Original Articles

Retinopathy, Glucose, and Insulin in an Elderly Population

The Rotterdam Study

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We studied the association between retinopathy and glucose metabolism in a population-based study of elderly men and women. Glucose metabolism was assessed by serum fructosamine and a nonfasting oral glucose tolerance test, and retinopathy was evaluated by fundus photography. Retinopathy was present in 296 of 6,191 subjects examined (4.8%; 120 men and 176 women). Serum glucose and fructosamine levels were higher in subjects with retinopathy compared with those without (8.4 vs. 6.8 mmol/l and 329.8 vs. 308.5 μmol/l, respectively, $P < 0.001$). Two-hour postload insulin levels and insulin resistance, assessed by the ratio of postload insulin over postload glucose level, did not differ between the two groups. These associations were similar in men and women and in subjects with and without diabetes and did not change after adjustment for body mass index or systolic blood pressure. Within the group of subjects who had retinopathy, serum glucose was significantly associated with the number of hemorrhages. These findings suggest that the presence and severity of retinopathy are associated with higher serum glucose levels, both in subjects with and without diabetes. *Diabetes* 44:11–15, 1995

A description of diabetes is found in Hindu manuscripts of the 5th century BC (1), but retinal hemorrhages and cotton-wool spots were first described in diabetes patients in 1856 (2). Studies in animals (3) and diabetes patients (4) have shown that a longer duration of the disease and a lower level of glycemic control are associated with a higher prevalence of diabetic retinopathy. Trials in patients with insulin-dependent diabetes mellitus (IDDM) have shown that improved glycemic control lowers the incidence of diabetic retinopathy (5). Consequently, it has been proposed that retinopathy is caused by hyperglycemia and not by other metabolic disturbances (6). As serum glucose level and the prevalence of non-insulin-dependent diabetes mellitus (NIDDM) increase with age (7), a high prevalence of diabetic retinopathy may be expected in elderly people. Until now, few population-based studies of retinopathy have included subjects without diabetes.

We evaluated the presence of retinopathy by fundus photographs in all participants of the population-based Rotterdam Study, while the glucose metabolism was assessed by serum fructosamine and an oral glucose tolerance test. This study describes the associations of retinopathy with serum glucose, fructosamine, and insulin resistance in 6,191 elderly nonhospitalized men and women.

RESEARCH DESIGN AND METHODS

The Rotterdam Study is a population-based, follow-up study of determinants of chronic disabling diseases in the elderly. All inhabitants of a suburb of Rotterdam, aged ≥55 years, were invited to participate. The design of the study and its objectives have been published previously (8). The participants attended the research center for several measurements. These included anthropometry, blood pressure measurements, and an extensive ophthalmological examination. In addition, an oral glucose tolerance test was performed. Informed consent was obtained from all subjects, and the study was approved by the medical ethics committee of the Erasmus University Medical School.

The ophthalmological examination was part of the measurements in the Rotterdam Study from March 1990 to the end of the baseline examination in July 1993. Totally, 7,983 subjects participated in the Rotterdam Study (response rate 78%), of whom 7,129 completed the examinations at the research center. In 6,251 people, it was possible to evaluate at least one fundus photograph. Significantly more women than men had absent or ungradable fundus photographs, and they were older than the remaining study population (75.3 vs. 68.9 years, $P < 0.001$). However, after adjustment for age and gender, the serum glucose level and the prevalence of diabetes and hypertension did not differ between those with and without gradable fundus photographs. Data on eyes with retinal vein occlusion or age-related macular degeneration were excluded. The analyses presented here were restricted to the remaining 6,191 people.

Retinopathy was assessed on fundus photographs. In each participant, both eyes were dilated with 0.5% tropicamide and 5% phenylephrine. After an average period of 45 min, two 35° color slides (Kodak Ektachrome 64 ASA, Topcon TRV-50VT fundus camera) centered on the macular area were taken of each eye (Diabetic Retinopathy Study standard field 2). The slides were examined on a portable stereo viewer with fluorescent back light (Philips PL-S 9W/84; 4,000°K) with 5× magnification. Combined with a 2.5× magnification of the fundus

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; sBP, systolic blood pressure; dBP, diastolic blood pressure; BMI, body mass index; CI, confidence interval.

