Blood Pressure, Lipids, and Obesity Are Associated With Retinopathy

The Hoorn Study

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OBJECTIVE — To study potential risk factors for retinopathy in diabetic and nondiabetic individuals.

RESEARCH DESIGN AND METHODS — The Hoorn Study is a population-based study including 2,484 50- to 74-year-old Caucasians. A subsample of 626 individuals stratified by age, sex, and glucose tolerance underwent extensive measurements during 1989–1992, including ophthalmologic examination and two-field 45-degree fundus photography. The prevalence of (diabetic) retinopathy was assessed among individuals with normal glucose metabolism (NGM) and impaired glucose metabolism (IGM) and individuals with newly diagnosed diabetes mellitus (NDM) and known diabetes mellitus (KDM) (new World Health Organization 1999 criteria).

RESULTS — The prevalence of retinopathy was 9% in NGM, 11% in IGM, 13% in NDM, and 34% in KDM. Retinopathy worse than minimal nonproliferative diabetic retinopathy was present in 8% in KDM and 0–2% in other glucose categories. The prevalence of retinopathy was positively associated with elevated blood pressure, BMI, cholesterol, and triglyceride serum levels in all glucose categories. The age-, sex-, and glucose metabolism category–adjusted odds ratios were 1.5 (95% CI 1.2–1.9), 1.3 (1.0–1.7), and 1.3 (1.0–1.6) per SD increase of systolic blood pressure, BMI, and total cholesterol concentration, respectively, and 1.2 (1.0–1.5) per 50% increase of triglyceride level. Elevated blood pressure and plasma total and LDL cholesterol levels showed associations with retinal hard exudates.

CONCLUSIONS — Retinopathy is a multifactorial microvascular complication, which, apart from hyperglycemia, is associated with blood pressure, lipid concentrations, and BMI.

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There is growing evidence that retinopathy is not only related to hyperglycemia and diabetes duration. Other cardiovascular risk factors have been shown to play an important role as well (1–4). The U.K. Prospective Diabetes Study (UKPDS) has shown that intensive blood pressure treatment in hypertensive subjects with type 2 diabetes prevented or delayed progression of retinopathy (5). There are also indications that elevated serum lipid levels promote retinopathy and especially hard exudates (6–8). Most of these studies, however, are restricted to diabetic patients. A number of population-based studies have reported the presence of retinopathy in nondiabetic subjects (9–14). However, there is only little information about risk factors for retinopathy in these individuals. We previously reported an association of hyperhomocysteinemia with retinopathy in the diabetic but not in the nondiabetic population (15). Therefore, the aim of the present study was to investigate the contribution of blood pressure, lipids, and obesity to retinopathy in diabetic and nondiabetic individuals. We also specifically analyzed associations of risk factors with hard exudates, a sight-threatening complication when associated with macular edema. In addition, we present the prevalence of retinopathy according to the new diagnostic criteria for diabetes of the World Health Organization (WHO 1999).

RESEARCH DESIGN AND METHODS

Subjects

The study population consisted of 626 Dutch citizens, aged 50–74 years, who underwent an ophthalmologic examination during 1989–1992. Subjects were selected from the Hoorn Study, which has been extensively reported elsewhere (16). Briefly, a random selection of 3,553 subjects, aged 50–74 years, from the population register of the town of Hoorn, the Netherlands, was invited, and 2,540 subjects (71.5%) participated. After exclusion of 56 non-Caucasians, the remaining 2,484 subjects formed the cohort of the Hoorn Study, a population-based study on glucose metabolism in a general Caucasian population. In this population, fasting plasma glucose was measured and all individuals not treated with oral blood

glucose–lowering agents or insulin underwent a 75-g oral glucose tolerance test (OGTT). All diabetic patients treated with oral glucose-lowering agents or insulin ($n = 76$) and all individuals with a 2-h postload glucose ≥11.1 mmol/l ($n = 122$), as well as two age- and sex-stratified random samples, from subjects with 2-h glucose levels <7.5 mmol/l ($n = 256$) and <11.1 mmol/l but ≥7.5 mmol/l ($n = 254$), respectively, were invited for an extensive physical examination, including ophthalmologic examination and fundus photography. Participants who did not receive pharmacological treatment for diabetes had a second OGTT within 3–5 weeks after the first OGTT.

