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Published in:
Quality of Life Research

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2003

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hart, HE., Bilo, HJG., Redekop, WK., Stolk, RP., & Meyboom-de Jong, B. (2003). Quality of life of patients with type I diabetes mellitus. *Quality of Life Research*, 12(8), 1089-1097.

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Quality of life of patients with type I diabetes mellitus

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Accepted in revised form 25 October 2002

Abstract

The objective of this study was to assess health related quality of life (QOL) in patients with type I diabetes mellitus (DMT1) and to compare their QOL with the QOL of persons of comparable age in the general population. Furthermore we wanted to investigate which factors mostly influence QOL. In a Dutch cohort of 281 patients with DMT1 QOL was assessed using two generic instruments: the EuroQol and the RAND-36. We performed regression analyses to investigate relationships between several demographic (e.g. sex, age, marital status) and diabetes-specific variables (e.g. HbA1c, frequency of insulin injection, presence of acute and chronic complications) and QOL. The Spearman rank correlations between RAND-36 domains and EuroQol were analysed. RAND-36 results showed, for almost all domains, a QOL comparable with persons of comparable age in the general population. In contrast the QOL measured with the EuroQol was lower for subjects with DMT1. Hyperglycaemic complaints and macrovascular complications had a profound negative influence on QOL. Most correlations between the RAND-36 results and the EuroQol results corresponded with our expectations. Longitudinal data and comparison with results of several diabetes-specific questionnaires should help to establish which instrument might be most appropriate to measure QOL in patients with DMT1.

Key words: EuroQol, Quality of life, RAND-36, Type I diabetes mellitus

Introduction

Diabetes mellitus type I (DMT1) is a chronic disease caused by auto-immune destruction of the insulin-producing pancreatic beta cells resulting in an absolute inability to produce insulin, necessary for the regulation of blood glucose [1].

The primary goal of treatment is to reach adequate metabolic control by daily insulin injections to avoid diabetic complications. The more intensive the treatment, the better the chance to delay the onset and the progression of complications [2]. Side effects of more intensive therapy are body weight gain and an increased frequency of hypoglycaemic episodes. In particular, the frequency of

hypoglycaemia can influence a patient's life [3]. It can be difficult to find a balance between food intake, exercise and insulin dose to reach a satisfactory metabolic control. This may affect health related quality of life (QOL) in many different ways [4].

In recent years, QOL consisting of physical, psychological and social aspects has become more important in health care. Different instruments have been developed to measure QOL in various patient categories: generic instruments to allow comparisons with other patient populations or samples of the general population and disease-specific instruments to assess the influence of different aspects of a specific disease and its treatment [5–9].

The attention paid to the QOL of patients with DMT1 is very important [4, 10–13]. The patients with DMT1 have a lifelong, chronic and serious disease and will develop several micro- and macrovascular complications, which will have a daily impact on their physical and psychological functioning. In addition to the fact that DMT1 is a serious chronic disease, it is a frequently occurring disease.

It is not clear, which factors influence QOL the most, how the individuals appraise the different aspects of the regimen, or which patients have the lowest QOL, or whether clinicians can influence those factors negatively influencing QOL. For these reasons it is of great importance to have good insight in the factors influencing the well being of this group of patients.

In this study we addressed the following questions: How do subjects with DMT1 assess their QOL compared to persons of comparable age from the general population? Which factors influence the QOL of patients with DMT1?

Methods

Patients

From January 1995 to January 1996, 293 consecutive DMT1 patients, treated at the outpatient clinic of the Isala Clinics in Zwolle, the Netherlands, were invited to participate in the study. A group of 281 patients agreed to participate and was investigated in 1995. DMT1 was defined as starting insulin therapy within 6 months after the first signs of diabetes mellitus and before the age of 30 years, or the absence of C-peptide secretion. Approval was obtained from the Hospital Scientific and Ethical Committee. All patients gave informed consent.

Quality of life

QOL was assessed using two generic instruments, the RAND-36-item Health Survey (RAND-36) and the EuroQol. Questionnaires were sent by mail to the patient's home address. Patients were asked to fill in the questionnaires at home. Upon the visit to the outpatient clinic, the patients returned the completed questionnaires to the diabe-

tes specialist nurse. Patients who did not return the completed questionnaires when visiting the clinic were asked to send their completed questionnaires afterwards.

