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ARTICLE

Prevalence of diabetic retinopathy in screening-detected diabetes mellitus: results from the Gutenberg Health Study (GHS)

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Abstract
Aims/hypothesis Individuals with type 2 diabetes mellitus may experience an asymptomatic period of hyperglycaemia, and complications may already be present at the time of diagnosis. We aimed to determine the prevalence of diabetic retinopathy in patients with newly diagnosed (screening-detected) type 2 diabetes.
Methods The Gutenberg Health Study is a population-based study with 15,010 participants aged between 35 and 74 years. We determined the weighted prevalence of diabetic retinopathy by assessing fundus photographs. Screening-detected type 2 diabetes was defined as an HbA_{1c} concentration of 6.5% (47.5 mmol/mol) or more, no medical diagnosis of diabetes and no intake of insulin or oral glucose-lowering agents.
Results Of 14,948 participants, 1377 (9.2%) had diabetes mellitus. Of these, 347 (25.2%) had newly diagnosed type 2 diabetes detected by the screening. Overall, the weighted prevalence of screening-detected type 2 diabetes was 2.1%. Fundus photos were evaluable for 285 (82.1%) participants with newly diagnosed diabetes. The weighted prevalence of diabetic retinopathy in screening-detected type 2 diabetes was 13.0%; 12% of participants had a mild non-proliferative diabetic retinopathy and 0.6% had a moderate non-proliferative diabetic retinopathy. Diabetic retinopathy was proliferative in 0.3%. No cases of severe non-proliferative diabetic retinopathy or diabetic maculopathy were found. Thirty (14.9%) of 202 and six (7.2%) of 83 individuals with and without concomitant arterial hypertension, respectively, had diabetic retinopathy (OR 2.54, 95% CI 1.06, 7.14). Visual acuity did not differ between individuals with and without diabetic retinopathy .
Conclusions/interpretation In this large European study, the prevalence of diabetic retinopathy in screening-detected type 2 diabetes was 13%. Only a very small proportion of participants with detected diabetic retinopathy needed treatment.

Keywords Diabetes mellitus · Epidemiology · Maculopathy · Microangiopathy · Retinopathy

Abbreviations

ADDITION	Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care
GHS	Gutenberg Health Study

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Introduction

The rise in prevalence of diabetes mellitus, especially type 2 diabetes, is a global health and economic problem. Diabetic retinopathy is a frequent complication of the disease and the leading cause of blindness among working-age populations in the developed world [1]. Type 2 diabetes is characterised by a long, often asymptomatic, period of hyperglycaemia. Therefore, end-organ damage, such as diabetic retinopathy, may already be present in individuals who are unaware that they have type 2 diabetes, and the likelihood of this increases with the duration of the diabetes [2, 3].

The analysis of retinal vessels provides the opportunity to observe early functional and morphological changes in the microvasculature before clinically significant microvascular and macrovascular complications arise [4]. Most guidelines recommend annual screening for diabetic retinopathy, but limited resources and the slow progression of diabetic retinopathy suggest that longer recall intervals should be considered if patients have no detectable lesions [5]. Screening procedures have advantages and disadvantages that must be considered [3, 4, 6]. It has been shown that healthcare costs increase with the severity of diabetic retinopathy , which suggests that preventing its progression may lower healthcare expenditure [7]. In addition, information technology based on epidemiological data may facilitate an individualised determination of screening intervals for diabetic retinopathy [8].

Models to determine a personalised screening frequency for diabetic retinopathy have been developed to help to reduce healthcare use and the costs of diabetes care. These models still require refinement as, for example, in a model proposed by van der Haijden et al, almost 12% of participants had developed sight-threatening diabetic retinopathy before the model-based time of screening [9]. Other outcome measures of screening procedures are psychosocial well-being and cardiovascular morbidity and mortality. In a targeted screening programme, the diagnosis of type 2 diabetes had no substantial adverse or positive effect on psychological well-being and perceived health status [10]. In summary, in contrast to macrovascular complications, some microvascular events, such as background retinopathy, could theoretically be prevented by earlier diagnosis and better glycaemic control [11]. Therefore, screening for diabetes may lead to the detection of retinopathy at an earlier stage before clinically evident complications occur. In line with this, it has been shown that patients who do not attend diabetic eye screenings are at increased risk of developing sight-threatening diabetic retinopathy [12].

