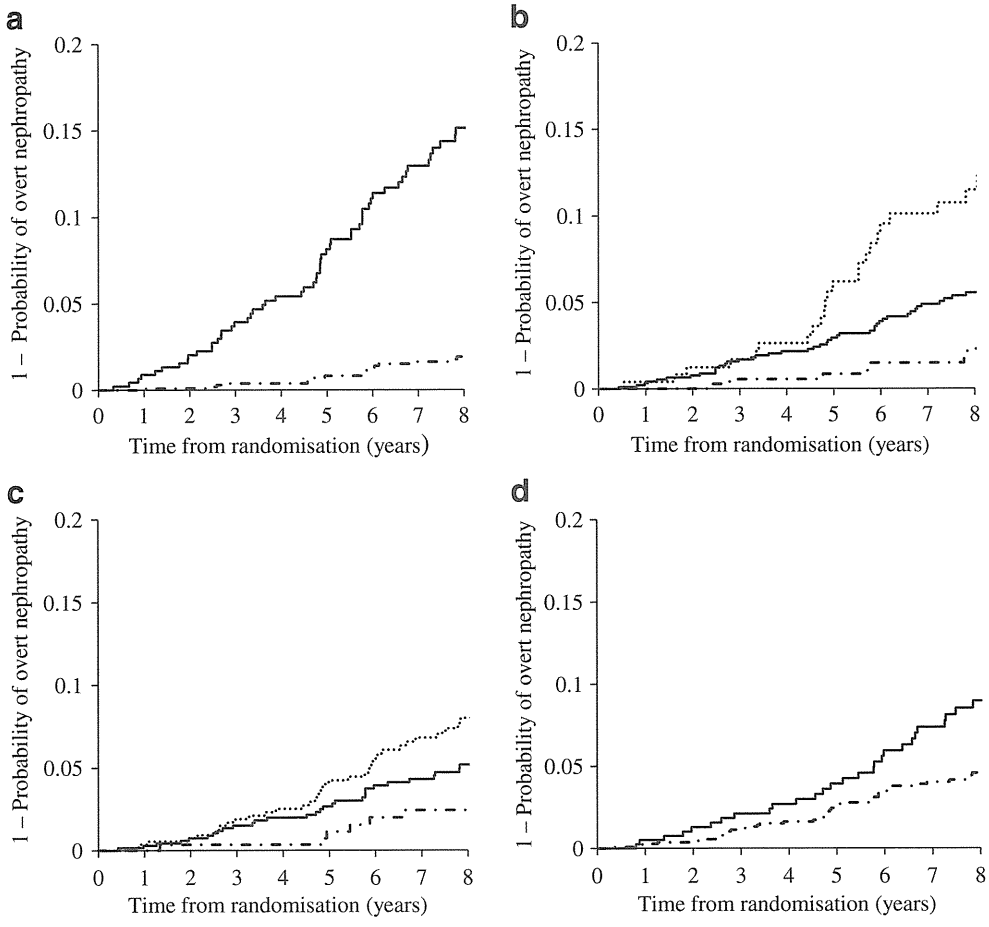

Fig. 1 Kaplan–Meier curves for progression to overt nephropathy according to: UACR (**a**), HbA_{1c} levels (**b**), SBP (**c**) and smoking status (**d**). **a** The hazard ratio for the low-microalbuminuric group (solid line) was 8.45 (95% CI 4.97–14.38, $p<0.01$) relative to the normoalbuminuric group (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