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ORIGINAL ARTICLE

Cross-sectional relationship between glycaemic control, hyperglycaemic symptoms and quality of life in type 2 diabetes (ZODIAC-2)

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ABSTRACT

Background: To describe the relationship between glycaemic control, hyperglycaemic symptoms and quality of life (HRQOL) in type 2 diabetic patients.
Methods: In a shared-care diabetes project HRQOL was assessed. A total of 1664 patients with type 2 diabetes were identified in 32 primary healthcare practices. Of these patients, 1149 were included. HRQOL was measured using a generic questionnaire (Rand-36), completed by 1006 of the 1149 participants.
Results: The number of hyperglycaemic symptoms was higher in women (1.88) compared with men (1.64), without differences in mean haemoglobin A_{1c} (HbA_{1c}) (7.5%). Univariate analyses showed negative relationships between all dimensions of the Rand-36 and hyperglycaemic symptoms ($p<0.001$), but between only one dimension and HbA_{1c} ($p=0.005$). Multivariate analyses showed no association between any of the dimensions of the Rand-36 and HbA_{1c}, but the relationship between hyperglycaemic symptoms persisted in all dimensions ($p<0.001$). Notwithstanding these results, the presence of hyperglycaemic symptoms was related to higher HbA_{1c}.
Conclusion: In type 2 diabetic patients, as assessed by a generic questionnaire, there is an evident relationship between hyperglycaemic symptoms and HRQOL and not between HbA_{1c} and HRQOL. Subjective hyperglycaemic symptoms are, independent of HbA_{1c}, important for HRQOL in type 2 diabetic patients, and should therefore not be neglected in the management of diabetes.

KEYWORDS

Cross-sectional studies, diabetes mellitus type 2, hyperglycaemia, primary health care, quality of life

INTRODUCTION

Over the past century, changes in human behaviour and lifestyle have led to a dramatic increase in the prevalence and incidence of diabetes mellitus type 2 worldwide. To effect a significant reduction in the resulting premature morbidity and mortality, an integrated approach to prevent diabetes mellitus type 2 and its complications is called for.[1]

Targets in diabetic treatment are to improve glycaemic symptoms and to reduce the risk of diabetes-related complications and as such improve patients' quality of life (HRQOL). To achieve treatment goals, physicians and patients must cooperate intensively; patients' compliance is essential. Patients can be expected to be more compliant when their HRQOL improves as a consequence. However, studies concerning the relationship between HRQOL and glycaemic control prove confusing. In patients with type 2 diabetes, an intensive regime to improve glycaemic control seemed to have no effect on the patient's HRQOL.[2] This was puzzling, since improved glycaemic control usually leads to a decrease in hyperglycaemic symptoms, which again is expected to improve HRQOL. The latter part is supported by Goddijn *et al.*[3] who found, in a longitudinal study with a small number of patients, that a reduction in hyperglycaemic symptoms leads to an improved HRQOL.

To optimise the treatment of diabetes mellitus, further study into the manner in which diabetes-related symptoms, glycaemic regulation and HRQOL are related is required. This study describes the cross-sectional relationship between glycaemic control, hyperglycaemic symptoms and HRQOL in a large cohort of patients with type 2 diabetes.

MATERIALS AND METHODS

Study population

In the region around Zwolle (the Netherlands), a large shared-care diabetes project was initiated in 1998, the Zwolle Outpatient Diabetes project Integrated Available Care (ZODIAC).
In this project, general practitioners (GPs) are supported by hospital-based diabetic specialist nurses (DSNs) in their care of type 2 diabetic patients.

In part of the project, all subjects with type 2 diabetes treated exclusively by their GPs in 32 practices are seen annually by DSNs. In the first year of the project, 1664 subjects with type 2 diabetes mellitus were identified in these practices. Patients treated by an internist (n=338) were excluded. Fifty-seven patients were excluded by their general practitioners because of a very short life expectancy or expected insufficient cognitive abilities to fill in the questionnaire. A total of 1269 patients were invited of whom 1149 (90.5%) participated.

