Isala Series, no. 47

Health Related Quality of Life in Patients with Diabetes Mellitus Type I

Bertien Hart

De uitgave van dit proefschrift kwam mede tot stand door financiële bijdragen van de Stichting Medisch Research Fonds Zwolle, Aventis Pharma BV, Bristol-Meyers Squibb BV, Eli Lilly Nederland, GlaxoSmithKline BV, Novo Nordisk Farma BV en Pfizer BV

Cover: Michiel Hennink
Printing: Optima Grafische Communicatie, Rotterdam

Isala series, no. 47
ISBN 90-74991-45-9
NUR 870

Health Related Quality of Life in Patients with Diabetes Mellitus Type I

Kwaliteit van leven van patiënten
met diabetes mellitus type I

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus

Prof. dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 18 juni 2004 om 13.30 uur

door

Huberta Emma Hart

geboren te Utrecht

Promotiecommissie

Promotoren	:	Prof.dr. M. Berg Prof.dr. B. Meyboom – de Jong
Overige leden	:	Prof.dr. J.P. Mackenbach Prof.dr. H.A.P. Pols Prof.dr. R. Sanderman
Copromotor	:	Dr. H.J.G. Bilo

Voor Lodi,
Michiel en Céline

Contents

Chapter 1

Diabetes Mellitus Type I and Health Related Quality of Life

Diabetes mellitus type I

Diabetes mellitus type I (DMT1) is a chronic disease caused by the autoimmune destruction of the insulin-producing beta cells in the pancreas, resulting in an absolute inability to produce the hormone insulin which is necessary for the regulation of blood glucose levels. The autoimmune destruction is postulated to result from an interaction between genetic and environmental factors, with the latter triggering the onset of the disease in genetically susceptible individuals (1). Various theories explaining the pathogenesis have been proposed in which environmental agents may serve as modifiers of pathogenesis rather than as triggers. These environmental risk determinants may be classified into three groups: viral infections, early postnatal diet, and toxins. Other non-genetic disease modifying factors include vaccine administration, psychological stressors, and climatic influences (2). The incidence of DMT1 is rapidly increasing in many parts of the developed world, and is showing a trend toward earlier age of onset. The incidence of DMT1 is highly variable among different ethnic populations, occurring most frequently in persons of north European descent, diminishing in southern direction, the 'North-South gradient', with the notable exception of Sardinia. The incidence of DMT1 is projected to be approximately 40 percent higher in 2010 than it was in 1997 (1, 2). The prevalence in The Netherlands is 0.3 percent (3).
Diabetes mellitus type I is characterized by hyperglycemia with the eventual development of micro- and macrovascular complications which define the degree of morbidity in these patients.
Microvascular complications which are generally accepted to be associated with diabetes mellitus are retinopathy, with the potential for blindness; peripheral neuropathy, with an increased risk of foot ulcers and amputation; autonomic neuropathy, with possible cardiac and gastrointestinal dysfunction; and nephropathy, with possible renal failure requiring renal replacement therapy. The most well-known macrovascular complications are angina pectoris, myocardial infarction, cerebrovascular accidents, and intermittent claudication.
Hyperglycemia is recognized as the primary causal factor in the development of these vascular complications associated with diabetes (4, 5). Hypertension and dyslipidemia often make an already grim picture even more serious.

Therapy for diabetes mellitus type I
The primary goal of treatment is to attain acceptable metabolic control by means of daily insulin injections in order to avoid acute and chronic diabetic complications. It has been shown that intensive treatment, compared to more conventional treatment, delays the onset and progression of microvascular complications in patients with DMT1 (6-11) . The Diabetes Control and Complications Trial (DCCT) also showed a reduction in some, but not all, cardiovascular risk factors, suggesting a potential beneficial effect of intensive therapy on the development of macrovascular complications in patients with DMT1 as well (12).
Intensive therapy implies that patients administer a minimum of three to four insulin injections per day (often with an insulin pen) or make use of an external or internal insulin pump, striving to keep blood glucose levels as close to normal as

possible. To achieve this goal, patients have to monitor their blood glucose level regularly. The side effects of a more intensive therapy are weight gain and an increased frequency of hypoglycemic episodes. The initial symptoms of hypoglycemia are sweating, tachycardia, dizziness, irritability, and restlessness. If these initial symptoms are not recognized, more serious sequelae will occur, including cognitive dysfunction, coma, convulsions, and even death. Recurrent episodes of grade I hypoglycemia are apparently well tolerated by the brain, and no cognitive impairment has been reported (13, 14). The occurrence of a severe hypoglycemic episode is a potentially dangerous and unpleasant event for both the patient and his/her environment and should be avoided if at all possible. Recent reports have suggested that the number of severe hypoglycemic episodes may be reduced by the implementation of pump therapy (15-17).
Furthermore, these new treatment options, such as the insulin pen and the insulin pump, give the patients more flexibility with respect to therapy and diet and greater freedom in lifestyle and in choosing a suitable job. Flexible insulin therapy and a liberal diet, facilitated by the use of the insulin pen/pump have been reported to be strongly associated with improved quality of life scores (18). Hanestad et al. reported that multi-injection treatment was associated with greater satisfaction in the domain of social life (19). The use of the insulin pump also helps to overcome the problems associated with preconception and pregnancy care (17).
To summarize, the primary goal in treating patients with DMT1 is to normalize blood glucose levels in an effort to prevent or delay the onset and progression of diabetes related chronic complications while, at the same time, keeping the patient's health related quality of life as normal as possible (see next section).

Health related quality of life

Health related quality of life (HRQOL) refers to those aspects of quality of life which are related to a person's health status. It is primarily concerned with that aspect of quality of life which may be affected by health and disease (20). HRQOL is a person's subjective perception and evaluation of his/her health status. If a person feels that his/her health status is poor, he/she may feel that his/her overall quality of life is also poor, although this is not necessarily the case. The converse situation may also not be valid (21).
In 1952, the World Health Organization (WHO) defined health as being not only the absence of disease, but also the presence of physical, mental, and social well-being (22). HRQOL issues, related to the physical, mental, and social domains of a person's health, have become increasingly important in health care and clinical practice (23). Since the meeting of the WHO and the International Diabetes Federation in St. Vincent, Italy, special goals have been set for the care of patients with diabetes in Europe which are described in the St. Vincent Declaration (1990). HRQOL is specified as an important element in the modern care of patients with diabetes (24).

In the particular case of DMT1, HRQOL refers to the patient's perception of the way diabetes affects his/her physical, psychological, and social functioning. It reflects the perceived burden of living with DMT1 (20).
It is important to have a good understanding of the various influences on HRQOL of patients with DMT1. The potential severity, the intensive therapy and its side effects, and the acute and chronic complications of diabetes make it essential that the patient, the clinicians and the associated health care workers have a clear picture of the factors associated with HRQOL.

Assessment of health related quality of life
HRQOL may be assessed with (semi-structured) interviews and checklists. These assessment methods are labor intensive. Alternatively, patients may be given questionnaires which can be self-administered. These questionnaires have a multiple-choice or check-box format, allowing the patient to choose the answer which best describes his/ her experience. This is the most widely used monitoring method used in daily clinical practice (25).
The questionnaires have to meet several practical, technical, and conceptual criteria (26). Practical criteria concern the *feasibility*: the burden for the patient when filling out the list, the time required to complete, the percentage correctly completed questionnaires, and the eventual relevance for both the clinician and the patient. Technical criteria concern the *reliability* of the measuring instruments. A reliable test will show a more or less similar result after repeated administration (test-retest reliability). The internal consistency of the instrument determines whether the items (of a single domain) measure the same construct (Cronbach's alpha). Conceptual criteria concern the *validity* of the measuring instrument. Does the instrument measure what it is supposed to be measuring? The *responsiveness* is a measure of the sensitivity in the ability to detect changes in HRQOL (26-28).
Furthermore, a questionnaire's discriminative and evaluative features are important. *Discriminative* features refer to the ability to assess cross-sectional differences in HRQOL *between patients* at a single point in time (27, 28) and *evaluative* features refer to the questionnaire's ability to assess changes in HRQOL longitudinally, *within patients*, over a period of time (27, 28). Both aspects of HRQOL are important for research and for clinical practice. There are specialized instruments for each type of task, and even the most minute changes can be measured with the correct evaluative instrument. Many different instruments have been developed to measure HRQOL for various categories of patient problems (28-33). There are two basic kinds of instruments for measuring HRQOL, specific and generic. *Specific instruments* focus on the most important aspects of the HRQOL of a specific group of patients (*disease-specific*), or on a specific problem, such as pain or sleep (*domain-specific*). Generic instruments approach HRQOL testing broadly, and are not restricted to any specific disease or domain aspects (27, 28). The different health states, provided by some generic instruments, have been assigned values, also called *utilities*, by the general public (34-36). These utilities have been scaled in such a way that a value of zero (0) is assigned to the worst health state (death) and a value of one (1) is equivalent to perfect health. These utilities facilitate cost-effectiveness studies (34-36).

The main advantage of specific instruments is their responsiveness, because the disease-specific items predominantly concern aspects of the HRQOL which are important for patients with a particular disease. Consequently, these instruments can play an important role in the evaluation of new therapies (in clinical trials, for example), and are therefore closely related to clinical practice (27).
The main advantage of the generic instruments is that they allow comparisons with subjects in the general population and with other patient populations.
Furthermore, the utilities, which are derived from some generic instruments, make it possible to compare the impact of various treatments for different diseases. These are therefore important for policymakers (27, 34).
One of the shortcomings of both types of instruments is that they are not always primarily focused on the patient. The number of possible answers is limited, and patient-respondents can not sufficiently emphasize which factors have the most influence on their HRQOL, when, in fact, HRQOL is by its very nature a subjective and individual construct (37). To address this, Gill and Feinstein have proposed a global rating, which gives patients the opportunity to rate the importance of their problems and the addition of a supplemental item in which patients can note additional important factors that have not been included elsewhere in the questionnaire (38). The Audit of Diabetes-Dependent Quality of Life (ADDQoL) gives the individual patient the opportunity to indicate the importance of each domain included in the questionnaire. Each domain is then weighted according to the patient's rating (29, 39).
It is evident that each type of instrument has advantages and limitations, and the choice of instrument will be dependent on the purpose of the assessment of HRQOL.

A model

Wilson and Cleary developed a model which conceptualises the relationship between traditional clinical variables and health related quality of life (HRQOL) (40). A part of this model will be applied here to a population of patients with diabetes mellitus type I (DMT1).
First the Wilson and Cleary model, shown in figure 1, will be explained, before the adaptations are discussed which were necessary for it to be applied to our study (figure 2).
Figure 1 shows a continuum, with at one end biological and physiological measures, and at the other end health status measures, such as physical functioning and general perceptions regarding health. Individual and environmental characteristics are shown to have an impact on this continuum. The ultimate outcome is overall quality of life (QOL), for which reason the impact of non-medical factors such as employment, housing, and personal relationships is also accounted for by this model (40).

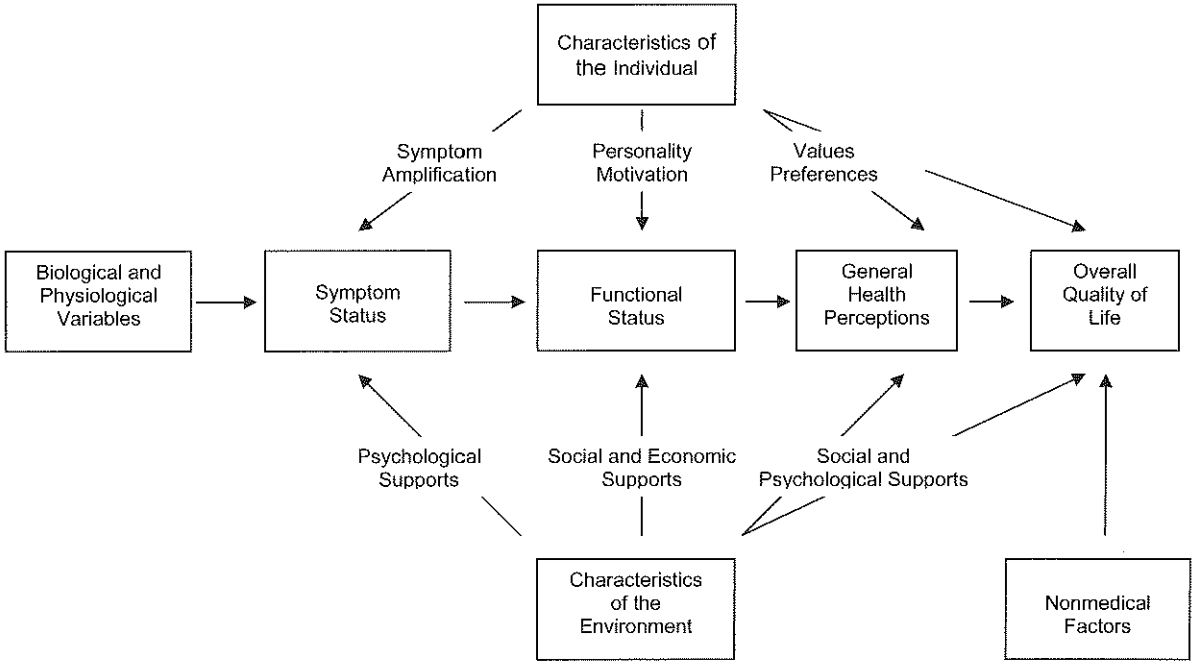


Figure 1
Relationships among measures of patient outcome in a health-related quality of life conceptual model [Wilson and Cleary: Linking clinical variables with health related quality of life. A conceptual model of patient outcomes (40)]

A symptom is a personal perception of an abnormal physical, emotional, or cognitive variable or state. The relationship between *Biological and Physiological Variables* and symptoms is a complex and inconsistent one. For example, patients with abnormal clinical values may experience no symptoms and conversely, patients with symptoms may show no evidence of any clinical abnormality. The *Symptom Status* is an important determinant of a person's *Functional Status*. Finally, this functional status is associated with a person's *General Health Perception*, which is, in turn, related to the *Overall Quality of Life* (40).

In the present study, the association of several patient characteristics and diabetes-specific factors with physical, mental, and social domains of a person's health related quality of life (HRQOL) were investigated in a cohort of patients with DMT1 (figure 2). DMT1 causes *symptoms of hyperglycemia* (thirst, tiredness, weight loss, polyuria, and polydipsia), because of the patient's inability to produce insulin which is necessary for the regulation of levels of blood glucose. DMT1 *therapy* may cause pain with its daily insulin injections and the associated self-monitoring of blood glucose. Possible *complications* of the therapy include hypoglycemic events and weight gain, which also have symptoms associated with them. The *chronic (micro- and macrovascular) complications* may present with a variety of symptoms ranging from loss of sight to foot ulcers and angina pectoris. Jacobson et al. reported that, also in patients with DMT1, symptoms are a patient's personal perception of an abnormal physical variable. He compared patients with DMT1 whose blood glucose levels were well controlled with those who were poorly controlled. He found that those patients with chronic poor control reported feeling physically better at higher glucose levels than patients with good control. He suggested that poorly controlled patients have underlying perceptions of hyperglycemic symptoms and physical well-being which are different from those experienced by patients with well controlled diabetes (41).
Although we did hypothesize that the presence of symptoms is an important determinant of functioning, and therefore indirectly associated with HRQOL, we did not investigate the presence or absence of symptoms independently, since no validated symptom check-list is available for patients with DMT1.
For example, a patient undergoing intensive treatment can experience episodes of severe hypoglycemia with the associated symptoms (i.e. sweating, irritability, etc.), which causes him/ her to avoid social contact. This impairment in (social) functioning will have a negative influence on his/ her daily HRQOL.
Whereas we did use Wilson and Cleary's conceptual model in our efforts to explain the associations between several demographic and diabetes-specific characteristics and HRQOL, we did not make the distinction between Functional Status and General Health Perceptions.
We predominantly used the RAND-36, which assesses HRQOL multidimensionally, containing subscales focusing primarily on physical, social, and emotional functioning and general health perceptions such as the subscales general health and vitality (42, 43).

