cohort in our hospitals after matching for sex and age. The assessment and definition of CVD were based on the following criteria. CHD was defined according to histories of physician-diagnosed ischemic heart disease. Strokes (ischemic cerebrovascular diseases) were diagnosed by means of neurological signs and symptoms, together with computed tomography or magnetic resonance imaging by neurologists. Only patients with a history of large vessel diseases and carotid stroke were enrolled, and patients with a history of cardioembolic and lacunar strokes were excluded. The study protocol and informed consent procedure were approved by the Ethics Committee of Nagoya University Graduate School of Medicine and Chubu Rosai Hospital and carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Evaluated Parameters

Body mass index (BMI) and blood pressure (BP) were measured. Fasting blood samples were obtained, and sera were stored at −80°C. Blood glucose, HbA_{1c}, insulin, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG) and creatinine were measured in our hospital laboratory. Adipocytokines and C-reactive protein (CRP) were also analyzed by an enzyme-linked immunoassay (ELISA) kit (R&D, Minneapolis, MN, USA or American Research Products, Belmont, MA, USA).

Genotyping of Polymorphisms

DNA-fragments of the single nucleotide polymorphism (SNP)-420 were amplified from genomic DNA using polymerase chain reaction with a previously described procedure[9].

Statistical Analyses

Statistical analyses were carried out using the program SPSS (SPSS, Chicago, IL, USA). The normally distributed parameters were expressed as means ± standard deviations and evaluated by Student's *t*-test. The parameters that were not normally distributed were expressed as median and interquartile range, and evaluated by Mann–Whitney *U*-test. Correlations were sought

Table 1 | Baseline clinical characteristics in patients with or without cardiovascular diseases

	Control	Case	*P*
n	178	89	
No. females	65	31	
Age (years)	65.5 ± 9.4	67.0 ± 10.0	0.86
Duration of diabetes (years)	13.7 ± 9.4	17.3 ± 9.9	0.47
Body mass index (kg/m^2)	23.0 ± 3.5	23.4 ± 3.5	0.41
HbA_{1c} (%)	7.2 ± 1.2	7.5 ± 1.2	0.45
FBG (mmol/L)	8.2 ± 2.4	7.9 ± 2.2	0.69
Fasting insulin (μU/mL)	6.7 ± 5.5	7.8 ± 5.4	0.73
HOMA-R	2.5 ± 2.4	2.6 ± 1.8	0.27
SBP (mmHg)	131 ± 16	134 ± 16	0.86
DBP (mmHg)	74 ± 11	74 ± 11	0.65
Total cholesterol (mmol/L)	5.15 ± 0.92	5.24 ± 0.87	0.44
Triglycerides (mmol/L)	1.18 (0.88–1.64)	1.35 (1.10–2.28)	0.05[a]
HDL (mmol/L)	1.36 ± 0.40	1.28 ± 0.38	0.82
LDL (mmol/L)	3.10 ± 0.82	3.18 ± 0.75	0.35
Creatinine (μmol/L)	71 (62–80)	80 (71–102)	<0.001[a]
Adiponectin (μg/mL)	7.8 (4.9–12.8)	8.7 (5.5–14.6)	0.32[a]
Resistin (ng/mL)	10.8 (6.9–17.6)	14.4 (8.1–22.2)	0.02[a]
CRP (mg/dL)	0.052 (0.018–0.139)	0.076 (0.035–0.180)	0.046[a]
Smoking history (%)	48.6	57.1	0.33[b]
Medications			
Insulin (%)	22.3	43.4	0.02[b]
Sulfonylurea (%)	34.2	36.1	0.77[b]
Glitazone (%)	10.7	6.7	0.09[b]
Statin (%)	26.4	37.1	0.38[b]
Aspirin (%)	5.4	28.9	<0.001[b]

Data are presented as means ± SD or median (interquartile range).
CRP, C-reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure.
[a]*P*-value by Mann–Whitney *U*-test.
[b]*P*-value by χ^2-test.
Non-labeled *P*-value by Student's *t*-test.

by use of Spearman's method. The association of serum resistin with stroke was assessed in multiple logistic regression models. A *P*-value <0.05 was considered statistically significant.

RESULTS

The baseline clinical characteristics of the study subjects are presented according to the presence or absence of CVD (Table 1). Cases had significantly higher TG, creatinine, resistin levels and CRP than controls. Other anthropometric data did not show any significant differences between the two groups. Serum resistin levels were significantly higher in patients with CVD than in those without CVD ($P = 0.024$). However, the levels of serum resistin were highest in patients with stroke among the CVD (stroke 16.5 [8.1–28.3] *vs* control, $P = 0.007$) (Figure 1a). The serum resistin levels had significantly univariate correlations with the levels of creatinine and CRP, but not with other anthropometric variables (Table 2).

As we reported previously, the serum resistin levels were significantly high ($P < 0.001$) according to the presence of the G allele (-420C/G). Next, we estimated serum resistin levels in multiple logistic regression analyses. The serum resistin levels were independently associated with stroke after adjustment for age, sex, BMI and genotype of *RETN* SNP -420 (Table 3; Model 1). After additional adjustment for HbA_{1c}, systolic BP, diastolic BP, LDL, HDL, triglyceride, and history of coronary disease (Table 3; Model 2), and even after further adjustment for creatinine, CRP, insulin treatment, sulfonylurea treatment and aspirin treatment (Table 3; Model 3), the significance still remained. Interestingly the genotype of *RETN* SNP -420 was not a significant factor in Model 1, but it was significant in Models 2 and 3 (CC *vs* GG).

Furthermore, we calculated the serum resistin levels in each genotype and found that serum resistin levels were significantly higher in cases of the CC and CG genotype groups than in controls (cases and controls; 14.2 ± 11.4 ng/dL *vs* 9.6 ± 6.1 [$P = 0.04$] in CC, 22.1 ± 13.1 *vs* 13.5 ± 6.9 [$P < 0.01$] in CG, 19.5 ± 12.2 *vs* 19.0 ± 11.0 [$P = 0.91$] in GG). In multiple regression analysis using serum resistin levels as the covariate in each genotype group, we found that high blood levels of resistin were a significant independent risk factor for stroke in the CG genotype group (odds ratio [OR] for stroke for 5-ng/mL increase in serum resistin levels, 1.66 [95% CI 1.03–2.68]) and showed a tendency for increased risk in the CC genotype group (OR 1.220, 95% CI 0.614–2.43). This means that, at least for diabetic patients with the CG genotype, measuring the serum resistin levels is more useful for detecting high-risk patients for susceptibility for stroke than just checking the genotype.

Based on these data, we divided the enrolled patients by their median serum resistin concentrations (High or Low) and their genotypes (CC, CG, GG) into six groups, just for an example. Odds ratios for stroke against the CC + Low group were calculated in each group by multivariate logistic-regression analysis (Figure 1b). The odds ratios increased according to the G allele mutation and high serum resistin concentration. Patients with the GG genotype and high serum resistin levels showed the highest odds ratio, 5.69 (95% CI 1.24–26.1), compared with the CC + Low group. However, we failed to show significance between High and Low within each genotype. Systolic blood pressure was also detected as a significant factor in this calculation.

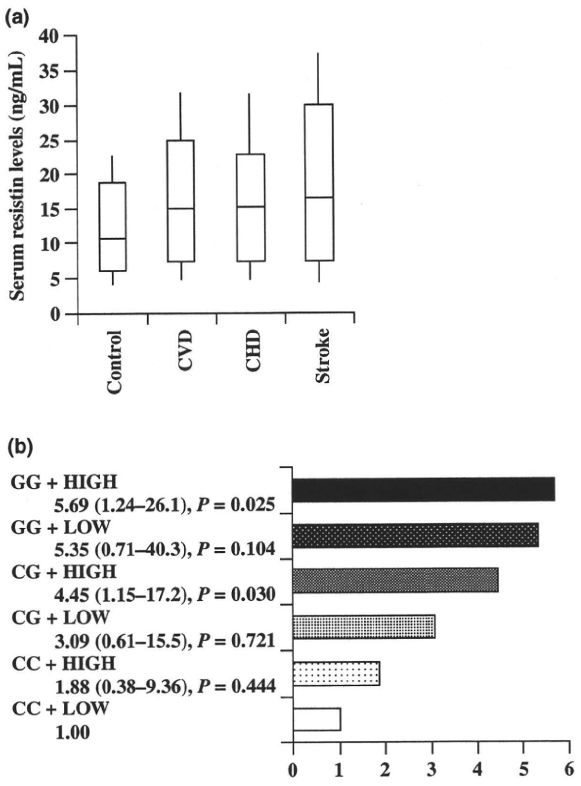

Figure 1 | (a) The resistin concentration (ng/mL) in control, total cardiovascular diseases (CVD) (coronary heart disease [CHD] + stroke) and each CVD. Box plots show median, interquartile range and non-outlier range. Extreme values are excluded from the box plots. (b) Odds ratio for stroke according to the combination of *RETN* genotype (-420C/G) and resistin levels (high or low) in multivariate logistic-regression analysis. The enrolled patients were divided by their serum resistin concentrations at median (high or low) and their genotypes (CC, CG, GG) into six groups. After adjustment for age, sex, body mass index, systolic blood pressure, serum levels of triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, C-reactive protein and creatinine, the multivariate logistic-regression analysis were made and each odds ratio against the CC + Low group was calculated. Right column shows odds ratio (confidence intervals).