camera, the total magnification was ~12.5×. The graders were blinded for the status of the glucose metabolism of the participants. The presence of cotton-wool exudates and the presence and number of dot/blot hemorrhages were graded, without differentiation between microaneurysms and hemorrhages. In an additional procedure, photographs with laser photocoagulation scars were categorized into either diabetic retinopathy or other diseases (most often retinal vein occlusion), using the photograph of the other eye and available clinical data. Retinopathy was defined as the presence of one or more hemorrhages/microaneurysms and/or cotton-wool spots (which corresponds to level 15–51 of the modified Airlie House classification [9]) or laser coagulation scars due to diabetic retinopathy. The eye with the most severe retinopathy was used in the analyses. The slides were graded by one of three graders. All questionable lesions were discussed and adjudicated by two of the authors (J.R.V., P.T.V.M.d.J.). A reproducibility study in 29 subjects revealed a κ of 0.71 between the observers and 0.86 within observers.

The participants came to the research center throughout the day. They were asked for the time of last food intake. Blood was drawn by venipuncture and allowed to coagulate for 30 min. Subsequently, serum was separated by centrifugation and quickly frozen in liquid nitrogen. Standard clinical chemistry measurements were performed in the stored serum, which included the measurement of fructosamine by test combination 1054686 (Boehringer Mannheim, Mannheim, Germany) during the first 2 years of the study (n = 4,458). Subjects not taking antidiabetes medication received a glucose drink of 200 ml, which contained 75 g glucose. Two hours later a second blood sample was obtained, which was processed in the same way as the random specimen. Glucose levels were measured in both samples by the glucose hexokinase method, while insulin was measured by radioimmunoassay (Medgenix, Brussels, Belgium) in the postload sample only. Diabetes was defined as use of antidiabetes medication and/or random or postload glucose value of ≥11.1 mmol/l. Insulin resistance was assessed by the ratio of 2-h postload serum insulin over postload serum glucose level.

Blood pressure was measured with a random-zero sphygmomanometer, and the mean of two measurements was used in the analyses. Hypertension was defined as systolic blood pressure (sBP) ≥160 mmHg or diastolic blood pressure (dBP) ≥95 mmHg or use of antihypertensive medication. For body mass index (BMI), weight divided by the square of height (kg/m^2) was used.

Statistical analysis. Mean levels of serum glucose, fructosamine, insulin, and insulin resistance were compared between subjects with and without retinopathy, adjusted for age by analysis of covariance. The analyses were performed in the whole population and in men and women separately and reported with corresponding 95% confidence intervals (CIs). Also, separate analyses were performed in those subjects who had not eaten for at least 3 h and in subjects with and without diabetes and hypertension. Associations between variables were evaluated using linear and logistic regression analysis. Odds ratios were calculated as an approximation of the relative risk. Adjustments were made for age, BMI, and sBP, if appropriate.

RESULTS

The baseline characteristics of the study population are given in Table 1. Retinopathy was found in 296 subjects (120 men and 176 women). Women were slightly older than men. After adjustment for age, random serum glucose and postload insulin levels were significantly higher in women compared with men. This was also found for dBP level and hypertension, but not for the presence of diabetes and retinopathy.

In Table 2, age-adjusted mean values of some metabolic parameters are given for subjects with and without retinopathy. Serum glucose and fructosamine levels were increased in subjects with retinopathy. The same differences were found in subjects with and those without diabetes. In the 128 men who had not eaten for at least 3 h before the venipuncture (fasting group), the age-adjusted glucose levels in those with and without retinopathy were 10.3 and 6.2 mmol/l, respectively ($P < 0.001$). In the 181 fasting women these values were 9.5 and 6.2 mmol/l ($P < 0.001$). When the analyses were performed in men and women separately, the results were essentially the same.