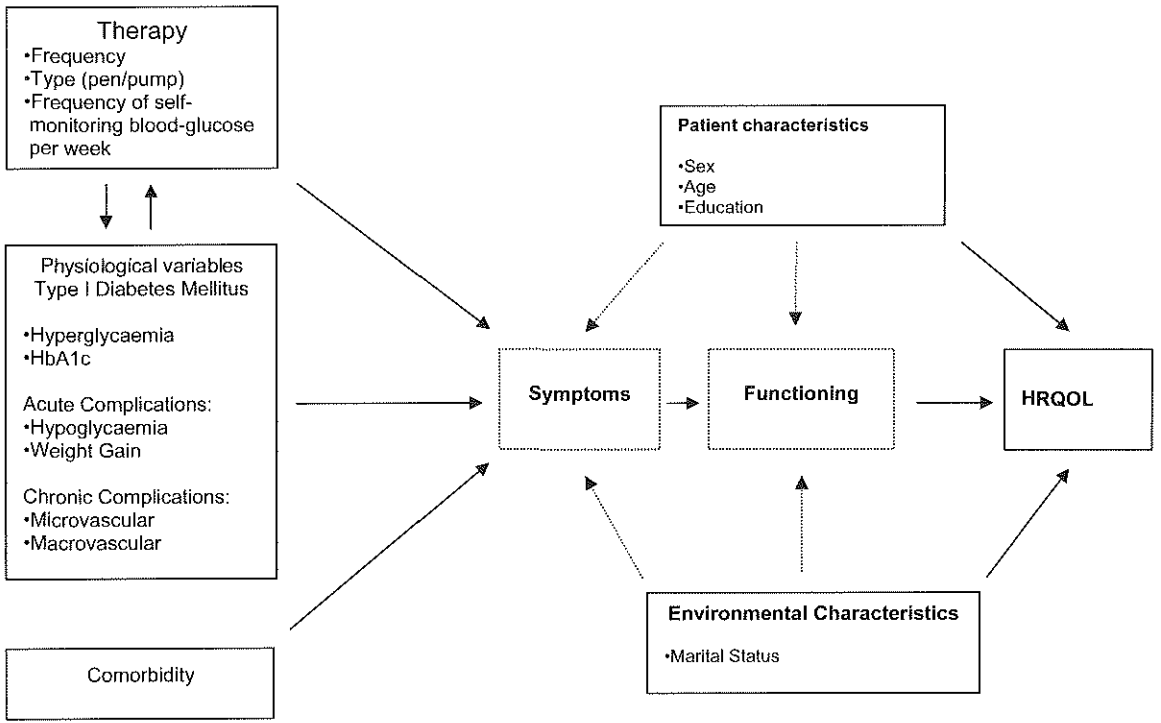


Figure 2
Relationships between disease and health related quality of life in patients with type I diabetes mellitus [model for current study, derived from Wilson and Cleary, (40)]

We believe that abnormal clinical findings and symptoms are associated with the functioning of an individual, but we do not believe they can *fully* explain a person's functioning (40).
Personality (the patient's character) and environment (family relationships, social support, life events) will, to a large extent, explain a person's perception of symptoms and affect how they function and in this way influence their HRQOL. Associations of sex, age, level of education (characteristics of the patient) and marital status (characteristics of the environment) with the HRQOL have been investigated. Studies by Rose et al. and Ormel et al. support views which emphasize the contribution of the patient's personality and his/her environment to the final HRQOL outcome (44-46).
Rose et al. developed a model which describes the different psychological influences on HRQOL in patients with DMT1. Their model explained 62% of the variance of the quality of life and 5% of the HbA1c values. They reported that the most significant determinants for the HRQOL were 'patient characteristics': patients with a more optimistic attitude, showing more belief in self-efficacy, and a generally more positive disposition had the higher HRQOL values (45, 46). Clinicians probably overestimate the impact of clinical variables on symptoms and patients' functioning, and underestimate the effect of the patient's personality and other characteristics (40).
Lindenberg proposed the Social Production Function (SPF) theory in which he attributes the task of maintaining their HRQOL largely to the patients themselves (44, 47, 48). There are differences in how people achieve physical and social well-being. There are different activity patterns or 'production functions' which can be used to produce well being. Different persons use different resources. Symptoms may also have an indirect effect on HRQOL by inhibiting functioning or diminishing specific activities, in accordance with Wilson et al.'s model (40). When symptoms negatively affect behavior, the patient may seek out alternatives which are similar (substitution) to prevent a decrease in their HRQOL. The patient's personal skills and social environment will partially determine to what degree substitution is possible (44).
Both Rose's model and the Social Production Function theory of Lindenberg support Wilson's model, which states that clinical variables and symptoms alone cannot satisfactorily explain a patient's HRQOL and associated level of functioning. Both also emphasize the importance of the patient's personality characteristics and his/her social environment (40, 44, 46).
In the present study, we primarily investigated the influence of clinical, disease-specific variables on HRQOL, although we did briefly consider the influence of demographic data as well (figure 2).
It is important to have adequate insight into the many factors which can influence the HRQOL of patients with DMT1. This will enable clinicians to take into account those factors which can negatively influence HRQOL, thereby practicing preventively by anticipating any decreases in HRQOL.

Aims of this study

In this study we investigated the HRQOL of patients with DMT1, the changes in HRQOL, and the factors associated with HRQOL, in order to answer the following two research questions:

I. What is the HRQOL of patients with DMT1?
II. Can we provide recommendations for the assessment of the HRQOL in patients with DMT1?

These questions lead to a number of other questions which are treated in the separate chapters.
To this purpose we have followed a cohort of 281 Dutch patients with DMT1 in the Isala Clinics in Zwolle, The Netherlands, for six years, from 1995 to 2001. During this period, the patients were examined annually by a physician according to a standardized protocol. Various clinical data were collected. Furthermore, each year, patients were seen by a nurse specialized in diabetes who conducted a semi-structured interview with the help of a standardized questionnaire which included questions about therapy, self-monitoring, education, employment, household, family, and social environment. All patients saw an ophthalmologist and podiatrist annually to monitor the presence or absence of retinopathy and neuropathy. Throughout the study period patients completed several disease-specific and generic HRQOL questionnaires.
The study population and the follow-up procedure are described in Chapter Two.

I. The HRQOL of patients with DMT1

In Chapter Three we answer the following questions: what is the HRQOL of patients with DMT1 compared with persons of comparable age from the general population (I.1); and which factors are associated with their HRQOL (I.2).
In Chapter Four we answer the following questions: what is the HRQOL of patients with newly diagnosed DMT1 during the first year post-diagnosis, and what is their HRQOL one year post-diagnosis, compared with subjects of comparable age from the general population, and compared with subjects with DMT1 with a longer (longer than one year) disease duration (I.3).
In Chapter Five we answer the following questions: how does the HRQOL of a patient with DMT1 develop and change over time, and how does this compare with subjects of similar age from the general population (I.4).
In Chapter Six we describe to what extent we can identify factors which are predictive for the degree of change in HRQOL (I.5).

II. The use of HRQOL questionnaires in patients with DMT1

In Chapter Seven we answer the following question: can we use the utilities from generic instruments for patients with DMT1 to make cost-effectiveness studies possible (II.1).
In Chapter Eight we answer the following questions: do generic instruments accurately measure changes in HRQOL over time in patients with DMT1 (II.2); do generic instruments provide information about diabetes-specific influences on

HRQOL in patients with DMT1 (II.3); and do diabetes-specific and generic instruments identify the same patients with a lower HRQOL (II.4).
Chapter Nine will contain the general discussion, conclusions and recommendations. Chapter Ten will summarize the thesis.

References

1. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus.
   NEnglJMed1994;331(21):1428-36.
2. Atkinson MA, Eisenbarth GS. Type I diabetes: new perspectives on disease pathogenesisand treatment. The Lancet 2001;358(9277):221-229.
3. Ballegooie Ev, Everdingen JJEv. CBO guidelines on diagnosis, treatment and prevention of complications of diabetes mellitus: retinopathy, foot ulcer, nephropathy
   and cardiovascular disease. Ned Tijdschr Geneeskd 2000;114(9):413-417.
4. EURODIAB. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994;37(3):278-85.
5. Klein R, Klein BE. Relation of glycemic control to diabetic complications and health outcomes. Diabetes Care 1998;21 Suppl 3:C39-43.
6. DCCT. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. Kidney Int 1995;47(6):1703-20.
7. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.
8. DCCT. The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 1995;122(8):561-8.
9. DCCT. Effect of intensive therapy on the microvascular complications of type I diabetes mellitus. JAMA 2002;287(19):2563-2569.
10. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U. Intensified conventional insulin treatment retards the microvascular complications of insulin dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. J Intern Med 1991;230(2):101-8.
11. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. NEngl J Med 1993;329(5):304-9.
12. DCCT. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75(14):894-903.
13. Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. Diabetes 1994;43:313-317.
14. DCCT. Effect of intensive diabetes therapy on neuropsychological function in adults in the diabetes control and complications trial. Ann Intern Med 1996;124:379-388.
15. Bode BW, Steed DR, Davidson PC. Redution in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. Diabetes Care 1996;19:324-327.
16. Haardt MJ, Berne C, Dorange C, al. e. Efficacy and indications of CSII revisited: the Hotel Dieu cohort. Diabet Med 1997;14:407-408.

17. Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion. A comprehensive review of insulin pump therapy. Arch Intern Med 2001;161(oct 22):2293-2300.
18. Bott U, Muhlhauser I, Overmann H, Berger M. Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes Care 1998;21(5):757-69.
19. Hanestad BR. Self-reported quality of life and the effect of different clinical and demographic characteristics in people with type 1 diabetes. Diabetes Res Clin Pract1993;19(2):139-49.
20. Polonsky WH. Understanding and assessing diabetes-specific quality of life. Diabetes Spectrum 2000;13:36-45.
21. Bradley C. Importance of differentiating health status from quality of life. The Lancet 2001;357(January 6):7-8.
22. World Health Organization. Constitution of the World Health Organization. 5th ed. Palais des Nations, Geneva; 1952.
23. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996;334(13):835-40.
24. Anonymous. Diabetes care and research in Europe: the Saint Vincent Declaration. Diabet Med 1990;7(4):360.
25. Hutchinson A, Bentzen N, Konig-Zahn C. Cross Cultural Health Outcome Assessment; a user's guide. Groningen, The Netherlands: Europian Research Group on Health Outcomes; 1996.
26. Essink-Bot ML, Krabbe PF, Bonsel GJ, Aaronson NK. An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. Med Care 1997;35(5):522-37.
27. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993;118(8):622-9.
28. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27(3 Suppl):S217-32.
29. Bradley C. Measuring quality of life in diabetes. The Diabetes Annual 1996;10:207 224.
30. Hirsch A, Bartholomae C, Volmer T. Dimensions of quality of life in people with non insulin-dependent diabetes. Qual Life Res 2000;9:207-218.
31. Coons SJ, Rao S, Keininger DL, Hays RD. A Comparative Review of Quality-of-Life Instruments. Pharmacoeconomics 2000;17(1):13-35.
32. Garratt AM, Schmidt L, Fitzpatrick R. Patient-assessed health outcome for measures for diabetes: a structured review. Diabet Med 2002;19:1-11.
33. Luscombe FA. Health-related Quality of Measurement in Type 2 Diabetes. Value in Health 2000;3(Supplement 1):15-28.
34. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
35. Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems: Health Utility Index. Pharmacoeconomics 1995;7:490-502.
36. Kaplan RM, Ganiats TG, Rosen P, Sieber W, Anderson JP. Development of a self administered Quality of Well-Being scale (QWB-SA). Qual Life Res 1995;4:443.
37. Carr AJ, Higginson IJ. Are quality of life measures patient centered? BMJ 2001;322:1357-1360.
38. Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. JAMA 1994;272(8):619-631.

39. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. Qual Life Res 1999;8(1-2):79-91.
40. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.
41. Jacobson AM, Adler AG, Wolfsdorf JI, Anderson B, Derby L. Psychological characteristics of adults with IDDM. Comparison of patients in poor and good glycemic control. Diabetes Care 1990;13(4):375-81.
42. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. Health Econ 1993;2:217-227.
43. Hays RD, Morales LS. The RAND-36 measure of health related quality of life. Ann Med 2001;33:350-357.
44. Ormel J, Lindenberg S, Steverink N, Vonkorff M. Quality of life and social production functions: a framework for understanding health effects. Soc Sci Med 1997;45(7):1051-1063.
45. Rose M, Burkert U, Scholler G, Schirop T, Danzer G, Klapp BF. Determinants of the quality of life of patients with diabetes under intensified insulin therapy. Diabetes Care 1998;21(11):1876-85.
46. Rose M, Fliege H, Hildebrandt M, Schirop T, Klapp BF. The network of psychological variables in patients with diabetes and their importance for quality of life and metabolic control. Diabetes Care 2002;25(1):35-42.
47. Lindenberg S, Frey B. Alternatives, frames and relative prices: a broader view of rational choice theory. Acta Sociol 1993;36:191-205.
48. Lindenberg S. The paradox of privatization in consumption. Heidelberg/ Wien: Physical; 1986.

A cohort of patients with Diabetes Mellitus Type I
- Long term clinical follow-up -

Abstract

Objective
The purpose of this study was to investigate long-term clinical follow-up, therapeutic trends in the late 1990s, and the development of chronic complications in a cohort of patients with diabetes mellitus type I (DMT 1).
Methods
234 Dutch patients with DMT 1 were followed from 1995 to 2001. Annually, patients underwent a physical examination, and data concerning therapy, therapeutic side effects, and complications were recorded. Data, at different moments, were compared with McNemar and T-tests using paired samples.
Results
In the six-year study period, therapy was intensified. The percentage of pump-users increased from 26.9% in 1995 to 32.6% in 1998 ($p=0.016$) to 43.6% in 2001 ($p<0.001$), which corresponded to a decrease in pen-users. The HbA1c level decreases, from 8.1% in 1995 to 7.9% in 1998 ($p=0.016$) to 7.6% in 2001 ($p<0.001$), were significant. The bodymass-index showed significant increases from 24.8 in 1995 to 25.6 in 1998 ($p<0.001$) to 26.1 kg/m^2 in 2001 ($p<0.001$). The percentage of patients reporting hypoglycaemic events tended to increase from 80.8% in 1995 to 87.4% in 2001. The percentage of patients with microvascular complications increased from 45.8% in 1995 to 58.1% in 1998 ($p=0.005$) to 65.7% in 2001 ($p=0.248$). The prevalence of macrovascular complications increased from 4.3% in 1995 to 9.8% in 2001 ($p<0.001$).
Conclusion
In the cohort of patients studied, therapy was intensified during the six year study period, and this was accompanied by an increase in the incidence of side effects. The percentage of patients with microvascular and macrovascular complications increased over time.

Introduction

A study was initiated at the Isala Clinics, Department of Internal Medicine, in Zwolle, the Netherlands, to investigate several disease factors in patients with diabetes mellitus type I (DMT I) including oxidative stress and health related quality of life (HRQOL) (1). From January 1995 through January 1996, 293 patients seen consecutively in the outpatient department were invited to participate in the study, of whom 281 agreed. After the initial investigations in 1995, the patients were followed for a period of six years (1995-2001). DMT 1 was defined in patients when insulin therapy was started within six months of onset of the first signs of diabetes and prior to age 30 or in the absence of C-peptide secretion. Approval for the study was granted by the Hospital Scientific and Ethics Committee. All patients provided informed consent.
This chapter concerns the clinical follow-up of the cohort with a focus on the therapy and on the development of chronic complications of diabetes.

Methods

Clinical data
All patients were examined according to a standardized 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, presence of hypoglycaemic events and hyperglycaemic complaints) were recorded annually. Patients recorded all *hypoglycaemic events* ('did you have a hypo in the past three months?') during the three months preceding the outpatient visit. Patients were asked to report whether they had one or more of six different *hyperglycaemic complaints* during the last three months (yes / no): tiredness, weight loss, pruritus, thirst, polyuria, and polydipsia. *Metabolic control* was assessed by measuring glycosylated haemoglobin A1c (HbA1c).
Comorbidity (presence of one or more diseases in addition to the diabetes) was assessed using a list of 26 chronic diseases (2).
Macrovascular complications
Patients were classified as having macrovascular complications when one or more of the following diagnoses were present: angina pectoris, myocardial infarction, intermittent claudication, transient ischaemic attack (TIA), or cerebrovascular accident (CVA). These diagnoses were, in 1995 and in 2001, recorded in the patient's dossier.
Microvascular complications
Patients with retinopathy, neuropathy, or nephropathy were classified as having microvascular complications.
Retinopathy
All patients received an annual ophthalmological examination. The degree of diabetic retinopathy was assessed by fundoscopy in mydriasis. Diabetic retinopathy was classified according to de Jong (3): no retinopathy (=0),

background retinopathy (=I) preproliferative (=II), proliferative diabetic retinopathy (=III).
The patient was scored positive for retinopathy when any type of retinopathy was present in either eye. When the degree was different in each eye, the highest degree was scored.
Neuropathy
The Semmes-Weinstein pressure aesthesiometer was used to test sensitivity (4). Six different monofilaments were used to test (left and right) foot sensitivity at five dorsal and plantar sites. The patient was diagnosed as having a neuropathy when the monofilament 5.07 was not felt at one of the ten test sites. In 2001, monofilament 5.07 was used as the test filament, and sensitivity was tested at four sites on the (left and right) feet.
Nephropathy
The 24-hour urinary excretion of albumin (UAER) was measured annually. UAER was considered abnormal when it was ≥ 30mg/ 24 hours. Micro-albuminuria was defined as 30-300 mg/ 24 hours, and macro-albuminuria as ≥300 mg/ 24 hours. All patients with abnormal UAER values were defined as having nephropathy (5-7). In 1995 patients with a micro-albuminuria >100 mg/24 hours were prescribed an angiotensin converting enzyme inhibitor (ACE-inhibitor) at the Isala Clinics. Patients using ACE-inhibitors were therefore classified as having nephropathy unless ACE-inhibition was initiated specifically for hypertension.