DISCUSSION

In the present study, both the serum resistin levels and its genotype at -420 (C>G) were associated with the prevalence of stroke in Japanese type 2 diabetic patients, even after adjustment for known atherosclerotic risk factors in the multiple logistic regression analysis. As serum resistin levels shows a significant odds ratio independently from its SNP-420, its measurement could

Table 2 | Spearman's correlation coefficients of serum resistin levels to anthropometric and biochemical variables in Japanese type 2 diabetic patients

	r	P
Age (years)	0.08	0.18
Duration of diabetes (years)	0.03	0.65
Body mass index (kg/m^2)	0.08	0.20
HbA_{1c} (%)	−0.03	0.60
Fasting blood glucose (mmol/L)	−0.15	0.08
Fasting insulin (μU/mL)	−0.06	0.57
HOMA-R	−0.13	0.21
Systolic blood pressure (mmHg)	0.05	0.41
Diastolic blood pressure (mmHg)	−0.07	0.25
Triglycerides (mmol/L)	−0.06	0.51
HDL-cholesterol (mmol/L)	−0.11	0.07
LDL-cholesterol (mmol/L)	−0.03	0.63
Creatinine (umol/L)	0.27	<0.001
Adiponectin	0.09	0.15
CRP	0.13	0.03

Spearman's *r* correlation across all cases and controls. *r* value with resistin. CRP, C-reactive protein; HDL, high density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein cholesterol.

also be helpful for the risk prediction of stroke in Japanese type 2 diabetic patients (Table 3).

Recent studies have shown that the resistin levels are significantly correlated with coronary artery calcification and are predictive of coronary atherosclerosis in humans[15,16]. Ukkola *et al.* and Norata *et al.*[17,18] described the association among this -420 (C>G) polymorphism, the resistin levels and cardiovascular risk factors. However, the association between the serum resistin levels and CHD seemed to be negative[10–13], and might be controversial for this polymorphism and CVD[17,19]. Differences in the cohorts might explain the different results, depending on which ethnic group was tested[8,20,21], or which diabetic cohort was explored. Indeed, methodological limitations in the commercially available ELISA assays might also result in variations among serum levels, which might cause difficulties when comparing results from different publications.

Although few studies have been carried out for stroke, our data showed that stroke was most strongly associated with the levels of resistin and its polymorphism (Figure 1).

After all, it is noteworthy that in a recent report by Efstathiou *et al.*[22], high resistin levels might have been strongly associated with an increased risk of 5-year mortality or disability after atherothrombotic ischemic stroke. However, because they did not measure the prestroke resistin levels, it is still unclear whether or not resistin is a key player in the pathogenesis of stroke or just a marker or indicator of the inflammatory status. To answer this, more studies will be required.

There are some limitations in the interpretation of the present study. First, we examined type 2 diabetic patients in Japan who were relatively lean compared with those in other developed countries. It would be hard to extrapolate the results of the present study to non-diabetic patients, obese diabetic patients or other

Table 3 | Multiple logistic regression analyses of serum resistin levels with history of stroke

Adjusted for	Model 1		Model 2		Model 3	
	Odds ratio (CI)	P	Odds ratio (CI)	P	Odds ratio (CI)	P
Resistin	1.32 (1.09–1.59)	0.004	1.34 (1.06–1.69)	0.013	1.33 (1.02–1.73)	0.039
Genotype of *RETN* SNP-420						
CC *vs* CG	1.55 (0.63–3.84)	0.34	1.34 (0.44–4.09)	0.61	1.43 (0.46–4.50)	0.54
CC *vs* GG	1.75 (0.56–5.42)	0.34	3.67 (1.02–13.2)	0.046	3.81 (1.03–14.1)	0.046
Age	1.03 (0.99–1.08)	0.13	1.02 (0.97–1.08)	0.38	1.03 (0.97–1.09)	0.35
Sex	1.18 (0.51–2.72)	0.69	1.03 (0.35–3.02)	0.96	1.02 (0.35–3.04)	0.97
BMI	1.06 (0.95–1.18)	0.32	1.01 (0.88–1.14)	0.93	1.02 (0.89–1.16)	0.81
HbA_{1c}			0.79 (0.51–1.22)	0.28	0.74 (0.46–1.20)	0.22
SBP			1.04 (1.01–1.07)	0.02	1.04 (1.00–1.07)	0.045
DBP			0.98 (0.93–1.04)	0.51	0.99 (0.94–1.04)	0.63
LDL			1.01 (0.99–1.02)	0.53	1.01 (0.99–1.02)	0.51
HDL			0.97 (0.94–1.01)	0.14	0.97 (0.94–1.01)	0.15
Triglycerides			1.00 (1.00–1.01)	0.33	1.00 (1.00–1.01)	0.31
History of CHD			1.95 (0.71–5.33)	0.20	1.68 (0.56–5.06)	0.36
Creatinine					0.95 (0.63–1.41)	0.78
CRP					1.01 (0.85–1.21)	0.89
Insulin therapy					1.95 (0.47–8.14)	0.36
Sulfonylurea therapy					1.80 (0.54–6.01)	0.34
Aspirin therapy					1.15 (0.34–1.41)	0.82

Odds ratio and 95% confidence interval (CI) for the existence of stroke for 5-ng/mL increase in serum resistin levels.
BMI, body mass index; CHD, coronary heart diseases; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; SNP, single nucleotide polymorphism.

ethnic groups. Second, this was a kind of cross-sectional study at the point of estimating serum resistin levels; we cannot determine any cause–effect relationship based on this study design. Third, the results were influenced by survivor effects, and the true prevalence of atherosclerotic diseases might be underestimated.

Some previous reports showed that the blood levels of resistin were positively related to the systemic inflammatory status. Although we cannot change our genotype to lower our susceptibility for stroke, there is the possibility of lowering the risk of stroke in diabetic patients, even those with the CG genotype, by multifactorial intervention aimed at reducing the systemic inflammation status, that is, by treatment with glitazone. Our results suggest that using the genotype and serum levels of resistin to discriminate between diabetic responders and non-responders will contribute to the development of effective strategies and improve the prognosis in this population. In conclusion, the present results suggest that serum resistin levels might be also a good marker of susceptibility to stroke as well as *RETN* polymorphism, and the measurement of both *RETN* gene polymorphism and serum resistin levels might be useful to detect the susceptibility to stroke and might provide an incremental value in the risk prediction for stroke, beyond the current approaches, among Japanese type 2 diabetic patients. Our findings need to be confirmed by further studies.

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連載
ガイドラインを考える
第4回

糖尿病診療のためのガイドライン

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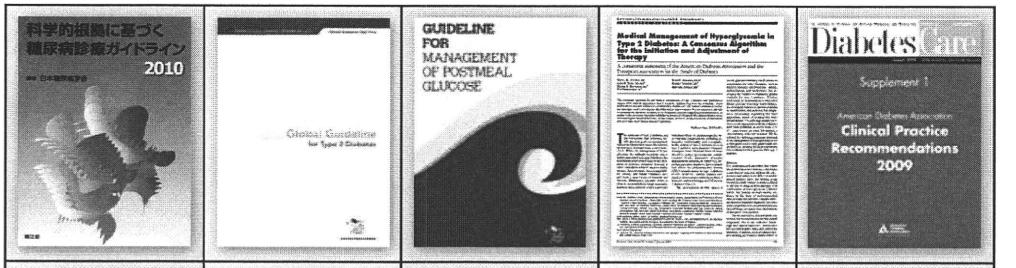
はじめに

糖尿病の増加は世界規模の脅威であり，世界各国では国を挙げて糖尿病対策に取り組んでいる．糖尿病対策として最も効果的なのは糖尿病の早期発見と早期からの適切な治療であるが，その際，適切な糖尿病診療の実践のためのガイドラインの存在は必須である．日常の臨床の現場で個別的な対応が求められるのは当然のことだが，基本的なガイドラインがあってこそ，患者一人ひとりにとって最も適切な選択肢を見極めることができる．ガイドラインなしに糖尿病診療に当たることは，羅針盤のない船を操縦するようなものである．

そこで，国際糖尿病連合(International Diabetes Federation；IDF)をはじめ，多くの国内外の糖尿病関連団体が，糖尿病診療のためのガイドラインを策定している[1-5](図1)．日本糖尿病学会でも，日常臨床のさまざまな場において活用できるように，数種類のガ



	科学的根拠に基づく糖尿病診療ガイドライン 2010[1]	Global Guideline for Type 2 Diabetes 2005(IDF)[2]	GUIDELINE FOR MANAGEMENT OF POSTMEAL GLUCOSE 2007(IDF)[3]	A consensus statement of ADA/EASD 2009(ADA)[4]	Clinical practice recommendation 2009(ADA)[5]
HbA1c	5.8～6.5%*	<6.5%	<6.5%	<7.0%	<7.0%
空腹時血糖値 (mg/dL)	110～130*	<110	<100	—	70～130
食後血糖値 (mg/dL)	140～180*	<145	<140	—	<180

図1　糖尿病診療ガイドライン(抜粋)の血糖コントロール指標とその目標値

*：血糖コントロール「良」の評価.

イドブックを発行してきたが，本稿では，「科学的根拠に基づく糖尿病診療ガイドライン2010」を中心に，糖尿病診療のためのガイドラインについて概説する．

「科学的根拠に基づく糖尿病診療ガイドライン 2010」の概要

1.「糖尿病治療ガイド」[6]と「科学的根拠に基づく糖尿病診療ガイドライン」

日本糖尿病学会は，糖尿病臨床の第一線にある実地医家，研修医，医学生そしてコメディカルスタッフのための糖尿病治療関連の小冊子である「糖尿病治療ガイド」を1999年に発行した．その後，本書は1～2年ごとに刊行され，現在では2010年度版が発行されている．2007年度版については英語版も刊行された．本書の核心部分は，「糖尿病治療のエッセンス」としてまとめられ，実地医家の先生方の外来で活躍している．その他，日本糖尿病学会は，「小児・思春期糖尿病管理の手びき」，「糖尿病専門医研修ガイドブック」を刊行し，さまざまな需要に対応してきた．

一方，「科学的根拠に基づく糖尿病診療ガイドライン」の発行は，evidence-based medicine(EBM)の実践が求められる時代を迎え，厚労省研究班による新しい視点でのガイドラインの策定が検討されたことに端を発している．この報告書は大きな反響を呼び，2年後の2004年に書籍として初版が刊行された．本書の特徴は，あくまでも糖尿病診療に関する国内外のエビデンスを基盤とし，ここから導かれる項目をステートメントとして掲げる，という姿勢を貫いていることである．改訂第2版(2007年)[1]を経て，2010年9月に改訂第3版が刊行された．

