Graefes Arch Clin Exp Ophthalmol (2009) 247:267–272
DOI 10.1007/s00417-008-0960-y

MEDICAL OPHTHALMOLOGY

Diabetic retinopathy and health-related quality of life

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Received: 28 July 2008 / Revised: 17 September 2008 / Accepted: 24 September 2008 / Published online: 17 October 2008

Abstract
Objective To describe the impact of co-morbidities, visual acuity, diabetic retinopathy (DR) grade, and macular edema (ME) on the health-related quality of life (HRQOL) among patients with diabetic retinopathy.
Methods Analysis of data of 207 patients with diabetic retinopathy from Germany in 2003. HRQOL assessment was done using the generic (SF-12) questionnaire. It was hypothesized that exogenous variables (co-morbidities, visual acuity impairment, DR, and ME) would have an impact on HRQOL. Using a structural equation modelling procedure, the effects of exogenous variables on endogenous variables physical component summaries (PSC) and mental component summaries (MCS) reflecting HRQOL were tested.
Results The number of co-morbidities had a negative effect on visual acuity (b=−0.26, standardized) and a similar negative effect on PCS (b=−0.27). DR grade had a negative effect on visual acuity (b=−0.19) and a positive effect on the variable ME (b=0.44). ME displayed a negative effect on visual acuity (b=−0.58) and also on MCS (b=−0.29). Visual acuity had a positive effect (b=0.48) on PCS.
Conclusions Presence of DR and ME, visual acuity impairment and patient co-morbidities lead to significant impairment of both the physical and mental components of HRQOL.

Keywords Diabetic retinopathy · SEM · SF-12

Abbreviations

DM	Diabetes mellitus
DR	Diabetic retinopathy
NPDR	Non-proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
ME	Macular edema
NCSME	No clinically significant macular edema
CSME	Clinically significant macular edema
SEM	Structural equation modelling
HRQOL	Health-related quality of life
RetDQoL	Retinopathy Dependent Quality of Life questionnaire
RetTSQ	Retinopathy Treatment Satisfaction Questionnaire
SF-12	Short-Form Health Survey
PSC	Physical Component Summaries
MCS	Mental Component Summaries
FIML	Full Information Maximum Likelihood
SD	Standard deviation
IQR	Interquartile range

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Introduction

Diabetic retinopathy (DR) is the leading cause of blindness in Germany [1]. Initially, most people with DR experience only mild vision symptoms. Visual loss in

patients with diabetes mellitus (DM) is often a late symptom of advanced retinopathy. In addition to the DR, patients can suffer from a macular edema (ME), which is caused by the breakdown of the blood–retinal barrier resulting in leakage of plasma and water from small vessels [2]. These leakages result in swelling and/or thickening of the retina around the macula, the central part of the retina in which fine visual discrimination occurs [3]. In patients with type 2 diabetes, ME is the primary cause for moderate and legal blindness [4]. About 10% of people after 15 years of DM are likely to develop a severe visual handicap [5]. Visual impairment related to DR may have serious consequences in diabetic patients, profoundly affecting health- and vision-related quality of life and leading to difficulties in treatment resulting from reduced ability of patients to manage their disease. Indeed, it has been reported that progression of DR impacts the health-related quality of life (HRQOL) [6]. Hypertension, a common comorbidity of diabetes, is a risk factor for microvascular complications such as retinopathy [7].

The objectives of this study were to describe the impact of co-morbidities, visual acuity, DR grade and macular edema on the HRQOL among patients with DR.

Material and methods

Study design

The study was non-interventional and cross-sectional, and was carried out in 2003 in Germany. Patients (n=207) with type 1 or type 2 DM, aged 18 years or older, being diagnosed with DR on January 1, 2002 or before and treated in 2002 in ophthalmologic practices, willing and able to provide written informed consent participated in this study. Severity classes of DR were based on the International Clinical Classification for Diabetic Retinopathy, developed in 2002 [8]. The severity of DR in the worst affected eye was used for retinopathy grading as follows: (1) mild non-proliferative diabetic retinopathy (NPDR); (2) moderate NPDR; (3) severe NPDR; and (4) proliferative diabetic retinopathy (PDR). Severity of ME in the worst affected eye was used as follows: no ME, no clinically significant ME (NCSME), and clinically significant ME (CSME). The details of the study methodology are published elsewhere [9]. To retrieve data on patient-reported outcomes, interviews with the patients were undertaken. Patients' demographic and medical data were collected from the medical charts. The study was performed in accordance with the Declaration of Helsinki (1996) and local ethics requirements.

