Hyperhomocysteinemia Is Associated With the Presence of Retinopathy in Type 2 Diabetes Mellitus

The Hoorn Study

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Background: Retinopathy is the leading cause of blindness among patients with type 2 diabetes mellitus (DM). Hyperhomocysteinemia is a recently recognized risk factor for cardiovascular disease, independent of established risk factors.

Objective: To study the association between the homocysteine level and retinopathy among subjects with and without DM.

Methods: We studied an age-, sex-, and glucose tolerance–stratified random sample of a 50- to 75-year-old general white population in the Hoorn Study (N=625). Retinal vascular changes (retinopathy) were assessed using ophthalmoscopy and/or fundus photography. Hyperhomocysteinemia was defined as a serum total homocysteine level greater than 16 µmol/L.

Results: The prevalence of retinopathy was 9.8% (28/285) in subjects with normal glucose tolerance, 11.8% (20/169) in those with impaired glucose tolerance, 9.4% (10/106) in those with newly diagnosed type 2 DM, and 32.3% (21/65) in those with known type 2 DM. The prevalence of retinopathy was 10.3% (39/380) in patients without hypertension and 16.3% (40/245) in subjects with hypertension; it was 12.0% (64/534) in subjects with a serum total homocysteine level of 16 µmol/L or less and 16.5% (15/91) in those with a serum total homocysteine level of more than 16 µmol/L. After stratification for DM and adjustment for age, sex, glycosylated hemoglobin, and hypertension, the odds ratio (95% confidence interval) for the relation between retinopathy and hyperhomocysteinemia was 0.97 (95% confidence interval, 0.42-2.82) in patients without DM and 3.44 (95% confidence interval, 1.13-10.42) in patients with DM (P = .08 for interaction).

Conclusion: The findings suggest that hyperhomocysteinemia may be a risk factor for retinopathy in patients with type 2 DM, but probably not in patients without DM.
SUBJECTS AND METHODS

STUDY POPULATION

The Hoorn Study, conducted from 1989 to 1992, is a cross-sectional survey of glucose tolerance and other cardiovascular risk factors in a 50- to 75-year-old general white population. A random sample of all men and women aged 50 to 75 years was drawn from the municipal population registry office of Hoorn, the Netherlands; 2484 subjects participated (response rate, 71%). All subjects, except previously diagnosed diabetic subjects with DM who were treated with oral glucose-lowering agents or insulin, underwent a 75-g oral glucose tolerance test and were classified according to the World Health Organization criteria. A second oral glucose tolerance test (participation rate, 93%) was performed, for reasons of efficiency, in a random subsample (n=1122), stratified by 2-hour glucose values of the first test, age, and sex. Finally, from this subsample another age-, sex-, and glucose tolerance-stratified random sample (n=708) was drawn. The presence of retinal vasculopathy (as defined below) was investigated (n=625; response rate, 88%) by 2 experienced ophthalmologists. The examination included both ophthalmoscopy and fundus photography (detailed below). Glucose tolerance was divided into 4 categories on the basis of the mean of the 2 oral glucose tolerance test results: subjects with normal glucose tolerance (n=285), subjects with impaired glucose tolerance (n=169), subjects with newly diagnosed DM (n=100), and subjects with known DM (n=65). The Hoorn Study was approved by the Ethical Review Committee of the University Hospital Vrije Universiteit, Amsterdam, the Netherlands. Informed consent was obtained from all participants.

OPHTHALMOLOGIC INVESTIGATION

Retinopathy was assessed by ophthalmoscopy and/or fundus photography. In each participant, both eyes were dilated with 0.5% tropicamide and 5% phenylephrine hydrochloride eye drops. After an average period of 13 minutes, indirect and direct ophthalmoscopy (N=625) was carried out by 2 ophthalmologists, and findings regarding the retinal status were reported on standard forms. Thereafter, two 45° standard field, 35-mm black-and-white fundus photographs (Kodak Tri-X 400 ASA; Eastman Kodak, Rochester, NY; Kowa Pro 1 fundus camera; Kowa Optical Industry, Tokyo, Japan) were taken of each eye. Photographs were taken with a green filter (to improve the contrast), centered on the macular area and the optic disc. Fundus photographs of 148 subjects were inadvertently lost. (The fundus photographs were randomly lost with regard to age, sex, hypertension, glucose tolerance category, and serum total homocysteine [tHcy] level of the subjects [data not shown].) Thus, for the present analysis fundus photographs of 477 subjects were available.