TABLE 1
Baseline characteristics of the study population

	Men	Women	Total
n	2,522	3,669	6,191
Age (years)	67.9 ± 8.0	69.4 ± 9.1	68.9 ± 8.8
Random glucose (mmol/l)	7.1 ± 2.6	6.8 ± 2.7	6.9 ± 2.7
Fructosamine (μmol/l)	309 ± 55	310 ± 50	310 ± 52
Postload insulin (pmol/l)	334 ± 295	399 ± 327	373 ± 316
Insulin resistance (pmol/mmol)	50.4 ± 39.6	55.8 ± 38.4	53.4 ± 39.0
Diabetes (%)	10.2	10.2	10.2
sBP (mmHg)	138.6 ± 21.9	139.9 ± 22.8	139.3 ± 22.4
dBP (mmHg)	74.5 ± 11.6	73.2 ± 11.5	73.7 ± 11.6
Hypertension (%)	25.7	32.1	29.5
Hemorrhages (%)	4.6	4.5	4.6
Diabetes laser coagulation scars (%)	0.1	0.3	0.2
Retinopathy (%)	4.8	4.8	4.8

Data are means ± SD. Postload insulin levels were only measured in subjects not taking antidiabetes medication (n = 5,049). Insulin resistance is the ratio of postload insulin over postload glucose. Diabetes was defined as the use of antidiabetic medication, a random glucose value ≥11.1 mmol/l, or a postload glucose value ≥11.1 mmol/l. Hypertension was defined as the use of antihypertensive medication, sBP ≥160 mmHg, or dBP ≥95 mmHg. Hemorrhages were defined as one or more dot/blot hemorrhages/microaneurysms or cotton-wool spots without retinal vein occlusion or macular degeneration. Retinopathy was defined as hemorrhages or diabetes laser coagulation scars.

Hypertension was more prevalent and blood pressure was higher in subjects with retinopathy compared with those without (age- and gender-adjusted levels were 146/75 and 138/74 mmHg, respectively). The differences in the serum glucose and fructosamine levels remained if the analyses were stratified to the presence of hypertension (Table 3). The differences in the postload insulin levels were only present in women with hypertension (Table 3).

The risk of retinopathy significantly increased with an increase in the serum glucose level. The age-adjusted relative risk in the whole study population was 1.13 per mmol/l (95% CI 1.10–1.16). When subjects with diabetes were excluded, the relative risk was 1.18 (95% CI 1.08–1.30). After further adjustment for sBP, the corresponding relative risks were 1.13 and 1.17, respectively. The postload insulin level was not associated with retinopathy: the relative risk was 1.00/50 pmol/l. The same result was found when the ratio of postload insulin over glucose was used. After adjustment for age, the relative risk of diabetes for the presence of retinopathy was

TABLE 2
Age-adjusted mean values of some metabolic parameters in subjects with and without retinopathy

	Retinopathy		Difference (95% CI)
	Absent	Present	
Random glucose (mmol/l)	6.8	8.4	1.6 (1.3–1.9)
Fructosamine (μmol/l)	309	330	21 (14–28)
Postload insulin (pmol/l)	370	422	52 (8–96)
Insulin resistance (pmol/mmol)	53.4	58.2	4.8 (−1.0–10.2)
Diabetes (%)	9.4	26.1	16.8 (11.6–21.9)
Hypertension (%)	28.7	44.1	15.4 (9.5–21.3)

Postload insulin level was measured 2 h after an oral glucose load of 75 g and only in subjects not taking antidiabetes medication. Insulin resistance is the ratio of postload insulin over postload glucose.

TABLE 3
Age-adjusted mean values of the glucose metabolism in subjects with and without retinopathy by the presence of diabetes and hypertension

	No hypertension			Hypertension		
	Retinopathy			Retinopathy		
	Absent	Present	Difference (95% CI)	Absent	Present	Difference (95% CI)
No diabetes						
Random glucose (mmol/l)	6.3	6.6	0.3 (0.1–0.5)	6.5	6.8	0.3 (0.1–0.7)
Fructosamine (μmol/l)	302	306	4 (−4–13)	305	299	−6 (−16–3)
Postload insulin (pmol/l)	338	359	21 (−33–75)	397	462	65 (−4–134)
Diabetes						
Random glucose (mmol/l)	12.4	13.9	1.5 (−0.4–3.4)	10.9	12.8	1.9 (0.5–3.4)
Frustosamine (μmol/l)	372	431	59 (23–95)	350	396	46 (17–76)
Postload insulin (pmol/l)	583	474	−109 (−509–291)	636	745	109 (−192–410)

Postload insulin level was measured 2 h after an oral glucose load of 75 g and only in subjects not taking antidiabetes medication.