2. ガイドラインの内容

本書の構成は，初版から同じである．糖尿病の全領域が項目別に分類され，それぞれの項で，診療上の指針となる重要なステートメント(推奨)が簡潔に記載されている．推奨の強さはグレードで評価し，グレードAは「行うよう強く勧める」，グレードBは「行うよう勧める」，グレードCは「行うように勧めるだけの根拠が明確でない」，グレードDは「行わないよう勧める」とされた．大多数はグレードAあるいはBであるが，妊婦に対する極端な食事制限などがC，Dとなっている．ステートメントに次いで解説が記されているため，ステートメントやグレードの背景が理解しやすい(図2)．また，これらの根拠であり，かつ解説のなかで引用されている臨床研究などの文献は，エビデンスとしての水

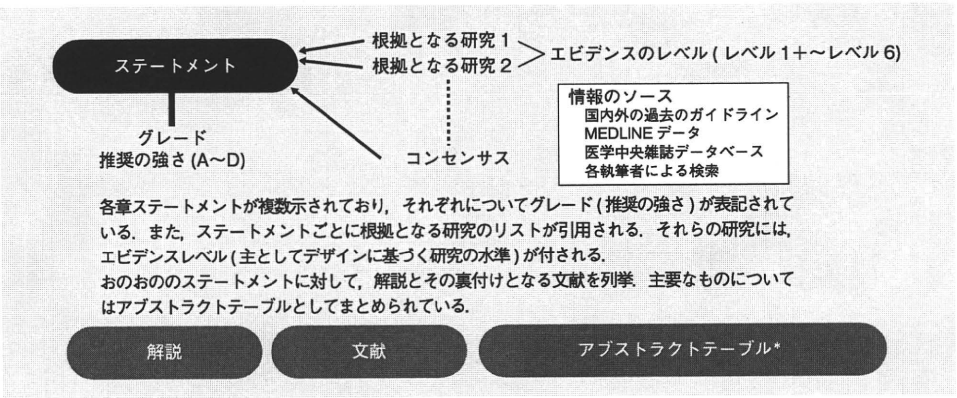


図2 ガイドラインの構成

*:文献の内容を要約したもの．（日本糖尿病学会編「科学的根拠に基づく糖尿病診療ガイドライン2010」より引用改変）

準が付されたうえで列挙され(表1)，最後にアブストラクトテーブルとしてコンパクトにまとめられている．

2010年度版の基本的な方針は，①糖尿病診療における実際的な治療ガイドよりは，糖尿病領域におけるエビデンス集とする，②積極的に日本発の新しいエビデンスを収載するが，臨床治験は原則として含めない，③文献検索の際の簡便な道しるべとなる「アブストラクトテーブル」を継続して掲載する，である(本書の序文より)．また「糖尿病と歯周病」および「糖尿病と感染症，シックデイ」が新章として加えられ，全25項目となった．その他の事項として，①ステートメントでは薬剤名は「分類名」による記載で，「商品名」は一切記載されていない，②全体の頁数が増大していない，③文献の執筆者の記載を「3名＋et al(ほか)」とするなど，細部にわたって配慮されている．

この版の策定委員会は糖尿病を専門とする医師26名，臨床疫学者1名で構成され，執筆協力者8名とともに23項目について分担執筆した．原稿のすべては複数の査読委員(50名)による査読を受け，再び執筆者に戻され意見交換をし，さらに最終段階では編集委員長と査読委員長が全体の統一を図ったという．このように多数の糖尿病や疫学を専門とする方々に支えられて本書が完成した．

3．2010年度版のトピックス

まず，2010年7月に新しい糖尿病診断基準がスタートしたが[7]，これが新しい内容として掲載された．これまでHbA1cに求められていた役割は，①血糖コントロールの指標(DCCT, Kumamoto Study, UKPDSなど)，②疫学調査における糖尿病診断の指標(国民健康栄養調査：厚労省1997年～)，③糖尿病の臨床診断における補助的指標(糖尿病の診断基準：日本糖尿病学1999年～)，④糖尿病のリスク判定の指標(特定健診・特定保健指導：厚労省2008年～)であったが，新しい糖尿病の診断基準ではHbA1cを補助的診断からより積極的に取り入れたのである(図3)．

HbA1c値については，「HbA1c(JDS値)」，「HbA1c(国際標準値)」そして「HbA1c(NGSP値)」の3種類が記

表1　ガイドラインで用いたエビデンスのレベル(各研究へ付された水準)

水準(レベル)	それに該当する臨床研究デザインの種類
1＋	水準1の規模を含むランダム化比較試験のシステマティックレビューまたはメタアナリシス
1	十分な症例数(全体で400例以上)のランダム化比較試験
2＋	水準2の規模を含むランダム化比較試験のシステマティックレビューまたはメタアナリシス
2	小規模(全体で400例未満)のランダム化比較試験
2－	さらに小規模(全体で50例未満)のランダム化比較試験，クロスオーバー試験(ランダム化を伴う)，オープンラベル試験(ランダム化を伴う)
3	非ランダム化比較試験，コントロールを伴うコホート研究
4	前後比較試験，コントロールを伴わないコホート研究，症例対照研究
5	コントロールを伴わない症例集積(10～50例程度)
6	10例未満の症例報告

注)文献情報に基づかず，対応する文献のない場合："コンセンサス"と記載．
注)括弧内の症例は目安である．

(科学的根拠に基づく糖尿病診療ガイドライン2010より引用)

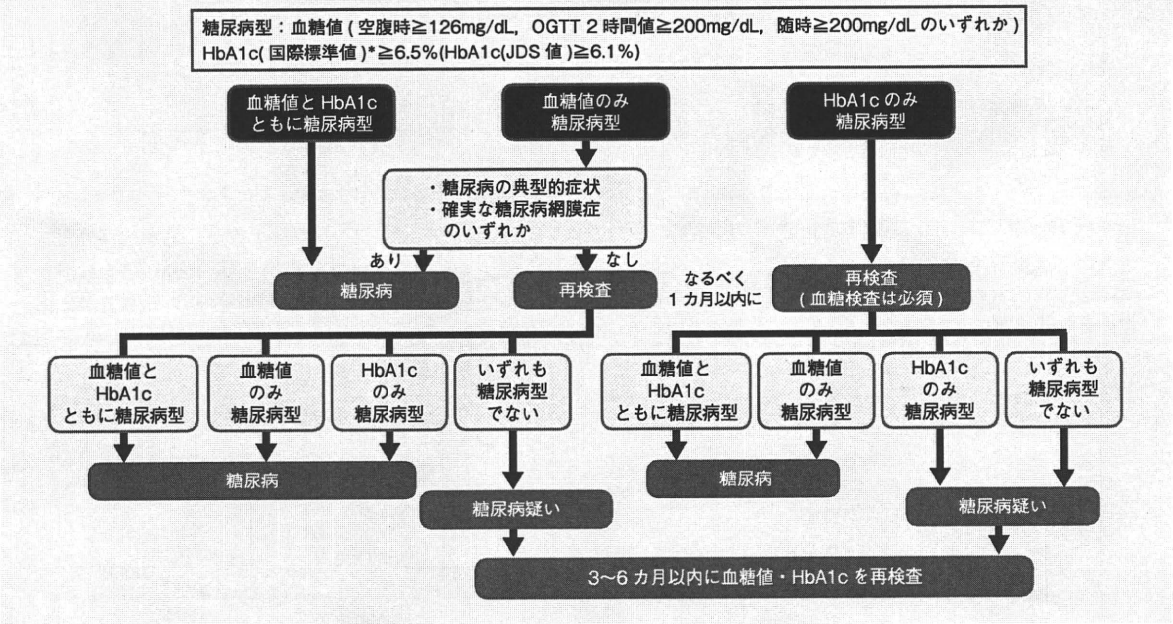


図3　糖尿病の新しい臨床診断（2010年7月1日施行）

＊：HbA1c(国際標準値)(%)は現行のJDS値で表記されたHbA1c(JDS値)(%)に0.4%を加えた値で表記する．

載されている．「HbA1c(JDS値)」とは従来どおりの値で，「HbA1c(国際標準値)」は日本以外の諸外国で現在用いられているHbA1c(JDS値)より0.4％高いNGSP値に相当する値である．新しいHbA1c(国際標準値)の臨床での運用時期については決定していないが，国際会議や論文発表などの際には，国際的に標準化された新しいHbA1c(国際標準値)を直ちに用いることが推奨されている(表2)．

表2　HbA1c の表記に関して

本書では HbA1c 値に関し，米国などにおける基準に基づく HbA1c(NGSP 値）との整合性を図るため，従来からの JDS(Japan Diabetes Society；日本糖尿病学会）標準検体に依拠した HbA1c 値に 0.4% を加えた値を HbA1c（国際標準値）として記述している．また，従来の HbA1c 値について記載する場合には，HbA1c(JDS 値）と記している．

近い将来，日常臨床，検診，健康診断等における表記は，すべて新しい HbA1c（国際標準値）を用いることになるが，その運用の開始は日本糖尿病学会が別途告示する日からとなる．

なお，英文論文や英文著書，国際学会の発表における HbA1c の記載は，平成 22 年 7 月 1 日より国際標準値による新しい表記法に移行している．

(科学的根拠に基づく糖尿病診療ガイドライン2010より引用)

IDF によるガイドライン

糖尿病に関連した国内外の代表的なガイドラインのうち，IDFによる2型糖尿病の診療ガイドライン(2005年)[2]は，リソースが限られている地域や国においても運用しうるという視点から策定されたもので，エビデンスに基づいていること，筋がとおっていること，実行可能であること，そして患者や主治医にとって到達可能であること，などを満たすことが念頭に置かれている．2010年度版の策定にあたり，血糖管理の到達目標および2型糖尿病治療のアルゴリズムに関する作業部会が開催され筆者も参加する機会を得た．会議では2日間にわたる白熱した討論が続いたが，血糖管理目標の指標とその目標値については，HbA1c,