Both ophthalmoscopic and fundus photographic findings were graded according to the modified Airlie House classification. The fundus photographs were independently graded by 2 ophthalmologists. The independent judgment of a third ophthalmologist was taken to be decisive in case of disagreement about the grading of retinopathy on the fundus photograph. For the present analysis “the worst eye” of each subject according to ophthalmoscopy or fundus photography was used. Any retinopathy (yes/no) was defined as the presence of 1 or more hemorrhages, microaneurysms, soft or hard exudates, neovascularization, and/or laser coagulation scars in 1 or both eyes. Diabetic retinopathy was defined as presence of 1 or more microaneurysms and/or laser coagulation scars in 1 or both eyes (there were no subjects with neovascularization), regardless of other abnormalities.

MEASUREMENT OF SERUM tHcy LEVEL

Fasting blood samples were centrifuged within 1 hour following collection. Serum samples were stored at −20°C for 6 years. There is good evidence that serum tHcy levels in frozen samples are stable for 10 years or longer. The serum tHcy (free plus protein-bound) level was measured using tri-n-butylphosphate as the reducing agent and ammonium 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate as the thiol-specific fluorochromophore, followed by high-performance liquid chromatography with fluorescence detection. The intra-assay and interassay coefficients are 2.1% and 5.1%, respectively.

OTHER MEASUREMENTS

Subjects were classified as either a current cigarette smoker or nonsmoker. The body mass index was calculated as weight

Continued on next page
(in kilograms) divided by height (in meters), squared. Blood pressure (BP) was measured, in total, as the mean of 4 measurements, performed on 2 different occasions, with a random 0 sphygmomanometer under standardized conditions. Hypertension was defined as a BP of 160 mm Hg or more systolic and/or 95 mm Hg or more diastolic and/or the current use of antihypertensive medication. Fasting and 2-hour postload venous plasma glucose levels were measured with a glucose dehydrogenase method (Merck, Darmstadt, Germany) and the glyco-sylated hemoglobin (HbA1c) level by ion-exchange, high-performance liquid chromatography, using a DM monitoring system (Modular Diabetes Monitoring System; Bio-Rad, Veenendaal, the Netherlands). The fasting serum total cholesterol level was measured by enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany). Hypercholesterolemia was defined as a total cholesterol level of 6.5 mmol/L or higher (≥251 mg/dL) and/or the current use of cholesterol-lowering medication. The serum creatinine level was measured by the modified Jaffe method. Estimation of the serum creatinine clearance was done according to the formula described by Cockcroft and Gault.25 Immunospecific insulin was measured in serum by a double-antibody radioimmunoassay (lot SP21, Lincoln Research, St Louis, Mo). The intraassay coefficient of variation was 6%. The lower limit of sensitivity was 12 pmol/L. Ophthalmologic investigations and laboratory measurements were carried out in a masked fashion for glucose tolerance status and other clinical data.

STATISTICAL ANALYSIS

Variables are presented as mean (SD), number (percentage of the total), or, in case of skewed distribution, median and interquartile range. For age, sex, and glucose tolerance category, standardized prevalence of any retinopathy and hyperhomocysteinemia was calculated, as described previously in detail.15 Briefly, the frequency was determined in 24 strata (age, sex, and glucose tolerance). To assess the standardized prevalence in the original population-based sample (standard, N=2484), the prevalence was calculated from the magnitude of each age, sex, and glucose tolerance category stratum. Coefficients were calculated to assess agreement with regard to

DM; it was 10.3% (39/380) in subjects without hypertension and 16.3% (40/245) in those with hypertension; it was 12.0% (64/534) in subjects with serum tHcy levels of 16 µmol/L or less and 16.5% (15/91) in those with serum tHcy levels higher than 16 µmol/L. The prevalence of diabetic retinopathy was 4.6% (13/285) in subjects with normal glucose tolerance, 5.9% (10/169) in subjects with impaired glucose tolerance, 4.7% (5/106) in subjects with newly diagnosed DM, and 23.1% (15/65) in patients with known DM. Figure 1 shows the prevalence of any retinopathy according to absence or presence of hyperhomocysteinemia (>16 µmol/L) in patients with and without DM. We chose this cutoff value since risk of retinopathy increased markedly above this value among subjects with DM (Table 2).