The 626 participants (88% of those invited) with an ophthalmologic examination or fundus photograph did not differ significantly from the nonattendees with respect to age, self-reported hypertension, and cardiovascular disease (data not shown). The Hoorn Study was approved by the Ethical Review Committee of the VU University Medical Center (VUMC) in Amsterdam, the Netherlands. Written informed consent was obtained from all participants.

Ophthalmologic examinations and definitions

The ophthalmologic examinations were performed by ophthalmologists in the Department of Ophthalmology of the VUMC. All examiners were unaware of the glucose metabolism status of the study participants.

After mydriasis with tropicamide and phenylephrine eye drops, the retina was examined by funduscopy, and (diabetic) retinopathy was graded following the Wisconsin grading system (modified Airlie House classification) (17). Fundus photography was performed with a 45-degree Kowa Pro fundus camera with green filter (Kowa Optical Industry, Tokyo). Of each eye, two black-and-white 35-mm photographs (Kodak Tri-X400 ASA; Eastman Kodak, Rochester, NY) were taken, one centered on the macula and one nasal on the optic disc. Photographs of 148 subjects were missing (not associated with age, sex, glucose tolerance category, hypertension, and worst eye visual acuity; data not shown). All photographs (11 × 11 cm) were recently regraded for (diabetic) retinopathy according to the Eurodiab standards independently by an ophthalmologically

trained physician and a senior ophthalmologist (H.A.v.L., B.C.P.P.). In case of disagreement, the independent judgment of another ophthalmologist was taken to be decisive (A.C.M.). We used the Eurodiab classification scheme for the photographs because this matches the available 45-degree two-field fundus photography and because it uses standard photographs to grade retinal lesions, whereas the Wisconsin grading system is based on seven fields of 30 degrees (17,18).

Retinopathy was considered present when at least one microaneurysm, hemorrhage, or hard exudate was present or in case of neovascularization, fibrous proliferation, or laser coagulation scars at photographs or funduscopy. Retinopathy worse than minimal nonproliferative diabetic retinopathy (NPDR) was present at Eurodiab grade 2 or more using photography or at Wisconsin grade 4.0 or more with funduscopy (17,18). Hemorrhages or exudates as symptoms of other pathology, such as retinal venous occlusion, were not considered as (diabetic) retinopathy but were analyzed separately. In each subject the "worst eye" was graded for each abnormality, according to ophthalmoscopy or fundus photography.

In five individuals, none of the photographs were gradable, because of poor quality. Of these, only one person had no complete funduscopy report and was excluded for analysis of retinopathy.

Laboratory and other medical assessments

Fasting and 2-h postload venous plasma glucose levels were determined with a glucose dehydrogenase method (Merck, Darmstadt, Germany). For statistical analyses, the mean of two fasting and two 2-h glucose levels (if present) was taken. HbA_{1c} and lipids were determined in the fasting blood sample at the first OGTT. HbA_{1c} was determined by ion exchange high-performance liquid chromatography using a DM monitoring system (Bio-Rad, Veenendaal, the Netherlands; normal range 4.3–6.1%). Total cholesterol, HDL cholesterol (after precipitation of the low- and very low–density proteins), and triglycerides were measured by enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany). The Friedewald formula was used to calculate the LDL cholesterol (except for subjects with triglycerides >4.55 mmol/l).

Systolic and diastolic (Korotkov V)

blood pressure was determined on the right arm of seated subjects, after at least 5 min resting, using a random-zero sphygmomanometer. The average of four measurements (duplicate recordings taken before the start of both OGTTs) was used for analysis. Height, weight, and waist and hip circumferences were determined to calculate waist-to-hip ratio (WHR) and BMI as described elsewhere (16). Use of medication was checked at the first visit.