With the invitation to visit the DSN, the patients received an HRQOL questionnaire (the Rand 36-Item Health Survey; Rand-36),[4] which they were requested to complete and hand in together with a list of their current medication. Their visit to the DSN included the following: (i) their medical history was taken and added to the history provided by the GP; (ii) height, weight and blood pressure were measured; (iii) the feet were examined thoroughly (data on the loss of sensibility were used in this study); and (iv) after the visit, blood and urine were collected. A cross-sectional analysis of the first-year data was made.

Measures

Medical history included year of onset diabetes, medication (general and diabetic), smoking, coronary heart disease and cerebrovascular disease. Coronary heart disease was considered to be present when the patient had a confirmed history of myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG). Cerebrovascular disease was considered to be present when there was a confirmed history of stroke or transient ischaemic attack (TIA). Neuropathy was defined as the inability to feel the 5.07 Semmes Weinstein monofilament at any one of three sites on each foot, which is a reasonably sensitive and specific assessment for diagnosing diabetic polyneuropathy.[5] The BMI was calculated from weight and length (kg/m^2).
The major endpoint for metabolic control was the haemoglobin A_{1c} (HbA_{1c}) level. Other laboratory measures were serum creatinine, total cholesterol, high-density lipoproteins (HDL), triglycerides, and albumin/creatinine ratio in urine. Creatinine clearance was calculated using the Cockcroft and Gault formula.[6]

The study group chose the Rand-36 to measure HRQOL based on previous experiences with this questionnaire. It is a reliable and valid generic measure, also in the Dutch population.[7,8] The Rand-36 contains nine health dimensions: physical functioning, social functioning, role limitations (physical), role limitations (emotional), mental health, vitality, pain, general health perception and health change. The nine dimensions were calculated in accordance with the Rand-36 manual,[4] except for 'social functioning' since one of the two items was measured on a six- instead of a five-point Likert scale. We used the formula as used by Van der Zee *et al.*[7] ((question 10j * 5 + question 6 * 6) - 11) * 100/49. To interpret the overall direction and importance of the HRQOL effects,[9] two summary measures were calculated: the Physical Component Summary and Mental Component Summary.[3] The range of the scales is from 0 to 100, a higher score meaning better HRQOL.

With the Rand-36, the patients received a list of glycaemic symptoms and were asked to indicate whether they had had any of six hyperglycaemic symptoms (fatigue, weight loss without clear cause, itching, thirst, increased fluid intake and increased urine production), or four hypoglycaemic symptoms (excessive sweating, shaky sensation, dizziness, and sudden appetite which disappeared when food was taken) in the preceding month.

Analysis

Due to skewed distribution of the Rand-36 scales, non-parametric statistics were used in the univariate analysis. To compare continuous variables with dichotomic or categorical variables, the Mann-Whitney test or Kruskal-Wallis test was used, respectively. The Spearman rank correlation was used to compare continuous variables. To compare normally distributed variables with dichotomic or continuous variables, (independent samples) the t-test or Pearson correlation was used, respectively. Multivariate analyses were performed using the parameter estimates of the general linear model (GLM). The assumption of the GLM that the distribution of the residual scores should be normal was checked by inspecting the distribution of the residuals using normal probability plots. The Rand-36 scores were used as dependent variables, the noncontinuous measures as fixed variables and the continuous measures

as covariates. The fixed or continuous variables were included for analysis whenever there was at least one significant univariate association with the Rand-36. SPSS 10.0 for windows was used for data analysis.

RESULTS

General characteristics

In *table 1* characteristics of the study population are summarised. Women (n=662) represent the majority (57.6%) of the study population. Mean age was 68.7 years, ranging from 21 to 97. Median diabetes duration was 5.3 years. Insulin was used by 195 (17.0%) patients. Mean HbA_{1c} (7.5) was in the intermediate range (7 to 8.5) according to the Dutch National Guidelines (upper limit of normal 6.0%).[10] No difference in HbA_{1c} was found between the sexes. The median number of hyperglycaemic symptoms, known from 823 subjects, was 1 for both men and women.