We therefore aimed to determine the prevalence of diabetic retinopathy in persons with type 2 diabetes that was newly detected within the framework of the population-based Gutenberg Health Study (GHS). Visual acuity served as a test for functional limitations caused by diabetic retinopathy. As micro- and macrovascular events have been shown to be related to age, sex, HbA_{1c} concentration, hypertension and dyslipidaemia [1, 13–15], we also analysed associations between these variables and diabetic retinopathy in screening-detected type 2 diabetes.

Methods

The GHS is a population-based, prospective, observational cohort study from midwestern Germany with a total of 15,010 participants aged between 35 and 74 years. Participants in the study undergo a standardised protocol that includes ophthalmic and complete general medical examinations focused on cardiovascular variables. The detailed protocol has previously been described [16].

Fundus images were taken by trained personnel at the GHS centre using a non-mydriatic fundus camera (Visucam PRO NMTM, Carl Zeiss, Jena, Germany) in a darkened room with the pupil's natural width. Three photographs were taken of each eye at 30° and 45° centred on the optic nerve, and at 30° centred on the macula. These images were evaluated by two certified graders (P. Raum, J. Lamparter) at the Reading Centre at Moorfields Eye Hospital, London, UK, using a specifically designed work station. The fundus images were the basis upon which we diagnosed whether diabetic retinopathy was present, and if it was, its stage. Grading of the fundus photographs was performed in line with the recommendations of the Early Treatment Diabetic Retinopathy Study.

In the present study, the term 'screening-detected diabetes' referred to screening of the general population for diabetes mellitus. Screening for type 2 diabetes in the GHS cohort was based on HbA_{1c} concentrations, with a cut-off value of 6.5% (47.5 mmol/mol) as recommended by the ADA [16, 17]. In line with this cut-off for the identification of individuals with type 2 diabetes, Sabanayagam et al found that cut-off points between 6.6% (48.6 mmol/mol) and 7.0% (53.0 mmol/mol) were also best for identifying individuals with mild and moderate retinopathy [18]. Exclusion criteria were a medical diagnosis of diabetes by a physician and/or the intake of insulin or oral glucose-lowering agents. Cardiovascular risk factors and visual acuity (in logMAR) were measured as previously reported [17].

For the current analyses, we used data on obesity, dyslipidaemia and arterial hypertension, assessed as follows. Arterial hypertension was diagnosed if antihypertensive drugs were being taken or if a mean systolic (and/or diastolic) blood pressure of ≥140 (≥90) mmHg was recorded from the second and third standardised measurements after resting. Diabetes was diagnosed if there was a definite diagnosis and treatment by a physician, a blood glucose level ≥7 mmol/l after

overnight fasting (≥8 h) or ≥11.1 mmol/l after a fasting period of less than 8 h. Obesity was defined as a BMI ≥30 kg/m^2. Dyslipidaemia was defined as a definite diagnosis of dyslipidaemia by a physician or an LDL:HDL-cholesterol ratio of ≥3.5.

Statistical analyses We performed statistical analyses using Statistical Analysis System (SAS) software, Version 9.4 of the SAS System for Windows (SAS Institute, Cary, NC, USA). Weighting for the age and sex distributions of the local population was based on census data as of 31 December 2009, coinciding approximately with the midpoint of our recruitment phase. As the distribution of missing values (arising from fundus photographs of insufficient quality) was not age- and sex-independent, weighting was conducted without these data.

Binary logistic regression analyses indicating ORs and 95% CIs were performed to assess age- and sex-adjusted associations between diabetic retinopathy and cardiovascular risk factors and diseases. We used a χ^2 test to assess the associations between categorical variables, and a Mann–Whitney *U* test for association analyses between binary and metric variables. Because of the small sample size, we did not perform Bonferroni's correction or multivariable analyses. Univariable associations with a two-sided $p < 0.05$ were considered statistically significant.

Results

Fundus photographs of sufficient quality were available for 14,948 (99.6%) of the participants. Overall, 1377 (9.2%) had type 2 diabetes. Of these, 25.2% (347/1377) had newly diagnosed type 2 diabetes (screening-detected disease). The weighted prevalence for screening-detected type 2 diabetes was 2.1% ($n = 306$; women [$n = 127$], 1.7%; men [$n = 179$], 2.4%).