表3　食後血糖値の管理に関するガイドライン

糖尿病の管理における血糖コントロールの目標
HbA1c＜6.5%
空腹時血糖＜100mg/dL
食後2時間血糖＜140mg/dL

- 血糖値を最適にコントロールするためには，空腹時血糖値と食後血糖値のどちらをも目標とした治療法が必要である．
- 血糖を最適にコントロールするためには，食後血糖値の適切な管理が不可欠である．
- したがって，空腹時及び食後高血糖の治療は，HbA1c値にかかわらず同時に開始すべきである．
- 適切な治療法を決定する上で費用は重要な要因であるが，血糖をコントロールすることは糖尿病の合併症治療よりも，はるかに安価である．

EBM：Evidence-based Medicine

根拠(エビデンス)を重視するが，患者さんの価値観も大切にし，最終的には主治医が専門的な技能や臨床経験を駆使して医療を実践する．医療経済に配慮する．

病気のみを診るのではなく，科学的な根拠に基づいて全人的に患者さんを診る．

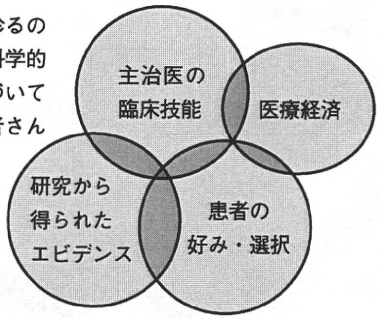


図4　「エビデンス」と「EBM」は同意語ではない

空腹時血糖値および食後2時間値とし，それぞれの到達目標をそれぞれ，7.0%未満，100mg/dL未満および140mg/dL未満とする，という案がまとまった．2007年にIDFが報告した「食後高血糖管理のためのガイドライン」[3](表3)に記されたHbA1c＜6.5%よりやや高い値が推奨された理由はいくつかあるが，安全に到達することが可能か，という点もそのうちの1つである．

治療のアルゴリズムは「生活習慣の改善のみ」が最初のステップであり，その後すべてのステップでも重要であることが強調された．日本，中国，インド以外の国では，HbA1cの到達目標に達したか否かで治療法をステップアップするtreatment-basedのアルゴリズムが使われている[4,5]．日本では病態に合わせたindividual-basedの治療が進められているが，年齢，糖尿病の罹病歴，病態，合併症，患者の受け入れなど個別化しうる要因のうち，何が重要かは明記されていない．また，IDFガイドラインでは薬剤のコストが重要な位置を占めており，エビデンスがあっても高価であれば選択肢として下位になる．IDFガイドラインが推奨するガイドラインが目指すところを理解し，日本の事情にあわせて共有しうるものは積極的に取り入れることも大切と思われた．

おわりに

2型糖尿病が世界中で爆発的に増えているのにもかかわらず，多くの国や地域ではまだ，糖尿病診療ガイドラインがない．あったとしても浸透していないので，糖尿病が診断されないまま放置されていたり，適切な治療を受けていない糖尿病患者が多数存在する．日本は糖尿病診療のためのリソースが豊富で，かつ，糖尿病をもつ人は皆が等しく適切な治療を受けることができるなど，恵まれた環境にある．にもかかわらず，到達目標であるHbA1c＜7.0% (国際標準値)に到達しているのは全糖尿病患者のうち40%程度といわれている．このギャップを埋めるために「科学的根拠に基づ

く糖尿病診療ガイドライン」は何ができるのだろうか．本書が提供しているのは，EBMの実践に必要な3つの要素[8]のうち，研究から得られたエビデンスのみである．主治医の臨床技能や患者の好み・選択，ましてや第4の大切な要因と認識されるようになった医療経済には触れられていない(図4)．

糖尿病診療に関するガイドラインが真にユーザーフレンドリーであるためには，コストの問題は避けて通れない．また，エビデンスを過信しすぎず，患者の価値観も配慮し，主治医の裁量権で最良の糖尿病診療を行うことの大切さも認識していかねばならない．

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Long-term mortality and causes of death among patients with type 1 diabetes in Japan

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INTRODUCTION

The Diabetes Epidemiology Research International (DERI) mortality study, beginning in 1986, is an international collaborative study that brought together diabetes researchers and clinicians from 4 countries (Finland, USA, Israel and Japan). In 1991 the study issued its first report demonstrating that Japanese patients with type 1 diabetes had a much worse prognosis than patients in Finland, USA and Israel, with the most frequent cause of death being diabetic nephropathy (1,2). The DERI study is still ongoing in Finland, USA, and Japan. In this presentation, we report on the prognosis of Japanese patients with type 1 diabetes by evaluating the latest data available as of January 1, 2005.

AIMS

To investigate long-term prognosis including causes of death among patients with type 1 diabetes in Japan.

METHODS

A total of 1,387 patients (556 males and 831 females) were enrolled in the study after being identified from two nationwide type 1 diabetes surveys in Japan. Subjects were diagnosed as having type 1 diabetes that developed prior to 18 years of age, during the period 1965-1979. Type 1 diabetes was defined as requiring initiation of insulin therapy, as a rule, within 1 month of diagnosis. All patients were tracked for survival status until January 1, 2005, with this status determined based on the questionnaires sent to their attending physicians or the residents' records. The cause of death was determined by the DERI mortality classification committee (MCC) (2) from the information of attending physicians or death certificates. The MCC consisted of three members from the USA, Finland, and Japan. The causes of death were divided into 9 groups.

1. diabetic renal disease
2. acute diabetic complications
3. accident/suicide
4. cardiovascular disease
5. infections
6. malignant neoplasms
7. other non-diabetic causes
8. other diabetic causes
9. unknown

Survival status as of January 1, 2005 was expressed in terms of standardized mortality ratio (SMR), crude mortality rate (CMR), and cumulative survival rates. Mortality was compared between male and female patients using the log rank test, and the Cox proportional-hazards model after adjustment for duration of disease prior to the start of follow-up.
Statistical analyses were performed using SAS 9.1. A P value of < 0.05 was considered as statistically significant (two-tailed).

RESULTS

Table 1. Characteristics of the subjects, crude death rate, and standardized mortality ratio (SMR) of patients with type 1 diabetes in Japan.

	Gender		Overall
	Male	Female	
No. of subjects (males/females)	556	831	1,387 (556/831)
Age at diagnosis (years)	8.7 ± 4.2	8.9 ± 4.0	8.8 ± 4.1
Attained age (years)	36.2 ± 7.2	37.0 ± 7.1	36.7 ± 7.1
Duration of diabetes (years)	27.6 ± 6.5	28.1 ± 6.4	27.9 ± 6.4
Follow-up (years)	24.3 ± 6.5	24.5 ± 6.3	24.4 ± 6.4
Follow-up (person-years)	13,491	20,377	33,868
No. of deaths	105	118	223
Crude death rate at 35-year follow-up (per 100,000 person-years) (95% CI)	778 (628-936)	579 (479-686)	658 (573-745)
SMR at 35-year follow-up (95% CI)	9.6 (7.7-11.5)	14.3 (11.8-16.9)	10.6 (9.3-12.0)

All data are expressed as mean ± SD. 95% confidence intervals (CI) calculated by using the Poisson distribution are given in parentheses.

One thousand one hundred and three patients were confirmed as alive as of January 1, 2005, and 223 deaths (16.1%) were observed (confirmation rate: 95.6%). The SMR was 10.6 (males, 9.6; females 14.3).

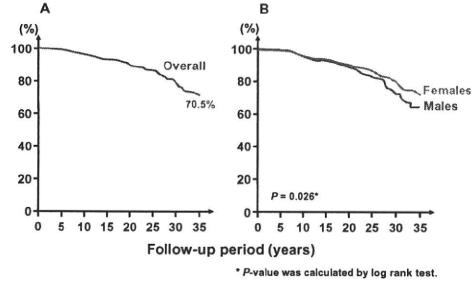

Figure 1. Cumulative survival rate of patients with type 1 diabetes in Japan. (A) All subjects; (B) Subjects by gender.

The cumulative survival rate at 35 years follow up was 70.5% (A). Males' cumulative survival rate was significantly lower than females' cumulative survival rate (P=0.026). Male patients were shown to be at 1.37-fold higher mortality risk compared to female patients by the Cox proportional-hazards model (95% CI, 1.02–1.85).

The time from the initiation of dialysis to death was 5.5 ± 4.8 years in 89 patients who died following initiation of dialysis.

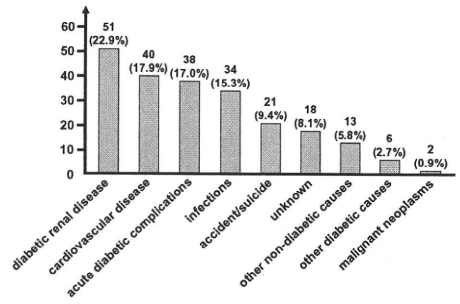

Figure 2. Number of deaths in Japanese patients with type 1 diabetes according to cause of death.

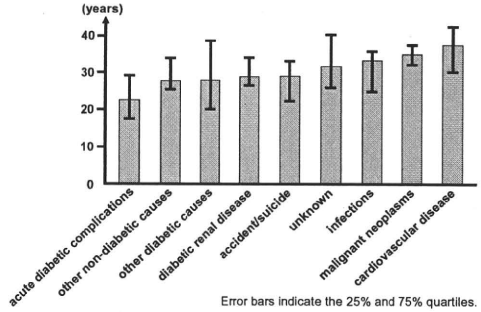

Figure 3. The median age of death in Japanese patients with type 1 diabetes according to cause of death.

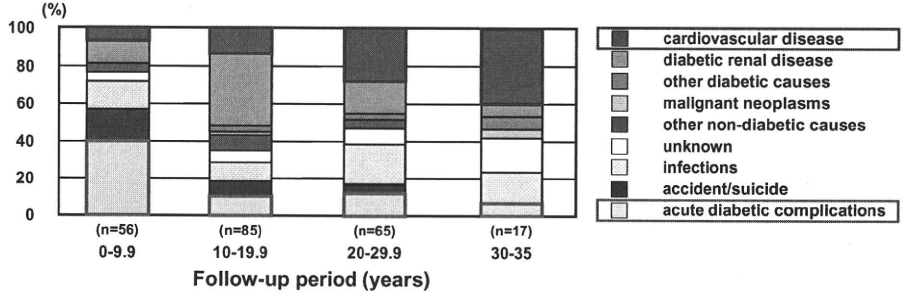

Figure 4. The causes of death according to follow-up period in patients with type 1 diabetes in Japan.

