Co-morbidity in patients with sight-threatening diabetic retinopathy

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CLINICAL STUDY

Abstract

Purpose **To describe the level of co-morbidity in patients with sight-threatening diabetic retinopathy in the United Kingdom.**
Methods **Questionnaires were completed by patients undergoing first photocoagulation treatment for diabetic maculopathy or proliferative retinopathy during a 2 month period throughout the UK.**
Results **Overall 15% of patients described angina, 9% had suffered a myocardial infarction and 6% a stroke. Self-reported renal disease was present in 8.5%. Foot ulceration was described by 10% of patients, and 4% had undergone an amputation. 35.5% of patients were on treatment for hypertension. 17.5% of patients had been hospitalised in the previous 6 months, and 3% of patients had died within 9 months of the laser treatment.**
Conclusions **There was significant co-morbidity in these patients, which may affect the management of their retinopathy.**

Key words Co-morbidity, Diabetic retinopathy, Maculopathy, Proliferative retinopathy

It is estimated that there are almost 1.4 million adults with diabetes in the United Kingdom[1] of whom 26–52% have diabetic retinopathy and 7–14% have sight-threatening retinopathy.[2–5] The multisystem effects of diabetes are well known, but few studies have specifically documented their prevalence in patients with sight-threatening diabetic retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy found that patients with proliferative retinopathy were at increased risk of cardiovascular disease, nephropathy and mortality,[6] and in the Diabetic Retinopathy Study at recruitment 10.2% of patients reported having kidney disease, 4.8% had suffered a myocardial infarction, 2.7% had had a stroke and 3.4% had had an amputation.[7] Systemic factors may not only affect the progression and severity of retinopathy (especially via glycaemic and blood pressure control)[8–10] but may also alter treatment and outcome for retinopathy if illness precludes adequate follow-up. This study aimed to describe the prevalence of co-morbidity in patients with sight-threatening diabetic retinopathy in a cohort of patients in the United Kingdom.

Materials and methods

This study was undertaken in conjunction with a national study throughout the UK examining photocoagulation treatment for diabetic retinopathy, the full methodology of which has been described elsewhere.[11] Patients eligible for inclusion in the study were those undergoing first laser treatment for diabetic maculopathy or proliferative retinopathy during a 2 month period throughout the UK. Questionnaires were completed by the ophthalmologist performing the laser treatment and by the patient prior to the initial laser treatment and at 9 month follow-up.

Disease-specific questionnaires were designed for completion by the patient and contained questions concerning the type and duration of diabetes, visual symptomatology and co-morbidity. Design of the questionnaire involved a period of initial research and design, to determine content, face and construct validity. An initial questionnaire was piloted on 15 patients, modifications were made, and it was then repiloted on 45 patients with diabetic retinopathy. The final version underwent a test–retest study in 40 patients for whom quadratic weighted kappa analysis showed levels of agreement ranging from +0.81 to +1.00, which was felt to show an acceptable degree of test–retest reliability. The patients were given their questionnaire to complete by the local ophthalmologist. The patient questionnaires were anonymous, but were confidentially coded to enable the information to be combined with the other questionnaires concerning each patient. The data from the questionnaires were double-entered, stored on a computerised database, and analysed using SPSS for Windows release 6.0.

Statistical analysis included the Mann–Whitney *U*-test and linear regression analysis where appropriate for continuous data, and chi-squared and logistic regression analysis where appropriate for categorical data.

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Table 1. *Demographic features*

Mean age (years)	Gender	Type of diabetes % (*n*)	Duration of diabetes (years)
All patients			
59.9 (range 17–94)	46.1% female	(a) Younger-onset disease: 15.5% (96) (b) Older-onset disease: 84.5% (523): Insulin treatment 36.7% (192) Oral agents 58.1% (304) Diet alone 5.2% (27)	(a) Younger-onset disease: 24.8 (range 7.3–71.1) (b) Older-onset disease: 12.3 (range 0.1–54)
Patients undergoing laser treatment for maculopathy			
62.2 (21–94)	48.2% female	(a) Younger-onset disease: 8.0% (30) (b) Older-onset disease: 92% (389): Insulin treatment 36.5% (142) Oral agents 58.6% (228) Diet alone 4.9% (19)	(a) Younger-onset disease: 25 (range 10–68.4) (b) Older-onset disease: 12.1 (range 0.1–57.4)
Patients undergoing laser treatment for proliferative retinopathy			
54.8 (17–85)	42.1% female	(a) Younger-onset disease: 31.6% (62) (b) Older-onset disease: 68.4% (134): Insulin treatment 43.3% (58) Oral agents 50.0% (67) Diet alone 6.7% (9)	(a) Younger-onset disease: 24.7 (range 7.3–54.9) (b) Older-onset disease: 13.1 (range 0.1–34.1)

Younger-onset disease: diabetes diagnosed under age 30 years and on insulin treatment; older-onset disease: diabetes diagnosed after age 30 years, or not on insulin treatment.

