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The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program

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Abstract

Aims—Retinopathy is considered the complication most closely associated with and characteristic of diabetes mellitus. Hyperglycaemia below levels diagnostic of diabetes, so called pre-diabetes, is associated with a low prevalence of 'diabetic' retinopathy. However, few longitudinal studies of non-diabetic populations have performed repeated measures of glycaemia and screened for retinopathy to determine its occurrence in the non-diabetic population and the onset of retinopathy in new-onset diabetic patients. We determined the prevalence of retinopathy characteristically seen in diabetes in persons with impaired glucose tolerance and in patients with new-onset diabetes of known duration in the Diabetes Prevention Program (DPP) cohort.

Methods—The DPP recruited persons with elevated fasting glucose (5.3 –6.9 mmol/l) and impaired glucose tolerance, and no history of diagnosed diabetes, other than gestational diabetes not persisting after pregnancy. Seven-field, stereoscopic fundus photography was completed a mean of 3.1 years after the development of diabetes in 594 of 878 participants who had developed diabetes during the DPP, and in a random sample of 302 participants who remained non-diabetic.

Results—Retinopathy consistent with diabetic retinopathy was detected in 12.6 and 7.9% of the diabetic and non-diabetic participants, respectively (P = 0.03, comparing prevalence in the two groups). Systolic blood pressure and HbA_{1c} were higher at baseline in the diabetic participants who had retinopathy compared with the diabetic participants without retinopathy.

Conclusions—Retinopathy characteristic of diabetes is present in persons with elevated fasting glucose and impaired glucose tolerance and no known history of diabetes. The prevalence of retinopathy is significantly higher in persons who develop diabetes, even within 3 years of diagnosis.

Keywords

impaired glucose tolerance; retinopathy; Type 2 diabetes

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Competing interests
None declared.

Introduction

The microvascular complications that accompany diabetes mellitus are sufficiently specific to diabetes that they have been utilized to establish the levels of hyperglycaemia, the defining feature of diabetes, that are diagnostic for the disease [1,2]. An Expert Committee on the diagnosis and classification of diabetes [2] identified levels of glycaemia, both fasting and 2 h after an oral glucose tolerance test, that were associated with retinopathy in epidemiological studies [3–5]. Fasting and 2-h glucose levels ≥ 7.0 and 11.1 mmol/l, respectively, have been adopted as diagnostic thresholds on the basis of these and other studies; glucose levels less than the diagnostic levels are considered to be either pre-diabetic (fasting 5.6–6.9 mmol/l or 2-h 7.8–11.0 mmol/l) or, if lower, normal. Of the micro-vascular complications, retinopathy was selected owing to the large volume of cross-sectional data available from several studies and the ability to detect lesions objectively with fundus photography.

The major importance of these diagnostic levels, based on risk for developing retinopathy, is twofold. First, the cut-points selected determine whether an individual is diagnosed as having diabetes or not and whether interventions are applied. Second, appreciating the time course of the development of retinopathy determines when we begin screening for it with regular ophthalmological examinations.

Relatively few studies have measured the occurrence of ‘diabetic’ retinopathy in non-diabetic populations [3–10], and only one study, in Pima Indians, has carefully screened ‘non-diabetic’ populations over time to ensure that they are in fact non-diabetic [7]. The relationship between subdiabetic levels of glycaemia and retinopathy therefore remains unclear.

The Diabetes Prevention Program (DPP), a clinical trial that established the salutary role of lifestyle intervention or metformin in preventing diabetes, studied persons with impaired glucose tolerance (IGT) and performed repeated measures of glycaemia over time [11,12]. The DPP provided the opportunity to examine whether retinopathy occurs in pre-diabetes, i.e. in the setting of glucose levels that are currently considered subdiabetic. In addition, we were able to examine the development of retinopathy in persons with recently diagnosed diabetes where the time of diagnosis could be established within a 6-month period.