Results

Study population
The characteristics of the study population are presented in Table 1. 54.4% of the study population was male. The mean patient age was 38.2 years. Mean diabetes duration was 17.2 years. At entry, almost one-third of the patient population smoked (29.9%) and 62.4% used alcohol.
Study drop-outs
The drop-out rate of the study was 16.7% (n=47). The reasons for withdrawal are presented in Table 2. In most cases, the reason for withdrawal was unknown (n=28). Five patients died: one in a motor vehicle accident, one due to a cerebrovascular accident, two because of cardiac problems, and in one case the cause was unknown.
Patients who withdrew from the study shared the following characteristics: there were more females than males (59.6% versus 42.7%, p=0.04), longer disease duration (20.6 versus 16.5 years, p=0.05), more often single (24.0% versus 9.2%, p=0.01), and a higher HbA1c (9.0% versus 8.1%, p=0.007). The drop-out group showed no other statistically significant differences in personal and disease related characteristics (Table 3).

Table 1
Personal and disease-specific characteristics of the study population; n = 281 (1995)

		(SD)	%
Gender (men)	153		54.4
Age (years/ SD)	38.2	(12.4)	
Duration of diabetes (years/SD)	17.2	(10.7)	
Married/ cohabiting	242		88.3
High level of education	90		32
Smoking	70		29.9
Alcohol consumption	146		62.4

SD - Standard deviation

Table 2
Withdrawal from study/ reasons for withdrawal (n = 47)

Reason unknown	28
Moved out of region Zwolle	10
Deceased	5
Pancreas transplantation	1
Car accident, comatose	1
Psychiatric admission	1
Passant [1]	1

[1]Patient came temporarily to Zwolle for a pump, but dropped out of the study when this did not take place

In the drop-outs the health related quality of life (HRQOL), assessed by the generic RAND-36 and EuroQol (EQ) instruments, was partially lower. The RAND-36 subscales physical functioning, bodily pain, general health, social functioning, role emotional, and mental health were lower than those of the patients continuing the study. Their mental component summary score (MCS) was significantly lower than those of the continuing patients as were their EuroQol scores (Table 4).

Therapy and self-management over time (Table 5)
Table 5 shows that the percentage of pump-users increased from 26.9% in 1995 to 32.6% in 1998 ($p = 0.016$) to 43.6% in 2001 ($p < 0.001$). There was a corresponding decrease in pen-users. The mean HbA1c decreased from 8.1% in 1995 to 7.9% in 1998 ($p = 0.016$) to 7.6% in 2001 ($p < 0.001$). The body mass index showed a statistically significant increase over both three-year periods.
The percentage of patients reporting hypoglycaemic events during the three months immediately preceding the visit to the outpatient clinic tended to increase from 80.8% in 1995 to 84.9% in 1998 ($p = 0.110$) to 87.4% in 2001 ($p = 0.736$).

Table 3
Personal and disease-specific characteristics of the study population
- Patients in the cohort versus patients withdrawn from the study –

	n = 234			n = 47			
		SD	%		SD	%	
Gender (men)	134		57.3	19		40.4	**0.038**
Age (years)	38.2	11.5		38.2	16.5		0.997
Diabetes duration (yrs)	16.5	10.1		20.6	13.1		**0.050**
Married/ cohabiting	207		90.8	35		76.0	**0.010**
High level of education	76		33.6	14		31.1	0.863
Smoking	70		29.9	21		44.7	0.060
Alcohol consumption	146		62.4	26		55.3	0.413
SBP (mm Hg)	138.9	17.8		140.0	21.6		0.709
DBP (mm Hg)	83.0	8.4		82.5	7.8		0.676
Pulse pressure	55.9	15.2		57.5	20.7		0.523
Cholesterol/ HDL ratio	3.8	1.2		3.8	1.2		0.889
Body mass index (kg/m^2)	24.8	3.2		24.2	3.1		0.197
Hba1c (%)	8.1	1.9		9.0	1.9		**0.007**
Insulin pump	63		26.9	9		19.1	0.360
Self monitoring blood glucose per week	12.0	11.3		11.4	12.7		0.775
Number of patients with:							
hypoglycaemic events	185		80.8	39		84.8	0.678
hyperglycaemic complaints	122		53.2	28		60.9	0.418
Prevalence of diabetic complications							
Microvascular	104		45.8	25		53.2	0.423
Retinopathy	79		34.6	18		44.9	0.492
Nephropathy	43		18.4	10		21.3	0.683
Neuropathy	24		10.7	8		17.0	0.211
Macrovascular	10		4.3	3		6.4	0.462
Comorbidity	133		58.1	28		60.9	0.746

SD - standard deviation
SBP - systolic blood pressure
DBP - diastolic blood pressure
For the continuous variables p values are result of independent sample T-tests
For the binary and categorical variables p values are from Fisher's Exact Test

Table 4
Health Related Quality of Life (HRQOL) of patients in the cohort compared with the HRQOL of patients who left the study (1995)

	Cohort n=234		Patients withdrawn n=47		p value
RAND-36					
Physical functioning	91.7	(12.9)	84.1	(20.6)	**0.021**
Role physical	84.4	(30.9)	75.0	(38.7)	0.127
Bodily pain	89.9	(16.8)	82.8	(21.5)	**0.040**
General health	69.3	(19.8)	61.4	(20.4)	**0.015**
Vitality	68.4	(19.4)	62.8	(22.4)	0.122
Social functioning	88.6	(19.2)	78.5	(22.2)	**0.006**
Role emotional	86.6	(29.7)	71.0	(38.2)	**0.012**
Mental health	78.3	(16.2)	68.0	(19.6)	**<0.001**
PCS	52.6	(7.0)	50.4	(8.5)	0.066
MCS	51.6	(9.7)	46.4	(10.9)	**0.001**
EuroQol					
Utility index	0.90	0.15	0.79	0.23	**0.003**
Visual analogue scale	82.1	14.1	74.8	19.0	**0.017**

Values are means with standard deviation in parentheses
P values are result of independent sample T-test
PCS - Physical Component Summary score
MCS - Mental Component Summary score

Over the six year period, the percentage of patients reporting hyperglycaemic complaints tended to increase from 53.3% to 58.3%.
The frequency of self monitoring blood glucose increased from 12.0 in 1995 to 18.2 in 1998 ($p<0.001$) to 20.0 in 2001 ($p=0.038$) per week.

Chronic diabetic complications and comorbidity (table 6)
The percentage of patients with microvascular complications increased from 45.8% in 1995 to 58.1% in 1998 ($p=0.005$), and increased again from 1998 to 2001 (from 58.1% to 65.7%), but this increase was not statistically significant ($p=0.248$).
The percentage of patients with retinopathy increased significantly during the first three-year period (34.6% to 44.9%, $p=0.007$), but showed only a modest, non-significant increase during the second, three-year period (44.9% to 48.5%, $p=0.442$). The percentage of patients with an increased urinary albumin excretion rate (used as a measure of nephropathy) decreased during the initial three years

(from 18.4% to 16.7%, $p=0.210$), but increased during the second three-year period (16.7% to 23.0%, $p=0.023$).
The percentage of patients with neuropathy increased between 1995 and 1998 ($p=0.004$), but declined during the second three-year period ($p=0.039$).
The number of patients with macrovascular complications increased from 10 (4.3%) in 1995 to 23 (9.8%) in 2001 ($p<0.001$). The most common diagnoses in 1995 were angina pectoris ($n=6$) and intermittent claudication ($n=4$). By the end of the study period (2001), myocardial infarction ($n=2$) and CVA ($n=4$) were also recorded.
The patients with comorbidity did not show statistically significant changes during the study period (Table 6).

Cardiovascular risk factors (Table 7)
During the first three-year period both systolic and diastolic blood pressure showed a significant decrease ($p<0.001$), whereas only diastolic blood pressure showed a further significant decrease during the second three year period ($p=0.029$). Pulse pressure decreased significantly during the first three years of the study ($p<0.001$), but tended to increase during the latter three-year period ($p=0.057$).
The cholesterol/ HDL ratio showed a decrease over both three-year periods ($p=0.031$, $p<0.001$).

Table 5
Therapy characteristics of the study population (n = 234); change over time

	1995		1998		p-value 1995 vs. 1998	2001		p-value 1998 vs. 2001
Insulin pump	63	(26.9%)	76	(32.6%)	**0.016**[1]	102	(43.6%)	**<0.001**[1]
Insulin pen	171	(73.1%)	157	(67.4%)		132	(56.4%)	
Frequency of insulin pen injection (per day)								
1-3	24	(14.0%)	22	(14.0%)		19	(14.4%)	
4	147	(86.0%)	128	(81.5%)		108	(81.8%)	
>4	0	(0.0%)	7	(4.5%)		5	(3.8%)	
Body mass index (kg/m^2)	24.8	(3.2)	25.6	(3.6)	**<0.001**[2]	26.1	(4.0)	**<0.001**
Hba1c (%)	8.1	(1.9)	7.9	(1.3)	**0.016**[2]	7.6	(1.1)	**<0.001**
Frequency of selfmonitoring blood glucose per week	12.0	(11.3)	18.2	(14.4)	**<0.001**[2]	20.0	(15.2)	**0.038**
Patients with:								
hypoglycaemic events last 3 months	185	(80.8%)	180	(84.9%)	0.110[1]	173	(87.4%)	0.736
hyperglycaemic complaints last three months	122	(53.3%)	105	(50.5%)	1.000[1]	116	(58.3%)	0.085

Values are number of patients (with valid percentages in parentheses) or means (with standard deviation in parentheses)
[1] p values are result of Mc Nemar test
[2] p values are result of paired samples T-test

Table 6
Diabetic complications and comorbidity of the study population (n = 234); change over time

	1995		1998		p-value 1995 vs. 1998	2001		p-value 1998 vs. 2001
Patients with diabetic complications								
Microvascular	104	(45.8%)	111	(58.1%)	**0.005**	119	(65.7%)	0.248
Retinopathy	79	(34.6%)	88	(44.9%)	**0.007**	99	(48.5%)	0.442
Nephropathy	43	(18.4%)	33	(16.7%)	0.210	45	(23.0%)	**0.023**
Neuropathy	24	(10.4%)	32	(15.2%)	**0.004**	23	(12.2%)	**0.039**
Macrovascular	10	(4.3%)	-	-	**<0.001**	23	(9.8%)	-
Comorbidity	133	(58.1%)	130	(62.5%)	0.212	107	(52.7%)	0.130

Values are number of patients (with valid percentages in parentheses)
P values are result of Mc Nemar test

Table 7
Cardiovascular risk factors in the cohort (n = 234)

	1995		1998		p-value 1995 vs. 1998	2001		p-value 1998 vs. 2001
Systolic blood pressure	138.9	(17.8)	131.1	(19.4)	**<0.001**	131.5	(19.2)	0.697
Diastolic blood pressure	*83.0*	(8.4)	79.4	(10.2)	**<0.001**	77.8	(10.4)	**0.029**
Pulse pressure	55.9	(15.2)	51.6	(15.9)	**<0.001**	53.7	(16.9)	0.057
Cholesterol/ HDL ratio	3.8	(1.2)	3.6	(1.3)	**0.031**	3.3	(1.1)	**<0.001**

Values are means with standard deviation in parentheses
P values are result of paired samples T-test

Discussion and conclusion

In this Dutch cohort of 234 patients with DMT1, treatment was intensified over the six year study period. The percentage of pump-users increased and HbA1c decreased at the cost of an increase in body mass index and an increased percentage of patients that reported hypoglycaemic events. Contrary to expectation, with the more intensive treatment the percentage of patients that reported hyperglycaemic complaints tended to increase during both three-year periods studied. The increased frequency of self-monitoring of blood glucose is inherent to the intensified therapy.

The decrease from 8.1 to 7.6% in the HbA1c levels is satisfactory, particularly considering the observational nature of the study. Comparatively, in the Diabetes Control and Complications Trial (DCCT), the patients in the intensive treatment group reached a median HbA1c level of 7.3% under very special study circumstances, whereas this level increased to 8.2% in the succeeding seven years, during the observational follow-up of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (8, 9).

Despite the intensified treatment in the six-year study period, the percentage of patients with micro- and macrovascular complications increased.

An increased incidence of nephropathy among diabetic patients may be expected. The decrease in urinary albumin secretion rate during the first three-year period may possibly be explained, however, by the reversibility, spontaneous remission, of the early stages of urinary albumin excretion (10). Improved metabolic control may also play a role.

The apparent decrease in the number of patients with neuropathy from 1998 to 2001 may be explained by the reduced number of test sites for the monofilament in 2001. An additional factor is the relatively large number of patients who did not visit the podiatrist in 2001 (19.2%).

The decreased prevalence of comorbidity during the second three-year period may be explained by the large percentage of missing records for 2001 (13.2%). The presence of complications related to the diabetes may have had a greater impact than the presence of non-diabetes related co-morbidities, causing the patients not to record the latter.

Although cardiovascular risk factors decreased during the study period, the percentage of patients with macrovascular complications increased. Comparing the percentages of micro- and macrovascular complications found in this study with other studies is complicated by variation in population characteristics and differences in assessment techniques (3, 5, 6, 8, 9, 11-13). The patient population of this study can be considered too small for definitive conclusions to be drawn. Nevertheless, the complication frequencies seen in the present cohort appear comparable to, or somewhat lower than those mentioned in the literature (14, 15).

Although many studies have shown the profound negative influence of smoking on the progression of nephropathy and retinopathy (14-18) , we made no specific interventions aiming to diminish the number of smokers.

The Steno-2 study showed that intensified multifactorial intervention, including behavior modification and pharmacologic therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, as well as secondary

prevention of cardiovascular disease with aspirin reduced the risk of cardiovascular and microvascular events by approximately 50 percent in patients with type 2 diabetes (19). Exercise has been shown to improve the vascular endothelial function in patients with DMT1. However, the beneficial effect on vascular function was not maintained when the exercise was discontinued (20).
Moreover, several studies showed that light to moderate alcohol consumption is associated with a decreased incidence of coronary heart disease in persons with diabetes (21).
In this observational study, too little attention has been paid to several potentially modifiable risk factors for the development of both types of complications. Lifestyle factors, such as smoking and exercise, can be influenced by lifestyle interventions, and offer new possibilities for slowing the onset and the progression of complications related to diabetes. Successful intervention in these areas is labour intensive and requires trained specialists. This type of intervention was not one of the aims of the present study.

Conclusion

In this Dutch cohort of patients with DMT 1, insulin therapy was intensified during the six-year study period, at the cost of the well-known side effects of this intensified therapy. The HbA1c level thus reached (7.6%) was satisfactory. Despite this reasonable HbA1c, the percentage of patients with micro- and macrovascular complications increased during the study period. More attention for other modifiable lifestyle factors, such as smoking, diet, and exercise, may offer more and better opportunities for lowering the incidence of chronic complications related to diabetes.