Results

Eight hundred and thirty patients were recruited into the study overall. Of these 546 (65.8%) were undergoing their first laser treatment for maculopathy (in the absence of proliferative retinopathy) and 34.2% were undergoing their first panretinal photocoagulation in the affected eye. A validation study showed that this represented 75.4% of all eligible patients.[11] Questionnaires were returned from 639 patients (76.9% of the patients recruited into the survey). There was no significant difference in the age ($p = 0.07$, Mann–Whitney *U*), gender (chi-squared 2.41, $p = 0.29$), visual acuity in the better eye ($p = 0.3$, Mann–Whitney *U*) or type of retinopathy (chi-squared 0.0009, $p = 0.97$) between the responders and the non-responders to the patient questionnaire. Table 1 shows the demographic features for these patients. The mean age of the patients was 59.9 years (range 17–94 years). Diabetes was diagnosed under the age of 30 years and required insulin treatment in 15.5% of patients. Table 2 shows the self-reported general health for these patients undergoing first laser treatment for diabetic retinopathy. Overall, 15% reported having angina, 8.8% had suffered a myocardial infarction, 5.9% had had a stroke and 8.5% reported having known renal disease. Thirty-four per cent reported symptoms of peripheral neuropathy, 10.5% had suffered foot ulceration, and 4.4% had undergone amputation of all or part of a limb. Of the 35.5% of patients who reported being on treatment for hypertension, 37.9% were taking an ACE inhibitor, 35.8% were on a calcium antagonist, 19.4% of patients were taking a beta blocker, 0.8% were on a combination of beta blocker and diuretic, and 5.9% were taking a thiazide diuretic alone.

Multiple logistic regression was performed to assess the risk factors for co-morbidity. Factors included in the analysis were age, gender, type and duration of diabetes and the type of retinopathy present. Ischaemic heart disease (angina and/or myocardial infarction) was associated with increased age ($p < 0.01$), increased duration of diabetes ($p < 0.01$), older-onset diabetes (OR = 3.2, $p = 0.04$) and the presence of proliferative retinopathy (OR = 1.7, $p = 0.03$) but not independently related to the gender of the patient. The presence of cerebrovascular disease (transient ischaemic attack and/or stroke) was significantly associated with increasing age ($p < 0.01$) and with increased duration of diabetes ($p < 0.01$) but not independently related to other factors. The presence of self-reported renal disease was significantly associated with proliferative retinopathy

Table 2. *Co-morbidity in patients with sight-threatening diabetic retinopathy*

			Type of retinopathy				Type of diabetes			
	All cases		Proliferative (214)		Maculopathy (425)		Younger-onset (96)		Older-onset (523)	
Symptom or disease	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Angina	99	15.5%	36	16.8%	63	14.8%	7	7.3%	81	15.5%
Myocardial infarction	56	8.8%	24	11.2%	32	7.5%	4	4.4%	43	8.2%
Cardiovascular accident	38	5.9%	13	6.1%	25	5.9%	4	4.4%	29	5.5%
Transient ischaemic attack	42	6.6%	17	7.9%	25	5.9%	3	3.1%	36	6.9%
Known renal disease	54	8.5%	30	14.0%	24	5.6%	15	15.6%	30	5.7%
Numbness in feet	217	34.0%	76	35.5%	141	33.2%	23	23.9%	178	34.0%
Foot ulcers	67	10.5%	28	13.1%	39	9.2%	7	7.3%	55	10.5%
Amputation	28	4.4%	7	3.3%	21	4.9%	5	5.2%	24	4.6%
Hypertension	227	35.5%	72	33.6%	155	36.5%	20	20.8%	190	38.3%

compared with maculopathy (OR = 2.9, $p < 0.01$) and increased duration of diabetes ($p = 0.03$), but not independently related to the age or gender of the patient, or the type of diabetes. Symptoms of peripheral neuropathy were not found to be significantly associated with any of the factors included in the analysis. The presence of treated hypertension was significantly related to older-onset diabetes (OR = 4.9, $p < 0.001$), the duration of diabetes (p = 0.01) and female sex (OR = 1.6, $p = 0.01$), but not independently to the age of the patient or the type of retinopathy present. Previous cataract surgery had been performed in 11.7% of patients.

No association was found between the outcome of treatment for proliferative retinopathy or maculopathy between those patients with or without self-reported ischaemic heart disease, cerebrovascular disease, renal disease, treated hypertension or smoking history, in terms of either visual acuity or morphological outcome.