Patients and methods

The design and conduct of the DPP have been described in detail [11,12]. In brief, the DPP recruited 3819 overweight or obese volunteers with impaired glucose tolerance between 1996 and 1999. They were randomly assigned to lifestyle intervention, with the goal of losing 7% of their initial body mass and achieving at least 150 min per week of moderate intensity activity, or to metformin, placebo, or troglitazone. The troglitazone arm of the study (n = 585) was suspended in June 1998 owing to safety concerns. At baseline, any history of diabetes, other than previous gestational diabetes mellitus (GDM), or past treatment with glucose-lowering medications, was an exclusion and all participants had elevated fasting glucose and impaired glucose tolerance on a standardized 75-g oral glucose tolerance test (OGTT) [11]. The specific glucose criteria were fasting glucose levels 5.6 –7.7 mmol/l during 1996– 97 and 5.3– 6.9 mmol/l thereafter. Two-hour glucose levels were 7.8–11.0 mmol/l. Participants had fasting glucose levels measured every 6 months and a 2-h OGTT performed annually. Any levels that were in the diabetic range had to be confirmed within 6 weeks of the initial test in order to establish the diagnosis of diabetes.

Participants

The participants for this retinopathy substudy of the DPP included a representative sample (n = 302) of the DPP cohort who remained non-diabetic throughout the study. The sample was

selected to include approximately equal representation from the three interventions (lifestyle, metformin, and placebo) that were maintained during the entire course of the DPP. In addition, as many of the participants as possible who had developed diabetes during the study were recruited for the retinopathy substudy, with the goal of obtaining fundus photography in approximately six hundred recently diagnosed diabetic participants. Fourteen participants who had fundus photography (all from the diabetic group) had been randomized to the troglitazone group and were excluded from the analysis, leaving a total of 896 participants (594 diabetic and 302 non-diabetic participants). The baseline characteristics of the non-diabetic and diabetic participants who joined the DPP follow-up study, with and without retinal photographs, are shown in Table 1. The DPP and the retinopathy substudy were approved by the Institutional Review Boards at all of the participating institutions, and all participants gave written informed consent.

Procedures

Oral glucose tolerance testing (annually) and fasting glucose testing (every 6 months) were performed after a 10 h or more overnight fast according to a standardized protocol and as previously described [11]. Glucose and HbA_{1c} [Diabetes Control and Complications Trial (DCCT) standardized assay] levels were measured in the DPP Central Biochemistry Laboratory at the University of Washington. Insulin secretion was estimated by the corrected insulin response (CIR), based on the plasma insulin and glucose concentrations at 30 min, with CIR = 100 × 30-min insulin/[30-min glucose × (30-min glucose minus 70 mg/dl)] [13]. Seven-field stereoscopic fundus photography was performed after informed consent was obtained. The standardized photography protocol, performed after pupillary dilation, was carried out by photographers who had received central training.

Analysis

The photographs were sent to a central fundus photography reading centre at the University of Wisconsin, where they were graded by trained readers masked to participant identification and treatment group assignment. Grading was performed using the modified Airlie House criteria [14]. All readings followed a strict protocol, that included masked re-readings by independent readers, with adjudication by a more senior reader if substantial disagreements occurred. In addition, 7% of all graded photographs were read independently, without knowledge of the original reading. The intergrading agreement was an unweighted kappa value of 0.87 (95% CI 0.76–0.98), which is considered highly acceptable.

Baseline characteristics are described using means ± SD for quantitative variables and percentages for categorical variables. The current updated mean values for covariates were determined by calculating the arithmetic mean of a specified value (e.g. HbA_{1c}), including all values measured from baseline to the time closest to the fundus photography. Comparisons between groups were carried out using the chi-square test of independence for categorical variables and the *t*-test for quantitative variables. Repeated measures analyses were performed using mixed models. A P-value < 0.05 was considered to be statistically significant. The Statistical Analysis Software (SAS) version 8.2 was used for all analyses (SAS Institute, Cary, NC, USA).

Results

Fundus photography was performed at a mean of 5.6 years (range 3.9–7.6) after study entry in 898 non-diabetic and diabetic participants. Two of the 898 participants had photographs that were of ungradable quality, leaving 896 participants for this study.