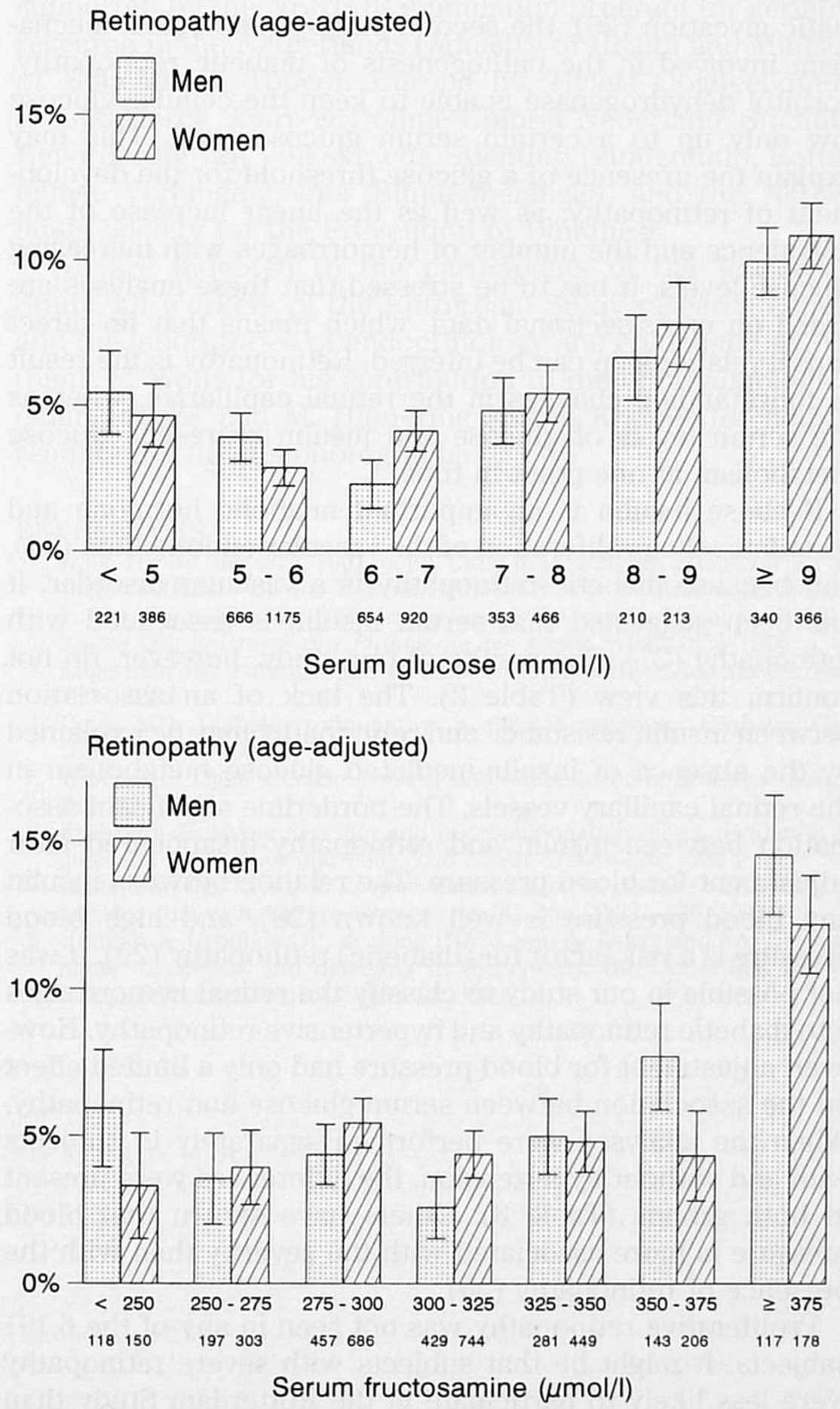

FIG. 1. The prevalence of retinopathy, adjusted for age, by categories of serum glucose and fructosamine. Figures at the bottom of each bar indicate the number of subjects in that category. Error bars indicate SE.