Statistical analysis

Subjects were classified in categories according to glucose metabolism. Known diabetic individuals (KDM) with oral glucose-lowering medication, insulin, or a diet were analyzed separately. The other subjects were classified in three groups according to the WHO 1999 with fasting plasma glucose <6.1 mmol/l and 2-h postload glucose <7.8 mmol/l for normal glucose metabolism (NGM), fasting glucose 6.1–7.0 mmol/l or 2-h glucose 7.8–11.1 mmol/l for impaired glucose metabolism (IGM), and fasting glucose ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l for newly diagnosed diabetes (NDM).

After stratification for glucose metabolism categories, the prevalences of retinopathy, retinopathy worse than minimal NPDR, and hard exudates were calculated. The prevalence of retinopathy was studied in approximate tertiles (based on the total study population distribution) of blood pressure, BMI, and cholesterol and triglyceride concentrations, separately in each glucose metabolism category. By logistic regression analysis, age- and sex-adjusted odds ratios for retinopathy were calculated for categories of glucose metabolism compared with NGM. Subsequently, age- and sex-adjusted odds ratios were calculated for tertiles of blood pressure, BMI, total cholesterol, and triglyceride concentrations in separate models, with the lowest tertile as the reference category. In this analysis, individuals with diabetes (NGM and KDM) and without diabetes (NGM and IGM) were taken together, with adjustment for IGM in the nondiabetic group and for KDM in the diabetic group. We tested for possible interactions of blood pressure, lipids, and BMI with the glucose metabolism categories. Finally, associations of retinopathy, retinopathy worse than minimal NPDR, and retinopathy with hard exudates, respectively, with blood pressure, choles-

Table 1—*General and ophthalmologic characteristics of the study population*

	NGM	IGM	NDM	KDM
n	256	177	115	78
Age (years)	63.3 ± 7.4	64.2 ± 7.3	65.7 ± 6.6	65.5 ± 6.8
Sex (% female)	51	49	51	62
Fasting glucose (mmol/l)	5.3 ± 0.4	6.0 ± 0.5	8.2 ± 2.9	10.6 ± 3.7
2-h glucose (mmol/l)	5.6 ± 1.4	8.6 ± 1.4	14.4 ± 5.6	15.8 ± 4.9*
HbA$_{1c}$ (%)	5.3 ± 0.5	5.6 ± 0.5	6.6 ± 1.7	7.8 ± 1.6
Total cholesterol (mmol/l)	6.6 ± 1.2	6.7 ± 1.1	6.5 ± 1.3	6.5 ± 1.3
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.3 ± 0.4†	1.1 ± 0.3	1.2 ± 0.3†
LDL cholesterol (mmol/l)	4.6 ± 1.1‡	4.6 ± 1.0§	4.4 ± 1.2‖	4.3 ± 0.9¶
Triglycerides (mmol/l)	1.3 (1.0–1.8)	1.6 (1.2–2.2)	2.0 (1.4–2.8)	1.9 (1.3–2.8)†
Systolic BP (mmHg)	133 ± 18	143 ± 20	145 ± 17	144 ± 21
Diastolic BP (mmHg)	81 ± 10	84 ± 10	84 ± 9	82 ± 11
% With antihypertensives	17	31	34	51
WHR	0.89 ± 0.08†	0.93 ± 0.09	0.95 ± 0.08‡	0.94 ± 0.07†
BMI (kg/m^2)	25.9 ± 3.2	27.5 ± 3.7	28.7 ± 4.0	28.8 ± 5.1†
Retinopathy (%)	9	11	13	34†
>Minimal NPDR (%)	1	2	0	8†
Hard exudates (%)	2	6	5	13†

Data are means or % ± SD and median (interquartile range) for triglycerides. BP, blood pressure; >Minimal NPDR, retinopathy worse than minimal nonproliferative diabetic retinopathy. *Subjects with diet only ($n = 12$); number of missing subjects: †1, ‡2, §4, ‖9, ¶7.

terol, triglycerides, BMI, and WHR as continuous variables were analyzed by logistic regression separately, after adjusting for age, sex, and the categories of glucose metabolism. Triglyceride levels were log-transformed for this analysis, because of its skewed distribution. Therefore, odds ratios for triglycerides were calculated per 50% increase of serum level. In all analyses SPSS 9.0 was used. P values <0.05 are considered to be statistically significant, and all odds ratios are presented with corresponding 95% confidence intervals.