The leading causes of death were diabetic renal disease, cardiovascular disease, and acute diabetic complications (Fig.2). The longer the duration of follow-up, the lower the mortality from acute diabetic complications, and the greater the mortality from cardiovascular disease (Fig. 4). Therefore, the age of death was younger in decedents with acute diabetic complications and older in those with cardiovascular disease (Fig. 3).

Conclusion

The mortality risk of Japanese patients diagnosed as having type 1 diabetes between 1965 and 1979 was 10.6-fold higher than that of the general population. Males had a 1.37-fold higher mortality risk than females. Diabetic renal disease, cardiovascular disease and acute diabetic complications were the leading causes of death. However, as the duration of follow-up increased, acute diabetic complications contributed less and cardiovascular disease contributed more to mortality.

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Acknowledgments

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Long-term mortality and causes of death among patients with type 1 diabetes in Japan

Aims: To investigate long-term prognosis including causes of death among patients with type 1 diabetes in Japan.

Methods: A total of 1,387 patients (556 males and 831 females) were registered from two nationwide type 1 diabetes surveys in Japan. They were diagnosed as type 1 diabetes at less than 18 years of age between 1965 and 1979. All patients were tracked for survival status until January 1, 2005, with this status determined based on the questionnaires sent to their attending physicians or the residents' records. Causes of death were identified through questionnaires or death certificates. Their survival status as of January 1, 2005 was expressed in terms of standardized mortality ratio (SMR) and crude mortality rate (CMR). Mortality was compared between the male and female patients by using the Cox proportional-hazards model. The causes of death for deceased cases were divided into 9 groups (1. diabetic renal disease; 2. acute diabetic complications; 3. accident/suicide; 4. cardiovascular disease; 5. infections; 6. malignant neoplasms; 7. other non-diabetic causes; 8. other diabetic causes; 9. unknown) and were also compared by duration of diabetes. Statistical analyses were performed by using SAS 9.1. This study was approved by the Institutional Review Board of Jikei University School of Medicine, Tokyo, Japan.

Results: The mean age at diagnosis was 8.8 ± 4.1 (SD) years, with a duration of diabetes of 27.9 ± 6.4 years. One thousand one hundred and three patients were confirmed as alive as of January 1, 2005, and 223 deaths (16.1%) were observed (confirmation rate: 95.6%). The SMR was 10.6 (males, 9.6; females 14.3), and the CMR was 658/100,000 person-years (males, 778; females, 579). The male patients were shown to be at 1.37-fold higher mortality risk compared to the female patients (95% CI, 1.02–1.85). The causes of death identified included diabetic renal disease (51 patients; 22.9%), cardiovascular disease (40; 17.9%), acute diabetic complications (38; 17.0%), infections (34; 15.3%), accidents and suicides (21; 9.4%), unknown cause (18; 8.1%), other non-diabetic causes (13; 5.8%), other diabetic causes (6; 2.7%), and malignant neoplasms (2; 0.9%). Leading causes of death included acute diabetic complications among those with less than 10 years' duration of disease, diabetic renal disease among those with 10 to 20 years' duration, infections among those with 20 to 30 years' duration, and cardiovascular disease among those with 30 to 40 years' duration. Thus, the longer the duration of disease, the less the mortality from acute diabetic complications, and the greater the mortality from cardiovascular disease. The time from the initiation of dialysis to death was shown to be 5.5 ± 4.8 years in 89 patients who were confirmed to have been dead after initiation of dialysis.

Conclusion: The mortality risk of patients diagnosed as type 1 diabetes between 1965 and 1979 in Japan was shown to be 10.6-fold higher than that of the general population. The males were found to be at 1.37-fold higher mortality risk than the females. Diabetic renal disease, cardiovascular disease and acute diabetic complications were found to be the leading causes of death. However, as the duration of disease became longer, acute diabetic complications contributed less and cardiovascular disease contributed more to mortality.

Blindness and laser photocoagulation in patients with childhood-onset type 1 diabetes in Japan

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ABSTRACT

Aim: The aim of the study was to investigate trends in the incidence of blindness and the association with laser photocoagulation in patients with type 1 diabetes in Japan.

Methods: Patients diagnosed between 1965 and 1979 aged under 18 years old were studied. The status of blindness and laser photocoagulation was identified as of 1 January 1995. To examine the time trend, we divided the cohort into two groups: 285 patients diagnosed between 1965 and 1969 (65–69 cohort) and 769 patients diagnosed between 1975 and 1979 (75–79 cohort). Survival analysis was performed using the Kaplan–Meier method. Cox proportional hazard models were used to assess the demographic characteristics.

Results: Blindness developed in 60 subjects in the 65–69 cohort and 15 subjects in the 75–79 cohort. The incidence of blindness in the 75–79 cohort was significantly lower than that in the 65–69 cohort ($p<0.0001$). In spite of no change in the use of laser photocoagulation in the 75–79 cohort compared with the 65–69 cohort, the hazard ratio for the blindness in those who received laser photocoagulation in the 75–79 cohort decreased significantly to 0.55 ($p<0.01$) compared with those in the 65–69 cohort when adjusted for the age of onset, sex, and time of diagnosis.

Conclusion: The incidence of blindness decreased significantly for the subjects diagnosed more recently. The change in quality and the earlier introduction of laser photocoagulation might have contributed to the decreased incidence of blindness observed over time.

Blindness is associated with a substantial reduction in quality of life among type 1 as well as type 2 diabetic patients.[1] An early study in Japan by Hibi *et al* in 1982 demonstrated that the prevalence of blindness was approximately 13.3% in 90 patients who were aged >25 years.[2]

The clinical application of laser photocoagulation for the treatment of advanced diabetic retinopathy was initiated in 1959.[3] Early treatment with scattered photocoagulation in the late 1980s did prove effective in type 2 diabetes, but was not effective in preventing advanced retinopathy in type 1 diabetes.[4] In the late 1990s and early 2000s a few reports started to provide evidence of improvements in visual outcome with photocoagulation therapy in type 1 diabetes.[5 6] However, there are no reports that have focused on the relationship between laser photocoagulation and the incidence of blindness.

The aim of the present study was to estimate the incidence of the use of laser photocoagulation and of blindness, and to examine whether or not laser photocoagulation contributed to the decreased incidence of blindness, if there was such a decrease.

PATIENTS AND METHODS

Subjects

The study subjects were selected from 1408 patients with childhood-onset type 1 diabetes in the Japanese cohort of the Diabetes Epidemiology Research International Study Group[7 8]. The subjects satisfied all of the following three criteria: (1) developed the disease before 18 years of age; (2) started insulin therapy within 1 month of diagnosis; and (3) diagnosed between 1965 and 1969 and alive at the end of 1969, or diagnosed between 1970 and 1979 and alive at the end of 1979. The Diabetes Epidemiology Research International Mortality Study was a population-based follow-up study initiated in 1986 to examine the mortality status of childhood-onset type 1 diabetes internationally.[7 8] The degree of the case ascertainment of the cohort was estimated to be 75% according to the reported incidence of type 1 diabetes during that period.[7–9] All attending physicians obtained informed consent from the patients at the time of questionnaire survey. The study was approved by the Institutional Review Board of Jikei University School of Medicine.

Methods

A questionnaire[10] was sent to the attending physicians on the clinical status of the patients: whether the patients "received or did not receive" laser photocoagulation and were "positive or negative" for blindness at the time point of January 1995. If the patient had "received" laser photocoagulation, we retraced and recorded the year and month of the first laser treatment. If the patient had been "positive" for blindness, we retraced and recorded the year and month of the diagnosis of blindness.

Statistical analysis

Out of the total cohorts we chose two groups according to the calendar year of diagnosis, namely those diagnosed between 1965 and 1969 (the 65–69 cohort) and those diagnosed between 1975 and 1979 (the 75–79 cohort). The group diagnosed between 1970 and 1974 was excluded from the analysis (n = 354), since we designed this study to analyse the follow-up period of the two cohorts on the basis that the relationship between the length of the recruitment period and the start time of the follow-up was the same. The follow-up time was calculated from 1970 for the 65–69 cohort and

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from 1980 for the 75–79 cohort. The cumulative incidence rates of laser photocoagulation and blindness in each group were analysed by the Kaplan–Meier method, and the log-rank test was used to compare the survival curves. In addition, to evaluate the cumulative incidence rates of blindness after receiving laser photocoagulation, the cumulative incidence rates of blindness in each group were analysed in those subjects who received laser photocoagulation. In this analysis, the follow-up time was calculated from the time when laser photocoagulation was performed. Using Cox proportional hazard models, the hazard ratio and its 95% confidence interval for the time of diagnosis for blindness were calculated after adjusting for age of onset and sex. The status of laser photocoagulation and its interaction with the year-of-diagnosis group were further included into models. The status of laser photocoagulation was analysed as a time-dependent covariant. A dummy variable was incorporated for the year-of-diagnosis groups. All statistical analyses were performed using SAS software (version 9; SAS Institute, Cary, North Carolina, USA). A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient background

The study subjects comprised 285 patients (115 male and 170 female) in the 65–69 cohort and 769 patients (316 male and 453 female) in the 75–79 cohort. Of those, 29 and 76 subjects in the 65–69 and 75–79 cohorts, respectively, died during the follow-up. These subjects were treated as censored at their deaths unless they had developed blindness or received laser photocoagulation before their deaths.

The history of laser photocoagulation was ascertained in 224 subjects (ascertainment rate 78.6%) in the 65–69 cohort and 692 subjects (90.0%) in the 75–79 cohort (table 1). The status of blindness was confirmed in 257 subjects (90.2%) in the 65–69 cohort and 703 subjects (91.4%) in the 75–79 cohort as of 1 January 1995 (table 1).