The randomly selected group of persons who had not developed diabetes at the time of photography had similar baseline characteristics as the participants without diabetes that did not have fundus photos (although older, with fewer Native Americans, and slightly but significantly higher systolic blood pressure; Table 1). The subgroup that developed diabetes and had fundus photography represented 68% (594 of 878) of all of the participants who developed diabetes up to the time of the photography protocol. The characteristics of the subgroup that developed diabetes and was photographed differed, again minimally but significantly, from the diabetic participants who were not photographed in the proportion that was female or Caucasian, and for the mean duration of diabetes and fasting glucose levels (Table 1). The baseline characteristics of the diabetic participants who were photographed were different from those in the non-diabetic sample who were photographed, reflecting the risk factors for diabetes development. Age, body mass index, and fasting and 2-h glucose, HbA_{1c}, high-density lipoprotein (HDL) cholesterol, insulin secretion as measured by CIR, fasting insulin and triglyceride levels were all significantly different between the two groups.

The frequency and characteristics of retinopathy detected by fundus photography are shown in Table 2. In the overall study group, 13.6% of the participants (9.9% of those without diabetes and 15.5% of those with diabetes) had evidence of retinopathy in at least one eye by fundus photography. However, approximately 19% of the retinal findings (20% for the non-diabetic group and 18% of the diabetic group) were considered less than definitive for diabetes by the Early Treatment of Diabetic Retinopathy Study scale (ETDRS; levels 14 and 15). Features such as haemorrhages, exudates, and intraretinal microvascular abnormalities were not considered diagnostic, whereas microaneurysms were. Ninety-nine participants (11.1%) had findings characteristic of diabetic retinopathy with at least one microaneurysm, the lesion considered most characteristic of diabetic retinopathy, in at least one eye (≥ ETDRS level 20). Seventy-eight participants had one or more microaneurysms in only one eye and eight had at least one microaneurysm in both eyes. Of note, none of the subjects had retinal changes (intraretinal microvascular abnormalities) that would be considered sight threatening according to the National Grading Protocols in the UK.

The frequency of diabetic retinopathy with at least micro-aneurysms (≥ ETDRS level 20) in the non-diabetic group was 7.9%, compared with 12.6% in the diabetic group ($P = 0.03$). The non-diabetic group was selected to include approximately the same number of participants from the placebo-treated ($n = 95$), metformin-treated ($n = 106$), and the lifestyle intervention ($n = 101$) groups. The relatively small numbers within each of the treatment groups precluded a meaningful comparison of retinopathy prevalence between the treatment groups.

The baseline characteristics of the participants who had retinopathy, compared with those who did not, stratified by the presence or absence of diabetes, are shown in Table 3. In the non-diabetic participants, none of the characteristics were significantly different between the participants with and without diabetic retinopathy. In the participants with diabetes, baseline HbA_{1c} (6.2 ± 0.54 vs. 6.1 ± 0.55%, $P < 0.05$) and systolic blood pressure (130 ± 18 vs. 125 ± 15 mmHg, $P < 0.05$) were the only two characteristics that were significantly different between the participants with retinopathy changes consistent with diabetes and those without. In both groups with such retinopathy, the baseline prevalence of hypertension was higher, although the differences were not statistically significant.

Comparisons between subgroups of participants were repeated using the current mean updated values for retinopathy risk factors (Table 4). In the non-diabetic participants, total cholesterol was significantly different between the participants who had diabetic retinopathy and those who did not. In the participants with diabetes, HbA_{1c}, and systolic and diastolic blood pressure were significantly higher in those with diabetic retinopathy compared with those without diabetic retinopathy, mirroring the analysis of baseline values.