References

1. Assink JH. Oxidative stress and health status in patients with insulin-dependent diabetes mellitus. Rotterdam, The Netherlands: Erasmus University Rotterdam; 1998.
2. Dutch Advisory on Health Research. Advice on chronic diseases: priorities for research. 's Gravenhage, the Netherlands; 1991.
3. de Jong PTVM. Screening op diabetische retinopathie [Screening for diabetic retinopathy]. Ned Tijdschr Geneeskd 1993;137(34):1701-1705.
4. Holewski JJ, Stess RM, Graf PM, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. J Rehabil Res Dev 1988;25(2):1-10.
5. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329(5):304-9.
6. EURODIAB. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994;37(3):278-85.
7. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Nederlandse Diabetes Federatie. Diabetische retinopathie, diabetische nefropathie, diabetische voet, hart- en vaatziekten bij diabetes mellitus [Diabetic retinopathy, diabetic nephropathy, diabetic foot, cardiac and vascular pathology in diabetes mellitus]. Utrecht: Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing; 1998.
8. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.
9. DCCT. Effect of intensive therapy on the microvascular complications of type I diabetes mellitus. JAMA 2002;287(19):2563-2569.
10. Hovind P, Rossing P, Tarnow L, Smidt UM, H.H. P. Remission and regression in the nephropathy of type i diabetes when blood pressure is controlled aggressively. Kidney Int 2001 2001;60(1):277-83.
11. Hahl J, Hamalainen H, Sintonen H, Simell T, Arinen S, Simell O. Health related quality of life in type I diabetes without or with symptoms of long-term complications. Qual Life Res 2002;11:427-436.
12. Nederlandse Diabetes Federatie. Richtlijnen en Adviezen voor goede diabeteszorg [The Dutch Federation for Diabetes. Guidelines and Recommendations for Diabetes Care]; 2000.
13. Zgibor JC, Songer TJ, Kelsey SF, Drash AL, Orchard TJ. Influence of Health care providers on the development of diabetes complications. Diabetes Care 2002;25(9):1584-1590.
14. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type I diabetic patients: a 10-year prospective observational study. Diabetes Care 2002;25(5):859-64.
15. Esmatjes E, De Alvaro F, Estudio Diamante. Incidence of diabetic nephropathy in Type I diabetic patients in Spain: Estudio Diamante. Diabetes Res Clin Pract 2002;57(1):35-43.
16. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ 1996;313(7060):779-84.

17. Gambaro G, Bax G, Fusaro M, Normanno M, Manani SM, Zanella M, et al. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. Diabetes Nutr Metab 2001;14(6):337-42.
18. Magrini A, Bottini N, Nicotra M, Cosmi E, Bottini E, Bergamaschi A. Smoking and the genetics of signal transduction: an association study on retinopathy in type I diabetes. Am J Med Sci 2002;324(6):310-3.
19. Gaede PH, Vedel P, Larsen N, Jensen G, Parving HH, Pederson OB. Multifactorial Intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348(5):383-459.
20. Fuchsjager-Mayrl G, Pleiner J, Wiesinger GF, Sieder AE, Quittan M, Nuhr MJ, et al. Exercise training improves vascular endothelial function in patients with type 1 diabetes. Diabetes Care 2002;25(10):1795-1801.
21. Howard AA, Arnsten JH, Gourevitch MN. Effect of Alcohol Consumption on Diabetes Mellitus; a systematic review. Ann Intern Med 2004;140:211-219.

Chapter 3

Health Related Quality of Life in patients with Diabetes Mellitus Type I

Published in Quality of Life Research:
Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res 2003;12(8):1089-1097.

Abstract

Objective
The objective of this study was to assess health related quality of life (HRQOL) in patients with type I diabetes mellitus (DMT1) and to compare their HRQOL with the HRQOL of persons of comparable age in the general population. Furthermore we wanted to investigate which factors mostly influence HRQOL.
Research design and methods
In a Dutch cohort of 281 patients with DMT1 HRQOL 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 HRQOL. The Spearman rank correlations between RAND-36 subscales and EuroQol were analysed.
Results
RAND-36 results showed, for almost all subscales, a HRQOL comparable with persons of comparable age in the general population. In contrast the HRQOL measured with the EuroQol was lower for subjects with DMT1. Hyperglycaemic complaints and macrovascular complications had a profound negative influence on HRQOL. Most correlations between the RAND-36 results and the EuroQol results corresponded with our expectations.
Conclusion
HRQOL in patients with DMT1 is comparable with that of a general population sample. The presence of hyperglycaemic complaints and macrovascular complications had the most pronounced negative association with HQOL. Longitudinal data and comparison with results of several diabetes-specific questionnaires should help to establish which instrument might be most appropriate to measure HRQOL in patients with DMT1.

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 (HRQOL) in many different ways [4].
In recent years, HRQOL consisting of physical, psychological and social aspects has become more important in health care. Different instruments have been developed to measure HRQOL 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 HRQOL 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 HRQOL the most, how the individuals appraise the different aspects of the regimen, or which patients have the lowest HRQOL, or whether clinicians can influence those factors negatively influencing HRQOL. 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 HRQOL compared to persons of comparable age from the general population? Which factors influence the HRQOL of patients with DMT1?

Methods

Patients
From January 1995 to January 1996, 293 consecutive DMT1 patients, treated at the outpatient internal 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 six 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.

Health Related Quality of Life

HRQOL 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 diabetes 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 subscales: 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 subscale, 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 ten minutes to complete. The instrument has been translated in Dutch [17] and validated for the Dutch population [18].

The EuroQol is a simple generic measure, consisting of two parts (EQ-5D and EQ-VAS), developed by a multidisciplinary group of researchers from five European countries [19]. 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 U.K. 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 [20]. 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 two minutes to complete and has been validated for the Dutch situation [21].

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 three months?') during the three 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 alpha 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 [22].

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 de Jong [23]: 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 [24]. At five dorsal and plantar sites on the feet sensitivity was tested using six different monofilaments. When the monofilament 5.07 was not felt at one of the ten test sites, patients were diagnosed as having neuropathy.

Nephropathy

The 24-hour urinary excretion of albumin (UAER) was measured yearly. UAER was considered abnormal when it was ≥ 30mg/ 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 [25-27].

At the time of the study (1995) patients with a micro-albuminuria >100 mg/ 24 hour 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

HRQOL of patients was compared with the HRQOL 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 HRQOL 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 subscales of the RAND-36 and the dimensions of the EuroQol. We expected correlations between 'Mobility' and the subscales 'physical functioning' and 'role physical', between 'Self-care' and 'physical functioning and 'role physical', between 'Usual activities' and most subscales of the RAND-36, between 'Pain/ discomfort' and 'bodily pain' and between 'Anxiety / depression' and the more

mental subscales 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 (87.9%) received intensive therapy (i.e. insulin pump or minimal 4 times daily pen injection) and self-monitored their blood glucose values. Almost half of the patients had microvascular complications (47.1%) (Table1). Most patients with retinopathy had grade 1 diabetic retinopathy, almost always in both eyes. Of the patients with nephropathy (n=53), 21% had 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 HRQOL questionnaires were completed by 274 patients (97.5%) (Table 2).
The RAND-36 subscale scores were comparable with those of persons of comparable age in the Dutch general population [14], except for the General Health subscale that was lower than in the general population ($p=0.022$) and the Bodily Pain subscale 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 U.K. general population [28].
Univariate analysis showed that females reported a lower HRQOL (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 than patients with 2-3 injections daily. Whereas patients with 4-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 HRQOL (PCS, MCS, EQ-5D, EQ-VAS). Patients having microvascular complications also reported a lower HRQOL (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 HRQOL (Table 3).

Table 1
Personal and disease-specific characteristics of the study population (n-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 consumption	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):	34	(12.1%)
2-3	175	(62.3%)
4	72	(25.6%)
Pump		
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		
Microvascular	129	(47.1%)
Retinopathy	97	(35.7%)
Nephropathy	53	(18.9%)
Neuropathy	32	(11.5%)
Macrovascular	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

Table 2
Comparison of health related quality of life scores seen in the study population with scores seen in the general population

	This study (DMT1)	General population [14]	
	n = 274	n = 195	
Age in years	38.2	35-44	
Percentage men	54.4%	31%	
RAND-36			
			p-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[1]	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
EuroQol			
	This study (DMT1)	**General population [28]**	
	n = 274	n = 561	
Age in 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**

DMT1 - Diabetes mellitus type I
EQ-5D - EuroQol utility
EQ-VAS - EuroQol Visual Analogue Scale

Values are means with standard deviations between parentheses
p-values concern T-test for independent samples
[1]Higher Bodily pain score indicates less pain

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

	PCS adjusted $R^2 = 0.278$ ß (p-value)	MCS adjusted $R^2 = 0.240$ ß (p-value)	EQ-5D adjusted $R^2 = 0.198$ ß (p-value)	EQ-VAS adjusted $R^2 = 0.228$ ß (p-value)
Females	-0.091 (p = 0.015)	0.118 (p = 0.021)		
Age (per year)		5.669 (p = 0.002)		
Married/ cohabiting				
High level of education				-5.432 (p = 0.006)
Hba1c (%)				-1.241 (p = 0.012)
Frequency of insulin injection:				
4-times a day relative to 2-3 times				
continuous relative to 2-3 times				
Self-monitoring a week	-0.167 (p < 0.001)			-0.224 (p = 0.005)
Hypoglycaemic complaints				
Hyperglycaemic complaints		-7.428 (p < 0.001)	-0.071 (p = 0.002)	-8.716 (p < 0.001)
Microvascular complications				
Macrovascular complications	-8.468 (p < 0.001)	-6.698 (p = 0.002)	-0.146 (p < 0.001)	-10.016 (p = 0.002)
Comorbidity	-2.323 (p = 0.0010)		-0.078 (p = 0.001)	

PCS - Physical Component Summary
MCS - Mental Component Summary
EQ-5D - EuroQol utility
EQ-VAS - EuroQol Visual Analogue Scale

Table 4
Spearman rank order correlations between subscales of the RAND-36 and the EuroQol

		EuroQoL				
		Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
RAND-36	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 ($p<0.001$)

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 per 10 years increase in age was seen. In contrast, younger age, unmarried status, hyperglycaemic 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 subscales of the RAND-36 and the EuroQol 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 subscales, while the Usual activities dimension was moderately/ strongly correlated with all subscales of the RAND-36. Pain/ discomfort was strongly correlated with the subscale 'bodily pain'. Anxiety/ depression was particularly correlated with the subscale 'mental health'.

Discussion and conclusion

HRQOL measured in our study population was comparable with the HRQOL of persons of comparable age in the Dutch general population (using the RAND-36), except for the subscales 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% versus 46%) and that females tend to report more symptoms such as bodily pain [14, 29]. The EuroQol gave lower HRQOL levels for subjects with DMT1 than patients in a U.K. sample of the general population. Wikblad et al reported a HRQOL equal to persons in the general population just as in our study (mean age 43.5 years) [30]. In the study of Wandell et al, diabetic patients reported a HRQOL lower than persons in a population sample [31]. However their cohort was older (mean 51.5 year) than our cohort (mean 38.2 years). Recently Hahl et al reported a lower HRQOL 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 [32].
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 [33]. 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 [34], 0.05 points for the EQ-5D and 5 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 HRQOL of patients with DMT1. We can conclude that the presence of macrovascular complications definitely has a large negative impact on the HRQOL of patients with DMT1. Other studies also reported a worse HRQOL, 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 [30, 35-37].

Hahl et al, also reported a significant negative influence on HRQOL by the symptoms of long-term micro- and macrovascular complications [32]. 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 HRQOL in our study. In the multivariate regression analyses these complications did not have a statistically significant influence on HRQOL. 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 HRQOL [38, 39]. Hanestad et al reported that the presence of nephropathy had a negative effect on HRQOL, whereas neuropathy was associated with a better HRQOL in her study. The severity of complications was not properly clarified. Wu et al observed a higher HRQOL (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 U.K. Prospective Diabetes Study (UKPDS) reported for patients with diabetes mellitus type 2 (DMT2) the same negative impact on HRQOL by the presence of long-term complications [40]. 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 HRQOL 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 however did find an association between microvascular complications and reduced HRQOL [41].

Another negative influence on HRQOL 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 HRQOL, by more symptomatic distress [3].

In our study, patients receiving continuous insulin pump therapy reported a lower MCS and EQ-5D. Such an intensive therapy obliges the patients to monitor their blood glucose levels more frequently. However, and especially, 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 HRQOL of patients using continuous therapy.

The finding that women, older patients and patients without a partner reported a lower HRQOL confirms the results of other studies [30, 35, 36, 38, 42]. The positive influence of age on the MCS has not been described before (Table 3). 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 HRQOL? 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 HRQOL. Concerning other factors, for example 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 subscales of the RAND-36 were as expected. Oddly enough the dimension 'self care' did not show any statistically significant correlation with any RAND-36 subscale. It is possible that this item, concerning washing and dressing oneself, is too specific to be reflected in the total score for a RAND subscale. 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 subscale, the RAND subscale with the highest correlation with the MCS [34].

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 HRQOL were assessed by both instruments, except for age and having a partner by the RAND-36 and the level of education and Hba1c 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 subscales) and the distinction between a 'physical score' and a 'mental score' are clear advantages of the RAND-36.

Conclusion

HRQOL in patients with DMT1 is comparable with that of a general population sample. The presence of hyperglycaemic complaints and macrovascular complications had the most pronounced negative association with HQOL.

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

References

1. Atkinson MA, Maclaren NK: The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med* 331:1428-36, 1994
2. DCCT: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977-86, 1993
3. DCCT: Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. *Diabetes Care* 19:195-203, 1996
4. Eiser C, Tooke JE: Quality-of-life evaluation in diabetes. *Pharmacoeconomics* 4:85-91, 1993
5. Coons SJ, Rao S, Keininger DL, Hays RD: A Comparative Review of Quality-of-Life Instruments. *Pharmacoeconomics* 17:13-35, 2000
6. Guyatt GH, Feeny DH, Patrick DL: Measuring health-related quality of life. *Ann Intern Med* 118:622-9, 1993
7. Hutchinson A, Bentzen N, Konig-Zahn C: *Cross Cultural Health Outcome Assessment; a user's guide*. Groningen, The Netherlands, Europian Research Group on Health Outcomes, 1996
8. Patrick DL, Deyo RA: Generic and disease-specific measures in assessing health status and quality of life. *Med Care* 27:S217-32, 1989
9. Testa MA, Simonson DC: Assessment of quality-of-life outcomes. *N Engl J Med* 334:835-40, 1996
10. Bradley C: Measuring quality of life in diabetes. *The Diabetes Annual* 10:207-24, 1996
11. Garratt AM, Schmidt L, Fitzpatrick R: Patient-assessed health outcome for measures for diabetes: a structured review. *Diabet Med* 19:1-11, 2002
12. Luscombe FA: Health-related Quality of Measurement in Type 2 Diabetes. *Value in Health* 3:15-28, 2000
13. Rubin RR, Peyrot M: Quality of life and diabetes. *Diabetes Metab Res Rev* 15:205-18, 1999
14. Zee vdKI, Sanderman R: *Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding [Measuring general state of health with the RAND-36. A guide]*. Groningen, University of Groningen, 1993
15. Hays RD, Sherbourne CD, Mazel RM: The RAND 36-item Health Survey 1.0. *Health Econ* 2:217-27, 1993
16. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A: Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 33:AS264-79, 1995
17. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 51:1055-68, 1998
18. Zee vdKI, Sanderman R, Heyink J, Haes dH: The psychometric qualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. *Int J Behav Med* 3:104-22, 1996
19. EuroQol Group: EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. *Health Policy* 16:199-208, 1990
20. Dolan P: Modeling valuations for EuroQol Health States. *Med Care* 35:1095-108, 1997