The onset age of diabetes was not different between the subjects with the missing information and the traced subjects on blindness and laser photocoagulation in the 65–69 cohort. Subjects in the 75–79 cohort with missing information on laser photocoagulation were younger at the onset age of diabetes (8.5 (SD 4.1) years) than the subjects traced (9.9 (SD 4.2) years, $p<0.01$) and the results were the same for those missing information on blindness (8.6 (SD 4.1) years) as the subjects traced (9.7 (SD 4.2) years, $p<0.05$). Sex distributions of blindness and laser photocoagulation were not different between the subjects with the missing information and the traced subjects in both the 65–69 and 75–79 cohorts.

Distribution of sex (135 male and 219 female) in the subgroup (354 patients) diagnosed between 1970 and 1974 that was excluded from the study showed no significant difference from those in the 65–69 cohort and 75–79 cohort ($p = 0.64$). The age at onset of diabetes (8.6 (SD 4.2) years old) in the subgroup diagnosed between 1970 and 1974 showed no significant difference from that in the 75–79 cohort (8.7 (SD 4.1) years old) ($p = 0.69$).

Response of attending physicians to the survey

A total of 735 attending physicians returned information on their patients' clinical status at the time point of questionnaire survey in 1995, including those who had treated multiple patients. No regional difference was observed in the number of answers from attending physicians who responded to our survey. It was confirmed that not only urban but also rural physicians were performing laser photocoagulation at the time point of this survey in Japan.

Cumulative incidence rate of laser photocoagulation

Laser photocoagulation was performed in 107 subjects (47.8%) in the 65–69 cohort and 112 subjects (16.2%) in the 75–79 cohort by the end of follow-up (table 2). In the 65–69 cohort, the cumulative incidence rates of the therapy (%) were 1.3 (95% CI 0 to 2.8), 5.9 (0.05 to 9.0), 22.8 (17.3 to 28.4), 39.4 (32.9 to 45.9) and 49.3 (42.6 to 56.0) at 5, 10, 15, 20 and 25 years follow-up, respectively. The rates were 0.7 (0.1 to 1.4), 5.9 (4.2 to 7.7) and 16.3 (13.6 to 19.1) at 5, 10 and 15 years follow-up in the 75–79 cohort, respectively. There was no statistically significant difference in the incidence of laser photocoagulation between the 65–69 cohort and the 75–79 cohort ($p = 0.51$) (fig 1A).

Cumulative incidence rate of blindness

Blindness developed in 60 subjects (23.3%) in the 65–69 cohort and 15 (2.1%) in the 75–79 cohort (table 2). The cumulative incidence rate of blindness (%) were 0.4 (95% CI 0 to 1.2), 3.6 (1.3 to 5.9), 13.0 (8.8 to 17.2), 22.0 (16.8 to 27.2) and 24.5 (19.1 to 29.9) at 5, 10, 15, 20 and 25 years follow-up in 65 to 69 cohort, respectively, and 0.1 (0 to 0.4), 0.7 (0.1 to 1.3) and 2.0 (1.0 to 3.1) at the follow-up at 5, 10 and 15 years follow-up in the 75–79 cohort, respectively. There was a statistically significant difference in the incidence of blindness between the 65–69 cohort and the 75–79 cohort ($p<0.0001$) (fig 1B).

Risk of blindness and age of onset

The risk of blindness significantly increased by 1.09 times (95% CI 1.03 to 1.15, $p<0.005$) with an increase in the age of onset by 1 year when adjusted for sex and time of diagnosis using a Cox proportional hazard model (table 3).

Risk for blindness and the calendar years of diagnosis

Using a Cox proportional hazard model, the risk of blindness by the calendar year of diagnosis was analysed after adjustment for age of onset, sex, and presence or absence of laser photocoagulation. The hazard ratio for blindness decreased significantly to 0.18 times (95% CI 0.09 to 0.33, $p<0.0001$) in the 75–79 cohort compared with the 65–69 cohort when adjusted for the age of onset and sex (table 3). The hazard ratio attenuated to 0.21 times (0.10 to 0.45, $p<0.0001$) after further adjustment

Table 1 Demographic characteristics by time of diagnosis for diabetes

	Laser photocoagulation			Blindness		
Characteristic	1965–9	1975–9	p Value	1965–9	1975–9	p Value
Number of subjects	224	692		257	703	
Sex (male) (%)	50 (46.7)	41 (36.6)	0.13	25 (41.7)	5 (33.3)	0.56
Onset age (years)	9.2 (4.2)	10.5 (3.5)	0.02	10.5 (4.0)	10.5 (3.3)	0.98

Values are mean (SD) or n (%).
p Values for sex and onset age were calculated by chi-square test and t test for the 1965–9 cohort vs 1975–9 cohort, respectively.

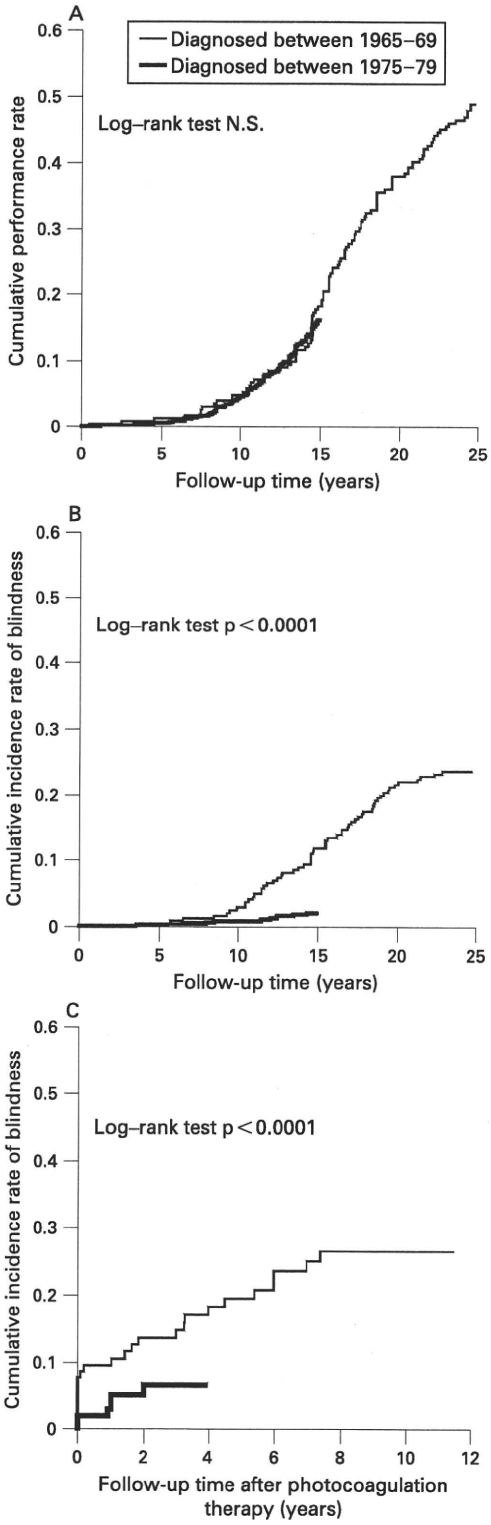

Figure 1 Cumulative performance rates of retinal photocoagulation therapy (A), cumulative incidence rates of blindness (B) and cumulative incidence rates of blindness after photocoagulation therapy (C). The data were followed-up by the Kaplan–Meier method for those diagnosed in 1965–9 and 1975–9. NS, not significant.

for the time-dependent status of laser photocoagulation (table 3).

Risk of blindness and receiving laser photocoagulation

The hazard ratio for the blindness significantly increased to 17.75 (95% CI 8.76 to 35.96, p<0.0001) for those receiving laser photocoagulation compared with those not receiving laser photocoagulation when adjusted for the age of onset, sex and time of diagnosis (table 3). The risk of blindness was significantly higher in subjects who needed laser photocoagulation than in those who did not, even after adjustment for the year of diagnosis.

Cumulative incidence rate of blindness in those who received laser photocoagulation

According to the subjects who received laser photocoagulation, blindness developed in 27 subjects (25.5%) in the 65–69 cohort and seven subjects (6.3%) in the 75–79 cohort. The cumulative incidence rate of blindness in those who received laser photocoagulation (%) were 20.2 (95% CI 12.2 to 28.1) and 26.9 (17.7 to 36.1) at 5- and 10-years follow-up, respectively, after receiving laser photocoagulation in the 65–69 cohort, and 7.9 (2.0 to 13.9) at 5-years follow-up after receiving laser photocoagulation in the 75–79 cohort. There was a statistically significant difference in the incidence of blindness between the 65–69 cohort and the 75–79 cohort (p<0.0001) (fig 1C).

Risk of blindness in those who received laser photocoagulation

The hazard ratio for blindness in those who received laser photocoagulation in the 75–79 cohort decreased significantly to 0.55 (95% CI 0.36 to 0.84, p<0.01) compared with those in the 65–69 cohort after adjusting for the age of onset, sex and time of diagnosis (table 4).

DISCUSSION

To our knowledge this study presents the first estimate of the incidence rate of blindness in Japanese type 1 diabetes patients with a large number of study subjects nationwide and with a high ascertainment rate.[9]

This study revealed that there was a significant improvement of blindness in the 75–79 cohort. A study based at Hvidore Hospital in Denmark showed a 7% cumulative incidence of blindness at 25-year follow-up, when the visual acuity of blindness was defined to be 0.1 or worse, in type 1 diabetes patients diagnosed in 1965–9, and 1% at 15-year follow-up in patients diagnosed in 1975–9.[11] In Japan, visual impairment, semi-blindness and blindness are defined according to the following decimal visual acuity scales: worse than 0.3 to a lower limit of 0.04, worse than 0.04 to a lower limit of 0.02, and worse than 0.02, in both eyes with the best possible correction. Considering that the definition of blindness in the present study was light perception level, we conclude that the incidence rate of 24.5% of blindness at the 25-year follow-up in the 65–69 cohort was extremely high compared with the similar data from the previous study.[11] The present study is based on a nationwide survey whereas Hvidore Hospital is a referral hospital. These differences indicate that there is room to improve prognosis or vision among Japanese patients.