3.13 (95% CI 2.37–4.14). For men and women, the relative risks were 2.94 (95% CI 1.87–4.60) and 3.21 (95% CI 2.24–4.59), respectively. Further adjustments for BMI or sBP did not substantially alter these risk estimates. In spite of the high risk of diabetes, most cases of retinopathy in the general population occur in subjects without diabetes (73.9%, Table 2). The reason is that subjects with diabetes are a minority of the study population (10.2%, Table 1).

In Fig. 1, the prevalence of retinopathy, adjusted for age, is given by different levels of the serum glucose and fructosamine. The figure suggests that the risk of retinopathy increased linearly when the serum glucose was >6 mmol/l. Within the fructosamine distribution >350 μmol/l, a linear increase of retinopathy was also found (data not shown). When the analyses were restricted to subjects who did not use antidiabetes medication, the same associations were found.

All subjects with laser coagulation scars used antidiabetes medication and had higher glucose and fructosamine levels than those with hemorrhages. Within subjects who had at least one hemorrhage/microaneurysm, the number of hemorrhages was significantly associated with the serum glucose level. In men, the regression coefficient was 0.41 per mmol/l (SE 0.13, $P < 0.01$) after adjustment for age, whereas in women, a coefficient of 0.18 per mmol/l (SE 0.06, $P < 0.01$) was found. The coefficients did not change after adjustment for BMI or sBP.

DISCUSSION

Retinopathy was found in 4.8% of the participants in the Rotterdam Study and was associated with higher serum glucose and fructosamine levels, but not with insulin resistance. These associations were similar in men and women with and without diabetes and did not change after adjustment for age, BMI, or sBP. The prevalence increased linearly in subjects with a random serum glucose level >6 mmol/l. Among subjects who had retinopathy, a significant association was present between serum glucose level and the number of hemorrhages.

The association between serum glucose and retinopathy is well known from clinical studies among diabetic patients, but there are few data from population-based studies that also include nondiabetic subjects. The results presented here are based on a population of nonhospitalized subjects aged ≥55 years, both with and without diabetes. The approach in our population-based study has certain limitations when

compared with a clinical study. For the assessment of retinopathy, fundus photographs of 35° from the macular area were used. There is ample evidence that fundus photography is superior over an examination by an ophthalmologist to detect diabetic retinopathy (10). The graders of the fundus photographs were blinded to all characteristics of the participants. Given the high reproducibility, it is unlikely that the results can be explained by misclassification in the assessment of retinopathy. Usually, more than one photograph is taken to cover an extended area of the retina, whereas stereo pictures are more liable to detect macular edema. Findings in a study that compared 30° fundus photographs of Diabetic Retinopathy Study fields 1 and 2 with all seven standard fields to detect any retinopathy showed a sensitivity of 0.87 (11). This limitation of the procedure used in the Rotterdam Study may have introduced only false-negative misclassification. As a consequence, the reported associations are likely to represent an underestimation.

In the Rotterdam Study, blood samples were obtained in a nonfasting state. However, the associations with the random glucose levels were essentially the same, both after adjustment for the time since the last meal and after restriction of the analyses to those subjects who had their last meal more than 3 h before the venipuncture. This indicates that recent food intake does not obscure the relation between serum glucose and retinopathy. Moreover, the same associations were found using serum fructosamine, which is not influenced by the time of last food intake. It is not possible, however, to compare the glucose levels measured in this study with those reported in studies based on a fasting blood sample. Insulin resistance was assessed by the insulin and glucose levels 2 h after an oral glucose load. The ratio of insulin over glucose after an oral glucose load given in the fasting state is a good measure of insulin resistance (12). We reported previously that nonfasting postload insulin levels are similar to fasting postload levels (13).

The duration of diabetes is associated with retinopathy. Furthermore, the prevalence of retinopathy has been shown to increase with age, even after adjustment for duration of disease (14). The importance of age was confirmed in the Beaver Dam Study (Wisconsin), in which the prevalence of retinopathy in elderly IDDM patients was about the same as in NIDDM patients of the same age (15). Because serum glucose also increases with age (16), all relations in this study were adjusted for age.