Discussion

The Diabetes Prevention Program recruited a population at high risk for developing diabetes by including participants who were overweight and had elevated fasting glucose and impaired glucose tolerance [11,12]. Except for prior gestational diabetes, a history of diagnosed diabetes was an exclusion criterion. Fasting and post-OGTT glucose levels were determined, which allowed a careful assessment of glycaemic status over the mean of 5.6 years of follow-up, and an accurate determination of the time of onset of diabetes. DPP participants who developed diabetes have a more accurate determination of its onset and duration than in other studies of diabetic retinopathy in persons with Type 2 diabetes. Fundus photography is an accepted objective method of detecting diabetic retinal changes [14]. In the DPP participants who did not develop diabetes, 7.9% had microaneurysms, the lesion that best characterizes diabetic retinopathy [14]. While previous studies [6–10,15–17] have assessed non-diabetic populations for the occurrence of 'diabetic' retinopathy, none has carefully assessed glycaemia over time to classify persons accurately as diabetic, non-diabetic or pre-diabetic. Seven population-based studies, five in the USA [8–10,15,16], one in Australia [6], and one in Sweden [16], have documented retinopathy in persons not known to be diabetic. Unfortunately, diabetes was not rigorously excluded with glucose tolerance testing in most of the studies, and individuals with undiagnosed diabetes and an unknown number of persons with impaired glucose tolerance were undoubtedly included in the study populations. The retinal lesions noted in these studies were often more consistent with hypertension than with diabetes, and advancing age and hypertension were associated with a higher prevalence of lesions. The prevalence of retinal lesions in 'non-diabetic populations' has ranged from < 1% in the Framingham [15], Evans County, Georgia [16], and Göteborg [17] studies, which used relatively less sensitive ophthalmoscopic methods (usually direct ophthalmoscopy), to 9.8% in the Blue Mountain Eye Study in Australia which used 6-field fundus photography [6]. In the latter study, 6.4% of the 'non-diabetic' population had microaneurysms. The Cardiovascular Health Study (CHS) examined an elderly population after excluding patients with previously diagnosed diabetes or with fasting hyperglycaemia [9]. Between 6.1 and 9.6% of the population had some form of retinopathy, although the prevalence of the more diabetes-specific lesions, such as microaneurysms, could not be ascertained from the published data. The Atherosclerosis Risk in Communities (ARIC) study performed non-mydriatic fundus photography, examining a single 45° field in more than 10 000 participants, after excluding those with previously diagnosed diabetes [10]. Microaneurysms were detected in 2% of the population. In all of these studies, the absence of rigorous screening for diabetes precludes the determination of the proportion of the population that had diabetes or IGT. A single study in the Pima Indian population, known for its extraordinarily high prevalence of diabetes, took retinal photographs after dilation in a population with diabetes diagnosed within the previous 4 years and in patients with impaired glucose tolerance [7]. Lesions consistent with diabetic retinopathy were found in 8.3% (4/48) of diabetic patients whose duration of diabetes was no greater than 4 years. Surprisingly, a higher percentage (11.8%; 8/68) of the patients with IGT had retinopathy. The small numbers of Pima Indians in this study makes interpretation and generalizability of these results problematic.

Our understanding of the time course of the development of retinopathy is based primarily on studies of persons with Type 1 diabetes [18–20], whose clinical (i.e. hyperglycaemic) onset is believed to be relatively acute and easily dated. Older studies using fundus photography detected typical diabetic retinopathy in 6–11% of patients with a duration of diabetes of 3 – 4 years [18,19]. The more recent DCCT identified micro-aneurysms (or more) in almost 18% of Type 1 diabetic persons with a duration of 1–3 years who were referred for the study [20]. Because of the gradual onset of Type 2 diabetes, the clinical course of retinopathy in Type 2 diabetes has largely been extrapolated from the studies of Type 1 diabetes. The estimated 9–12 years delay in diagnosing Type 2 diabetes was predicated on the occurrence of retinopathy

in newly diagnosed Type 2 diabetes and the unsupported assumption that the prevalence of retinopathy in non-diabetic persons is zero [21]. The current DPP results, with more than 12% of the participants with diabetes having retinopathy within approximately 3 years of diagnosis, suggest that the development of retinopathy over time is comparable with that in Type 1 diabetes. However, the finding that approximately 8% of the pre-diabetic population also has retinopathy confirms that retinopathy may start during what is now considered the pre-diabetic state, and then increases by approximately 50% shortly after diabetes develops. A similar pattern of development of microalbuminuria, an early indicator of diabetic nephropathy, in the setting of subdiabetic levels of hyperglycaemia, has also been noted [22]. As has been suggested in other studies, hypertension and dyslipidaemia may contribute to the risk of developing retinopathy [23,24].

There are potential shortcomings in our study that require comment. We only took photographs of a sample of the DPP population, 68% of the diabetic participants and approximately 16% of our non-diabetic participants. Although the randomly selected sample of non-diabetic participants was generally similar to the entire cohort, we plan to take photographs of the entire cohort, which will allow more detailed subset and covariate analyses. The presence of retinopathy characteristic of diabetes in our non-diabetic population reinforces the results of previous studies [1–10] by providing a more carefully characterized population with repeated testing of glucose tolerance. Although unlikely, some members of the DPP cohort might have had undiagnosed diabetes prior to study entry, although they had no evidence of diabetes on repeated OGTT testing during the DPP. There is no way of determining this short of performing glucose tolerance testing over the entire lifespan. Finally, during the first year of the DPP recruitment, inclusion criteria were changed to match the criteria established by the American Diabetes Association in 1997 [11]. A small number of subjects (< 2% of the entire cohort) who fulfilled, at baseline, the new criteria for diabetes was recruited before the change in criteria. Given the small number of such volunteers included in the current study (two of the 302 IGT subjects), there was no difference in the results when taking these subjects into account.