The median serum tHcy level was 12.2 µmol/L (interquartile range, 10.0-15.3) in men and 10.7 µmol/L (interquartile range, 9.0-13.3) in women. Serum tHcy levels correlated with age (r=0.17; P<.001). After adjustment for age and sex, the serum tHcy level correlated with the serum creatinine level (r=0.4; P<.001), inversely with creatinine clearance (r=-0.3; P<.001), but there was no substantial correlation between the serum tHcy levels and the following variables: systolic BP (r=0.06; P=.1), diastolic BP (r=-0.03; P=.5), body mass index (r=-0.02; P=.7), fasting glucose level (r=-0.07; P=.07), fasting insulin level (r=0.05; P=.2), HbA1c level (r=-0.02; P=.6), serum total cholesterol level (r=0.04; P=.3), or duration of DM in subjects with known DM (r=-0.03; P=0.8).

After adjustment for age and sex, the OR (95% CI) for any retinopathy was 1.37 (1.18-1.59) per percentage of increment of HbA1c level, 1.76 (1.07-2.90) for DM (yes/no), 1.37 (0.97-2.55) for hypertension (yes/no), 1.46

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The OR per 5-µmol/L increment of serum tHcy level was 0.89 (95% CI, 0.60-1.34) in subjects without DM and 1.50 (95% CI, 0.93-2.41) in subjects with DM. Additional adjustment for serum creatinine level, serum creatinine clearance, hypercholesterolemia, current smoking, body mass index, and/or fasting insulin level did not markedly change the results (data not shown).

To reduce the effect of possible misclassification, we repeated the analysis after classifying subjects with only hemorrhages in one or both eyes as having no retinopathy in an additional analysis. After adjustment for age, sex, and HbA1c level, the OR for hyperhomocysteinemia was 1.11 (95% CI, 0.46-2.68) in subjects without DM and 5.28 (95% CI, 1.67-16.67) in subjects with DM, and per 5-µmol/L increment of serum tHcy level it was 0.96 (95% CI, 0.62-1.48) and 1.64 (95% CI, 1.00-2.71), respectively. If diabetic retinopathy (see “Subjects and Methods” section) was taken as the dependent variable, the OR for hyperhomocysteinemia was 1.11 (95% CI, 0.36-3.41) in subjects without DM and 4.45 (95% CI, 1.21-16.37) in subjects with DM, and per 5-µmol/L increment of serum tHcy level it was 0.96 (95% CI, 0.55-1.66) and 1.45 (95% CI, 0.84-2.53), respectively. Additional adjustment of the previous analyses for hypertension or BP revealed similar results (data not shown). Among subjects with DM, after stratification for hypertension and adjustment for age and sex, the OR for hyperhomocysteinemia was 6.00 (95% CI, 0.37-96.80) among subjects with normotension and 4.11 (95% CI, 0.95-17.79) among subjects with hypertension. These ORs did not differ significantly from each other, which suggests that the association between hyperhomocysteinemia and retinopathy is independent of the presence of hypertension.

This population-based study indicates that hyperhomocysteinemia is associated with retinopathy in subjects with type 2 DM, independent of known determinants, ie, DM duration, glycemic level, and hypertension. We found a dose-response relation between the serum tHcy level and retinopathy among subjects with type 2 DM (Table 2). For each 5-µmol/L (about 1 SD) increment in serum tHcy level, the risk of retinopathy rose by about 50% (95% CI, −7 to 141) in the subjects with DM. Hyperhomocysteinemia