21. Essink-Bot ML, Stouthard ME, Bonsel GJ: Generalizability of valuations on health states collected with the EuroQol-questionnaire. *Health Econ* 2:237-46, 1993
22. Dutch Advisory on Health Research: *Advice on chronic diseases: priorities for research*. 's Gravenhage, the Netherlands, 1991
23. de Jong PTVM: Screening op diabetische retinopathie [Screening for diabetic retinopathy]. *Ned Tijdschr Geneeskd* 137:1701-05, 1993
24. Holewski JJ, Stess RM, Graf PM, Grunfeld C: Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. *J Rehabil Res Dev* 25:1-10, 1988
25. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304-9, 1993
26. EURODIAB: Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. *Diabetologia* 37:278-85, 1994
27. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Nederlandse Diabetes Federatie: Diabetische retinopathie, diabetische nefropathie, diabetische voet, hart- en vaatziekten bij diabetes mellitus [Diabetic retinopathy, diabetic nephropathy, diabetic foot, cardiac and vascular pathology in diabetes mellitus]. Utrecht, Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, 1998
28. Kind P, Hardman G, Macran S: *UK Population Norms for EQ-5D*. York, United Kingdom, 1999
29. Kind P, Dolan P, Gudex C, Williams A: Variations in population health status: results from a United Kingdom national questionnaire survey [see comments]. *BMJ* 316:736-41, 1998
30. Wikblad K, Leksell J, Wibell L: Health-related quality of life in relation to metabolic control and late complications in patients with insulin dependent diabetes mellitus. *Qual Life Res* 5:123-30, 1996
31. Wandell PE, Brorsson B, Aberg H: Quality of life among diabetic patients in Swedish primary health care and in the general population: comparison between 1992 and 1995. *Qual Life Res* 7:751-60, 1998
32. Hahl J, Hamalainen H, Sintonen H, Simell T, Arinen S, Simell O: Health related quality of life in type I diabetes without or with symptoms of long-term complications. *Qual Life Res* 11:427-36, 2002
33. Duijn NPG, K. Schuling, J. Weert, van H. Meyboom-de Jong, B.: The sensitivity to change of the COOP charts. *Huisarts Wet* 38:139-43, 1995
34. Ware JE, Kosinki M: Interpreting SF-36 summary health measures: A response. *Qual Life Res* 10:405-13, 2001
35. Aalto AM, Uutela A, Aro AR: Health related quality of life among insulin-dependent diabetics: disease-related and psychosocial correlates. *Patient Educ Couns* 30:215-25, 1997
36. Bott U, Muhlhauser I, Overmann H, Berger M: Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. *Diabetes Care* 21:757-69, 1998
37. Jacobson AM, de Groot M, Samson JA: The evaluation of two measures of quality of life in patients with type I and type II diabetes. *Diabetes Care* 17:267-74, 1994
38. Hanestad BR: Self-reported quality of life and the effect of different clinical and demographic characteristics in people with type 1 diabetes. *Diabetes Res Clin Pract* 19:139-49, 1993
39. Wu SY, Sainfort F, Tomar RH, Tollios JL, Fryback DG, Klein R, Klein BE: Development and application of a model to estimate the impact of type 1 diabetes on health-related quality of life. *Diabetes Care* 21:725-31, 1998

40. U.K. Prospective Diabetes Study Group: Quality of life in Type 2 Diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). *Diabetes Care* 22:1125-36, 1999
41. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GEH, Niessen LW: Health related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. *Diabetes Care* 25:458-63, 2002
42. Reviriego J, Millan MD, Millan M: Evaluation of the diabetes quality-of-life questionnaire in a Spanish population. An experience of translation and reliability. *Pharmacoeconomics* 10:614-22, 1996

Chapter 4

Health Related Quality of Life in patients with newly diagnosed Diabetes Mellitus Type I

Partly published in Diabetes Care:
Hart HE, Redekop WK, Assink JH, Meyboom-de Jong B, Bilo HJG: Health-Related Quality of Life in Patients with Newly Diagnosed Type I Diabetes. Diabetes Care 2003; 26(4):1319-20.

Abstract

Objective
The aim of this study was to investigate the health related quality of life (HRQOL) of patients with newly diagnosed diabetes mellitus type I (DMT1) during the first year after diagnosis and to compare their HRQOL, one year after diagnosis, with people of comparable age from the general population and with other patients who were diagnosed with DMT1 longer than one year prior to the start of the study period.
Research design and methods
We used the RAND-36 and the EuroQol to assess the HRQOL of fifteen patients who had been newly diagnosed with DMT1. To compare HRQOL scores, we converted the individual raw scores into percentiles based on the average scores of the comparison population.
Results
The improvements in the subscales role physical, vitality, and mental health as well those seen in the physical summary score and in the EQ-VAS were statistically significant within the first six months of diagnosis. The next half-year did not show any further significant changes in HRQOL. After one year, the HRQOL of the newly diagnosed patients was comparable with that of persons in the general population and with patients with a longer disease duration.
Conclusion
The HRQOL improved in newly diagnosed patients during the first six months following diagnosis. One year after diagnosis the HRQOL is comparable with persons from the general population and with patients with DMT1 with a longer disease duration.

Introduction

The diagnosis of diabetes mellitus type I (DMT1) permanently changes a person's life. The transition from being a healthy person to a person with a chronic illness can have a considerable impact (1). Newly diagnosed patients have to consider their diet, insulin therapy, exercise and daily self-monitoring of their blood glucose which will likely affect their health related quality of life (HRQOL) (2). The aim of the present study was to investigate the HRQOL in patients newly diagnosed with DMT1(1), to follow their progress during the year following the diagnosis to monitor the effect on their HRQOL (2), and to determine which factors are important in influencing the HRQOL during those first twelve months after the diagnosis has been made (3). We also compared the patients' one year HRQOL reports with those obtained from age matched controls from the general population (4.1) and from patients with DMT1 with a longer duration of disease (4.2).

Methods

Patients

During 1995 and 1996, 15 patients who were diagnosed with diabetes mellitus type I (DMT1) at the outpatient clinic of the Isala Clinics in Zwolle, The Netherlands were included in this study. They were followed for a period of twelve months from the time of diagnosis. The diagnosis of DMT1 was based on the initiation of insulin therapy within six months of the manifestation of the diabetes mellitus, with the diagnosis occurring before the age of thirty, or on the absence of C-peptide secretion. Approval for the study was obtained from the Hospital Scientific and Ethics Committee. All patients gave informed consent.

Clinical data

Demographic data such as gender, age, and level of education were recorded at baseline.

Patients underwent a physical examination at the time of diagnosis (baseline), and at six and twelve months. *Metabolic control* was assessed by measuring levels of glycosylated hemoglobin A1c (HbA1c) at baseline, monthly during the first six months, at nine months, and then again after twelve months. The lipid profile and micro-albuminuria were measured at the same time intervals.

Comorbidity was assessed using a list of 26 chronic diseases, on which patients were asked to indicate any which applied to them (3). When they indicated one or more chronic diseases apart from their diagnosis of DMT1, they were scored positive for *comorbidity*.

During each of the three outpatient visits, one at baseline, one at six months, and one at twelve months, patients were asked to report whether they had experienced one of a list of six *hyperglycaemic complaints*, including fatigue, weight loss, pruritus, thirst, polyuria, and polydipsia. They were also asked, at baseline and at

twelve months, whether they experienced any problems with the *activities of daily living* such as shopping, work, school, and household chores.
Any acute complications arising from the therapy were recorded: the patients recorded all *hypoglycaemic* events during the three months preceding the outpatients visits at six and twelve months.

Health Related Quality of Life:
Health related quality of life (HRQOL) was assessed at baseline, at six months, and at twelve months, using two generic instruments. Generic instruments were chosen to facilitate comparisons with persons from the general population. The questionnaires were mailed to the patient's home address shortly before a scheduled outpatient visit. Patients were directed to complete the questionnaires at home before coming in for their appointment and to return the completed questionnaire to the nurse when they came in.
The RAND-36-item Health Survey (RAND-36)
The RAND-36 is a self-administered, generic, multi-dimensional questionnaire consisting of 36 items, which measures HRQOL, and takes approximately ten minutes to complete (4, 5). The response alternatives vary from 2 ('yes' and 'no') to 6 (Likert scale). The reference period is four weeks. The 36 items are divided into eight subscales: 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 subscale scores were coded, summed, and converted to a scale from zero (worst health) to one hundred (best health) (6). Physical and mental component summary scores were also determined (Physical Component Summary [PCS]/ Mental Component Summary [MCS]) (7). The instrument has been translated into the Dutch language (8), and has been validated for the Dutch population (9).
The EuroQol (EQ)
The EuroQol was developed by a multidisciplinary group of researchers from five European countries to describe and evaluate state of health (10). It is a simple, generic, multidimensional measure, consisting of two parts, which takes the patient about two minutes to complete. The reference period is the day of the measurement. Part one consists of five questions covering the areas Mobility, Self-Care, Usual Activities, Pain/ Discomfort, and Anxiety/ Depression. The patient is asked to choose from three levels of functioning: 'no problem', 'some/ moderate problems', and 'extreme/ unable to'. The respondent's state of health is described by combining the levels indicated for each of the dimensions (EQ-5D). A total of 243 possible states of health can be defined using this method. The UK general public has used a valuation technique called a time trade-off to make valuations of these health states (utility indices). The set of possible values has a range of –0.549 to 1, where 1 indicates perfect health, 0 indicates death, and –0.549 indicates the worst possible health state, which is viewed as considerably worse than death by the UK general public (11). The EuroQol utility index facilitates economic evaluation. Furthermore, part two, a single overall score, can also be obtained from the EuroQol thermometer: a self-rated health-status using a graduated (0-100) visual analogue scale, similar to a thermometer (EQ-VAS). With the thermometer, 0

indicates the worst HRQOL and 100 indicates the best possible HRQOL. The EuroQol has been validated for the Dutch population (12).

Analysis

We performed Wilcoxon signed ranks tests to compare clinical data (i.e. HbA1c, body mass index) and HRQOL at different points in time. We also carried out univariate and multivariate stepwise regression analyses, with HRQOL as the dependent variable, to investigate the relationship between HRQOL and demographic data (sex, age, marital status, and level of education) and diabetes related data (HbA1c, hyperglycaemic complaints, hypoglycaemic events).

To compare the HRQOL of the study patients with age matched controls from the general population we converted individual scores into percentiles based on the general population average and standard deviation. A similar procedure was used when comparing the HRQOL of newly diagnosed patients with the HRQOL of patients with a longer disease duration, with the exception that no adjustment was made for age differences. A T-test for independent samples was used to compare the HRQOL of patients newly diagnosed with DMT1 with the HRQOL in the general population. The Mann Whitney U test was used to compare the HRQOL between newly diagnosed patients and patients with DMT1 of longer duration.

We considered relationships to be statistically significant when p-values were ≤ 0.05. Data were analyzed using SPSS for Windows, version 10.0.7.

Results

Fifteen patients were included in this study, one third of which was men. The mean age was 29.2 with a standard deviation of 12.0, and a range of fourteen to 54 years (table 1). In the first six months following diagnosis, HbA1c levels declined significantly, from 14.3% to 5.9% ($p < 0.001$; table 2). The percentage of patients that reported hyperglycaemic events showed a similar trend, decreasing from 93% to 53% ($p = 0.014$). Body mass index increased significantly during the first six months of the study, from 22.2 to 23.9 kg/m^2 ($p = 0.001$). During the latter half of the year, there was no further significant change in either HbA1c levels or reported hyperglycaemic complaints (table 2).

Table 1
Characteristics of patients with newly diagnosed diabetes mellitus type I (n = 15)

Gender (men)	5	(33.3%)
Age (years)	29.2	(12.0)
Married/ cohabiting	12	(80.0%)
High level of education	2	(13.3%)
Comorbidity (one or more chronic medical condition)*	9	(69.0%)

Values are number of patients or means with percentage or standard deviation between parentheses.
*In addition to diabetes mellitus type I

Table 2
Clinical data during the first year following diagnosis (n = 15)

	Baseline	6 months	12 months	p value 0-6	p value 6-12
HbA1c (%)	14.3 (3.7)	5.9 (0.8)	6.9 (1.5)	**0.001**	0.075
Cholesterol/ HDL ratio	4.5 (1.8)	3.3 (1.0)	3.5 (1.4)	**0.001**	0.068
Body mass index (kg/m^2)	22.2 (3.7)	23.9 (3.7)	23.3 (3.0)	**0.001**	0.441
Micro-albuminuria (mg/24 hr)	9.3 (6.7)	10.7 (12.4)	12.3 (14.8)	0.955	0.454
Number of patients with:					
hyperglycaemic complaints	14 (93 %)	8 (53 %)	9 (60 %)	**0.014**	0.564
hypoglycaemic events	[1]	12 (80 %)	10 (67 %)	-	0.317
problems with ADL*	4 (27 %)	[2]	3 (20 %)	-	-

Values are means with standard deviations (SD) in parentheses
P values are result of Wilcoxon signed ranks tests.
[1] Not applicable
[2] Not measured
*Activities of Daily Living

The same was true for the body mass index. Hypoglycaemic events were reported by twelve patients (80%) at the six month point and ten patients (66.7%) at the twelve month point in the study. Table 3 gives a detailed overview of the follow-up of the HbA1c levels for the first six months following diagnosis. The first three months showed significant declines, which tapered off entirely during months four, five, and six.

Table 3
Follow up of HbA1c during the first six months following diagnosis

	Mean	SD	Range	p-value
Baseline	14.3	3.7	8.2 - 21.9	-
Month 1	9.6	2.0	6.9 - 13.1	**0.001**
Month 2	7.0	0.8	5.6 - 8.7	**0.001**
Month 3	5.9	1.0	4.4 - 8.0	**0.006**
Month 4	5.8	0.6	4.9 - 6.9	0.533
Month 5	6.0	0.8	4.7 - 7.2	0.211
Month 6	5.9	0.8	4.8 - 7.3	0.972

Mean - mean HbA1c
SD - standard deviation
Range - range of the HbA1c values
P values are the result of Wilcoxon signed ranks test

HRQOL – from baseline to six months after diagnosis
RAND-36 All subscales and both summary scores showed an increase during the first six months after diagnosis. The increases of the subscales 'role physical', 'vitality', and 'mental health', and the PCS were statistically significant (table 4).
EuroQol Both the EQ-5D and the EQ-VAS showed an increase during the first six months. The increase of the EQ-VAS was statistically significant.
HRQOL – from six to twelve months after diagnosis
There were no statistically significant changes in the HRQOL (i.e. all RAND-36 and EuroQol outcomes) during the last six months of the twelve month study period.
HRQOL – from baseline to twelve months after diagnosis
RAND-36 The subscales 'physical functioning' and 'role physical' and the PCS showed an increase immediately following diagnosis and continued to increase significantly during the entire twelve month period. The subscale 'vitality' tended to decrease during the last six months of the twelve months study period, but reached a value (70.0 with a standard deviation 21.6) that was significant higher than at baseline. The other RAND subscales and the MCS did not change (table 4).
EuroQol The EQ-5D did not show statistically significant changes during the overall study period. The EQ-VAS increased significantly from its baseline value.

Associations with HRQOL at the moment of diagnosis
The univariate analysis showed that patients who were either married or cohabiting reported a higher EQ-5D and a lower EQ-VAS than other respondents. Patients who were positive for comorbidity reported a lower MCS (table 5). These associations were still present following multivariate regression analysis (table 5).