The fundus photographs of at least one eye from 285 (82.1%) of these 347 participants were eligible for analysis. The prevalences of the various stages of diabetic retinopathy in these participants are listed in Table 1. The weighted prevalence of diabetic retinopathy (all stages) was 13.0% (12.1% in men and 14.2% in women). Twelve per cent of participants had a mild non-proliferative diabetic retinopathy, and 0.6% a moderate non-proliferative diabetic retinopathy. Diabetic retinopathy was proliferative in 0.3% of the individuals.

The median HbA_{1c} was 6.8% (50.8 mmol/mol) in both individuals with (range 6.5–15.0% [47.5–140.4 mmol/mol]) and without (range 6.5–13.8% [47.5–127.3 mmol/mol]) diabetic retinopathy ($p = 0.228$). Overall, 202/285 (70.9%) participants with screening-detected type 2 diabetes had arterial hypertension. Obesity and dyslipidaemia were found in 51.4% (146/284; missing data in $n = 1$) and 43.8% (124/283; missing data in $n = 2$) of those with screening-detected type 2 diabetes. The (age- and sex-adjusted) associations between these cardiovascular risk factors and the presence of diabetic retinopathy are summarised in Table 2.

The median visual acuity (logMAR) of both eyes was 0.00 (range: left eye −0.1 to +0.5, right eye –0.1 to +0.7) in participants with diabetic retinopathy, and 0.10 (range: left eye −0.1 to +3.0, right eye –0.3 to +2.0) in those without it ($p = 0.16$).

Discussion

This large European population-based study reports on the prevalence of diabetic retinopathy in individuals with diabetes mellitus newly detected from a screening examination. Furthermore, we assessed the associations of arterial hypertension, dyslipidaemia, obesity, and visual acuity with diabetic retinopathy in this subgroup of people with type 2 diabetes.

Prevalence of screening-detected diabetic retinopathy In the present study of a mid-European, west-German cohort, one in 50 participants and one quarter of all diabetic individuals were newly diagnosed as having type 2 diabetes. In this subgroup, there were 1.5 times more men than women. Approximately 13% of those with screening-detected type 2 diabetes had signs of diabetic retinopathy. Nevertheless, mostly mild forms of non-proliferative diabetic retinopathy were found in these subgroups. Only one person had proliferative diabetic retinopathy, and no case of severe non-proliferative or diabetic maculopathy was found. This means that very few patients from those newly diagnosed with diabetes in a screening setting had stages of diabetic retinopathy that needed treatment.

Until now, no data from European population-based studies on this topic have been published. Nevertheless, the present results are in line with those from studies that have used targeted screening procedures or assessed the prevalence of diabetic retinopathy in patients who were newly diagnosed in general practice. In a European population-based targeted screening procedure, the prevalence of diabetic retinopathy in screening-detected type 2 diabetes was 7.6%, compared with 1.9% in patients who were newly diagnosed in general practice [19]. In the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION), patients with screen-detected diabetes had a low prevalence (6.8%) of diabetic retinopathy and no vision-threatening lesions. The ADDITION study from Denmark was the first to describe the prevalence of diabetic retinopathy in a population of newly diagnosed type 2 diabetic patients in general practitioners' practices who were

Table 1 Prevalence of diabetic retinopathy in diabetic individuals detected by screening