Table 1. Characteristics of the Subjects*

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<thead>
<tr>
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<th>Subject With</th>
<th>Subjects With</th>
<th>P†</th>
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<tbody>
<tr>
<td></td>
<td>No Diabetic</td>
<td>Diabetic</td>
<td></td>
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<tr>
<td></td>
<td>Retinopathy</td>
<td>Retinopathy</td>
<td></td>
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<tr>
<td>Sex, %</td>
<td>49.1</td>
<td>41.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.1 (7.3)</td>
<td>65.7 (6.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 (3.9)</td>
<td>28.0 (4.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>28.7</td>
<td>28.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>138 (19)</td>
<td>147 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82 (10)</td>
<td>85 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>37.5</td>
<td>50.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose tolerance, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>47.1</td>
<td>35.4</td>
<td></td>
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<tr>
<td>Impaired</td>
<td>27.3</td>
<td>25.3</td>
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<tr>
<td>Newly diagnosed diabetes mellitus, %</td>
<td>17.6</td>
<td>12.7</td>
<td></td>
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<tr>
<td>Known diabetes mellitus, %</td>
<td>8.1</td>
<td>26.6</td>
<td>&lt;.001‡</td>
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<td>Duration of diabetes mellitus, y</td>
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<td></td>
<td>5.9 (2.0-9.5)</td>
<td>9.4 (4.3-16.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting glucose level, mmol/L</td>
<td>6.5 (2.3)</td>
<td>7.8 (3.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, % hemoglobin</td>
<td>5.8 (1.2)</td>
<td>6.6 (1.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fasting insulin level, pmol/L</td>
<td>83 (62-116)</td>
<td>93 (72-143)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total serum cholesterol level, mmol/L</td>
<td>6.6 (1.2)</td>
<td>6.8 (1.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>53.5</td>
<td>63.3</td>
<td>.1</td>
</tr>
<tr>
<td>Total serum homocysteine level, µmol/L</td>
<td>11.5 (9.3-14.1)</td>
<td>11.1 (8.4-14.0)</td>
<td>.99</td>
</tr>
<tr>
<td>Serum creatinine level, µmol/L</td>
<td>91 (17)</td>
<td>94 (30)</td>
<td>.5</td>
</tr>
<tr>
<td>Serum creatinine clearance, mL/min]</td>
<td>75 (17)</td>
<td>74 (19)</td>
<td>.6</td>
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*Data are presented as mean (SD), percentage of the total or median (interquartile range). Ellipsis indicates not applicable.
†Tested with t test or Wilcoxon rank sum test for continuous variables and Pearson χ² test for frequencies.
‡χ² Test for trend.
§Diabetes duration since diagnosis of those subjects with known diabetes mellitus.
∥Estimated creatinine clearance.

(0.89-2.39) for hypercholesterolemia (yes/no), 1.09 (0.64-1.86) for current smoking (yes/no), and (among subjects with known DM) 7.31 (2.69-19.85) for a DM duration of more than 10 years.

After stratification by DM (yes/no) and adjustment for age, sex, HbA1c level, and hypertension, we observed a substantial difference between the 2 strata with regard to relative risk of retinopathy. The OR of retinopathy associated with hyperhomocysteinemia (>16 µmol/L) was 0.97 (95% CI, 0.42-2.82) in subjects without DM and 3.44 (95% CI, 1.13-10.42) in subjects with DM (P=.08 for interaction); after additional adjustment for serum creatinine clearance it was 1.01 (95% CI, 0.44-2.33) in subjects without DM and 3.33 (95% CI, 0.99-11.19) in subjects with DM, respectively. The results per category increment of serum tHcy level are shown in Table 2 and Figure 2 (P=.03 for interaction). This indicates that hyperhomocysteinemia is associated with retinopathy in subjects with DM but not in subjects without DM. After adjustment for age, sex, HbA1c level, and hypertension, the OR per 5-µmol/L increment of serum tHcy level was 0.89

**Figure 1.** Prevalence of retinopathy according to the absence or presence of hyperhomocysteinemia (>16 µmol/L) in subjects with and without diabetes mellitus (DM). Error bars represent the upper half of the 95% confidence intervals.
teinemic response to a low intake of folic acid. In contrast, enzyme activity, leading to an exaggerated hyperhomocys-
lemia, defined as a serum tHcy level of 16 μmol/L or higher, was also related to retinopathy among subjects with type 2 DM (OR, 3.4 [95% CI, 1.1-10.6]). The results of the present study are in line with 2 studies that reported a higher serum tHcy level in subjects with type 1 and type 2 DM,38 this may make them more susceptible to hyper-
Figure 2. Odds ratio for retinopathy among subjects with and without diabetes mellitus (DM), according to the serum total homocysteine level adjusted for age, sex, glycosylated hemoglobin level, creatine clearance, and hypertension. The reference category was serum total cholesterol values 9 to 16 μmol/L (>348 to >619 mg/dL). The error bars represent the upper or lower half of the 95% confidence intervals. Asterisk indicates P<.05 for trend.