Table 4
Health related quality of life during the first year after the diagnosis of diabetes mellitus type I (n = 15)

	Baseline	6 months	12 months	P value 0-6 months	P value 6-12 months	P value 0 -12 months
RAND – 36						
Physical functioning	82.3 (22.0)	89.0 (18.2)	93.7 (9.7)	0.081	0.168	**0.018**
Role physical	56.7 (44.8)	83.3 (34.9)	88.3 (18.6)	**0.034**	0.518	**0.001**
Bodily pain	86.8 (14.8)	90.8 (16.6)	87.8 (21.5)	0.360	0.416	0.506
General health	68.0 (20.2)	80.7 (14.5)	78.3 (16.9)	0.063	0.428	0.214
Vitality	50.3 (23.9)	71.7 (19.3)	70.0 (21.6)	**0.005**	0.860	**0.004**
Social functioning	80.0 (25.8)	90.0 (17.8)	85.0 (27.6)	0.200	0.290	0.389
Role emotional	80.0 (35.2)	84.4 (30.5)	86.7 (30.3)	0.607	0.783	0.276
Mental health	68.3 (26.1)	80.8 (16.3)	77.1 (23.5)	**0.037**	0.404	0.082
Physical Component Summary	48.8 (7.3)	53.4 (6.1)	54.4 (3.4)	**0.009**	0.730	**0.004**
Mental Component Summary	47.1 (12.5)	52.8 (7.8)	50.8 (11.5)	0.088	0.331	0.173
EuroQol						
Utility index	0.79 (0.19)	0.88 (0.19)	0.88 (0.19)	0.154	0.917	0.061
Visual Analogue Scale	74.0 (19.8)	87.6 (11.5)	84.9 (12.4)	**0.005**	0.331	**0.036**

Values are means with standard deviation in parentheses
P-values are result of Wilcoxon signed ranks tests

Table 5
Results of the uni- and multivariate regression analyses during the first year after diagnosis

	Univariate at baseline	**Univariate** at 6 months	**Univariate** at 12 months	**Multivariate** at baseline	**Multivariate** at 6 months	**Multivariate** at 12 months
Age		-0.410 (MCS) [p=0.011]	-0.195 (PCS) [p=0.004]			-0.247 (PCS) [p=0.002]
Married/cohabiting	0.290 (EQ-5D) [p=0.010] -26.25 (EQ-VAS) [p=0.035]			0.290 (EQ-5D) [p=0.010] -26.25 (EQ-VAS) [p=0.035]		
HbA1c			-5.002 (MCS) [p=0.017] -0.098 (EQ-5D) [p=0.002]			-5.626 (MCS) [p=0.022] -0.105 (EQ-5D) [p=0.005]
Bodymass index		-1.150 (MCS) [p=0.037]				-
Hyperglycaemic complaints						-12.03 (EQ-VAS) [p=0.049]
Problems activities of daily living			-4.267(PCS) [p=0.045]			
Comorbidity	-14.46 (MCS) [p=0.021]			-14.46 (MCS) [p=0.021]		

PCS: physical component summary; MCS: mental component summary; EQ-5D: EuroQol utility; EQ-VAS: EuroQol Visual Analogue Scale
* no significant associations found between health related quality of life and sex, level of education and presence of hypoglycaemic events

Table 6
Comparison of HRQOL of patients newly diagnosed with DMT1 with that of persons from the general population and that of patients with DMT1 with a longer disease duration

	This study at 12 months	General population sample[1]	I	Patients with DMT1 with a longer disease duration[2]	II	Patients with a longer disease duration: < 40 yrs. old and without macrovascular complications	III
RAND-36							
Physical functioning	93.7 (9.7)	89.4 (4.0)	0.60 (0.20)	90.4 (14.7)	0.59 (0.23)	94.7 (8.0)	0.53 (0.29)
Role physical	88.3 (18.6)	83.7 (2.5)	0.56 (0.20)	82.8 (32.4)	0.57 (0.21)	88.6 (26.5)	0.52 (0.23)
Bodily pain	87.8 (21.5)	85.3 (2.7)	0.57 (0.25)	88.7 (17.8)	0.55 (0.27)	91.6 (15.6)	0.50 (0.28)
General health	78.3 (16.9)	75.8 (2.1)	0.54 (0.26)	68.0 (20.1)	0.65 (0.26)	71.6 (18.3)	0.61 (0.29)
Vitality	70.0 (21.6)	68.5 (0.9)	0.56 (0.32)	67.5 (20.0)	0.56 (0.31)	68.5 (18.1)	0.56 (0.33)
Social functioning	85.0 (27.6)	87.1 (2.1)	0.55 (0.28)	86.9 (20.0)	0.55 (0.28)	89.6 (17.6)	0.52 (0.28)
Role emotional	86.7 (30.3)	82.8 (2.3)	0.58 (0.25)	84.0 (31.8)	0.58 (0.25)	88.2 (28.1)	0.55 (0.25)
Mental health	77.1 (23.5)	75.6 (2.3)	0.56 (0.31)	76.6 (17.3)	0.56 (0.33)	77.2 (16.1)	0.55 (0.34)
PCS	54.4 (3.4)	-	-	52.2 (7.3)	0.61 (0.17)	54.1 (5.9)	0.52 (0.20)
MCS	50.8 (11.5)	-	-	50.8 (10.1)	0.54 (0.31)	51.1 (9.9)	0.54 (0.31)
EuroQol							
EQ-5D	0.88 (0.19)	0.92 (0.03)	0.47 (0.29)	0.88 (0.17)	0.55 (0.27)	0.92 (0.13)	0.49 (0.31)
EQ-VAS	84.9 (12.4)	86.0 (1.6)	0.49 (0.28)	80.8 (15.3)	0.59 (0.27)	82.9 (13.3)	0.55 (0.30)

I Percentiles in comparison with general population sample
II Percentiles in comparison with patients with a longer disease duration
III Percentiles in comparison with patients a longer disease duration, but <40 years and without macrovascular complications
Values are means with standard deviations in parentheses
[1] Age adjusted with Dutch general population (RAND-36) and with age and sex adjusted UK General population (EQ) (6, 13)
[2] Mean duration of diabetes 17.2 years (10.7), mean age 38.2 years (12.4) (14)

Associations with HRQOL six months after diagnosis
Older patients reported a lower MCS. Patients with a higher body mass index (which increased during the first six months) reported a lower MCS. No significant associations were found following multivariate analysis, however (table 5).
Associations with HRQOL twelve months after diagnosis
Older patients and patients having problems with the activities of daily living reported a lower PCS. The age-related difference remained apparent following multivariate regression analysis (table 5). Patients with a higher HbA1c reported a lower MCS and EQ-5D. The same result was found with the multivariate analysis (table 5). Patients with hyperglycaemic complaints reported a lower EQ-VAS (table 5).

Comparison in HRQOL with the general population
One year post-diagnosis, we compared the RAND-36 scores of the patient population with scores obtained from age matched controls from the general population (6). The mean percentiles for the RAND-36 ranged from 0.54 to 0.60 for the eight subscales. This meant that patients newly diagnosed with DMT1 were reporting a HRQOL that tended to be somewhat higher than that being reported by persons from the general population. These differences were not statistically significant, however.
We also compared the one year post-diagnosis EuroQol scores of the study population patients with those obtained from age matched controls from the general population (13). The mean percentiles were 0.47 (EQ-5D) and 0.49 (EQ-VAS). This meant that the patients were reporting their HRQOLs to be marginally lower than persons in the general population. Here again, however, the differences were not statistically significant.
Comparison in HRQOL with diabetes patients with a longer disease duration
One year after diagnosis, we compared the HRQOL of the study population patients with the HRQOL of patients who had been diagnosed with DMT1 an average of 17.2 years earlier (14). The mean percentiles for the RAND-36 and the EuroQol were 0.54-0.65. This meant that the patients who were newly diagnosed were reporting a HRQOL which was somewhat higher than that reported by the patients who had had the disease for a longer time duration. These differences were not statistically significant.
We expected the HRQOL of the newly diagnosed patients to be similar to the scores of patients with a longer disease duration who were younger (<40 years), and who were without complications (macrovascular) from their diabetes (2, 15). In fact, when we compared the HRQOL of the study population with that of a subgroup of patients without macrovascular complications and who were younger than 40 years, the differences largely disappeared, except in the subscale of 'general health', where the newly diagnosed group tended to score higher.

Discussion

After the diagnosis DMT1 is made, all HRQOL scores improved during the first half year of the study period. One year post-diagnosis all HRQOL scores are higher than at baseline. Whether this result is due to the use of a generic instrument instead of a disease-specific instrument remains to be investigated.
All the cumbersome aspects of the disease, such as diet, insulin injections, and daily blood glucose monitoring, appear to be accepted fairly quickly, and incorporated in daily lifestile, within twelve months of the diagnosis.
It should be noted that the presence of comorbidity and hyperglycaemic complaints had a measurable negative influence on HRQOL, however. We concluded that the presence of DMT1 does not decrease HRQOL, unless there are symptoms present.
Although the sample size included of the present study is limited, we think that the results obtained are representative.
After one year, when in a stable situation, the patients in the study population reported a HRQOL which tended to be somewhat higher (RAND-36) and marginally lower (EuroQol) than that of the age matched controls. These differences were not significant, however. Unfortunately, only the EuroQol allowed for comparisons on the basis of gender.
When comparing on the basis of disease duration, the newly diagnosed patients tended to report a somewhat better HRQOL, though these results, too, were not significant. The patients in our study were generally somewhat younger, and did not yet have any of the macrovascular complications, which affect HRQOL (15).
The HRQOL improves during the first six months after a patient is diagnosed with diabetes mellitus type I. One year after the diagnosis the HRQOL of the patient is comparable to that of persons in the general population and patients with DMT1 of longer duration.

Acknowledgements: *We thank the Northern Centre for Healthcare Research of the University of Groningen for providing data to compare our data with those of a sample of the general Dutch population.*

References

1. Jacobson AM. The psychological care of patients with insulin-dependent diabetes mellitus. N Engl J Med 1996;334(19):1249-1253.
2. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15(3):205-18.
3. Dutch Advisory on Health Research. Advice on chronic diseases: priorities for research. 's Gravenhage, the Netherlands; 1991.
4. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. Health Econ 1993;2:217-227.
5. Hays RD, Morales LS. The RAND-36 measure of health related quality of life. Ann Med 2001;33:350-357.
6. Zee vdKI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding [Measuring general state of health with the RAND-36. A guide]. Groningen: University of Groningen; 1993.
7. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33(4 Suppl):AS264-79.
8. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.
9. Zee vdKI, Sanderman R, Heyink J, Haes dH. The psychometric qualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-122.
10. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
11. Dolan P. Modeling valuations for EuroQol Health States. Med Care 1997;35(11):1095-108.
12. Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol-questionnaire. Health Econ 1993;2(3):237-46.
13. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. York, United Kingdom; 1999.
14. Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res 2003;12(8):1089-1097.
15. Hahl J, Hamalainen H, Sintonen H, Simell T, Arinen S, Simell O. Health related quality of life in type I diabetes without or with symptoms of long-term complications. Qual Life Res 2002;11:427-436.

Chapter 5

Change in Health Related Quality of Life over time in patients with Diabetes Mellitus Type I

Accepted for publication in Quality of Life Research:
Hart HE, Redekop WK, Bilo HJG, Berg M, Meyboom-de Jong B: Change in health related quality of life over time in patients with type I diabetes mellitus. Qual Life Res 2004; in press.

Abstract

Objective
The objective of this study was to investigate the health related quality of life (HRQOL) of patients with type I diabetes mellitus (DMT1) over time and to compare change in perceived HRQOL with that of a sample of the general population.
Methods
In a Dutch cohort of 234 patients with DMT1 we assessed, over a period of six years, the HRQOL with two generic instruments: RAND-36 and EuroQol. We applied multilevel modelling to estimate the change in HRQOL over the years 1995-2001. We compared change in HRQOL with the change estimated from a comparably aged sample from the general population using a one sample T-test.
Results
Patients reported a statistically significant decrease in HRQOL for most RAND-36 subscales and the PCS. Mean changes in RAND-36 scores ranged from –0.09 per year (mental health) to –1.18 per year (bodily pain). EQ scores decreased significantly as well. Patients in the cohort had a faster decrease over time in five RAND-36 subscales, the PCS and MCS, and the EQ-VAS than the estimated decrease in the general population.
Conclusion
This study showed that patients with DMT1 have a faster decrease in HRQOL over time than comparably aged persons from the general population. The generic instruments used in our study were sensitive enough to measure changes in HRQOL over time in an adult diabetes population.

Introduction

Type I diabetes mellitus (DMT1) is a chronic disease with an onset in childhood or adolescence. The total inability to produce insulin obliges patients to administer (multiple) daily insulin injections to regulate their blood glucose properly (1, 2). Despite such efforts, many patients will develop chronic diabetic complications, both microvascular and macrovascular.
The Diabetes Control and Complications Trial (DCCT) has shown that the more intense the treatment, the better the chances to delay the onset and the progression of microvascular complications (3). For this reason, patients have to administer insulin injections at least four times daily or use an insulin pump, besides regularly monitoring blood glucose levels.
Throughout their entire lives, patients will need to find a balance between food intake, exercise and insulin dose in order to reach and maintain a good glucose control. Thus, DMT1 and its therapy may have a considerable impact on health related quality of life (HRQOL).
For afflictions like DMT1, with its onset in youth and a lifelong therapy and self-management regime, it is important to be able to assess and interpret factors influencing HRQOL properly (4). Indeed, many studies have investigated influences on HRQOL. Most HRQOL measurements were at one moment (cross-sectional), showing that patients with DMT1 have slightly poorer scores than persons in the general population, especially women, the older and the less educated patients, and patients without a partner (5-20). Furthermore, patients with complications have a lower HRQOL (9, 16, 19, 21-24).
Very little has been published regarding the long-term changes in HRQOL amongst type 1 diabetes patients. Only two studies, the study of Wändell et al (n = 20) and the DCCT study (n = 1441) have examined HRQOL over time in adult patients with DMT1 (18, 25). Both reported no change in HRQOL over time, over three and six years respectively. While Wändell et al used a generic instrument, the DCCT study used a diabetes-specific instrument.
The aim of this study was (1) to measure the HRQOL of patients with DMT1 over time and (2) to compare changes in HRQOL over time, with changes expected in the general population.

Methods

Patients
From January to July 1995 293 consecutive DMT1 patients, treated at the outpatient department of the Isala Clinics in Zwolle, the Netherlands, were invited to participate in this study. Of these patients 95.6% (n = 281) agreed to participate and was included in the study. DMT1 was defined as starting insulin therapy within six 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 Ethics Committee. All patients gave informed consent. This cohort has been followed for six years (1995-2001).

Health Related Quality of Life

HRQOL was assessed using two generic instruments, the RAND-36-item Health Survey (RAND-36) and the EuroQol.

The *RAND-36* is a self-administered questionnaire containing 36 items involving eight different subscales: 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 subscale, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health) (26, 27). In addition, physical and mental component summary scores were determined (PCS/ MCS) (28). Both summary scales are based on all eight calculated subscales. These subscales are factor analysed, using Principal Component Analysis, followed by an orthogonal rotation. Each of the summary scales were standardized and transformed, so that both PCS and MCS had a mean of 50 and a standard deviation of 10 (28). The subscales physical functioning, role physical and bodily pain contribute most to the scoring of the PCS. Mental health, role emotional and social functioning subscales contribute most to the scoring of the MCS (29). The questionnaire takes about ten minutes to complete. The instrument has been translated into Dutch and validated for the Dutch population (30, 31). The RAND-36 was completed annually.

The *EuroQol* is a simple generic measure, consisting of two parts (EQ-5D and EQ-VAS), and was developed by a multidisciplinary group of researchers from five European countries (32). 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 the status regarding 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 U.K. 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 (33). 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 two minutes to complete and has been validated for the Dutch situation (34). The EuroQol was completed in the years 1995 to 1998 and in the year 2001.

Questionnaires were sent by mail to the patient's home address. Patients were asked to fill in the questionnaires at home. At the time of the visit to the outpatient clinic, the patients returned the completed questionnaires to the diabetes specialist nurse. Patients who did not return the completed questionnaires when visiting the clinic were asked to send their completed questionnaires afterwards.

Clinical data

One trained physician examined all patients according to a standardised protocol at the entry of the study. Demographic data (marital status, level of education) and data concerning therapy (frequency of insulin injection, frequency of self monitoring of blood glucose) were recorded annually. Patients recorded all *hypoglycaemic events* ('did you have a hypo in the past three months?') during the three months preceding the outpatient visit and were asked to report whether they had one or more of six different *hyperglycaemic complaints* during the last three months (yes/ no): tiredness, weight loss, pruritus, thirst, polyuria and polydipsia.

Metabolic control was assessed by measuring glycosylated haemoglobin A1c (HbA1c).

The presence of *comorbidity* (one or more diseases besides diabetes or diabetic complications) was assessed using a list of 26 chronic diseases in the years 1995, 1998 and 2001 (35).

Macrovascular complications

Macrovascular complications comprised angina pectoris, myocardial infarction, intermittent claudication, transient ischaemic attack (TIA), and cerebrovascular accident (CVA). The physician recorded these diagnoses in the clinical status of all patients in 1995 and 2001.

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 de Jong (36): 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 (37). At five dorsal and plantar sites on the feet sensitivity was tested using six different monofilaments. When the monofilament 5.07 was not felt at one of the ten test sites, patients were diagnosed as having neuropathy. Patients were examined by the podotherapist in the years 1995, 1998 and 2001.

Nephropathy

The 24-hour urinary excretion of albumin (UAER) was measured annually. UAER was considered abnormal when it was ≥ 30mg/ 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 (38-40). At the start of the study (1995) patients with micro-albuminuria >100 mg/ 24 hour received an angiotensin converting enzyme inhibitor (ACE-inhibitor). We classified ACE-inhibitor users as having nephropathy, unless ACE-inhibition was started specifically for hypertension.

Analysis

To compare the dropouts with the patients who continued in the study we used an independent sample T-test for the continuous variables and the Fishers Exact Test for the categorical variables.

We applied multilevel modelling to investigate the change in HRQOL over the years 1995 – 2001 (41). This method, also known as growth curve analysis, enables the use of all HRQOL values for an individual patient, unlike repeated measures analysis where only patients with complete data can be included in the analysis (42). In simple terms, the approach can be likened to a linear regression approach. If the HRQOL scores for a single patient are drawn on a graph where the x-axis represents time and y-axis represents HRQOL and if a line is drawn through these scores, the slope of this line can be seen to represent the rate of change in HRQOL over time for that individual patient. If this process is repeated for all patients, the average rate of change in HRQOL over time in the study population can be estimated. One general assumption in the analysis is that missing values are missing at random. As well, we assumed that change in HRQOL was linear in form since there was no reason to assume a more complex form.