The RAND-36 is a self-administered questionnaire containing 36 items involving eight different domains: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. For each domain, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health) [14, 15]. In addition, physical and mental component summary scores were determined (PCS/MCS) [16]. The questionnaire takes about 10 min to complete. The instrument has been translated in Dutch [17] and validated for the Dutch population [18].

The EuroQol is a simple generic measure, developed by a multidisciplinary group of researchers from five European countries, consisting of two parts (EQ-5D and EQ-VAS). For the EQ-5D part, there are five questions covering the areas mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is divided into three levels: no problem, some/moderate problems and extreme problems/unable to perform. A respondent's health state is defined by combining one level from each of the five dimensions (EQ-5D). A total of 243 possible health states can be defined in this way. Valuations of these health states have been made by the UK general public, using a valuation technique called time trade-off. The values, or utilities, are scaled on a scale on which 0 is the value of dead and 1 is the value of perfect health [19]. Furthermore a single overall score can be elicited using the EuroQol thermometer, a self-rated health status using a graduated (0–100) visual analogue scale, similar to a thermometer (EQ-VAS). The EuroQol takes about 2 min to complete and has been validated for the Dutch situation [20].

Clinical data

One trained physician (J.H.A.) examined all patients according to a standardised protocol. Demographic data (age, sex, married/having a partner, level of education) and data concerning therapy (HbA1c, frequency of insulin injection,

frequency of self-monitoring of blood glucose and presence of *hyperglycaemic complaints*) were recorded. Patients recorded all *hypoglycaemic events* ('did you have a hypo in the past 3 months?') during the 3 months preceding the outpatient visit. Patients were asked to report whether they had one of six different *hyperglycaemic complaints* during the last three months (yes/no): tiredness, weight loss, pruritus, thirst, polyuria and polydipsia (Cronbach's α 6-items 0.74). Metabolic control was assessed by measuring glycosylated haemoglobin A1c (HbA1c). The presence of comorbidity (one or more diseases besides diabetes) was assessed using a list of 26 chronic diseases [21].

Macrovascular complications

Patients were classified as having macrovascular complications when one or more of the following diagnoses was present: angina pectoris, myocardial infarction, intermittent claudication, transient ischaemic attack (TIA), or a cerebrovascular accident (CVA). The physician recorded these diagnoses in the clinical status of all patients.

Microvascular complications

Patients with retinopathy, neuropathy or nephropathy were diagnosed as having microvascular complications.

Retinopathy

The ophthalmologist examined all patients annually. The degree of diabetic retinopathy was assessed by fundoscopy in mydriasis. The classification of diabetic retinopathy used was based on Jong [22]: no retinopathy (= 0), background retinopathy (= I), preproliferative (= II), and proliferative diabetic retinopathy (= III).

Retinopathy was scored positive, when any type of retinopathy was present in either eye. When the degree of retinopathy was different in two eyes, the highest degree was scored.

Neuropathy

Sensitivity was tested by the Semmes-Weinstein pressure aesthesiometer [23]. At five dorsal and plantar sites on the feet sensitivity was tested using six different monofilaments. When the monofila-

ment 5.07 was not felt at one of the 10 test sites, patients were diagnosed as having neuropathy.

Nephropathy

The 24-hours urinary excretion of albumin (UAER) was measured yearly. UAER was considered abnormal when it was ≥ 30 mg/24 hours. Micro-albuminuria was defined as 30–300 mg/24 hours and macro-albuminuria as ≥ 300 mg/24 hours. All patients with micro-albuminuria or macro-albuminuria were defined as having nephropathy [24–26].

At the time of the study (1995) patients with a micro-albuminuria > 100 mg/24 hours received an angiotensin converting enzyme inhibitor (ACE-inhibitor) in the Isala Clinics. We classified ACE-inhibitor users as having nephropathy, unless ACE-inhibition was started specifically for hypertension.