RESULTS — Table 1 shows the main characteristics of our study population in the four categories of glucose metabolism. The prevalence of retinopathy increased from 9% in individuals with NGM to 13% in individuals with NDM and was significantly higher (34%) among individuals with KDM. Only five individuals had symptoms of proliferative retinopathy or retinopathy with photocoagulation scars. The prevalence of retinopathy with hard exudates was 2% in those with NGM, 5–6% in those with IGM or NDM, and 13% in subjects with KDM (Table 1). After adjustment for age and sex, the odds ratios for the presence of retinopathy were 1.23 (95% CI 0.66–2.31), 1.42 (0.71–2.84), and 4.72 (2.50–8.93) in IGM, NDM, and KDM, respectively, compared with NGM.

Figure 1 shows the prevalence of retinopathy in categories of systolic blood pressure, total cholesterol and triglyceride concentrations, and BMI after stratification for glucose metabolism category. The prevalence of retinopathy was associated with systolic blood pressure. Especially in NGM and KDM groups, we established a positive trend (P values for trend 0.05 and 0.07, respectively; Fig. 1A). The results for diastolic blood pressure were similar (data not shown). We found a positive association of total and LDL cholesterol with retinopathy, especially in the IGM and NDM groups (P values for trend 0.01 and 0.31, respectively, for cholesterol; Fig. 1B; data for LDL cholesterol not shown but similar). Positive trends in the prevalence of retinopathy for BMI and triglyceride levels were less consistent in the different glucose metabolism groups (Figs. 1C and 1D).

Logistic regression analysis showed that in individuals with (but also in individuals without) diabetes, the highest risks for retinopathy were present in the highest tertiles of blood pressure and total cholesterol and triglyceride concentration (Table 2). Actual blood pressure, but not the use of antihypertensives, was positively associated with retinopathy. Associations of lipid levels and blood pressure with retinopathy were somewhat stronger in individuals without diabetes than in individuals with diabetes. BMI was posi-

tively associated with retinopathy in individuals with diabetes.