In summary, the DPP cohort of IGT participants and new-onset diabetic patients, whose date of onset can be determined within 6 months, provided the opportunity to determine the prevalence of retinopathy in the setting of subdiabetic hyperglycaemia and early in the course of diabetes. Retinal lesions characteristic of diabetes are present before the onset of diabetes by current criteria and increase in prevalence very early in the course of diabetes. The more careful characterization of long-term glycaemia in the DPP cohort and documentation of retinopathy in the pre-diabetic state support the notion that retinopathy may occur over a wider continuum of glycaemia than is encompassed by current diagnostic criteria. These findings suggest that the current diagnostic criteria for diabetes, based predominantly on the associated risk for retinopathy, may require reconsideration. At this time, earlier screening for retinopathy in the pre-diabetic state, keeping in mind the clinically benign characteristics of such lesions and the considerable effort and expense required, does not seem warranted and requires further study.

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Abbreviations

BMI
body mass index

CIR
corrected insulin response

DCCT
Diabetes Control and Complications Trial

DPP
Diabetes Prevention Program

DPPOS
Diabetes Prevention Program Outcomes Study

ETDRS
Early Treatment of Diabetic Retinopathy Study

GDM
gestational diabetes mellitus

HDL
high-density lipoprotein

IGT
impaired glucose tolerance

IRMA
intra-retinal microvascular abnormalities

LDL
low-density lipoprotein

NIDDK
National Institute of Diabetes and Digestive and Kidney Diseases

NPDR
non-proliferative diabetic retinopathy

OGTT
oral glucose tolerance test

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Table 1

Baseline characteristics[*] of Diabetes Prevention Program Outcomes Study (DPPOS) participants with and without retinal photographs taken 3.9–7.6 (mean = 5.6) years after baseline

Characteristic	No diabetes		Diabetes	
	No photos	Photos[†]	No photos	Photos[‡]
n	1551	302	282	594
Age (years)	51.1 ± 10.4	52.5 ± 10.2[‡‡]	49.9 ± 11.0	51.1 ± 10.1[§§]
Sex (% female)	68.5%	66.6%	75.2%	63.3%[‡‡]
Race (% Caucasian)	56.5%	55.3%[‡‡]	46.8%	52.9%[‡‡]
History of GDM (% of women)	13.4%	13.4%	16.5%	19.9%
BMI (kg/m^2)	33.4 ± 6.3	32.9 ± 5.5	35.4 ± 6.9	34.9 ± 7.0[§§]
HbA_{1c} (%)[§]	5.8 ± 0.47	5.9 ± 0.43	6.1 ± 0.55	6.1 ± 0.55[§§]
Glucose (mmol/l)				
Fasting	5.8 ± 0.40	5.8 ± 0.40	6.0 ± 0.49	6.2 ± 0.51[‡‡§§]
2-h	9.0 ± 0.89	9.0 ± 0.92	9.5 ± 0.97	9.5 ± 0.94[§§]
Blood pressure (mmHg)				
Systolic	123 ± 14.3	124 ± 14.6[‡‡]	125 ± 15.1	126 ± 15.2
Diastolic	78 ± 9.0	79 ± 9.3	79 ± 10.1	79 ± 9.8
Hypertension (% yes)[¶]	24.8%	29.8%	33.3%	34.5%
Smoking (% never)	60.6%	58.3%	56.7%	55.9%
Cholesterol (mmol/l)[**]				
Total	5.3 ± 0.94	5.3 ± 0.92	5.2 ± 0.93	5.3 ± 0.90
LDL	3.3 ± 0.85	3.2 ± 0.83	3.2 ± 0.80	3.3 ± 0.85
HDL	1.21 ± 0.32	1.22 ± 0.30	1.16 ± 0.29	1.14 ± 0.29[§§]
Triglycerides (mmol/l)[**]	1.78 ± 1.05	1.79 ± 1.08	1.89 ± 1.11	1.95 ± 1.08[§§]
Duration of diabetes (years)	—	—	2.8 ± 1.6	3.1 ± 1.5[‡‡]
Fasting Insulin (pmol/l)[**]	150.6 ± 87.4	150.3 ± 87.6	171.0 ± 85.0	180.0 ± 94.4[§§]
Corrected insulin response[††]	0.68 ± 0.46	0.64 ± 0.43	0.57 ± 0.36	0.53 ± 0.32[§§]