The prevalence of retinopathy increased linearly with an increase of serum glucose and fructosamine levels. Fructosamine reflects the average serum glucose level of the last 3 days (17). Importantly, when subjects with diabetes were excluded from the analyses, the same associations were found. The risk associated with increasing serum glucose level for retinopathy found in this study was of the same magnitude as observed in the elderly population of the Beaver Dam Study (15). However, the frequency of retinopathy found in the latter study was higher than found in the Rotterdam Study. This difference may be explained by the fact that in the Beaver Dam Study, a larger area of the retina was photographed than in the Rotterdam Study and stereographic pictures were used. In the elderly nondiabetic study population in Rancho Bernardo (California), the prevalence of retinopathy was lower than in the Rotterdam Study population, and there was no association found with the serum glucose level (18). In that study, only a single photograph, taken with a 45° nonmydriatic camera, of the foveal area was used to detect retinopathy, which might account for these differences. Apart from the difficulties associated with the assessment of nonmydriatic photographs, a number of early small lesions may be missed on 45° fundus photographs compared with photographs using a smaller angle.

In several population-based studies of diabetic patients, an association has been found between serum glucose level and the severity of retinopathy (19). Findings in trials conducted in IDDM patients aiming at increased metabolic control have suggested that improved glucose control leads to a decrease of the incidence and progression of retinopathy (20,21). The central role of serum glucose in the etiology of diabetic retinopathy is supported by findings in animals and biochemical studies using cultures of retinal pericytes (3,22). Diabetic retinopathy is a vascular disorder, a thickening of the basement membrane. The uptake of glucose by the pericytes of the retinal capillaries is not insulin mediated (23). As a consequence, with an increasing serum glucose level, the intracellular glucose level increases. This causes a stimulation of the polyol pathway, leading to the accumulation of sorbitol in the cells of the capillary wall (24). The increased glucose levels also cause an acceleration of the nonenzymatic glycation (25), the second pathophysiological mechanism involved in the pathogenesis of diabetic retinopathy. Sorbitol dehydrogenase is able to keep the cellular glucose low only up to a certain serum glucose level. This may explain the presence of a glucose threshold for the development of retinopathy, as well as the linear increase of the prevalence and the number of hemorrhages with increasing glucose levels. It has to be stressed that these analyses are based on cross-sectional data, which means that no direct causal relationship can be inferred. Retinopathy is the result of longstanding changes in the retinal capillaries, whereas the serum levels of glucose and insulin represent glucose metabolism at one point in time.

Because insulin is an important anabolic hormone and stimulates the proliferation of the vascular endothelium (26), and because diabetic retinopathy is a vascular disorder, it has been suggested that serum insulin is associated with retinopathy (27). The results of our study, however, do not confirm this view (Table 2). The lack of an association between insulin resistance and retinopathy may be explained by the absence of insulin-mediated glucose metabolism in the retinal capillary vessels. The borderline significant association between insulin and retinopathy disappeared after adjustment for blood pressure. The relation between insulin and blood pressure is well known (28), and high blood pressure is a risk factor for (diabetic) retinopathy (29). It was not possible in our study to classify the retinal hemorrhages into diabetic retinopathy and hypertensive retinopathy. However, adjustment for blood pressure had only a limited effect on the association between serum glucose and retinopathy. When the analyses were performed separately in subjects with and without hypertension, the differences were present in both groups (Table 3). Others have shown that blood pressure is more associated with the severity than with the presence of retinopathy (30).

Proliferative retinopathy was not seen in any of the 6,191 subjects. It might be that subjects with severe retinopathy were less likely to participate in the Rotterdam Study than subjects without retinopathy of the same age. In addition, the limited area visualized on the fundus photographs may have

contributed to the absence of proliferative retinopathy, although new vessels most frequently develop within 45° of the optic disk (4). Also, the progression from background retinopathy to proliferative retinopathy is less common in the elderly, especially neovascularization of the disk (31,32). Moreover, current clinical practice in the Netherlands is to treat macular edema and proliferative retinopathy with laser photocoagulation (33). As a consequence, some of the subjects with laser coagulation scars will have had proliferative retinopathy in the past. Subjects with diabetes laser photocoagulation scars had higher serum glucose and fructosamine levels, which suggest a more severe form of diabetic retinopathy.

In conclusion, in this nonhospitalized elderly population we found that the presence and severity of retinopathy were associated with increased serum glucose and fructosamine levels. These linear associations were present in diabetic and nondiabetic subjects. There was no association with serum insulin levels obtained after an oral glucose load.

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