Analysis

QOL of patients was compared with the QOL of the general population using the *T*-test for independent samples. Univariate and multivariate stepwise regression analyses (with the PCS, MCS, the EuroQol 5-D, and the EuroQol-VAS being the dependent variables) were performed to investigate the relationships between QOL scores (RAND-36 and EuroQol) and demographic data (sex, age, marital status, level of education) and data concerning the disease and its therapy (e.g. frequency of insulin injection, HbA1c, acute and chronic complications). Furthermore we calculated the Spearman rank order correlations between the domains of the RAND-36 and the dimensions of the EuroQol. We expected correlations between 'mobility' and the domains 'physical functioning' and 'role physical', between 'self-care' and 'physical functioning' and 'role physical', between 'usual activities' and most domains of the RAND-36, between 'pain/discomfort' and 'bodily pain' and between 'anxiety/depression' and the more mental domains of the RAND-36. We considered correlations < 0.39 as weak, 0.40–0.59 as moderate and > 0.60 as strong.

Relationships were considered statistically significant when *p*-values ≤ 0.05 were reached. Data were analysed using SPSS for Windows version 10.0.7.

Results

A total of 281 adult patients with DMT1 entered the study. Baseline characteristics of the study population are shown in Table 1. Mean age in the study population was 38.2 years and 54.4% were men. Most patients received intensive therapy (87.9%) and self-monitored their blood glucose values. Almost half of the patients had microvascular complications (47.1%) (Table 1). Most patients with retinopathy had grade I diabetic retinopathy, almost always in both eyes. Of the patients with nephropathy ($n = 53$), 21% had

Table 1. Personal and disease-specific characteristics of the study population

Number of patients	281	
Gender (men)	153	(54.4%)
Age (years)	38.2	(12.4)
Duration of diabetes (years)	17.2	(10.7)
Married/cohabiting	242	(88.3%)
High level of education	90	(32%)
Smoking	91	(32.4%)
Alcohol use	172	(61.2%)
Systolic blood pressure (mm Hg)	139.1	(18.4)
Diastolic blood pressure (mm Hg)	82.9	(8.3)
Ratio of total cholesterol (mmol/l)/HDL-cholesterol (mmol/l)	3.8	(1.2)
Body mass index (kg/m ²)	24.7	(3.2)
HbA1c (%)	8.3	(1.9)
Frequency of insulin injection (per day):		
2–3	34	(12.1%)
4	175	(62.3%)
Infusion	72	(25.6%)
Self-monitoring of blood glucose	275	(100%)
Number of control measurements per week	11.9	(11.6)
Number of patients with		
Hypoglycaemic events last 3 months	224	(81.5%)
Hyperglycaemic complaints last 3 months	150	(54.5%)
Prevalence of diabetic complications		
<i>Microvascular</i>	129	(47.1%)
Retinopathy	97	(35.7%)
Nephropathy	53	(18.9%)
Neuropathy	32	(11.5%)
<i>Macrovascular</i>	27	(9.6%)
Comorbidity (one or more chronic medical condition)	161	(58.5%)

Values are number of patients or means with valid percentage or standard deviation between parentheses.

macro-albuminuria ($n = 11$), the others micro-albuminuria. About 10% of the patients had macrovascular complications, the most frequently reported diagnoses being angina pectoris and intermittent claudication. Most patients with comorbidity had one or two other chronic medical conditions besides their diabetes.

The QOL questionnaires were completed by 274 patients (97.5%) (Table 2). The RAND-36 QOL domain scores were comparable with those of persons of comparable age in the Dutch general population [15], except for the General Health domain that was lower than in the general population ($p = 0.022$) and the Bodily Pain domain that was higher than in the general population ($p = 0.010$). The EQ-5D and the EQ-VAS-score were lower in our study group compared to persons of comparable age from the UK general population [27].

Univariate analysis showed that females reported a lower QOL (MCS and EQ-5D) than males. Older patients had lower scores for the PCS, the EQ-5D and the EQ-VAS. Patients having a partner and patients using alcohol reported a higher MCS and EQ-VAS. A higher HbA1c was associated with a lower EQ-VAS. Patients with continuous insulin therapy had a lower MCS and a lower EQ-5D, whereas patients with four-times daily insulin injection reported a higher PCS, than patients with 2–3 injections daily. Patients with a high frequency of self-monitoring had lower scores for the PCS, the EQ-5D and the EQ-VAS. Patients having hyperglycaemic complaints, macrovascular complications and comorbidity reported a lower QOL (PCS, MCS, EQ-5D, EQ-VAS). Patients having microvascular complications also reported a lower QOL (MCS, EQ-5D and EQ-VAS).