The cumulative incidence of laser photocoagulation was the same for those diagnosed in the 1965–9 and 1975–9 cohorts. The finding is consistent with the aforementioned report of the Hvidore Hospital: the cumulative incidence of proliferative retinopathy was 11–16% and that of laser-treated retinopathy

Table 2 Laser photocoagulation and blindness outcomes in total and 15-year observation periods by the year of diagnosis of diabetes

Variable	Laser photocoagulation		Blindness	
	1965–9	1975–9	1965–9	1975–9
As of the end of 1994				
Number of events (%)	107 (47.8)	112 (16.2)	60 (23.3)	15 (2.1)
Duration of diabetes at event (years)	16.1 (4.9)	11.3 (2.9)	15.2 (4.5)	9.9 (4.4)
Age at event (years)	27.5 (5.7)	24.3 (3.8)	28.3 (5.8)	23.6 (4.8)
Calendar year at event (years)	1985.7 (4.9)	1990.9 (2.9)	1984.7 (4.5)	1989.4 (4.4)
Follow-up period (years)	24.1 (2.6)	14.9 (0.7)	20.3 (4.8)	13.9 (2.3)
At 15-year follow-up				
Number of events (%)	53 (18.6)	112 (14.6)	33 (11.6)	15 (2.0)
Duration of diabetes at event (years)	12.4 (3.6)	11.3 (2.9)	12.0 (3.0)	9.9 (4.4)
Age at event (years)	24.6 (4.9)	24.3 (3.8)	25.3 (4.5)	23.6 (4.8)
Calendar year at event (years)	1981.9 (3.6)	1990.9 (2.9	1981.4 (3.0	1989.4 (4.4)

Values are mean (SD) or n (%).

was 12–21% at 15 years of diabetes duration among type 1 diabetes patients diagnosed in 1965–9, 1970–4 and 1975–9.[11] The cumulative incidence of laser photocoagulation was a little higher in our population. Regarding the subgroup excluded from the study, we confirmed that there was no significant difference in the distribution of sex compared with the 65–69 and 75–79 cohorts, and no significant difference in the onset age compared with the 75–79 cohort. These findings suggest that this excluded subgroup did not differ in any other important demographic or clinical features from the groups investigated further in this study.

The risk of advanced retinopathy and blindness increased significantly with an increase in age of onset when adjusted for sex and time of diagnosis. There seems to be no established agreement on an increased risk of advanced retinopathy and blindness in age of onset.

In the subjects who received laser photocoagulation, the cumulative incidence rate of blindness after receiving the therapy decreased significantly in the 75–79 cohort compared with the 65–69 cohort. Given that there was no change in the frequency of laser photocoagulation, we consider two possible explanations.

First, the change in quality of laser photocoagulation could explain the decreased incidence of blindness observed over time. The results of two large clinical trials[12 13] of laser photocoagulation showed that the technical advances in laser photocoagulation prevented the progression of retinopathy. In Japan, the laser coagulation instrument was first introduced in 1968 and spread rapidly throughout the country during the 1970s through 1990s.[16] The long-term prognosis for blindness may have been improved by technical advances in laser photocoagulation in the late 1980s and early 1990s in Japan.[14]

Second, the earlier introduction of laser photocoagulation relative to the disease process may also have contributed to the reduction of the incidence of blindness, on which our data do not provide any detailed information. The early introduction of laser photocoagulation was optimally timed by the development of fluorescein fundus angiography.[15] It rapidly became available in Japan in the late 1970s[16] and made early diagnosis of proliferative retinopathy possible.

As a result, the risk of blindness was significantly higher in subjects who received laser photocoagulation than in those who did not, even after adjustment for the year of diagnosis. It is appropriate that patients receiving laser photocoagulation have advanced retinopathy, and this may explain the markedly higher risk of blindness compared with those not receiving the therapy. Zaninetti *et al* emphasised that eyes requiring vitrectomy because of vitreous haemorrhage or retinal detachment in proliferative retinopathy after laser photocoagulation were often a result of incomplete photocoagulation.[17] Various surgeries introduced by Machemer in 1971[18] were performed from about 1979 in Japan.[19] Photocoagulation therapy and progress in the treatment of advanced retinopathy, such as the technical improvement in vitreous surgery, might have contributed to the reduced incidence of blindness.

This study has the following limitations. First, information evaluated in this study was limited to reports on the status of blindness, any type of laser photocoagulation therapies and presence or absence of vitreous surgery. Second, our data did not include other known clinical risk factors for retinopathy, including hyperglycaemia,[20] hypertension[21] and so on. Better management of clinical risk factors may play an important role in reducing the progression of retinopathy in this study.

Table 3 Analyses of risk factors for blindness using Cox proportional hazard models

Variable	Model 1		Model 2		Model 3	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age at onset (per year)	1.09 (1.03 to 1.15)	0.0047	1.04 (0.96 to 1.11)	0.35	1.03 (1.00 to 1.11)	0.38
Sex (female/male)	1.14 (0.71 to 1.82)	0.58	1.05 (0.59 to 1.89)	0.86	1.04 (0.58 to 1.87)	0.91
Calendar time period of diagnosis (1975–9/1965–9)	0.18 (0.09 to 0.33)	<0.0001	0.21 (0.10 to 0.45)	<0.0001	0.16 (0.05 to 0.50)	0.002
Laser photocoagulation (presence/absence)	–	–	17.75 (8.76 to 35.96)	<0.0001	15.45 (6.91 to 34.52)	<0.0001
Calendar time period of diagnosis × laser photocoagulation	–	–	–	–	1.65 (0.38 to 7.17)	0.51

Laser photocoagulation was analysed as a time-dependent covariant.
Three levels of adjustment were made as follows. Model 1: age at onset (per year), sex (female/male) and calendar time period of diagnosis (1975–9/1965–9); Model 2: Model 1+ laser photocoagulation (presence/absence); Model 3: Model 2 + calendar time period of diagnosis × laser photocoagulation].

Table 4 Analyses of risk factors for blindness after laser photocoagulation using Cox proportional hazard model

Variable	Hazard ratio (95% CI)	p Value
Age at onset (per year)	1.06 (0.97 to 1.15)	0.23
Sex (female/male)	1.25 (0.62 to 2.54)	0.54
Calendar time period of diagnosis (1975–9/1965–9)	0.55 (0.36 to 0.84)	<0.01

In summary, the incidence of blindness has decreased significantly for the subjects observed over time. This decrease might partially be attributed to technical advances in laser photocoagulation.

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Hemoglobin A1c in predicting progression to diabetes☆

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ABSTRACT

The predictive value of hemoglobin A1c (HbA1c) in comparison to fasting plasma glucose (FPG) is evaluated for 5-year incident diabetes (DM), as HbA1c may be more practical than FPG in the screening for DM in the future. Of 1189 non-DM subjects aged 35–89 years old from the Funagata Study, 57 subjects (4.8%) had developed DM on the WHO criteria at 5-year follow-up. The odds ratio (95% confidence interval: CI) for a one standard deviation increase in FPG/HbA1c was 3.40 (2.44–4.74)/3.49 (2.42–5.02). The area under the receiver operating characteristic curve for FPG/HbA1c was 0.786 (95% CI: 0.719–0.853)/0.785 (0.714–0.855). The HbA1c corresponding to FPG 5.56 mmol/l was HbA1c 5.3%. There was no statistical difference in sensitivity between FPG 5.56 mmol/l and HbA1c 5.3% (61.4% vs. 56.1%), while specificity was higher in HbA1c 5.3% than FPG 5.56 mmol/l (87.8% vs. 82.5%, p-value < 0.001). 0.001). The fraction of incident case from those with baseline IGT was similar between the groups, however the fraction of people above the cut-off was significantly lower in HbA1c 5.3% than FPG 5.56 mmol/l (14.3% vs. 19.6%, p-value < 0.001). HbA1c is similar to FPG to evaluate DM risk, and HbA1c could be practical and efficient to select subjects for intervention.

1. Introduction

The prevalence of type 2 diabetes (T2DM) is increasing rapidly worldwide, and emerging as a serious health issue [1]. Recent clinical trials have demonstrated that lifestyle or pharmacological interventions in subjects with impaired glucose tolerance (IGT) can delay or prevent T2DM [2–4]. More recent epidemiological study [5] and clinical trial [6] have shown that aggressive glycemic control should be started as early as possible to delay or prevent serious diabetes-related complications in subjects with DM. Thus, high-risk subjects for T2DM should be identified at early stage of the disease for intensive interventions.

In Japan, people with possible (hemoglobin A1c [HbA1c] 5.6–6.0%) and probable (HbA1c ≥6.1% and under treatment of diabetes) DM increased from 16.2 million in 2002 to 22.1 million in 2007 among the general population over 20 years old, representing an average 7.3% increase in rate per year [7]. The high-risk approach where either FPG or HbA1c is

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Abbreviations: ADA, American Diabetes Association; CI, confidence intervals; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; JDS, Japan Diabetes Society; OGTT, oral glucose tolerance test; OR, odds ratio; ROC, receiver operating characteristic; Wc, Waist circumference; WHO, World Health Organization; 2 h PG, 2 h plasma glucose.

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incorporated into the general health check targeted future lifestyle-related diseases including DM has been launched in 2008 [8]. Although 2 h plasma (2 h PG) on an oral glucose tolerance test (OGTT) is a better predictor of DM than FPG [9,10], an OGTT is abandoned at opportunistic screening for DM. The simple and inexpensive substitutes would be required at primary health care. To date, both HbA1c and FPG are significant predictors of DM in some studies [11,12]. However, these studies used the American Diabetes Association (ADA) criteria [13] for the diagnosis of DM and the impact of HbA1c on incident DM based on 2 h PG was not taken into account. Thus, the aim of the current study was to assess the predictabilities of baseline FPG and HbA1c for DM based on the World Health Organization (WHO) criteria [14] at 5-year follow-up, by comparing baseline 2 h PG on an OGTT. Moreover, the cut-off points on baseline HbA1c were examined with respect to the prediction of DM at 5-year follow-up.

2. Subjects and methods

Funagata Study has been described previously [15]. Briefly, the Funaga Study is a population-based study conducted in an agricultural area 400 km north of Tokyo to clarify the risk factors, related conditions, and consequence of type 2 DM. The baseline data from the 2nd survey performed between 18th June1995 and 6th July 1997 consisted of 2154 subjects aged 35–89 years (participation rate: 48.4%). Of those, 1189 subjects without DM on the 1999-WHO criteria [14] were repeatedly performed an OGTT at the 3rd survey conducted between 16th June 2000 and 7th June 2002.