HRQOL assessment

To assess HRQOL, generic and disease-specific instruments were used in this study. As a generic instrument, the Short-Form Health Survey (SF-12) questionnaire [10] was used. The SF-12 contains 12 items from the eight scales of the SF-36 [11] and measures physical and mental dimensions of HRQOL. Six of the 12 items create the physical component summary score (PCS) and the remaining six items create the mental component summary score (MCS).

In addition to SF-12, information of patient-reported outcomes according to the disease-specific instrument Retinopathy Dependent Quality of Life questionnaire (RetDQoL) [12] and Retinopathy Treatment Satisfaction Questionnaire (RetTSQ) [13] was collected. All HRQOL questionnaires used in this study had previously undergone cultural and linguistic validation into German. However, only SF-12 was used in the current modeling of the data. We were interested in general HRQOL assessment (rather than retinopathy-specific HRQOL), because the patients with diabetic retinopathy have co-morbidities the burden of which on a patient may not be adequately captured by using a retinopathy-specific HRQOL instrument.

Model

It was hypothesized that co-morbidities, visual acuity impairment, progression of DR and ME would have an impact on PCS and MCS. We applied structural equation modelling approach (SEM) [14, 15] because it enables to test in one model the effects of several exogenous variables on several endogenous variables at the same time. The main endogenous variables are PCS and MCS, reflecting quality of life. Clinical characteristics (co-morbidities, DR, ME, visual acuity) were modelled as exogenous observed variables.

The modelling was done in Mplus version 3.13 [16]. In order to allow our estimator to take into account the fact that our variables violate the distributional assumptions of normality, we analyzed the model using robust WLS. This estimator performs well with ordinal data, where the normality assumption is violated [17]. The missing values were imputed by the ME algorithm in the SPSS program [18]. Descriptive analysis of data was done in SAS version 8.2 (SAS Institute Inc, Cary, NC, USA).

Results

General information about participating patients (N=207) in terms of socio-demographic, clinical, and HRQOL characteristics is summarized in Table 1. The study population had an average duration of diabetes of 20 years

Table 1 Socio-demographic, clinical, and HRQOL characteristics of sample (*N*=207)

Age (years) – Median (IQR)	64 (55–71)
Sex, females –*n* (%)	104 (50.2)
Marital status, currently married –*n* (%)	148 (71.5)
Living with partner/family –*n* (%)	144 (69.6%)
Currently smoke –*n* (%)	44 (21.3)
Main activity –*n* (%)	
Early retired[a]	26 (12.6)
Retired	95 (45.9)
Unemployed	6 (2.9)
Working for pay	50 (24.2)
Caring for family	16 (7.7)
Unknown	14 (6.8)
Reduction in earning capacity due to diabetic retinopathy –*n* (%)	36 (17.4)
Type of diabetes –*n* (%)	
Type 1	54 (26.1)
Type 2	153 (73.9)
Years since diagnosis with diabetes – Median (IQR)	18 (13–27)
Years since diagnosis with diabetic retinopathy – Median (IQR)	6 (3–10)
Most recent HbA1c – Median (IQR)	7.2 (6.5–7.9)
Concomitant diseases –*n* (%)	165 (79.7)
Best corrected visual acuity, binocular[b] – Median (IQR)	0.80 (0.50–1.00)
No clinically significant macular oedema –*n* (%)	6 (2.9)
Clinically significant macular oedema –*n* (%)	40 (19.3)
Blindness –*n* (%)[c]	7 (3.4)
Body mass index – mean (SD)	27.9 (4.4)
25–29.9 –*n* (%)	74 (35.7)
≥ 30.0 –*n* (%)	59 (28.5)
Treatment of diabetes –*n* (%)[d]	
Diet only	2 (1.0)
Treatment with oral hypoglycemic	15 (7.3)
Treatment with insulin alone or with oral hypoglycemics	170 (82.1)
Present HRQOL from RetDQoL	
(In general, my present quality of life is) –*n* (%)	
Excellent	2 (1.0)
Very well	22 (10.6)
Well	106 (51.2)
Indifferent	60 (29.0)
Bad	10 (4.8)
Very bad	1 (0.5)
Extremely bad	1 (0.5)
NA	5 (2.4)
Retinopathy-dependent HRQOL from RetDQoL –*n* (%) (If I did not have diabetic eye problems, my quality of life would be)	
Very much better	41 (19.8)
Much better	55 (26.6)
A little better	59 (28.5)
The same	49 (23.7)
NA	3 (1.5)
Satisfaction with treatment of diabetic retinopathy from RetTSQ – mean (SD) (How satisfied you are with treatment of your diabetic eye problems, on a scale 0 to 6, 0-very disappointed, 6 – very satisfied)	5.2 (1.3)
SF-12 physical component summary score - mean (SD)	40.0 (11.6)
SF-12 mental component summary score - mean (SD)	47.3 (11.0)