Table 1 *Characteristics of study population 1998 (n=1149)*

Male	487 (42.4)
Age (years)	68.7 ± 11.5 (21-97)
Diabetes duration (years)‡	5.3 (2.5,10.4) (0-58)
Diabetes therapy	
- Diet only	148 (12.9)
- Oral medication	806 (70.1)
- Insulin	169 (14.7)
- Insulin + oral medication	26 (2.3)
Metabolic regulation	
- HbA_{1c} (%)	7.5 ± 1.3 (4.8-13.1)
Macrovascular complications	
- CHD	233 (20.3)
- Stroke/TIA	145 (12.6)
Microvascular complications	
- Albuminuria*	460 (41.7)
- Neuropathy	333 (29.2)
Cockcroft (ml/min)	72.1 ± 28 (15-215)
Blood pressure (mmHg)	
- Systolic	155 ± 25 (95-240)
- Diastolic	84 ± 11 (45-135)
Body mass index (kg/m²)	28.9 ± 4.8 (16-48)
Cholesterol/HDL	5.3 ± 1.6 (1.9-13.6)
Triglycerides (mmol/l)	2.6 ± 1.6 (0.5-15.2)
Smokers	207 (18.2)
No. hyperglycaemic symptoms (n=823)‡	1 (0,3) (0-6)
No. hypoglycaemic symptoms (n=820)‡	1 (0,2) (0-4)

Data are means ± SD (range) or n (% of known data). ‡Data are median (P_{25},P_{75}) (range). *Albuminuria ≥3 mg/mmol creatinine.

Determinants of quality of life

Univariate analysis

In the total study population of 1149 subjects, 1006 (87.6%) completed the Rand-36. No differences in HbA_{1c} were found between patients who completed the Rand-36 and those who did not. Univariate analysis was undertaken for all measures. *Table 2* shows the results of the Rand-36 in relation to HbA_{1c}. One dimension (health change) correlates significantly with HbA_{1c} (r=-0.093, p=0.005). *Table 3* shows the results of the Rand-36 in relation to the number of hyperglycaemic symptoms. For all scales the correlation coefficients are at least -0.310 (p< 0.001), the dimension 'vitality' having the strongest correlation (r=-0.546).

All measures show at least one significant association with the Rand-36, except for smoking, blood pressure and cholesterol/HDL ratio (data not shown). When compared with males, females showed lower scores on the Rand-36 (on eight scales). Patients with neuropathy showed lower scores than patients without neuropathy (eight scales). Increasing age was also related to lower scores (six scales). An increase in the number of hypoglycaemic symptoms was associated with lower scores on all Rand-36 scales, with lower correlation coefficients (range (r)=-0.238 to 0.468) as compared with the number of hyperglycaemic symptoms. Coronary heart disease and duration of diabetes both were related significantly to two scales.

Table 2 *Results RAND-36 divided for HbA_{1c}*

HbA_{1c} category	Good	Inter-mediate	Poor	Spearman correlation*
Range	<7%	7-8.5%	>8.5%	
Total completed questionnaires	441	473	239	
Physical functioning	57.2	55.7	53.2	-.029
Social functioning	80.8	76.6	78.8	-.039
Role limitations (physical problem)	64.4	62.2	65.5	.024
Role limitations (emotional problem)	73.5	73.7	73.5	.021
Mental health	74.8	72.6	73.8	.003
Pain	71.7	69.7	70.7	-.009
Vitality	60.6	60.8	59.1	-.008
General health perception	61.9	61.5	60.6	-.006
Health change	48.5	47.0	42.4	-.093‡
Physical component summary	66.7	64.9	65.3	-.014
Mental component summary	70.6	69.6	70.0	.003