In both baseline and 5-year follow-up, blood samples were drawn from the antecubital vein after overnight fasting for measurement of FPG and lipids (enzymatic and direct methods) followed by an 75 g OGTT (Trelan-G®, Shimizu Pharmaceutical, Shimizu) in subjects without a treatment of DM. HbA1c was measured after the calibration standardized of the Japan Diabetes Society (JDS) [16,17] and the JDS assigned HbA1c values, which is 0.3% lower than the National Glycoprotein Standardization Program assigned values [18], were used in the present study. Intra-assay coefficient of variation for HbA1c was 1.0% at values 5.2% and 10.5%. Waist circumference (Wc) was measured at the navel level at the end of expiration under normal breathing in a standing position. Systolic and diastolic blood pressures were measured in the sitting position after a 5 min rest using a mercury sphygmomanometer. All participants were questioned about their smoking and alcohol habits.

2.1. *Statistical analyses*

McNemar's test was used to compare proportions between dependent samples. The 5-year cumulative incidence of DM was calculated as the number of subjects who developed DM at 5-year follow-up divided by the sum of duration of follow-up for each subject, in the three glucose categories for FPG, 2 h PG and HbA1c, respectively, as follows: FPG <5.05, 5.05–5.55, 5.56–6.99 mmol/l, 2 h PG <5.60, 5.60–7.79, 7.80-11.09 mmol/l, and HbA1c <5.0, 5.0–5.2, ≥5.3%. The FPG 5.56 mmol/l and 2 h PG 7.80 mmol/l were chosen, as they are defined as the lower limit of abnormal glucose metabolism in non-DM glucose range [14]. The HbA1c 5.3% was chosen, as it corresponds to FPG 5.56 mmol/l in the receiver operating characteristic (ROC) curve analysis [19] described below. The below these cut-offs, subjects were equally divided into cited group for FPG, 2 h PG and HbA1c, respectively.

Odds ratios (ORs) for the presence of DM at 5-year follow-up were estimated by using logistic regression analysis and reported with their 95% confidence intervals (CIs). The model adjusted for age (continuous), sex (categorical), Wc (continuous), FPG, 2 h PG or HbA1c (categorical) was made and tested by one by one for following explanatory variables: systolic blood pressure (continuous), cholesterol (continuous), triglyceride (continuous), high density lipoprotein cholesterol (continuous), smoking status (categorical, none/past smoker/current smoker), alcohol habits (categorical, none/drink occasionally/drink regularly) and family history of DM (categorical, none/present in first degree relatives). A variable of family history of DM, which came out to be significant in the former model, was fitted in a final model with age, sex, Wc and variables for FPG, 2 h PG or HbA1c. The subsequent logistic regression model, in which a continuous variable for a one standard deviation increase in FPG (0.58 mmol/l), 2 h PG (1.83 mmol/l) or HbA1c (0.4%) was entered, was fitted to see which of the glucose index has the strongest impact on the development of DM.

2.1.1. *Performance of three glucose indices as screening tests for DM at 5-year follow-up*

The ability of baseline FPG, 2 h PG and HbA1c to predict the incidence of DM at 5-year follow-up was determined by computing sensitivity and specificity and plotting them in a ROC curve [19]. The optimal cut-off maximizing sum of sensitivity plus specificity was explored for each glucose indicator. The sensitivity, specificity, positive predictive value (PPV) and false negative predictive value (NPV) for DM at 5-year follow-up and the proportion of subjects above the cut-off were calculated at baseline FPG 5.56 mmol/l and 2 h PG 7.80 mmol/l. The same calculation was made for HbA1c 5.1%, 5.2%, 5.3% and 5.4%.

The study was approved by the Institutional Review Board of Yamagata University and the informed consent to participate was obtained from all participants. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). A p-value < 0.05 was considered as statistically significance.

3. Results

During a 5-year follow-up period, 34 men (6.8% [95% CI: 4.6–9.0]) and 23 women (3.3% [2.0–4.7]) developed DM. The overall cumulative 5-year incidence density of DM was 12.1 (95% CI: 8.9–15.2) per 1000 person years of follow-up for men and women combined (Table 1).

3.1. *Incidence density and risk prediction of DM at 5-year follow-up from baseline FPG, 2 h PG, or HbA1c*

The 5-year cumulative incidence density and the multivariate ORs of DM at 5-year follow-up were significantly higher in subjects with the highest glucose category than the lowest

Table 1 – Incidence density and adjusted odds ratios for the presence of DM at 5-year follow-up according to baseline glucose categories.

	Number of subjects (%)	Number of incident case (incident case from IGT)	Incidence density of DM 1000 person-years (95% CI)	[a] Adjusted ORs for DM (95% CI)
Fasting plasma glucose (mmol/l)				
<5.05	507 (42%)	8 (1)	4.0 (1.2–6.7)	1.00
5.05–5.55	449 (38%)	14 (9)	7.9 (3.8–12.0)	1.72 (0.71–4.19)
5.56–6.99	233 (20%)	35 (25)	37.8 (25.5–50.1)	7.53 (3.35–16.93)
2 h plasma glucose (mmol/l)				
<5.60	512 (43%)	6 (0)	3.0 (0.6–5.3)	1.00
5.60–7.79	541 (46%)	16 (0)	7.5 (3.8–11.1)	2.38 (0.91–6.26)
7.80–11.09 (IGT)	136 (11%)	35 (35)	64.8 (44.1–85.6)	20.64 (8.13–52.37)
HbA1c (%)				
<5.0	559 (47%)	8 (2)	3.6 (1.1–6.1)	1.00
5.0–5.2	460 (39%)	17 (7)	9.3 (4.9–13.7)	2.14 (0.91–5.05)
≥5.3	170 (14%)	32 (26)	47.4 (31.4–63.4)	10.06 (4.44–22.79)
Total				
	1189 (100%)	57 (35)	12.1 (9.0–15.2)	

[a] Adjusting for age, sex, waist circumference, and family history of DM.

glucose category for FPG, 2 h PG and HbA1c (Table 1). There was no difference in the 5-year cumulative incidence density between three glucose indicators for each of the lowest, middle and the highest glucose category.

Modeling with continuous FPG, 2 h PG or HbA1c, the risk for DM at 5-year follow-up related to a one standard deviation increase in FPG, 2 h PG and HbA1c were 3.40 (2.44–4.74), 4.76 (3.30–6.86) and 3.49 (2.42–5.02), respectively.

3.2. *ROC curve analyses predicting DM from baseline FPG, 2 h PG, or HbA1c*

The area under the ROC curve for DM at 5-year follow-up was not statistically different across three glucose indicators: 0.830 (0.767–0.893) for 2 h PG, 0.786 (0.719–0.853) for FPG and 0.785 (0.714–0.855) for HbA1c (Fig. 1). The optimal cut-offs for FPG, 2 h PG and HbA1c were 5.36 mmol/l, 7.52 mmol/l and 5.1%, respectively. The HbA1c 5.3% gave the same sum of sensitivity plus specificity as FPG 5.56 mmol/l/l.

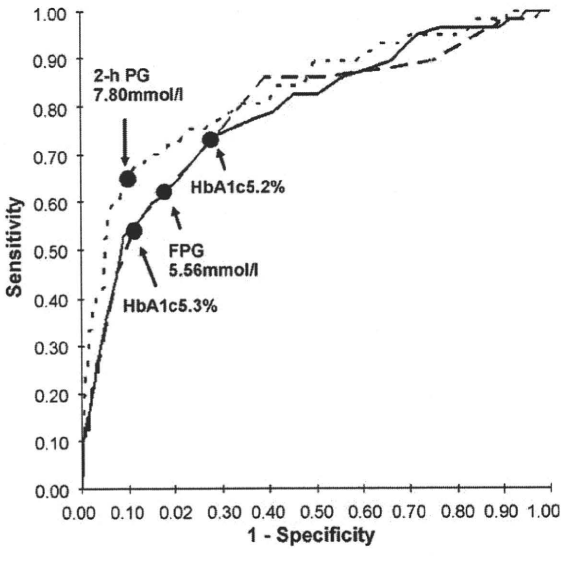

Fig. 1 – Receiver operating characteristic curves for incident diabetes at 5-year follow-up: baseline FPG (solid line), 2 h PG (dotted line) and HbA1c (solid and dotted line) among 1189 non-diabetes subjects at baseline.

3.3. *Performance as the screening test for future DM at various Pre-DM glucose cut-offs*

There was no statistical difference in sensitivity and 100-PPV between FPG 5.56 mmol/l, 2 h PG 7.80 mmol/l, HbA1c 5.2% and HbA1c 5.3%. The specificity was the highest in 2 h PG 7.80 mmol/l, the second highest in HbA1c 5.3%, followed by FPG 5.56 mmol/l, and the lowest in HbA1c 5.2% (all p-values <0.01). There was a precise reverse order in the proportion of subjects above the cut-off (all p-values <0.05).

The distribution of incident case of DM from subjects with baseline IGT was almost similar between the categories for baseline FPG and baseline HbA1c (Table 1). The proportion of incident case of DM from subjects with baseline IGT was significantly higher in those with baseline HbA1c 5.2% (89%, 31/35)(p-values <0.001) than that in those with baseline FPG 5.56 mmol/l (71%, 25/35) or baseline HbA1c 5.3% (74%, 26/35).

4. Discussion

The FPG is an established predictor of DM and considered as a relevant screening test for DM in the future [9–12]. However, blood sampling at fasting state in the morning is oftentimes difficult to perform in general population. Our study has shown that HbA1c has a similar ability to FPG for evaluating future DM risk and for detecting incident cases of DM, especially from the group of subjects with IGT at baseline. Obtained data also demonstrated that 2 h PG on an OGTT had a slightly better predictability for future DM than FPG or HbA1c, which is partly accordance with European reports [9,10]. However, its use as an initial screening test is unrealistic. In the screening at non-fasting state, HbA1c could be practically