Abbreviations: *IQR*, interquartile range; *HRQOL*, health-related quality of life; *RetDQoL*, Retinopathy Dependent Quality of Life Questionnaire; *NA*, not available; *RetTSQ*, Retinopathy Treatment Satisfaction Questionnaire

[a] Retirement before the generally accepted age of 65

bVisual acuity is reported as a proportion in Germany (1.00 in Germany=6/6 in UK)

[c] Persons considered legally blind in Germany, i.e., those whose vision can not be corrected to better than 0.1 (20/200)

[d] For some patients (n=20, 9.7%) the treatment of diabetes was not specified

(SD 10.3) and a median duration of time in years since the diagnosis of DR of 6 (Interquartile range, IQR 3–10). Of 207 patients with DR, 78 (37.7%) had diabetic neuropathy and 28 (13.5%) diabetic nephropathy. The average age of the patients was 65 (SD 12.7), 50.2% (n=104) were female, the most recently measured HbA1c was 7.4 on average (SD 1.3), and the majority of patients were overweight (BMI: 25.0–29.9, 35.7%) or obese (BMI ≥ 30.0, 28.5%) (Table 1). About 60% of patients were non-smokers (n=120), smoking status of one patient was unknown, and the remaining patients (n=86, 41.5%) were tobacco users currently or at some time during their life.

Of the 207 patients, 44 (21.3%) had mild NPDR, 48 (23.2%) had moderate NPDR, 52 (25.1%) severe NPDR and 63 (30.4%) had PDR. A total of 161 patients had no ME, six (2.9%) had NCSME, and 40 (19.3%) had CSME. Seven patients (3.4%) were considered legally blind, which means that visual acuity in these patients cannot be corrected to better than 0.1 (or 20/200). Of these seven patients, four had no ME, and three others had CSME. The best corrected binocular visual acuity averaged 0.70 (SD, 0.32). The variable number of co-morbidities reflected the number of co-morbidities accompanying the DR and included nephropathy (n=28, 13.5%), neuropathy (n =78, 37.7%), hypertension (n =132, 80.0%), hypercholesterinaemia (n=71, 43.0%), hyperlipidemia (n =26, 15.8%), coronary heart disease (n =52, 31.5%), coronary insufficiency (n=27, 16.4%), peripheral vascular disease (n =15, 9.1%), cerebrovascular disease (n =13, 7.9%), psychiatric conditions (n=14, 8.5%) and other accompanying conditions (n =29, 17.6%). Of 29 patients in category ‘other co-morbidities’ one had a renal carcinoma, another patient was on long-term dialysis, four others had episodes of cerebral apoplexy in the past, and the remaining 23 had uncomplicated medical conditions. Patients had on average 2.35 co-morbidities (SD 1.63).

The model is displayed in Fig. 1.

Both the unstandardized and the standardized direct regression coefficients are presented in Table 2.