Patients were asked how many times they had visited a variety of health care workers in the previous year. The total number of visits to any health care worker in the previous year was a mean 15.6 (range 1–188, SD 14.5). One hundred and twelve patients (17.5%) had been admitted to hospital in the previous 6 months (median 0 times, range 0–22 for all cases). The number of nights as an inpatient in the previous 6 months was a mean 2.6 (range 0–112).

Overall 56.3% (360) of respondents said that they had been smokers at some stage in their lives and 12.2% (78) of respondents said that they were still smoking. For those who had stopped smoking, 57.2% had stopped prior to the diagnosis of diabetes whilst 42.8% had stopped after the diagnosis was made. For those who were still smoking the mean number of cigarettes smoked per day was 12.6 (range 2–35), whilst for those who had previously been smokers, the mean number of cigarettes was 19.9 (range 1–100). In response to the question about the patients' understanding of the risk of smoking to their health, 56.1% (330) responded that they thought the risk to their health from smoking was greater because they were diabetic, 17.7% (104) said that they thought the risk to their health from smoking was the same as for someone who was not diabetic, 0.5% (3) felt that the risk to their health was less and 25.7% (151) said that they did not know. For the group who were still smoking, 42.3% (33) said that they were aware that the risk to their health was greater because they were diabetic, and 28.2% (22) said that they did not know.

Discussion

This study highlights the high prevalence of co-morbidity in this group of patients with sight-threatening diabetic retinopathy. Overall 28% described angina, myocardial infarction, transient ischaemic attack or stroke, and this was 12% for the group of patients aged less than 65 years. The presence of ischaemic heart disease or cerebrovascular disease was found to be associated with increasing age and increasing duration of diabetes, but not with the gender of the patient. The prevalence of macrovascular complications in diabetic patients has been shown to be increased 2- to 3-fold in men and 4- to 5-fold in premenopausal women, and the fact that the presence of macrovascular complications in this study was not related to the gender of the patient highlights the fact that diabetes abolishes the protective effect of being female.[12,13] Renal disease was reported by 8.5% of patients overall and in 14% of patients with proliferative retinopathy. The presence of renal disease was found to be associated with proliferative retinopathy rather than maculopathy and with increased duration of diabetes. These self-reported figures will certainly be an underestimate of the number of patients with any degree of nephropathy. Although the incidence of nephropathy is thought to be declining, particularly for type I diabetes, it is thought that renal disease will develop in 20–25% of patients with diabetes.[14]

Twenty-four per cent of patients were aware of numbness in their feet, 10.5% had suffered foot ulceration and 4.4% had undergone amputation of all or part of a limb. A community survey found a prevalence of neuropathy of 16% compared with 3% in the non-diabetic population, and that past or present foot ulceration was present in 7.4% in people with diabetes compared with 2.5% in the control group.[15,16] The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found a prevalence of foot ulceration in 9.5% of the younger-onset group of patients with diabetes, and 10.5% of the older-onset group. The 4 year incidence of lower-limb amputation was 2.2% overall.[17]

Higher rates of co-morbidity would be expected in our survey, since these patients had more severe degrees of retinopathy than a community sample of patients with diabetes and might thus be expected to have higher levels of other diabetes-related complications.

Nabarro reported a series of 6780 patients with diabetes mellitus, of whom 20.8% had type I diabetes.[18] This was a highly selected group of patients who were seen in a hospital diabetes clinic between 1954 and 1988. He found clinically important neuropathy in 17.4% of patients with type I diabetes and in 11.6% of those with type II diabetes. Foot ulceration occurred in 5.7% of patients, and major amputations were needed in 1.2% of patients. Coronary artery disease was found in 9% of patients with type I diabetes, and was as common in women as men.

In the Diabetic Retinopathy Study (DRS) at recruitment, 10.2% reported having kidney disease, 4.8% had suffered a myocardial infarction, 2.7% had had a stroke and 3.4% had had an amputation.[7] However, one of the eligibility criteria for the DRS was that 'the outlook for survival and availability for 5 years of follow-up was judged good by the examining physician' and patients over 70 years were not eligible. It is therefore not surprising that the levels of co-morbidity are higher in our group of patients with proliferative retinopathy.

Two hundred and twenty-seven of the patients in our study (35.5%) reported being on treatment for hypertension, and this was related to the duration of diabetes, older-onset diabetes and female gender. These

figures are in accord with other studies. A population study from the USA showed that 41% of the patients with diabetes were on treatment for hypertension compared with 22.4% of the controls.[19] Among patients with diabetes on oral hypoglycaemic agents, 52.9% of the women were on treatment for hypertension compared with 39% of the men. In the DRS 29.3% of patients were on antihypertensive treatment at baseline, and this was more common in women than men (37.4% vs 22.8%).