Data are means ± SD, unless otherwise stated.

[*] All characteristics are at DPP baseline except for duration of diabetes.

[†] Selected randomly from participants who remained non-diabetic throughout study.

[‡] Participants who developed diabetes during the DPP and enrolled in DPPOS were recruited for the retinopathy study with a goal of 600 participants.

[§] Information was only available for *n* = 300 in the non-diabetic sample with photos, for *n* = 1548 in the non-diabetic cohort without photos, and for *n* = 592 in the diabetic sample with photos.

[¶] Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or hypertension medication.

[**] Information was only available for *n* = 1548 in the non-diabetic cohort without photos, for *n* = 593 in the diabetic sample with photos, and for *n* = 281 (*n* = 282 for fasting insulin) for the diabetic sample without photos.

[††] Information was only available for *n* = 297 in the non-diabetic sample with photos, for *n* = 1515 in the non-diabetic cohort without photos, for *n* = 592 in the diabetic sample with photos, and for *n* = 277 for the diabetic sample without photos.

[‡‡] $P < 0.05$ for difference between the non-diabetic participants with vs. without fundus photos or for difference between the diabetic participants with vs. without fundus photos.

[§§] $P < 0.05$ for difference between the diabetic and the non-diabetic sample.

Table 2

Prevalence of retinopathy (number and percentage affected)

	ETDRS levels	Overall (*n* = 896)	Non-diabetic sample (*n* = 302)	Diabetic sample (*n* = 594)
Any retinopathy*	14–43	122 (13.6%)	30 (9.9%)	92 (15.5%)
Non-diabetic retinopathy	14–15	23 (2.5%)	6 (2.0%)	17 (2.9%)
Exudates or IRMA	14	3 (0.3%)	1 (0.3%)	2 (0.4%)
Haemorrhages	15	20 (2.2%)	5 (1.7%)	15 (2.5%)
Diabetic retinopathy	20–43	99 (11.1%)	24 (7.9%)	75 (12.6%)‡
Microaneurysms only	20	85 (9.5%)	21 (6.9%)	64 (10.8%)§
Mild/moderate NPDR†	35–43	14 (1.6%)	3 (1.0%)	11 (1.8%)

*Includes all retinopathy (non-specific, i.e. no microaneurysms, and diabetic retinopathy).

†Mild/moderate non-proliferative diabetic retinopathy (NPDR)—microaneurysms plus one or more of the following: venous loops > 0/1; soft exudates, intraretinal microvascular abnormalities or venous beading; retinal haemorrhages; hard exudates > 0/1; or soft exudates > 0/1.

‡P = 0.035 by Chi square, compared with the non-diabetic sample.

§P = 0.065 by Chi square, compared with the non-diabetic sample.

Table 3

Baseline characteristics of participants with and without diabetic retinopathy (ETDRS level ≥ 20) taken 3.9–7.6 (mean = 5.6) years after baseline