Variable number of co-morbidities had a negative effect on visual acuity (b=−0.26, standardized) and a similar negative effect on PCS (b=−0.27). The variable DR grade had a negative effect on visual acuity (b=−0.19) and a positive effect on the variable ME (b=0.44). In other words, higher DR grade was associated with a worse visual acuity and a worse ME. ME displayed a strong negative effect on visual acuity (b=−0.58) and also on MCS (b=−0.29). The visual acuity had a positive effect (b=0.48) on PCS. DR grade had no direct effect on PCS and MCS, and its negative effect was mediated by visual acuity as well as by ME.

The global fit measures suggested a very good fit to the data according to which we did not reject the model [19, 20]

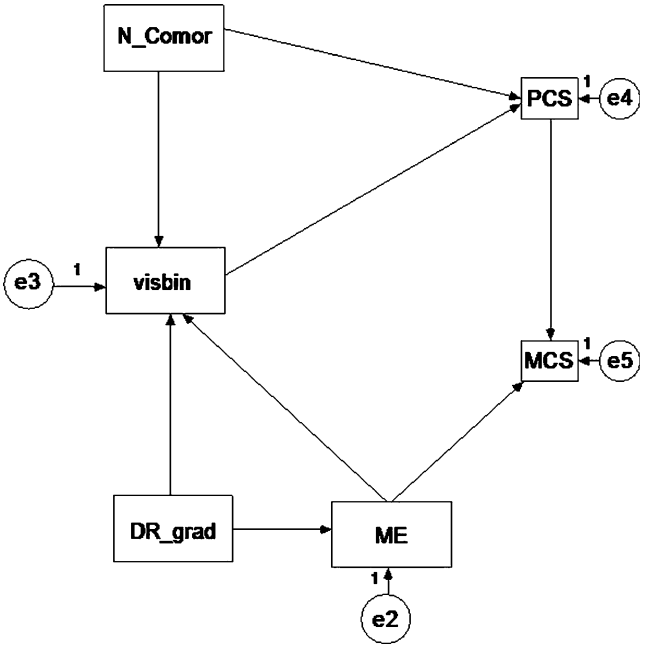

Fig. 1 The SEM model. *N_Comor*, number of co-morbidities; *visbin*, binocular vision acuity; *DR_grad*, severity grade of diabetic retinopathy; *ME*, macular edema; *PCS*, physical component summaries; *MCS*, mental component summaries, *e2–e5*, prediction errors; ←, a direct causal relation

(Chi-square/degrees of freedom=1.00, P level=0.42). There were no modification indices suggested by the program. Therefore we can conclude that the structural model specified is consistent with the data.

Discussion

Diabetic retinopathy is thought to have great impact on the HRQOL in adults with type 1 or type 2 diabetes. This study reflects the direct and indirect effects of different aspects of DR, namely co-morbidities, visual acuity, ME and severity grade of DR on the HRQOL of patients. Diabetes complications have a significant impact on HRQOL [21, 22]. It has been reported that patients with more diabetes complications, particularly having three or more complications, are likely to report poor HRQOL [23].

In this study, having co-morbidities was inversely associated with the visual acuity and the HRQOL. This may possibly be explained by the following reasons: first, patients with co-morbidities were significantly older than those without them (median age 65 vs. 55, respectively, p= 0.0011, by Wilcoxon test). Furthermore, patients with co-morbidities tended to have worse visual acuity than patients without them (median 0.67 vs. 1.0, respectively, p<0.0001, by Wilcoxon test). Patients may experience visual acuity loss not only because of diabetes but also because of

Table 2 Unstandardized and standardized effects

			Estimate, unstandardized	SE	*P*	Estimate, standardized
ME	←	DR grade	.435	.110	<0.05	.440
Visual acuity, binocular	←	Number of co-morbidities	−.049	.012	<0.05	−.263
Visual acuity, binocular	←	DR grade	−.051	.019	<0.05	−.190
Visual acuity, binocular	←	ME	−.158	.021	<0.05	−.580
PCS	←	Visual acuity, binocular	16.435	2.469	<0.05	.475
PCS	←	Number of co-morbidities	−1.727	.350	<0.05	−.270
MCS	←	ME	−2.551	0.796	<0.05	−.288
MCS	←	PCS	.102	.061	0.10	.108

Abbreviations: *ME*, macular edema; *DR*, diabetic retinopathy; *PCS*, physical component summaries; *MCS*, mental component summaries; *SE*, standard error; *P*, *p*-value

conditions such as age-related macular degeneration, cataract, or glaucoma [24, 25].