The prevalence of current smoking of 12.2% for the patients in this survey can be compared with a national American survey in 1989 which showed that 27% of people with diabetes reported currently smoking cigarettes.[20] In the DRS at baseline 32.4% of patients were current cigarette smokers and 20.1% were former smokers.[7] The levels of current smoking in our survey compare favourably with these other studies. However, it is of note that only 56.1% of patients (and 42.3% of smokers) were aware that smoking was a greater risk to their health because they had diabetes. This would suggest the need for better education about the risks of smoking for these patients.

This study found no association between the systemic health of these patients and the outcome of photocoagulation treatment. However, the study was not specifically designed to address this issue, self-reporting is likely to underestimate the level of disease (especially renal) and the group on treatment for hypertension may well not have significantly different levels of blood pressure compared with the group not requiring treatment.

In conclusion, this study highlights the high prevalence of co-morbidity in patients undergoing laser treatment for diabetic retinopathy in the UK. This may affect the treatment of their retinopathy, as the patients may be frequently hospitalised or unwell, causing them to miss or postpone their appointments, and may alter the threshold for panretinal photocoagulation treatment if careful follow-up cannot be maintained.[21,22] Moreover, poor systemic health may exacerbate diabetic macular oedema, and control of systemic factors rather than laser treatment may be a necessary initial treatment option. It is therefore very important to be aware of the systemic status of diabetic patients with retinopathy, since this may affect their management. This study details the prevalence of associated disease in patients undergoing laser treatment for diabetic retinopathy.

References

1. Amos A, McCarty D, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to 2010. Diabet Med 1997;14(Suppl5):S16.
2. McLeod B, Thompson J, Rosenthal A. The prevalence of retinopathy in the insulin-requiring diabetic patients of an English country town. Eye 1988;2:424–30.
3. Sparrow JM, McLeod BK, Smith TD, Birch MK, Rosenthal AR. The prevalence of diabetic retinopathy and maculopathy and their risk factors in the non-insulin-treated diabetic patients of an English town. Eye 1993;7:158–63.
4. Foulds WS, McCuish A, Barrie T, *et al*. Diabetic retinopathy in the west of Scotland: its detection and prevalence, and the cost-effectiveness of a proposed screening programme. Health Bull 1983;41:318–26.
5. Neil H, Thompson A, Thorogood M, Fowler G, Mann J. Diabetes in the elderly: the Oxford community diabetes study. Diabet Med 1989;6:608–13.
6. Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. Diabetes Care 1992;15:1875–91.
7. Diabetic Retinopathy Study Research Group. Report 6. Design, methods, and baseline results. Invest Ophthalmol Vis Sci 1981;21:149–209.
8. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
9. Stratton IM, Adler AI, Neil HA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35). BMJ 2000;321:405–12.
10. Adler AI, Stratton IM, Neil HA, *et al*. Association of sytolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36). BMJ 2000;321:412–9.
11. Bailey CC, Sparrow JM, Grey RHB, Cheng H. The National Diabetic Retinopathy Laser Treatment Audit. I. Maculopathy. Eye 1998;12:69–76.
12. Fuller J, Shipley M, Rose G. Coronary heart disease risk and impaired glucose tolerance: the Whitehall Study. Lancet 1980;I:1373–6.
13. Morrish N, Stevens L, Fuller J, Keen H, Jarrett R. Incidence of macrovascular disease in diabetes mellitus: the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics. Diabetologia 1991;34:584–9.
14. British Diabetes Association Report. Diabetes in the United Kingdom 1996.
15. Walters DP, Gatling W, Mullee MA, Hill RD. The prevalence of diabetic distal sensory neuropathy in an English community. Diabet Med 1992;9:349–53.
16. Walters DP, Gatling W, Mullee MA, Hill RD. The distribution and severity of diabetic foot disease: a community study with comparison to a non-diabetic group. Diabet Med 1992;9:354–8.
17. Moss SE, Klein R, Klein BE. Prevalence of lower limb amputation in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Intern Med 1992;152:610–6.
18. Nabarro JDN. Diabetes in the United Kingdom: a personal series. Diabet Med 1990;8:59–68.
19. Dupree EA, Meyer MB. Role of risk factors in complications of diabetes mellitus. Am J Epidemiol 1979;112:100–12.
20. Ford ES, Malarcher A, Herman W, Aubert R. Smoking and diabetes: findings from the 1989 National Health Interview Survey. Diabetes Care 1994;17:688–92.
21. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of diabetic retinopathy study findings. DRS report 8. Ophthalmology 1981;88:583–600.
22. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report 9. Ophthalmology 1991;98:766–85.