Group	Total (all stages)		Stages of diabetic retinopathy					
			Non-proliferative				Proliferative	
			Mild		Moderate			
	% (*n*)	95% CI	% (*n*)	95% CI	% (*n*)	95% CI	% (*n*)	95% CI
Total (*n* = 285)								
Study sample[a]	12.6 (36)	9.00–17.06	11.6 (33)	8.13–15.93	0.7 (2)	0.09–2.52	0.4 (1)	0.09–1.95
Study population[b]	13.0 (32.8)	9.15–17.64	12.0 (30.3)	8.31–16.61	0.6 (1.4)	0.05–2.31	0.3 (0.8)	0.01–1.92
Men (*n* = 171)								
Study sample[a]	11.7 (20)	7.29–17.48	10.5 (18)	6.36–16.13	1.2 (2)	0.14–4.16	0.6 (1)	0.01–3.22
Study population[b]	12.1 (18.1)	7.41–18.27	11.0 (16.5)	6.54–17.10	1.0 (1.4)	0.08–3.83	0.6 (0.8)	0.01–3.18
Women (*n* = 114)								
Study sample[a]	14.0 (16)	8.24–21.79	13.2 (15)	7.62–20.95	0	N/A	0	N/A
Study population[b]	14.2 (14.7)	8.30–22.21	13.5 (13.7)	7.67–21.36	0	N/A	0	N/A
Age <65 years (*n* = 174)								
Study sample[a]	13.2 (23)	8.57–19.17	12.6 (22)	8.10–18.51	0	N/A	0.6 (1)	0.01–3.16
Study population[b]	13.5 (22.5)	8.64–19.81	13.0 (21.6)	8.21–19.25	0	N/A	0.5 (0.8)	0.01–3.05
Age ≥65 years (*n* = 111)								
Study sample[a]	11.7 (13)	6.39–19.19	9.0 (10)	5.10–17.19	1.8 (2)	0.22–6.41	0	N/A
Study population[b]	11.9 (10.3)	6.52–19.43	10.1 (8.7)	5.16–17.29	1.7 (1.4)	0.18–6.19	0	N/A

To determine the prevalence of diabetic retinopathy in the population, data from the study sample were weighted for the age- and sex distributions of the local population. No cases of severe diabetic retinopathy or diabetic maculopathy were found

[a] Study sample: number of cases/observations in the study cohort

[b] Study population: to determine the prevalence in the study population, data from the study sample were weighted for the age and sex distributions of the local population (region of Mainz/Mainz-Bingen, Germany)

representative of the background population [20]. In comparison, in a Danish population-based study, the prevalence of diabetic retinopathy in the population with type 2 diabetes was 31.5% [21]. As in the GHS, no cases of severe non-proliferative or proliferative diabetic retinopathy were found. In the Diabetes Prevention Program (DPP) cohort, the prevalence of diabetic retinopathy in new-onset diabetes was 12.6% [22], whereas the median prevalence of diabetic retinopathy in newly diagnosed diabetes was 10.5% across 26 population-based studies (all from outside Europe) [23]. The lowest prevalence was found in African-American individuals (1.5%) and the highest in a population from China (30.6%). In the Hoorn study, the prevalence of diabetic retinopathy was higher in screening-detected type 2 diabetic individuals than in those newly diagnosed in general practice [19]. In the Beaver Dam Eye Study, the prevalence of sight-threatening diabetic retinopathy in screening-detected diabetes was only 2%, and the authors therefore concluded that asymptomatic individuals discovered to have diabetes during epidemiological studies may not need immediate ophthalmoscopic examination at the time of their diagnosis because they have a relatively low risk of danger of visual loss at that time [24].

Table 2 Effect of concomitant arterial hypertension, obesity and dyslipidaemia on the presence of diabetic retinopathy/ diabetic maculopathy in screening-detected type 2 diabetes

Screening-detected type 2 diabetes with the following risk factors	Diabetic retinopathy/ maculopathy (all stages)		
	n (%)	OR	95% CI[a]
Arterial hypertension			
Yes (*n* = 202)	30 (14.9)	2.54	1.06–7.14
No (*n* = 83)	6 (7.2)		
Obesity			
Yes (*n* = 146)	20 (13.7)	1.20	0.60–2.46
No (*n* = 139)	16 (11.5)		
Dyslipidaemia			
Yes (*n* = 124)	11 (8.9)	0.52	0.23–1.07
No (*n* = 159)	25 (15.7)		

Age- and sex-adjusted ORs according to binary logistic regression analysis (including age, sex and one further variable, respectively)