***Spearman correlation was measured for continuous variable. ‡p=0.005.**

Table 3 *Results RAND-36 divided for number of hyperglycaemic symptoms*

Number of symptoms	0	1-2	3-6	Spearman correlation
Total completed questionnaires	211	368	237	
Physical functioning	74.5	53.9	41.7	-.386‡
Social functioning	91.4	77.1	67.9	-.374‡
Role limitations (physical problem)	88.0	61.4	44.8	-.404‡
Role limitations (emotional problem)	91.5	72.3	58.7	-.328‡
Mental health	84.6	72.7	64.4	-.391‡
Pain	87.3	69.8	55.8	-.396‡
Vitality	79.2	58.7	45.6	-.546‡
General health perception	70.2	60.8	53.8	-.379‡
Health change	54.9	45.7	39.5	-.310‡
Physical component summary	82.2	64.3	52.3	-.500‡
Mental component summary	83.9	69.0	58.3	-.499‡

‡p<0.001.

Multivariate analysis

Table 4 shows the influence that each parameter had on the different Rand-36 dimensions after correction for all other included parameters by using the 95% confidence interval and the proportion variance explained (eta squared). The negative influence of the number of hyperglycaemic symptoms remained significant on all Rand-36 scales (all p<0.001). Six other parameters also showed an independent significant influence on some of the Rand-36 scales: increasing age (five scales), BMI (four scales), coronary heart disease (five scales), cerebrovascular disease (three scales), neuropathy (two scales) and being female was negatively associated with seven scales. In multivariate analyses, the remaining parameters lost their influence on the Rand-36 scales (data not shown).

When the number of hypoglycaemic symptoms is added as a parameter to the multivariate analyses, it is significant on all scales (data not shown), as is the number of hyperglycaemic symptoms. When the eta squared values of the number of hypoglycaemic and hyperglycaemic symptoms

Table 4 *Clinical parameter estimates of Rand-36 dimensions*

		Physical functioning	Social functioning	Role limitations (physical problem)	Role limitations (emotional problem)	Mental health	Pain	Vitality	General health	Health change	Physical component summary	Mental component summary
Age	LB	-1.14	-.45	-.92	-.74	-.09	-.33	-.20	-.07	-.34	-.46	-.27
	UB	-.79	-.12	-.38	-.22	.17	.03	.08	.14	-.09	-.19	-.00
	eta	.133‡	.014†	.030‡	.018‡	.000	.003	.001	.001	.014†	.030‡	.006*
BMI	LB	-1.63	-.82	-1.36	-.85	-.32	-0.99	-.49	-.34	-.46	-.85	-.46
	UB	-.84	-.08	-.12	.36	.30	-.16	.17	.14	.13	-.22	.15
	eta	.045‡	.007*	.007*	.001	.000	.009†	.001	.001	.002	.015†	.001
CDV	LB	9.39	3.20	-.28	-.81	-3.99	-4.05	.73	-2.33	-.53	1.39	-.63
	UB	21.18	14.49	18.70	17.67	5.09	8.25	10.45	4.84	8.18	10.90	8.47
	eta	.032‡	.012†	.005	.004	.000	.001	.007*	.001	.004	.009*	.004
Neuro-	LB	4.44	-2.44	-6.28	-3.58	-.97	.82	-2.47	-1.02	-.60	-.13	-.90
pathy	UB	12.60	5.37	6.50	8.88	5.35	9.39	4.25	3.93	5.42	6.31	5.28
	eta	.021‡	.001	.000	.000	.002	.007*	.000	.002	.003	.005	.003
CHD	LB	6.48	-.70	-3.78	-7.29	-2.07	.08	.19	1.08	-3.45	1.28	-1.39
	UB	16.06	8.52	11.41	7.52	5.40	10.16	8.13	6.89	3.65	8.98	6.02
	eta	.027‡	.004	.001	.000	.001	.005*	.005*	.009†	.000	.009†	.002
No.	LB	-8.13	-6.43	-11.99	-9.50	-5.62	-7.90	-8.74	-4.52	-4.39	-7.59	-6.76
hypergly-	UB	-5.81	-4.19	-8.37	-6.00	-3.82	-5.47	-6.82	-3.13	-2.67	-5.77	-5.03
caemic	eta	.152‡	.101‡	.142‡	.095‡	.123‡	,130‡	.247‡	.129‡	.076‡	.223‡	.203‡
symptoms												
Male/	LB	5.17	.79	1.44	4.26	3.11	4.34	.80	-1.86	-1.49	3.15	2.36
female	UB	12.81	8.13	13.36	15.81	9.07	12.35	7.12	2.77	4.16	9.17	8.11
	eta	.027‡	.007*	.008*	.016†	.021‡	.021‡	.008*	.000	.001	.022‡	.018‡