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lemia, defined as a serum tHcy level of 16 μmol/L or higher, was also related to retinopathy among subjects with type 2 DM (OR, 3.4 [95% CI, 1.1-10.6]). The results of the present study are in line with 2 studies that reported a higher serum tHcy level in subjects with type 1 and type 2 DM who have diabetic retinopathy than in those without DM.29,30 However, these studies did not investigate the strength of the association between serum tHcy level and retinopathy, nor has additional adjustment for important risk factors for retinopathy been performed. Another study showed an association between the presence of diabetic retinopathy and C677T polymorphism of the methylenetetrahydrofolate reductase among patients with type 2 DM.31 This mutation in the methylenetetrahydrofolate reductase gene was found in 5% to 15% of the general population. Persons who are homo-
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zeyme activity, leading to an exaggerated hyperhomocys-
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### Table 2. Odds Ratios (95% Confidence Intervals) for Diabetic Retinopathy

| Total Homocysteine Level, μmol/L | Prevalence of Diabetic Retinopathy, %* | Adjusted for Age and Sex | Adjusted for Age, Sex, HbA1c† Level, and Hypertension | Adjusted for Age, Sex, HbA1c†, Hypertension, and Serum Creatinine Clearance | Adjusted for Age, Sex, HbA1c†, Level, Hypertension, and Diabetes Duration
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<tr>
<td>≤9.0</td>
<td>10.0 (4/40)</td>
<td>0.53 (0.16-1.71)</td>
<td>0.56 (0.17-1.85)</td>
<td>0.56 (0.17-1.87)</td>
<td>0.54 (0.15-1.90)</td>
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<tr>
<td>9.1-16.0‡</td>
<td>18.0 (20/111)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>&gt;16.0</td>
<td>35.0 (7/20)</td>
<td>2.68 (0.92-7.80)</td>
<td>3.05 (0.99-9.42)</td>
<td>3.09 (0.92-10.38)</td>
<td>3.00 (0.95-9.51)</td>
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<td>Per category increment</td>
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<tr>
<td>P for trend</td>
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<tr>
<td>≤9.0</td>
<td>12.1 (11/91)</td>
<td>1.38 (0.64-2.98)</td>
<td>1.52 (0.69-3.34)</td>
<td>1.47 (0.66-3.25)</td>
<td></td>
</tr>
<tr>
<td>9.1-16.0‡</td>
<td>9.9 (29/292)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;16.0</td>
<td>11.3 (8/71)</td>
<td>1.19 (0.52-2.74)</td>
<td>1.05 (0.45-2.46)</td>
<td>1.08 (0.46-2.54)</td>
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<tr>
<td>Per category increment</td>
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<td>P for trend</td>
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*For parenthetic values, the numerator indicates the number of subjects; denominator, the total number in the subpopulation.
†HbA1c indicates glycosylated hemoglobin.
‡Indicates reference category.
Hyperhomocysteinemia is associated with retinopathy among subjects with type 2 DM, but probably not in subjects without DM. If the finding of the present study can be confirmed in a prospective study, this may have implications for the clinical management of subjects with type 2 DM since the serum tHcy level can be lowered substantially with folic acid supplementation.

We evaluated a possible dose-response relation between the serum tHcy level and retinopathy, because it is unknown whether this relation is graded or has a certain threshold. The limited number of subjects with retinopathy, however, did not allow for a precise assessment of the presence of a possible threshold, which may be at 16 µmol/L among subjects with type 2 DM, but this result clearly needs to be confirmed in other studies. The boundaries of the serum tHcy level categories were quite broad and chosen post hoc. Another limitation is that, owing to the limited number of subjects with retinopathy, we could not explore the association between the serum tHcy level and the separate degrees of diabetic retinopathy. Since we did not assess B vitamins and the present study is cross sectional, we cannot rule out the possibility that low vitamin B levels may cause diabetic retinopathy or that diabetic retinopathy per se can raise serum tHcy levels, although the latter appears biologically implausible.

CONCLUSIONS

Hyperhomocysteinemia is associated with retinopathy among subjects with type 2 DM, but probably not in subjects without DM. If the finding of the present study can be confirmed in a prospective study, this may have implications for the clinical management of subjects with type 2 DM since the serum tHcy level can be lowered substantially with folic acid supplementation.47

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18. Hoogeveen RJ, Kostense PJ, Jager A, et al. Serum homocysteine level and progression of retinopathy of 4.8%, as detected by grading 1 standard photographic field, which is lower than the 10.7% we found. The difference in reported prevalences may partly be explained by less sensitive methods used to detect retinopathy in the Rotterdam Study. In the present study both ophthalmoscopical and photographic findings were used to assess the presence of retinopathy. The poor agreement we found between retinal photography and ophthalmoscopy is comparable with other studies.45,46