Because the associations between prevalence of retinopathy and risk factors were similar in most categories of glucose metabolism and no consistent significant interactions were observed, we subsequently combined all glucose metabolism categories (Table 3). After adjustment for age, sex, glucose metabolism category, and use of antihypertensive medication, the odds ratios for retinopathy per 1 SD increase of systolic or diastolic blood pressure were 1.48 and 1.39, respectively. Odds ratios were even higher when we considered retinopathy worse than minimal NPDR. Use of antihypertensive medication was positively associated with retinopathy worse than NPDR, although not statistically significant. An increase of total or LDL cholesterol, triglyceride levels, or BMI was associated with elevated risks for retinopathy as well. Lipid levels and BMI, however, were not associated with retinopathy worse than minimal NPDR. Systolic and diastolic blood pressure, as well as total and LDL cholesterol, were positively associated with the presence of retinopathy with hard exudates; all with odds ratios of 1.6 per SD increase (Table 3). HDL cholesterol and WHR, however, did not show a clear relationship with retinopathy. Finally we combined glucose metabolism categories, systolic blood pressure, use of antihyper-
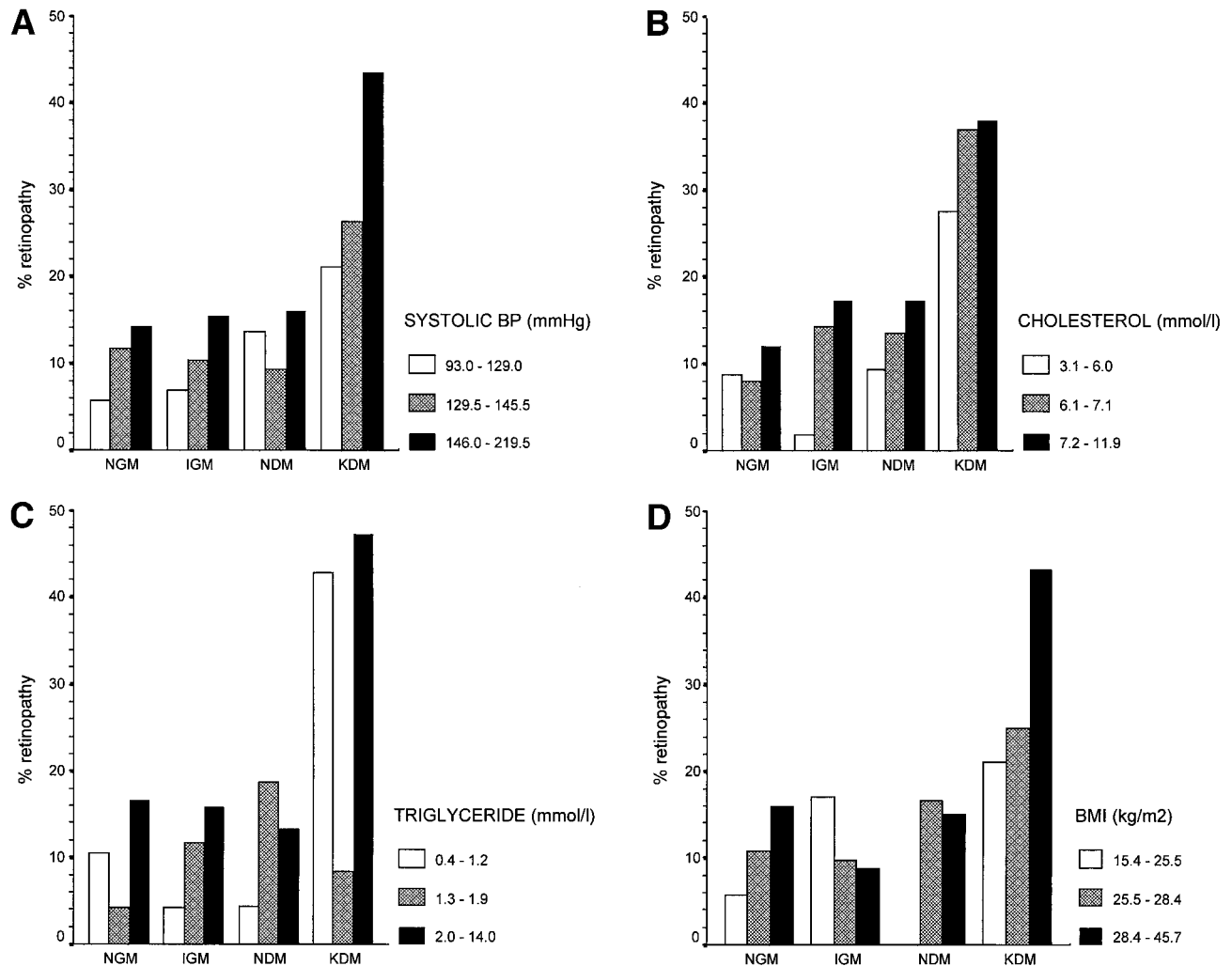
Figure 1—*Prevalence of retinopathy among tertiles of systolic blood pressure (A), total cholesterol (B), triglycerides (C), and BMI (D), stratified for glucose metabolism.*

tensive medication, BMI, and total cholesterol and triglyceride levels in one model, in which we adjusted for age and sex (data not shown). Both KDM and systolic blood pressure were significantly and independently associated with retinopathy. BMI and triglyceride and cholesterol concentrations did not reach statistical significance, but the odds ratios were only slightly lower than in the age-, sex-, and glucose metabolism category–adjusted model of Table 3.

CONCLUSIONS — This population-based cross-sectional study showed that, in addition to glycemic variables, blood pressure, BMI, and cholesterol and triglyceride concentrations are associated with retinopathy as well.