*p<0.05, †p<0.01, ‡p<0.001. CDV = cerebrovascular disease; CHD = coronary heart disease. The first and second numbers represent the lower (LB) and upper bound (UB) respectively of the 95% confidence interval of the regression coefficient (B). A negative number means the parameter has a negative relationship with the Rand-36 dimension. The third number represents the partial eta squared (it describes the proportion of total variability of the Rand-36 dimension attributable to a parameter).

are compared, the former scores higher on two scales: mental health (eta squared 0.137 *vs* 0.051) and pain (eta squared 0.085 *vs* 0.066).

Symptoms *vs* HbA_{1c}

Table 5 shows the quintiles of HbA_{1c} divided for the number of hyperglycaemic and hypoglycaemic symptoms. These data show that the number of hypoglycaemic symptoms is not related to HbA_{1c}, not even within the lowest quintile. However, the number of hyperglycaemic symptoms correlates significantly with HbA_{1c} (p=0.033). The average number of hyperglycaemic symptoms was 2.11 for patients in the highest quintile, and 1.62 to 1.71 for patients in the lower four quintiles. *Table 6* shows the mean HbA_{1c} divided for presence or absence of separate hyperglycaemic symptoms. HbA_{1c} was significantly higher in the group of persons with the presence of the symptoms thirst (p=0.002) and increased fluid intake (p=0.011).

Table 5 *Quintiles of HbA_{1c} divided for number of hyperglycaemic and hypoglycaemic symptoms*

HbA_{1c}	Hyperglycaemic symptoms (n)†	Hypoglycaemic symptoms (n)‡
4.8-6.4 (243)	1.71 ± 1.57	1.15 ± 1.17
6.5-7.0 (231)	1.71 ± 1.54	1.19 ± 1.13
7.1-7.6 (208)	1.71 ± 1.47	1.27 ± 1.18
7.7-8.5 (228)	1.62 ± 1.65	1.16 ± 1.13
8.6-13.1 (236)	2.11 ± 1.56	1.24 ± 1.17

†Correlation with HbA_{1c}: 0.064 (p=0.033). Correlation was measured for continuous variable. ‡Correlation with HbA_{1c}: 0.023 (p=0.261). Correlation was measured for continuous variable.

Table 6 *HbA_{1c} divided for each type of hyperglycaemic symptom*

Symptoms	Yes	No	P
Fatigue	7.48 ± 1.2 (441)	7.50 ± 1.3 (348)	.937
Weight loss	7.51 ± 1.3 (64)	7.27 ± 1.3 (717)	.109
Itching	7.58 ± 1.3 (221)	7.44 ± 1.2 (561)	.251
Thirst	7.73 ± 1.3 (196)	7.39 ± 1.2 (585)	.002
Increased fluid intake	7.76 ± 1.5 (191)	7.39 ± 1.2 (595)	.011
Increased urine production	7.55 ± 1.3 (332)	7.43 ± 1.2 (451)	.243

Data are means ±SD (number of patients).