[a] CIs based on the profile likelihood method

Association with HbA_{1c}, hypertension and variables suggestive of the metabolic syndrome In the present study,

the majority of participants with screening-detected type 2 diabetes and diabetic retinopathy had systemic hypertension. Approximately one half of the population with diabetic retinopathy were obese, and one third had dyslipidaemia. This observation is in line with earlier studies (that were not population-based) in which high levels of serum lipids and blood pressure were identified as risk factors for diabetic retinopathy [25]. In our study cohort of screening-detected type 2 diabetes, the presence of diabetic retinopathy was associated with neither the HbA_{1c} concentration nor the presence of arterial hypertension, obesity and dyslipidaemia. In the ADDITION study (screening in general practices), patients with diabetic retinopathy had significantly higher HbA_{1c} and systolic and diastolic blood pressures than those without retinopathy [20]. In a disease cohort of diabetic individuals in which systolic blood pressure and Hb_{A1c} concentrations were higher in those with than those without diabetic retinopathy, Spijkerman et al [26] did not find an association between HbA_{1c} levels and diabetic retinopathy in participants with screening-detected diabetes, but higher rates of arterial hypertension and dyslipidaemia were observed. In a study of the prevalence of and risk factors for diabetic retinopathy in people with newly diagnosed type 2 diabetes mellitus using Scottish national data, diabetic retinopathy was associated with male sex, systolic blood pressure, time to screening and obesity [27].

In terms of dyslipidaemia, intraretinal modified LDLs have been implicated in diabetic retinopathy, and it has been shown that extravascular modified LDLs may promote retinal pigment epithelium injury through oxidative stress, endoplasmic reticulum autophagy and apoptosis, whereas modified HDL-cholesterol had protective effects [28, 29]. The same holds true for other novel risk markers such as serum apolipoprotein AI [30]. Unfortunately, these variables were not measured in the GHS.

There is controversy regarding the effect of screening on overall mortality. In a study by Jansson et al, no reduction in total mortality or cardiovascular disease outcomes was found in patients with type 2 diabetes who were detected by screening compared with those diagnosed clinically [31]. The Hoorn study, on the other hand, found that the mortality risk increased with increasing duration of diabetes [32]. In individuals whose diabetes is of short duration, the mortality risk could largely be attributed to other risk factors, whereas in those with a longer duration of diabetes, the elevated mortality risk was independent of cardiovascular risk factors.

Visual acuity in screening-detected diabetes In the present study, visual acuity was not impaired in the vast majority of participants, and no cases of severe non-proliferative diabetic retinopathy or maculopathy were observed. This finding was in line with other studies [23] and reflects the fact that type 2 diabetes may be asymptomatic even when end-organ damage is already detectable.

Limitations and perspectives One limitation of the present study is that non-mydriatic fundus photos were taken, and we were only able to take three fundus photos instead of the gold standard of seven. This limitation may have led to an underestimation of the prevalence of diabetic retinopathy because more peripheral lesions (e.g. microaneurysms) were not detected with this method. Nevertheless, it has recently been shown that 14/35 studies on diabetic retinopathy have not applied pupil dilation [33]. Furthermore, it has been shown that even taking two 45° photographic fields per eye is a promising alternative to the routine ophthalmologist's examination when screening for diabetic retinopathy. In a study by Stellingwerf et al, the sensitivity of two-field photography in identifying diabetic individuals with sight-threatening diabetic retinopathy was 95% (specificity 99%), and the sensitivity for detecting any diabetic retinopathy was 83% (specificity 88%) [34].

Another limitation of this study has previously been published. For quality control purposes, we assessed the fundus images of 218 age- and sex-matched controls who did not have diabetes [17]. Approximately 10% of these control participants had retinal changes that would have been assessed as a mild stage of diabetic retinopathy. This can be attributed to the definition of diabetic retinopathy (i.e. that is already present when one microaneurysm is visible), to image quality and to other retinal microangiopathies.

A further limitation of the present study is that microalbuminuria was not assessed in the GHS. It would have been interesting to assess associations between microalbuminuria and diabetic retinopathy, especially because it has been shown that diabetic retinopathy is useful in diagnosing or screening for diabetic nephropathy in patients with diabetes and renal disease [35]. Furthermore, in a study on an elderly cohort of Icelanders (≥67 years), over three-quarters of cases of retinopathy occurred in individuals without diabetes, and a strong association was found between microalbuminuria and non-diabetic retinopathy [36]. Therefore, microalbuminuria should be tested in future population-based studies.

The results of this study have clearly highlighted the high number of individuals in the community who have undetected diabetes mellitus, and have indicated the need for screening for type 2 diabetes to detect early complications and prevent severe ophthalmic complications and visual impairment.

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