We tested the null hypothesis that there was no change in HRQOL over time. The developers of both the RAND-36 and the EuroQol do not provide cut-off points for clinically important changes in HRQOL scores. However, changes of > 2-5 points for the RAND-subscales and > 1 point for the RAND summary scores are sometimes considered as the smallest clinically significant changes (44-46). For the EQ-5D and the EQ-VAS, 0.05 points and five points can be used as a rough guide although formally the EuroQol Group has not published any minimally significant values.

HRQOL of patients was compared with the HRQOL of a sample from the general population by comparing the annual change in HRQOL in the cohort with the expected annual change in the general population using a one-sample t-test (27, 47). Since no longitudinal HRQOL data were available for the general population, we compared data from persons in two consecutive age categories (age groups 35-44 and 45-54 years). We divided the difference in HRQOL of these two age categories by ten to estimate the expected change per year.

Additionally we performed univariate regression analyses, HRQOL scores in 2001 being the dependent variable, to investigate associations of the presence of comorbidity, microvascular and macrovascular complications in 2001 with HRQOL scores in 2001.

Changes were considered statistically significant when p-values less than 0.05 were observed. Data were analysed using SAS version 8.2.

Results

A total of 281 adult patients with DMT1 entered the study in 1995.

The dropout rate over these six years was low (16.7%, n=47). Dropouts from the study were more frequently female (59.6% vs. 42.7%, p=0.04), were patients with

a longer disease duration (20.6 vs. 16.5 years, p=0.05), were more often single (24.0% vs. 9.2%, p=0.01) and had a higher HbA1c (9.0% vs. 8.1 %, p=0.007) than the patients who remained in the study period for six years.
Dropouts reported a lower baseline HRQOL for the following RAND-36 subscales: physical functioning, bodily pain, general health, social functioning, role emotional, mental health and the MCS. The PCS was not statistically significant lower. EuroQol scores were also significantly lower.
With regarding to the parameters shown in Table 1, dropouts showed no other statistically significant differences from the patients who completed the total study period. Of the dropouts, five patients died for the following reasons: motor vehicle accident (n=1), cerebrovascular accident (n=1), cardiac problems (n=2), reason unknown (n=1).
Personal and disease-specific characteristics of the 234 patients followed for the total study period of six years are shown in Table 1.

Table 1
Personal and disease-specific characteristics of the study population (n = 234)

	1995		2001	
Gender (men)	134	(57.3%)	134	(57.3%)
Age (years)	38.2	(11.5)	44.2	(11.5)
Duration of diabetes (years)	16.5	(10.1)	22.5	(10.1)
Married/ cohabiting	207	(90.8%)	189	(87.9%)
High level of education	76	(33.6%)	76	(35.5%)
Systolic blood pressure (mm Hg)	138.9	(17.8)	131.5	(19.2)
Diastolic blood pressure (mm Hg)	83.0	(8.4)	77.8	(10.4)
Pulse pressure	55.9	(15.2)	53.7	(16.9)
Ratio cholesterol/ HDL(mmol/l)	3.8	(1.2)	3.3	(1.1)
Body mass index (kg/m^2)	24.8	(3.2)	26.1	(4.0)
Hba1c (%)	8.1	(1.9)	7.6	(1.1)
Insulin pump	63	(26.9%)	102	(43.6%)
Number of control measurements per week	12.0	(11.3)	20.0	(15.2)
Number of patients with:				
hypoglycaemic events	185	(80.8%)	173	(87.4%)
hyperglycaemic complaints	122	(53.2%)	116	(58.3%)
Prevalence of diabetic complications				
Microvascular	104	(45.8%)	119	(65.7%)
Retinopathy	79	(34.6%)	99	(48.5%)
Nephropathy	43	(18.4%)	45	(23.0%)
Neuropathy	24	(10.4%)	23	(12.2%)
Macrovascular	10	(4.3%)	23	(9.8%)
Comorbidity	133	(58.1%)	107	(52.7%)

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

Mean age in the study population at the start of the study was 38.2 years and 57.3% were men. A quarter of the patients used a pump (26.9%).
Almost half of the patients had microvascular complications (45.8%, up to 65.7% in 2001), whereas only 4.3 % had macrovascular complications (mainly angina pectoris and intermittent claudication), up to 9.8% in 2001. Those patients with comorbidity (58.1%) mostly had one or two other chronic medical conditions besides their diabetes. This percentage did not show statistically significant changes during the study period (McNemar test, $p = 0.526$).
Table 2 shows the changes in RAND-36 and EuroQol scores over time. The response rate, the percentage of patients from the study population (n = 234) that

completed the questionnaires, was high, ranging from 97.4 % in 1995 to 91.0 % in 2001.

RAND-36

Change per year: patients reported a statistically significant decrease per year, for six of the eight RAND subscales and the PCS (table 3). The subscales role emotional and mental health and the MCS did not show statistically significant changes over time.

Change per year compared with Dutch general population: for five RAND subscales and the PCS, patients with DMT1 reported a decrease in HRQOL, which was faster than that seen in the general population. The expected changes per year of the subscales vitality and role emotional and the MCS were positive in the general population, whereas these were slightly negative in the cohort. The differences were statistically significant ($p<0.001$ and $p=0.05$) for the subscale vitality and the MCS. Changes in the subscales physical functioning, role emotional and mental health were not statistically significant between the study population and the general population sample (table 3) (27).

EuroQol

Change per year: the EQ-5D and the EQ-VAS showed a statistically significant decrease per year (table 3). The five dimensions of the EQ-5D all changed statistically significantly over time. A large percentage (46.6 – 59.0%) of the patients reported the highest possible EQ-5D score of one.

Change per year compared with U.K. general population: patients with DMT1 reported a faster decrease in EQ-VAS over time than the estimated change in the general population (table 3) (47).

HRQOL in 2001

We checked the association of comorbidity and microvascular or macrovascular complications in 2001 with HRQOL scores in 2001. The presence of macrovascular complications in 2001 was associated with lower EQ-5D (-0.205, $p<0.001$), EQ-VAS (-14.681, $p<0.001$), PCS (-10.796, $p<0.001$) and MCS (-4.876, $p=0.026$) scores. The presence of microvascular complications was only associated with lower EQ-VAS scores (-4.361, $p=0.049$). While the presence of comorbidity was associated with lower EQ-5D (-0.083, $p<0.001$), EQ-VAS (-4.300, $p=0.021$) and PCS scores (-4.636, $p<0.001$).

Table 2
Health related quality of life over time of patients with diabetes mellitus type I (n = 234)

	1995		1996		1997		1998		1999		2000		2001	
Response rate	97.4%		98.3%		94.0%		92.7%		91.5%		92.7%		91.0%	
RAND-36	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Physical functioning	91.7	12.9	91.2	14.7	90.6	15.1	91.0	15.8	88.7	19.0	87.4	19.0	87.3	19.0
Role physical	84.4	30.9	85.3	29.3	80.3	34.0	81.2	33.3	78.4	36.6	81.1	34.1	76.2	37.8
Bodily pain	89.9	16.8	88.3	17.7	87.9	18.1	87.5	19.9	83.3	24.6	83.7	22.9	83.6	20.2
General health	69.3	19.8	69.3	18.5	67.8	17.6	66.8	18.9	65.6	20.6	65.5	20.0	64.4	20.3
Vitality	68.4	19.4	67.6	17.7	66.3	17.5	68.3	19.8	65.8	21.6	65.0	22.0	61.6	20.0
Social functioning	88.6	19.2	88.3	18.5	88.5	17.4	86.5	18.6	88.2	18.8	86.3	19.6	84.2	20.3
Role emotional	86.6	29.7	88.3	28.3	87.7	29.4	83.0	35.5	83.2	33.9	85.5	31.1	83.5	32.6
Mental health	78.3	16.2	79.0	15.2	78.5	14.2	79.9	15.9	78.7	16.0	78.9	15.8	77.1	16.1
PCS	52.6	7.0	52.2	7.0	51.4	7.5	51.5	7.6	50.1	9.6	50.1	9.3	49.8	9.1
MCS	51.6	9.7	52.0	8.5	51.9	8.6	51.7	9.5	51.8	9.5	51.9	9.3	50.9	9.3
EuroQol														
EQ-5D	0.90	0.15	0.88	0.16	0.87	0.17	0.87	0.18	[1]	[1]	[1]	[1]	0.85	0.19
EQ-VAS	82.1	14.1	78.6	15.1	76.8	14.1	77.1	14.4	[1]	[1]	[1]	[1]	76.0	13.5

[1] The EuroQol was not assessed in 1999 and 2000
PCS: Physical Component Summary score - MCS: Mental Component Summary score - EQ-5D: EuroQol utility index - EQ-VAS : EuroQol Visual Analogue Scale

Table 3
Mean changes in health related quality of life over time

	Mean change per year in cohort[1]	Confidence interval 95%	p value[2]	Estimated change per year in general population sample (27, 47)	p value[3]
RAND-36					
Physical functioning	- 0.791	(-1.184, -0.397)	<0.001	- 1.01	0.2743
Role physical	- 1.118	(-1.810, -0.425)	0.002	- 0.40	0.0424
Bodily pain	- 1.180	(-1.616, -0.744)	<0.001	- 0.33	0.0001
General health	- 0.904	(-1.253, -0.555)	<0.001	- 0.24	0.0002
Vitality	- 0.916	(-1.279, -0.554)	<0.001	+ 0.04	<0.0001
Social functioning	- 0.598	(-1.009, -0.187)	0.004	- 0.19	0.0516
Role emotional	- 0.298	(-1.594, 0.999)	0.653	+ 0.14	0.5083
Mental health	- 0.093	(-0.465, 0.162)	0.344	- 0.02	0.4114
PCS	- 0.504	(-0.688,-0.320)	<0.001	- 0.31	0.0386
MCS	- 0.088	(-0.305, 0.128)	0.425	+ 0.13	0.0486
EuroQol					
Utility index	- 0.007	(-0.011, -0.003)	<0.001	- 0.006	0.5435
Visual analogue scale	- 0.934	(-1.230, -0.638)	<0.001	- 0.453	0.0015

[1] Change per year estimated using multilevel modeling
[2] p value based on multilevel modeling to test the null hypothesis that there is no change in HRQOL over time
[3] p value based on one sample T test to test the null hypothesis that there is no difference in change in HRQOL over time between the cohort and the general population sample
PCS: Physical Component Summary - MCS: Mental Component Summary

Discussion and conclusion

In this longitudinal study, a cohort of 234 adult patients with DMT1 was followed for six years. These patients showed a statistically significant decrease per year for the majority of HRQOL scales. The question remains of course, whether these statistically significant changes are of clinical relevance. When applying the arbitrary cut-off points described in the methods paragraph, changes over time in RAND subscale scores can be seen as clinically relevant too, after two to four years time, except for the subscales role emotional and mental health. The EQ-5D did not show a clinically relevant decline in HRQOL over these six years, whereas the EQ-VAS showed this only after six years. However, the EuroQol group has never officially reported the minimally important change in EQ-5D or EQ-VAS we used, since there is no need to establish such thresholds. The main function of the EQ-5D is for use in cost-effectiveness analyses, which result in an estimate of the additional costs needed in order to gain one quality-adjusted life-year (QALY), where health related quality of life can be based on the EQ-5D. Since no Dutch EQ-5D scores were available to compare with scores in our cohort, we compared our data with the available UK data. However, preliminary evidence suggests that there are few prominent differences between western countries in the ranking of health states that are representative of HRQOL dimensions (48).

The finding that patients with DMT1 had a partially steeper decline in HRQOL over time than the general population, can possibly be explained by the growing percentage of patients with microvascular and macrovascular complications. Indeed, we know that in 2001 in our cohort almost 66% (up from 45.8%) of the patients had microvascular complications, whereas almost 10% (up from 4.3%) had macrovascular complications and that these complications were negatively associated with HRQOL scores. These chronic complications may elicit symptoms, which will influence patients functioning negatively and result in a decrease in HRQOL scores (49). The symptoms due to comorbidity (non-diabetes morbidity) will be present in both the study population and the general population sample and their influence will be measured in both populations by the generic instruments we used. For this reason, Woodcock et al have argued for the complementary use of generic and diabetes-specific instruments to distinguish between the impact of diabetes-specific morbidity and non-diabetes-specific morbidity on HRQOL (50).

The dropout patients had statistically significant lower baseline scores than other patients. This might have caused an underestimate of the decrease in scores over time if all subjects had been studied. Moreover, the mean MCS score of the dropouts was lower than patients who continued in the study. This fact might partly explain the fact that the subscales role emotional and mental health did not decrease statistically significantly in the study population.

In our study particularly the physical subscales and the PCS decreased statistically significantly over time and not the more mental subscales and the MCS. The more mental subscales remained more or less stable over time. This lack of change in MCS over time may be related to other observations regarding the relationship between age and mental health. In a previous cross-sectional study we reported

that older patients reported higher MCS scores (24). In a cross-sectional study, Lloyd et al. reported that older patients reported lower Short Form-36 scores on average, except for the subscales role emotional and mental health (21). Parkerson et al. described a mixed effect of age on HRQOL as well, where older patients tended to show less social worry but also reported lower physical and current health (16). Perhaps the fact that these patients with DMT1 have learned to cope with a chronic disease like DMT1, positively influences their mental health. The ability of older patients to be able to attribute their health problems to ageing might also explain this phenomenon (51).

The changes in questionnaire scores that we found were often not only statistically significant but could be viewed as clinically relevant. However, Wändell et al and the DCCT did not find such changes (18, 25). The follow-up of the study of Wändell et al might have been too short (3 years) to measure a significant change over time. Moreover, their sample of patients with DMT1 was too small (n=20), resulting in a reduced ability to detect changes in HRQOL (i.e., low statistical power). In contrast, the DCCT study had a mean follow-up duration of 6.5 years and a large study population (n=1.441). Nevertheless, they too did not find a change in HRQOL using the Diabetes Quality of Life Measure (DQOL), a diabetes-specific instrument.

In our study we used two generic HRQOL instruments to allow comparisons with samples from the general population. Despite the fact we did not use a diabetes-specific instrument (considered to be more sensitive to changes in diabetes populations) we still found a significant change in HRQOL in our study. Moreover, the RAND-36 gave, by its further differentiation into eight subscales and its use of 36 items, more detailed insight into which aspects of HRQOL changed and which did not. Since the individual dimensions of the EQ-5D all changed over time, the EQ-5D instrument did not show the kind of change over time seen with the RAND-36. Furthermore the EQ-5D utility index showed a large ceiling effect, with half of the patients reporting the highest possible score.

Conclusion

This longitudinal, observational study in a large cohort of 234 patients with DMT1 showed that patients with DMT1 have a clinically relevant loss of predominantly physical aspects of HRQOL over time and have a faster decrease over time, for most subscales, than comparably aged persons from the general population. This faster decline in HRQOL is probably due to the development of chronic diabetic complications. Further studies should investigate which factors are mostly associated with these changes in HRQOL over time to give a more detailed insight in this decline in HRQOL.

The generic instruments used in our study were responsive to change in HRQOL over time in an adult DMT1 population. Future studies should investigate the possibilities and limitations of generic and diabetes-specific instruments in patients with DMT1. Studies including both type of instruments could help to distinguish between the impact of diabetes-specific factors and the impact of more general factors on HRQOL.