Multivariate analysis for the RAND-36 and the EuroQol showed that the presence of a macrovascular complication had the most pronounced negative influence on QOL (Table 3). Older age, higher frequency of self-monitoring a week, macrovascular complications and comorbidity were associated with lower PCS scores (Table 3). The assessment of the impact of age and frequency of self-monitoring is based on a combination of the beta coefficient with the observed range in values. For example, a decrease in PCS score of 0.91/10 years increase in age was seen. In contrast, younger age, unmarried status, hyper-

Table 2. Comparison of QoL scores seen in the study population with scores seen in the general population

	This study DMT1 N = 274	General population [15] N = 195	
Age (years)	38.2	35–44	
Percentage men	54.4%	31%	
RAND-36			<i>p</i> -Values
Physical functioning	90.4 (14.7)	90.0 (14.4)	0.769
Role physical	82.8 (32.4)	82.9 (32.0)	0.974
Bodily pain ^a	88.7 (17.8)	83.8 (21.7)	0.010
General health	68.0 (20.1)	74.0 (20.7)	0.002
Vitality	67.5 (20.0)	67.1 (18.9)	0.826
Social functioning	86.9 (20.0)	88.0 (17.6)	0.529
Role emotional	84.0 (31.8)	82.2 (33.5)	0.558
Mental health	76.6 (17.3)	76.9 (18.0)	0.857
	DM type n = 274	General population [27] n = 561	
EuroQoL			
Age (years)	38.3	35–44	
Percentage men	54.4%	45.6%	
EQ-5D	0.88 (0.17)	0.91 (0.16)	0.052
EQ-VAS	80.8 (15.2)	86.6 (13.8)	<0.001

Values are means with standard deviations between parentheses. *p*-Values concerns *T*-test for independent samples.

^aHigher bodily pain score indicates less pain.

Table 3. Results of the multivariate analyses for the RAND-36 and the EuroQoL

	β (<i>p</i> -value)			
	PCS adjusted $R^2 = 0.289$	MCS adjusted $R^2 = 0.240$	EQ-5D adjusted $R^2 = 0.200$	EQ-VAS adjusted $R^2 = 0.228$
Females				
Age (per year)	−0.091 (<i>p</i> = 0.015)	0.118 (<i>p</i> = 0.021)		
Married/cohabiting		5.669 (<i>p</i> = 0.002)		
High level of education				−5.432 (<i>p</i> = 0.006)
HbA1c (%)				−1.241 (<i>p</i> = 0.012)
Frequency of insulin injection:				
Four-times a day relative to 2–3 times				
Continuous relative to 2–3 times				−0.224 (<i>p</i> = 0.005)
Self-monitoring a week	−0.167 (<i>p</i> < 0.001)			−0.224 (<i>p</i> = 0.005)
Hypoglycaemic complaints				
Hyperglycaemic complaints		−7.428 (<i>p</i> < 0.001)	−0.071 (<i>p</i> = 0.002)	−8.716 (<i>p</i> < 0.001)
Microvascular complications				
Macrovascular complications	−8.468 (<i>p</i> < 0.001)	−6.698 (<i>p</i> = 0.002)	−0.146 (<i>p</i> < 0.001)	−10.016 (<i>p</i> = 0.002)
Comorbidity	−2.323 (<i>p</i> = 0.0010)		−0.078 (<i>p</i> = 0.001)	

glycaemic complaints and macrovascular complications were associated with lower MCS scores (Table 3). The presence of hyperglycaemic complaints, macrovascular complications and comorbidity were associated with lower EQ-5D scores (Table 3). High level of education, higher HbA1c,

higher frequency of self-monitoring, hyperglycaemic complaints and macrovascular complications were associated with lower EQ-VAS scores (Table 3).

The Spearman rank correlations between the domains of the RAND-36 and the EuroQoL

Table 4. Spearman rank order correlations between domains of the RAND-36 and the EuroQoL