Characteristic	No diabetes		Diabetes	
	No diabetic retinopathy	Diabetic retinopathy	No diabetic retinopathy	Diabetic retinopathy
n	278	24	519	75
Age (years)	52.5 ± 10.1	52.7 ± 11.7	51.1 ± 10.2	51.3 ± 9.0
Sex (% female)	65.8%	75.0%	64.5%	54.7%
Race (% Caucasian)	54.0%	70.8%	52.2%	57.3%
History of GDM (% of women)	12.6%	22.2%	20.6%	14.6%
BMI (kg/m^2)	32.8 ± 5.5	33.4 ± 5.7	34.7 ± 6.8	35.9 ± 8.8
HbA_{1c} (%)*	5.9 ± 0.43	5.8 ± 0.44	6.1 ± 0.55	6.2 ± 0.54**
Glucose (mmol/l)				
Fasting	5.8 ± 0.39	5.9 ± 0.49	6.2 ± 0.50	6.2 ± 0.61
2-h	9.0 ± 0.90	9.2 ± 1.12	9.5 ± 0.93	9.3 ± 0.97
Blood pressure (mmHg)				
Systolic	125 ± 14.6	124 ± 15.8	125 ± 14.7	130 ± 18.2**
Diastolic	79 ± 9.2	78 ± 10.4	79 ± 9.8	80 ± 9.7
Hypertension (% yes)†	29.1%	37.5%	34.1%	37.3%
Smoking (% never)	58.3%	58.3%	56.5%	52.0%
Cholesterol (mmol/l)‡				
Total	5.2 ± 0.93	5.5 ± 0.64	5.3 ± 0.91	5.2 ± 0.84
LDL	3.2 ± 0.85	3.4 ± 0.65	3.3 ± 0.86	3.3 ± 0.79
HDL	1.22 ± 0.29	1.16 ± 0.32	1.15 ± 0.29	1.11 ± 0.30
Triglycerides (mmol/l)‡	1.75 ± 1.03	2.22 ± 1.47	1.95 ± 1.03	1.96 ± 1.39
Fasting insulin (pmol/l)§	151.2 ± 90.0	138.9 ± 52.7	181.6 ± 95.7	169.3 ± 84.5
Corrected insulin response¶	0.65 ± 0.44	0.51 ± 0.35	0.53 ± 0.33	0.52 ± 0.27

Data are means ± SD, unless otherwise stated.

*Information was only available for *n* = 276 in the non-diabetic no diabetic retinopathy sample and for *n* = 517 in the diabetic no diabetic retinopathy sample.

†Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or hypertensive medication. ‡Information was not available for one participant in the diabetic with diabetic retinopathy sample.

§Information was not available for one participant in the diabetic without diabetic retinopathy sample.

¶Information was only available for *n* = 274 in the non-diabetic no diabetic retinopathy sample, *n* = 23 in the non-diabetic diabetic retinopathy sample, and *n* = 517 in the diabetic no diabetic retinopathy sample.

**$P < 0.05$ between the diabetic retinopathy and the no diabetic retinopathy group.

Table 4

Current mean updated characteristics of participants with and without retinopathy

Characteristic	Non-diabetic participants		Diabetic participants	
	No diabetic retinopathy	Diabetic retinopathy	No diabetic retinopathy	Diabetic retinopathy
n	278	24	519	75
Duration of diabetes (years)	—	—	3.1 ± 1.5	3.3 ± 1.6
BMI (kg/m^2)	31.9 ± 5.7	32.8 ± 6.0	34.4 ± 6.9	36.1 ± 9.1
HbA_{1c} (%)	5.9 ± 0.37	5.8 ± 0.39	6.2 ± 0.63	6.4 ± 0.55*
Glucose (mmol/l)				
Fasting	5.7 ± 0.34	5.7 ± 0.32	6.6 ± 0.88	6.7 ± 0.86
2-h	8.2 ± 1.17	8.3 ± 1.42	10.1 ± 1.40	10.0 ± 1.57
Blood pressure (mmHg)				
Systolic	122 ± 11.2	121 ± 11.7	124 ± 10.4	128 ± 12.9*
Diastolic	76 ± 6.6	76 ± 7.2	77 ± 6.6	79 ± 7.8*
Hypertension (%)†	52%	54%	65%	71%
Cholesterol (mmol/l)				
Total	5.1 ± 0.79	5.2 ± 0.51*	5.1 ± 0.71	5.1 ± 0.68
LDL	3.1 ± 0.69	3.2 ± 0.54	3.1 ± 0.64	3.2 ± 0.62
HDL	1.23 ± 0.28	1.16 ± 0.29	1.15 ± 0.28	1.09 ± 0.25
Triglycerides (mmol/l)	1.61 ± 0.77	1.76 ± 0.86	1.87 ± 0.87	1.81 ± 1.02

Data are means ± SD.

*$P < 0.05$ between the diabetic retinopathy and the no diabetic retinopathy group.

†Hypertension over time defined as blood pressure > 140/90 or treatment with anti-hypertensive medications, either at baseline or during the study.