DISCUSSION

This study shows a negative relationship between HRQOL and glycaemic symptoms as well as a positive relationship between hyperglycaemic symptoms and HbA_{1c}. However, no association between HRQOL and HbA_{1c} was found. Moreover, we found a negative association of HRQOL with female gender, age, BMI, CHD, cerebrovascular disease and neuropathy. Independent of each other, hypoglycaemic as well as hyperglycaemic symptoms have a strong influence on HRQOL. The influence on HRQOL by hyperglycaemic symptoms is stronger and associated with HbA_{1c}, whereas hypoglycaemic symptoms are not.

Goddijn *et al.*[3] concluded in a longitudinal study with 94 patients that in type 2 diabetic patients reduction of hyperglycaemic symptoms improved HRQOL. Earlier studies using the Rand-36, SF-20 or SF-36 were unable to find a relationship between HRQOL and HbA_{1c}.[11-14] We found only health change to be univariately and negatively associated with HbA_{1c} as did Johnson *et al.* in the Pima Indians.[15] This also applies to the longitudinal studies in which the above-mentioned questionnaires were used.[3,16] However, when other questionnaires were used, the association between HbA_{1c} and HRQOL showed mixed results, such as a significant negative association[12,14,17,18] or no clear relation.[2,14,19-22] The relation with glucose levels was also unambiguous.[23,24]

The negative relationships between HRQOL and complications are what we expected:[25,26] having a complication relates to worse HRQOL. And although care providers work hard to improve the risk profile for complications by monitoring the HbA_{1c}, blood pressure and lipid profile, other (modifiable) factors should also be addressed. In order to improve 'quality of care', some of the efforts should also be directed to factors such as BMI and hyperglycaemic symptoms, since our results show that they relate directly to HRQOL. At the moment a large part of diabetes management is directed by objective measures such as HbA_{1c}, which are not directly related to HRQOL. Hyperglycaemic symptoms receive far less attention. As Hanestad *et al.*[27] already postulated, this means that important aspects of the patient's life are neglected in diabetes care.

The absence of a relationship between HRQOL and HbA_{1c} is hard to explain, especially when considering the relationship between HRQOL and hyperglycaemic symptoms and HbA_{1c} and hyperglycaemic symptoms. One would expect that if one of these three parameters is high, it would relate positively to both other parameters. It may be debatable whether the symptoms chosen (as used by Goddijn *et al.*[3]) are truly hyperglycaemic.

According to Van der Does *et al.*,[22] fatigue is the dimension most directly related to the present glycaemic status. However, fatigue is a general and frequently occurring symptom present in both patients with diabetes and with depression. People with diabetes suffer more often from depression compared with people without diabetes,[28-30] and depression appears to be a good effect indicator of HRQOL,[31,32] in particular among female patients.[30] The presence of depression has not been assessed and may have been of influence on our results.[33] Except for the symptom fatigue, the presence of all other hyperglycaemic symptoms was associated with a higher HbA_{1c}. Polyuria, polydipsia and unexplained weight loss are classic symptoms of diabetes mellitus.[34] Moreover, most hyperglycaemic symptoms were found in patients with the highest HbA_{1c}, supporting the fact that they are indeed hyperglycaemic symptoms.

The limitations of our study are that the symptoms that were chosen were not taken from a validated symptom list, and that the number of missing values for the hypoglycaemic and hyperglycaemic symptoms was quite substantial. This may present an inaccurate representation of the symptoms within the study population. For the longitudinal follow-up of our population, validated symptom score lists have been introduced. And although the Rand-36 is closely related to the SF-36, the Rand-36 has not been as extensively validated as the SF-36.[35]

Improving glycaemic control decreases the risk of complications. Whether it increases HRQOL directly will have to be further studied longitudinally now that our cross-sectional results suggest that this is not the case. As such, physicians and DSNs have to be more aware of the importance of motivating treatment adherence, as stated earlier by Goddijn *et al.*[3] If the association between hyperglycaemic symptoms and HRQOL in the absence of a relation between HbA_{1c} and HRQOL is confirmed in a longitudinal design, caregivers will have to consider these symptoms as a separate treatment objective. This cross-sectional study of a large cohort is a basis for future longitudinal analyses.

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