Due to increased impairment by those additional diseases, the HRQOL of patients may be decreased. The grade of DR has also a negative effect on the visual acuity. As the severity level of diabetic retinopathy increases, patients are at greater risk for incorrigible vision loss [26]. ME also has a negative effect on the binocular vision since it has a causal role in vision loss which could partially explain its negative effect on HRQOL. Indeed, vision loss is of tremendous concern to patients with diabetes, and if it does occur, it has a substantial negative impact on HRQOL [27]. Interestingly, the severity grade of DR had no direct effect on the HRQOL but an indirect through visual acuity impairment and ME.

Positive effects could be observed for the severity grade of DR on ME, as indicated above, this positive effect indirectly influences the HRQOL in a negative way. The more severe the grade of DR, the more severe the ME is expected to be, which was associated with impaired HRQOL in our model. As expected, a strong positive effect was shown for the binocular vision acuity on HRQOL.

We have found that variables diabetic retinopathy severity grade, macular edema, visual acuity, and patient co-morbidities influence both the physical and mental components of HRQOL. Furthermore, the physical component of HRQOL in our model was affected to a greater degree than was the mental component.

We assumed that the relation between DR and MCS is indirectly mediated by ME and by visual acuity and PCS. We tested whether this is empirically supported by the data and found no modification indices, suggesting adding a direct effect from DR to MCS. In other words, the direct effect is not statistically significant. Thus, based on the present analysis, the relation between DR and MCS seems to be indirect. In order to generalize it to other cases, the model should be replicated with other data sets.

Our study has the following limitations: first, the causes of visual impairment in this study were not assessed. Due to cross-sectional design of this study, we do not know whether vision acuity in patients was impaired before the diabetes onset, and if it was, what was the further decrease in visual acuity attributed to diabetic retinopathy. Second, HRQOL questionnaires were in majority of cases interviewer-administered (in patients with impaired vision) and in some cases self-administered. It has been reported that mode of administration may impact the HRQOL assessment, e.g., it has been reported that interviewer-administered mode may introduce the interviewer bias with HRQOL questionnaires, because interviewed patients may alter their responses to present themselves in a favorable light and therefore lead to higher than expected HRQOL in certain domains [28]. However, exclusive reliance on self-administered mode would introduce selection bias, as patients with impaired vision may not be able to complete the questionnaires by themselves and therefore be underrepresented in this study. Third, it may be possible that ophthalmologic practices randomly selected from the physicians database may not be representative of all ophthalmologic practices in Germany due to small number (n=41 practices), which may possibly introduce selection bias. Forth, patient selection in a practice which was done by ophthalmologist according to predefined scheme was not monitored, so we cannot assess whether ophthalmologists followed patient selection scheme as expected. Fifth, results of our study apply to aggregated data on patients with type 1 and type 2 DM, which we justify based on comparable data between type 1 and type 2 DM patients in our study. But since retinopathies in type 1 and type 2 DM patients are different entities, separate analyses for each type of DM are recommended. Further limitation is that we did not consider the laterality of DR or ME and vision in study subjects. Therefore, if visual impairment and DR/ME is not in the same side of the eye in a subject, that might not be due to DR or ME. In other words, by using binocular vision, we dilute the association between DR/ME and vision. And finally, a validation of the sociodemographic

structure of our sample with an external database of patients with diabetic retinopathy in Germany was not done because of unavailability of such a database.

Despite these weaknesses, the strength of this study is that it is the first study that examined the impact of important clinical characteristics in patients with diabetic retinopathy in Germany on HRQOL. We conclude that diabetic retinopathy severity grade, macular edema, visual acuity, and patient co-morbidities significantly influence both the physical and mental components of HRQOL. Further studies are warranted to investigate HRQOL in patients with visual impairment due to DR/ME compared to patients with visual impairment due to other causes.

Acknowledgements The authors would like to thank two anonymous reviewers for their valuable comments on the paper. This research was supported by Lilly Germany GmbH, Bad Homburg.

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