RAND-36	EuroQoL				
	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Physical functioning	-0.490 ($p < 0.001$)	-0.025 ($p = 0.686$)	-0.509 ($p < 0.001$)	-0.475 ($p < 0.001$)	-0.218 ($p < 0.001$)
Role physical	-0.401 ($p < 0.001$)	-0.062 ($p = 0.309$)	-0.700 ($p < 0.001$)	-0.390 ($p < 0.001$)	-0.389 ($p < 0.001$)
Bodily pain	-0.343 ($p < 0.001$)	-0.039 ($p = 0.523$)	-0.478 ($p < 0.001$)	-0.717 ($p < 0.001$)	-0.279 ($p < 0.001$)
General health	-0.324 ($p < 0.001$)	-0.079 ($p = 0.195$)	-0.480 ($p < 0.001$)	-0.431 ($p < 0.001$)	-0.323 ($p < 0.001$)
Vitality	-0.227 ($p < 0.001$)	-0.001 ($p = 0.993$)	-0.573 ($p < 0.001$)	-0.337 ($p < 0.001$)	-0.408 ($p < 0.001$)
Social functioning	-0.272 ($p < 0.001$)	-0.048 ($p = 0.434$)	-0.558 ($p < 0.001$)	-0.388 ($p < 0.001$)	-0.484 ($p < 0.001$)
Role emotional	-0.166 ($p = 0.006$)	-0.066 ($p = 0.280$)	-0.700 ($p < 0.001$)	-0.314 ($p < 0.001$)	-0.389 ($p < 0.001$)
Mental health	-0.196 ($p = 0.001$)	0.020 ($p = 0.737$)	-0.402 ($p < 0.001$)	-0.332 ($p < 0.001$)	-0.531 ($p < 0.001$)

dimensions are shown in Table 4. The correlations between mobility and 'physical functioning' and 'role physical' were moderate. The dimension self-care did not show any significant correlation with one of the RAND-36 domains, while the usual activities dimension was moderately/strongly correlated with all domains of the RAND-36. Pain/discomfort was strongly correlated with the domain 'bodily pain'. Anxiety/depression was particularly correlated with the domain 'mental health'.

Discussion

QOL measured in our study population was comparable with the QOL of persons of comparable age in the Dutch general population, when using the RAND-36, except for the domains of 'bodily pain' and 'general health', which were respectively higher and lower than in the general population. We cannot explain why patients with DMT1 reported less pain (i.e. higher RAND-36 bodily pain scores) than patients in the general population. A possible explanation is the fact that the percentage of females in the general population sample was higher than in our cohort (69 vs. 46%) and that females tend to report more symptoms such as bodily pain [15, 28]. The EuroQoL gave lower QOL levels for subjects with DMT1 than patients in a UK sample of the general population. Wikblad et al. [29] reported a QOL equal to persons in the general population just as in our study (mean age 43.5 years). In the study of Wandell et al. [30], diabetic patients reported a QOL lower than persons in a population sample. However their cohort was older (mean 51.5 year) than our cohort (mean 38.2 years). Recently Hahl et al. [31]

reported a lower health related QOL for patients with DMT1 (in the age groups 35–44 and 45–54) compared to the general population, measured with the 15-D, a generic measure.

The frequency of macrovascular complications was relatively low (9.6%) in our cohort, whereas microvascular complications were more prevalent (47.1%), as could be expected with this duration of diabetes (mean 17.2 years). Almost by definition, the early stages of microvascular complications will not have an impact on daily life. Most complications were in the early stages in our patient group.

When considering our results of the uni- and multivariate regression analyses it is important to remember that statistically significant associations are not the same as clinically important relationships. The problem is the interpretation of one's statistical exercises [32]. Although the developers of the instruments do not promote the use of the smallest change which is still considered clinically significant, score changes of >1 point for the summary scores [33], 0.05 points for the EQ-5D and five points for the EQ-VAS (EuroQoL group) can be used as a guide. If we apply these arbitrary cut-off points, the components found in the regression models have a clinically important negative impact on the health related QOL of patients with DMT1. We can conclude that the presence of macrovascular complications definitely has a large negative impact on the health related QOL of patients with DMT1. Other studies also reported a worse QOL, measured with generic as well as diabetes-specific instruments, when late complications were present, but these studies did not differentiate between microvascular and macrovascular complications [29, 34–36].