Our study had some limitations. It is well known that volunteers who participate in a population study are generally healthier than nonparticipants. Therefore, we may have underestimated the true prevalence of retinopathy. We combined findings of funduscopy with those of fundus photography to enhance the sensitivity. Fundus photography has been shown to be valuable in detecting early retinopathy, while on the other hand, lesions outside the two central fundus fields and small lesions on 45-degree fundus photographs might be missed (19,20). Therefore, the two methods are complementary.

In the present study, the prevalence of retinopathy among non-KDM individuals was higher than that reported in the Californian Rancho Bernando and Finnish Oulu Studies and in Pima Indians, in which prevalences <4% were reported (12–14). The prevalence of retinopathy

among 3,654 subjects without diabetes aged ≥45 years in the Blue Mountains Eye Study was similar to that in our study (9.8%) (10). The prevalence of retinopathy in the Beaver Dam Eye Study population without diabetes was 7.8%, while among Hispanic Americans without diabetes aged ≥40 years, the prevalence was 17.5% (9,11). Differences between studies may be due to differences in population characteristics (like age and ethnicity), techniques and definitions used to detect retinopathy, and the definition of diabetes. In our study, individuals with only one to three microaneurysms or dot hemorrhages were already considered to have retinopathy, because even one or two microaneurysms have been reported to be predictive for progression of retinopathy (21). Indeed the prevalence of retinopathy worse than minimal NPDR

Table 2—*Odds ratios for retinopathy in persons without diabetes (NGM and IGM) and with diabetes (NDM and KDM) for each risk factor separately*

Risk factor	No diabetes	Diabetes
Age (per 10 years)	1.01 (0.66–1.55)	1.31 (0.77–2.22)
Sex (female vs. male)	1.34 (0.71–2.51)	1.50 (0.74–3.05)
Systolic BP* (mmHg)		
93–129	1	1
129.5–145.5	2.03 (0.87–4.77)	0.93 (0.30–2.87)
146–219.5	3.01 (1.24–7.28)	1.85 (0.69–4.99)
Use of antihypertensives	0.76 (0.34–1.66)	0.90 (0.42–1.93)
Diastolic BP* (mmHg)		
52.5–78	1	1
78.5–85.5	1.95 (0.82–4.63)	0.66 (0.25–1.79)
86–127	2.63 (1.13–6.12)	1.80 (0.74–4.38)
Use of antihypertensives	0.79 (0.36–1.72)	0.87 (0.40–1.89)
Total cholesterol (mmol/l)		
3.1–6.0	1	1
6.1–7.1	1.85 (0.77–4.48)	1.47 (0.59–3.63)
7.2–11.9	2.61 (1.10–6.21)	1.76 (0.69–4.49)
Triglycerides (mmol/l)		
0.4–1.2	1	1
1.3–1.9	0.82 (0.36–1.88)	0.65 (0.21–2.03)
2.0–14.0	2.24 (1.03–4.91)	1.52 (0.57–4.04)
BMI (kg/m^2)		
15.4–24.5	1	1
25.5–28.4	1.14 (0.54–2.45)	2.55 (0.71–9.11)
28.4–45.7	1.27 (0.57–2.83)	3.52 (1.05–11.8)

Data are odds ratios (95% CI) among tertiles of blood pressure (BP), lipids, and BMI, related to the lowest tertile; adjusted for age and sex (age and sex not adjusted), for IGM in no diabetes and for KDM in diabetes. *For blood pressure additionally adjusted for use of antihypertensives.

ing that blood pressure is also associated with retinopathy in individuals with NGM (Fig. 1). Antihypertensive medication was not associated with higher risk of retinopathy. In contrast, retinopathy worse than minimal NPDR did show a positive association, although not statistically significant (Table 3). Possibly these more severe levels of retinopathy are due to long-lasting hypertension, resulting in current use of antihypertensives. Furthermore, we showed that retinopathy, and hard exudates in retinopathy in particular, are related to elevated serum (LDL) cholesterol levels, which supports earlier results from diabetic patients in the Wisconsin Epidemiologic Study of Diabetic Retinopathy and the Early Treatment Diabetic Retinopathy Study, and expands these findings to individuals without diabetes (6,7). Lipid lowering may have beneficial effects on ocular morbidity, as has been mentioned before in an above-mentioned study with diabetic patients (7). Associations between triglyceride levels or BMI and retinopathy, as observed in this study, were reported among type 1 diabetic patients in the EURODIAB Study (8). Other studies, however, showed no statistically significant or even inverse associations between BMI and retinopathy (1–3,12).