Hahl et al. [31], also reported a significant negative influence on QOL by the symptoms of long-term micro- and macrovascular complications. In this study however, they used self-reported symptoms of the complications instead of the objective scoring of complications in our cohort. The presence of microvascular complications seemed to be of minor influence on the QOL in our study. In the multivariate regression analyses these complications did not have a statistically significant influence on QOL. Perhaps this finding can be explained by the fact that a light to moderate degree of neuropathy, retinopathy and/or nephropathy will not even cause minor symptoms or complaints and thus will not interrupt daily life in subjects with DMT1. In contrast, macrovascular complications will virtually always cause manifest symptoms or complaints. However, two studies described an influence of microvascular complications on QOL [37, 38]. Hanestad et al. reported that the presence of nephropathy had a negative effect on QOL, whereas neuropathy was associated with a better QOL in her study. The severity of complications was not properly clarified. Wu et al. observed a higher QOL (measured with the SF-36) for patients with retinopathy and concluded that further study was needed to explore the underlying reasons for this surprising finding. The UK Prospective Diabetes Study (UKPDS) reported for patients with diabetes mellitus type 2 (DMT2) the same negative impact on QOL by the presence of long-term complications [39]. Patients with macrovascular complications reported a lower EQ-5D, while patients with microvascular complications reported more tension and a total mood disturbance (Profile of Mood State). In this study, too, the generic measure (EQ-5D) did not measure a lowered QOL by microvascular complications. Perhaps the generic instruments, such as the EQ-5D, are not sensitive enough to measure the sometimes mild symptoms associated with the microvascular complications. Redekop et al. [40] however did find an association between microvascular complications and reduced QOL.

Another negative influence on QOL is the presence of hyperglycaemic complaints. These had a negative association with the RAND-36 and the EuroQol scores, whereas remarkably the presence of hypoglycaemic events was of less importance.

Only the univariate analysis for the EQ-VAS showed a significant negative influence of the presence of hypoglycaemic events. However, in the intensive treatment group of the Diabetes Control and Complications Trial the presence of hypoglycaemia was the only factor which tended to cause a decreased QOL, by more symptomatic distress [3].

In our study, patients receiving continuous insulin therapy reported a lower MCS and EQ-5D. Such an intensive therapy obliges the patients to monitor their blood glucose levels regularly. However, it was the frequency of self-monitoring, which remained of significant negative influence in the multivariate analysis of both the PCS and the EQ-VAS. The correlation between the frequency of self-monitoring and continuous insulin therapy was moderate (0.503, $p = 0.010$). Therefore, the obligatory high frequency of self-monitoring associated with continuous insulin therapy could explain the perceived lower QOL of patients using continuous therapy.

The finding that women, older patients and patients without a partner reported a lower QOL confirms the results of other studies [29, 34, 35, 37, 41]. The positive influence of age on the MCS has not been described before. Perhaps the fact that these patients have learned to cope with a chronic disease like DMT1, positively influences mental state. The finding that patients with a higher education reported a lower EQ-VAS score is new. The reason for this finding is unclear.

What is the relevance of knowing these relationships between patient characteristics and QOL? Many personal characteristics such as sex and age cannot be influenced.

Nevertheless it is of great importance for clinicians to be aware of patients likely to have a lower QOL. For other factors, such as the frequency of self-monitoring, it might be possible to try to reduce the frequency to what is absolutely necessary.

Most correlations between the dimensions of the EQ and the domains of the RAND-36 were as expected. Oddly enough the dimension 'self-care' did not show any statistically significant correlation with any RAND-36 domain. It is possible that this item, concerning washing and dressing oneself, is too specific to be reflected in the total score for a RAND domain. Usual activities are shown to be influenced by both physical and mental factors.

The highest correlation of the dimension anxiety/depression was with the mental health domain, the RAND domain with the highest correlation with the MCS [33].

The response rates for both instruments were equal, so the length of the RAND-36 did not seem to be a problem for this group of patients, but this is likely due to their incorporation into one questionnaire. Most relationships between patient characteristics and QOL were assessed by both instruments, except for age and having a partner by the RAND-36 and the level of education and HbA_{1c} by the EuroQol. The shortness and simplicity of the EuroQol as well as its capacity to make economic evaluations possible are major advantages of this instrument. Still, the more detailed information (eight different domains) and the distinction between a 'physical score' and a 'mental score' are clear advantages of the RAND-36.

Longitudinal data and comparison with results of several diabetes-specific QOL questionnaires should help to establish which instrument might be most appropriate to measure QOL in patients with DMT1.

Acknowledgements

We thank the Northern Centre for Healthcare Research of the University of Groningen for comparing our data with those of a sample of the general Dutch population. We also thank the diabetes specialist nurses of the Isala Clinics for their help and an anonymous reviewer for the constructive comments and suggestions. The study was partly funded through grants from the Dutch Prevention Fund and the Medical Research Foundation Zwolle.

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