This cross-sectional study suggests that retinopathy is a multifactorial microvascular complication, involving not only glucose metabolism but also lipid metabolism, blood pressure, and BMI. Increased capillary permeability, microaneurysm formation, capillary closure, and retinal ischemia are probably due to the combined effects of the various risk factors.

was only 0–2% in individuals without KDM. Small hemorrhages could mimic nonspecific early symptoms of hypertensive vascular changes. In diabetic subjects these lesions are usually classified as retinopathy. Such lesions were observed in nondiabetic individuals in our study and in other studies and indicate that risk factors other than hyperglycemia may also

play a role (9–14). Blood pressure, but not lipids or (central) obesity, however, appears to be a risk factor for retinopathy worse than minimal NPDR.

In the UKPDS, associations were found between retinopathy and blood pressure in subjects with a fasting glucose level of at least 6.1 mmol/l (3–5). Our study extends this observation by show-

Table 3—*Odds ratios for retinopathy, retinopathy worse than minimal nonproliferative diabetic retinopathy, and hard exudates for each risk factor separately*

Risk factor	Retinopathy	> Minimal NPDR	Hard exudates
Systolic BP (19.5 mmHg)*	1.48 (1.17–1.86)	2.14 (1.21–3.80)	1.60 (1.13–2.25)
Use of antihypertensives	0.85 (0.50–1.47)	1.84 (0.51–6.61)	0.75 (0.33–1.70)
Diastolic BP (10.0 mmHg)*	1.39 (1.10–1.76)	1.84 (1.08–3.12)	1.62 (1.16–2.26)
Use of antihypertensives	0.89 (0.52–1.51)	2.06 (0.59–7.23)	0.79 (0.35–1.78)
Total cholesterol (1.19 mmol/l)	1.29 (1.02–1.62)	1.02 (0.57–1.85)	1.59 (1.13–2.23)
HDL cholesterol (0.36 mmol/l)	0.98 (0.75–1.28)	1.05 (0.56–1.96)	1.03 (0.69–1.53)
LDL cholesterol (1.05 mmol/l)	1.25 (0.98–1.59)	1.12 (0.58–2.13)	1.63 (1.12–2.37)
Triglycerides (50%)	1.24 (1.03–1.51)	0.96 (0.61–1.49)	1.23 (0.93–1.62)
BMI (3.96 kg/m^2)	1.31 (1.04–1.66)	1.05 (0.59–1.88)	0.98 (0.69–1.40)
WHR (0.0864)	1.15 (0.84–1.57)	1.15 (0.52–2.56)	1.40 (0.87–2.27)

Odds ratios (95% CI) per 1 SD increase (between brackets) or per 50% increase (triglycerides) after adjustment for age, sex, and glucose metabolism category. *For blood pressure additionally adjusted for use of antihypertensives; BP, blood pressure.

Subjects with cardiovascular risk factors, like elevated blood pressure, BMI, or serum lipid levels, should be given more frequent ophthalmologic examinations.

Alternatively, diagnosis of abovementioned vascular retinal changes should lead to further examination for risk factors like hypertension, dyslipidemia, and accompanying atherosclerosis. Thus, appropriate (combined) therapy in an early phase not only prevents symptomatic cardiovascular morbidity and mortality, but may also contribute to the prevention of retinopathy.

In conclusion, the present study shows that besides hyperglycemia, also blood pressure, obesity, and elevated serum cholesterol and triglyceride levels are associated with (prevalent) retinopathy.

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