Acknowledgements: *We thank the Northern Centre for Healthcare Research of the University of Groningen for providing data of a sample of the general Dutch population. We also thank the diabetes specialist nurses of the Isala Clinics for their help.*

References

1. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 1994;331(21):1428-36.
2. Atkinson MA, Eisenbarth GS. Type I diabetes: new perspectives on disease pathogenesis and treatment. The Lancet 2001;358(9277):221-229.
3. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.
4. Bradley C. Importance of differentiating health status from quality of life. The Lancet 2001;357(January 6):7-8.
5. Klein R, Klein BE. Relation of glycemic control to diabetic complications and health outcomes. Diabetes Care 1998;21 Suppl 3:C39-43.
6. Aalto AM, Uutela A, Aro AR. Health related quality of life among insulin-dependent diabetics: disease-related and psychosocial correlates. Patient Educ Couns 1997;30(3):215-25.
7. Aalto AM, Uutela A, Kangas T. Health behaviour, social integration, perceived health and dysfunction. A comparison between patients with type I and II diabetes and controls. Scand J Soc Med 1996;24(4):272-81.
8. Bardsley MJ, Astell S, McCallum A, Home PD. The performance of three measures of health status in an outpatient diabetes population. Diabet Med 1993;10(7):619-26.
9. Bott U, Muhlhauser I, Overmann H, Berger M. Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes Care 1998;21(5):757-69.
10. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L. Quality of life and associated characteristics in a large national sample of adults with diabetes. Diabetes Care 1997;20(4):562-7.
11. Hanestad BR. Self-reported quality of life and the effect of different clinical and demographic characteristics in people with type 1 diabetes. Diabetes Res Clin Pract 1993;19(2):139-49.
12. Jacobson AM, de Groot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. Diabetes Care 1994;17(4):267-74.
13. Jacobson AM, de Groot M, Samson JA. The effects of psychiatric disorders and symptoms on quality of life in patients with type I and type II diabetes mellitus. Qual Life Res 1997;6(1):11-20.
14. Kent LA, Gill GV, Williams G. Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis. Lancet 1994;344(8925):778-81.
15. Muhlhauser I, Overmann H, Bender R, Bott U, Jorgens V, Trautner C, et al. Social status and the quality of care for adult people with type I (insulin-dependent) diabetes mellitus--a population-based study. Diabetologia 1998;41(10):1139-50.
16. Parkerson GR, Jr., Connis RT, Broadhead WE, Patrick DL, Taylor TR, Tse CK. Disease-specific versus generic measurement of health-related quality of life in insulin-dependent diabetic patients. Med Care 1993;31(7):629-39.
17. Reviriego J, Millan MD, Millan M. Evaluation of the diabetes quality-of-life questionnaire in a Spanish population. An experience of translation and reliability. Pharmacoeconomics 1996;10(6):614-22.

18. Wandell PE, Brorsson B, Aberg H. Quality of life among diabetic patients in Swedish primary health care and in the general population: comparison between 1992 and 1995. Qual Life Res 1998;7(8):751-60.
19. Wikblad K, Leksell J, Wibell L. Health-related quality of life in relation to metabolic control and late complications in patients with insulin dependent diabetes mellitus. Qual Life Res 1996;5(1):123-30.
20. Wu SY, Sainfort F, Tomar RH, Tollios JL, Fryback DG, Klein R, et al. Development and application of a model to estimate the impact of type 1 diabetes on health-related quality of life. Diabetes Care 1998;21(5):725-31.
21. Lloyd CE, Orchard TJ. Physical and psychological well-being in adults with Type 1 diabetes. Diabetes Res Clin Pract 1999;44(1):9-19.
22. Pouwer F, van der Ploeg HM, Ader HJ, Heine RJ, Snoek FJ. The 12-item well-being questionnaire. An evaluation of its validity and reliability in Dutch people with diabetes. Diabetes Care 1999;22(12):2004-10.
23. Hahl J, Hamalainen H, Sintonen H, Simell T, Arinen S, Simell O. Health related quality of life in type I diabetes without or with symptoms of long-term complications. Qual Life Res 2002;11:427-436.
24. Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res 2003;12(8):1089-1097.
25. DCCT. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. Diabetes Care 1996;19(3):195-203.
26. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. Health Econ 1993;2:217-227.
27. Zee vdKI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding [Measuring general state of health with the RAND-36. A guide]. Groningen: University of Groningen; 1993.
28. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33(4 Suppl):AS264-79.
29. Ware J. SF-36 Health Survey Update. Spine 2000;25(24):3130-3139.
30. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.
31. Zee vdKI, Sanderman R, Heyink J, Haes dH. The psychometric qualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-122.
32. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
33. Dolan P. Modelling valuations for health states: the effect of duration. Health Policy 1996;38(3):189-203.
34. Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol-questionnaire. Health Econ 1993;2(3):237-46.
35. Dutch Advisory on Health Research. Advice on chronic diseases: priorities for research. 's Gravenhage, the Netherlands; 1991.
36. de Jong PTVM. Screening op diabetische retinopathie [Screening for diabetic retinopathy]. Ned Tijdschr Geneeskd 1993;137(34):1701-1705.

37. Holewski JJ, Stess RM, Graf PM, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. J Rehabil Res Dev 1988;25(2):1-10.
38. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Nederlandse Diabetes Federatie. Diabetische retinopathie, diabetische nefropathie, diabetische voet, hart- en vaatziekten bij diabetes mellitus [Diabetic retinopathy, diabetic nephropathy, diabetic foot, cardiac and vascular pathology in diabetes mellitus]. Utrecht: Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing; 1998.
39. EURODIAB. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994;37(3):278-85.
40. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329(5):304-9.
41. Singer J. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. J. Educ Behav Stat 1998;24(4):323-355.
42. Crosby R, Kolotkin R, Williams G. Defining clinically meaningful change in health-related quality of life. J. Clin Epidemiol 2003;56:395-407.
43. Rubin D. Inference and missing data. Biometrika 1976:581-592.
44. Brook RH, Ware JE, Rogers WH, Keeler EB, Davies AR, Donald CA, et al. Does free care improve adults' health? Results from a Randomized Controlled Trial. N Engl J Med 1983;309(23):1426-1434.
45. Hays RD, Morales LS. The RAND-36 measure of health related quality of life. Ann Med 2001;33:350-357.
46. Ware JE, Kosinki M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10:405-413.
47. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. York, United Kingdom; 1999.
48. Anderson RT, Aaronson NK, Bullinger M, McBee WL. A review of the progress towards developing health related quality of life instruments for international clinical studies and outcomes research. Pharmacoeconomics 1996;10(4):336-355.
49. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.
50. Woodcock A, Julious SA, Kinmouth AL, Campbell MJ. Problems with the performance of the SF-36 among people with type 2 diabetes in general practice. Qual Life Res 2001;10:661-670.
51. Leventhal E, Prohaska T-. Age, symptom interpretation, and health behavior. J Am Geriatr Soc 1986;34(3):185-91.

Chapter 6

Factors predicting rate of change in Health Related Quality of Life in patients with Diabetes Mellitus Type I

Hart HE, Redekop WK, Berg M, Bilo HJG, Meyboom-de Jong B: Factors predicting the rate of change in health related quality of life in patients with diabetes mellitus type I. 2004;submitted

Abstract

Objective
The aim of this study was to investigate whether sociodemographic and diabetes-specific characteristics in 1995 can predict the rate of change in health related quality of life (HRQOL) over time in patients with diabetes mellitus type I (DMT1).
Methods
A Dutch cohort of 234 patients with DMT1 was followed for six years (1995-2001). HRQOL (RAND-36 and EuroQol) and several patient characteristics (demographic and clinical) were recorded annually during the study period. Baseline characteristics associated with rate of change in HRQOL were identified using multilevel modelling.
Results
Patients showed a statistically significant decrease over time in most HRQOL scales. Higher baseline diastolic blood pressure was predictive of a faster decrease in RAND-36 PCS score (-0.025, $p=0.02$), whereas higher baseline systolic blood pressure was predictive of a slower decrease in RAND-36 MCS score (0.015, $p=0.0034$). Patients with macrovascular complications at baseline showed a faster decrease in EQ-VAS score −1.678 ($p=0.016$).
Conclusion
In this cohort of patients with DMT1, it was possible to identify factors predicting change in HRQOL. Late diabetic complications and a higher diastolic blood pressure are predictive of a lower HRQOL in the coming years.

Introduction

Many associations with the health related quality of life (HRQOL) of patients with diabetes mellitus have been described (1-3). All these associations were reported cross-sectionally.
In a previous study we reported that adult patients with diabetes mellitus type I (DMT1) reported a statistically significant and clinically relevant decrease in HRQOL, and we found that these patients had a faster decrease in HRQOL over time than persons from the general population (4).
Although we know that the HRQOL of patients with DMT1 decreases faster over time than in people without DMT1, we do not know in which patients HRQOL decreases faster over time and which factors are associated with it. To date, no studies have investigated the associations between patient characteristics and changes in HRQOL.
More knowledge about patient and/ or disease-specific characteristics predictive of change in HRQOL for the individual patient with DMT1 provides possibilities to identify which patients are likely to experience a faster decrease in HRQOL than other patients.
When it is possible to more accurately predict such changes for the individual patient, it is worth trying to prevent a future decrease in HRQOL or act quickly and effectively on changes in HRQOL. This might benefit patients with DMT1.
We hypothesized that patients with microvascular and macrovascular complications already at study entry, will lose HRQOL faster due to the development of symptoms of these long-term complications (5, 6).
To test this hypothesis we followed a cohort of patients with DMT1 over six years, measured HRQOL yearly and investigated which baseline characteristics could predict for the degree of change in HRQOL over time.

Methods

Patients
In early 1995, 293 consecutive DMT1 patients, treated at the outpatient clinic of the Isala Clinics in Zwolle, the Netherlands, were invited to participate in this study. In total 281 patients agreed to participate and were included in the study. DMT1 was defined as starting insulin therapy within six 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 Ethics Committee. All patients gave informed consent. This cohort has been followed for six years (1995-2001).

Health Related Quality of Life
HRQOL 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 diabetes 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 subscales: 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 subscale, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health) (7, 8). In addition, physical and mental component summary scores were determined (PCS/ MCS) (9). The questionnaire takes about ten minutes to complete. The instrument has been translated in Dutch (10) and validated for the Dutch population (11). The RAND-36 was completed yearly.
The *EuroQol* is a simple generic measure, consisting of two parts (EQ-5D and EQ-VAS) , developed by a multidisciplinary group of researchers from five European countries (12). 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 U.K. 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 (13). 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 two minutes to complete and has been validated for the Dutch situation (14). The EuroQOl was completed in the years 1995 till 1998 and in the year 2001.

Clinical data
One trained physician examined all patients according to a standardised protocol at the entry of the study. Demographic data (age, sex, married/ having a partner, level of education) and data concerning therapy (frequency of insulin injection, frequency of self monitoring of blood glucose) were recorded yearly. Patients recorded all *hypoglycaemic events* ('did you have a hypo in the past three months?') during the three months preceding the outpatient visit and were asked to report whether they had one or more of six different *hyperglycaemic complaints* during the last three months (yes/ no): tiredness, weight loss, pruritus, thirst, polyuria and polydipsia.
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 (15).
Macrovascular complications:

In 1995 and 2001 the physician recorded the presence, or absence, of macrovascular complications of all patients. Macrovascular complications comprised angina pectoris, myocardial infarction, intermittent claudication, transient ischaemic attack (TIA), and cerebrovascular accident (CVA).

Microvascular complications:

Presence, or absence, of microvascular complications was recorded annually. 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 the method described by de Jong (16): 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 (17). At five dorsal and plantar sites on the feet sensitivity was tested using six different monofilaments. When the monofilament 5.07 was not felt at one of the ten test sites, patients were diagnosed as having neuropathy.

Nephropathy

The 24-hour urinary excretion of albumin (UAER) was measured yearly. UAER was considered abnormal when it was ≥ 30mg/ 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 (18-20). At the time of start of the study (1995) patients with a micro-albuminuria >100 mg/ 24 hour 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

We applied multilevel modelling to investigate the change in HRQOL over the years 1995 – 2001 (21). This method, also known as growth curve analysis, enables the use of all HRQOL values for an individual patient, unlike repeated measures analysis where only patients with complete data can be included in the analysis (22). In simple terms, the approach can be likened to a linear regression approach. If the HRQOL scores for a single patient are drawn on a graph where the x-axis represents time and y-axis represents HRQOL and if a line is drawn through these scores, the slope of this line can be seen to represent the rate of change in HRQOL over time for that individual patient. If this process is repeated for all patients, the average rate of change in HRQOL over time in the study population can be estimated. One general assumption in the analysis is that missing values are missing at random. As well, we assumed that change in

HRQOL was linear in form since there was no reason to assume a more complex form.
Factors associated with the change in HRQOL were identified using this technique. This type of analysis has previously been used in diabetes research (23). In a backward stepwise fashion we excluded variables (with a p-value >0.05) from the model, where a p-value ≤ 0.05 provided a guideline for a variable to remain in the model.
Data were analysed using the statistical computer package SAS for Windows version 6.12. Changes were considered statistically significant when p-values less than or equal to 0.05 were reached.

Results

A total of 281 adult patients with diabetes mellitus type I entered the study in 1995.
The dropout rate over the six-year study period was 16.7% (n=47). Patients who withdrew from the study were more frequently female (59.6% vs. 42.7%, p=0.04), had a longer disease duration (20.6 vs 16.5 years, p=0.05), were more often single (24.0% vs 9.2%, p=0.01), had a higher HbA1c (9.0 vs 8.1, p=0.007) and reported a lower baseline HRQOL.
Personal and disease-specific characteristics of the 234 patients who fulfilled the study period of six years are shown in table 1. Mean age at entry in the study population was 38.2 years and 57.3% were men. A quarter of the patients used a pump (26.9%). Almost half of the patients had microvascular complications (45.8%), whereas only 4.3 % had macrovascular complications. The most frequently recorded macrovascular diagnoses were angina pectoris and intermittent claudication. Most patients with comorbidity had one or two other chronic medical conditions besides their diabetes.
Table 2 shows the change in HRQOL over time, assessed by the RAND-36 and the EuroQol. Patients reported a statistically significant decrease per year, over the six year study period, for six of the eight RAND-subscales and the Physical Component Summary (PCS). The decreases in the subscales role emotional and mental health and the Mental Component Summary were not statistically significant (table 2). The EQ-5D and the EQ-VAS showed a statistically significant decrease per year (table 2).
Table 3 shows the socio-demographic and diabetes-specific factors associated cross-sectionally with HRQOL at baseline. For all four outcomes (PCS, MCS, EQ-5D, EQ-VAS) hyperglycaemic symptoms were associated with a lower HRQOL. Comorbidity was associated with a reduced PCS, MCS and EQ-5D. Other factors were mainly associated with a lower baseline PCS score: having a partner, a longer duration of disease since diagnosis, a higher frequency of self monitoring blood glucose per week and the presence of microvascular and macrovascular complications, particularly neuropathy and intermittent claudication. The presence of retinopathy was associated with a lower EQ-5D (table 3).
The baseline HRQOL value (alpha) in 1995 is estimated on the basis of the constant combined with the factors associated with HRQOL. For example, a

patient without hyperglycaemic symptoms, retinopathy or comorbidity, has an estimated EQ-5D of 0.982 (constant). A patient with retinopathy will have an EQ-5D of 0.982-0.048 = 0.934.

Table 1
Personal and disease-specific characteristics of the study population (1995, n = 234)

Gender (men)	134	(57.3%)
Age (years)	38.2	(11.5)
Duration of diabetes (years)	16.5	(10.1)
Married/ cohabiting	207	(90.8%)
High level of education	76	(33.6%)
Smoking	70	(29.9%)
Alcohol use	146	(62.4%)
Systolic blood pressure (mm Hg)	138.9	(17.8)
Diastolic blood pressure (mm Hg)	83.0	(8.4)
Pulse pressure	55.9	(15.2)
Ratio cholesterol/ HDL(mmol/l)	3.8	(1.2)
Body mass index (kg/m^2)	24.8	(3.2)
Hba1c(%)	8.1	(1.9)
Use of insulin pump	63	(26.9%)
Frequency of self-monitoring blood glucose per week	12.0	(11.3)
Number of patients with:		
hypoglycaemic events	185	(80.8%)
hyperglycaemic complaints	122	(53.2%)
Prevalence of diabetic complications		
Microvascular	104	(45.8%)
Retinopathy	79	(34.6%)
Nephropathy	43	(18.4%)
Neuropathy	24	(10.4%)
Macrovascular	10	(4.3%)
Comorbidity	133	(58.1%)

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

Table 2
Health related quality of life over time in a cohort of patients with diabetes mellitus type I

	Mean change per year in cohort[1]	Confidence interval (95%)	p value[2]
RAND-36			
Physical functioning	- 0.791	(-1.184, -0.397)	< **0.001**
Role physical	- 1.118	(-1.810, -0.425)	**0.002**
Bodily pain	- 1.180	(-1.616, -0.744)	< **0.001**
General health	- 0.904	(-1.253, -0.555)	< **0.001**
Vitality	- 0.916	(-1.279, -0.554)	< **0.001**
Social functioning	- 0.598	(-1.009, -0.187)	**0.004**
Role emotional	- 0.298	(-1.594, 0.999)	0.653
Mental health	- 0.093	(-0.465, 0.162)	0.344
PCS	- 0.504	(-0.688,-0.320)	< **0.001**
MCS	- 0.088	(-0.305, 0.128)	0.425
EuroQol			
Utility index	- 0.007	(-0.011, -0.003)	< **0.001**
Visual analogue scale	- 0.934	(-1.230, -0.638)	< **0.001**

Values are means with standard deviations between parentheses
[1] Change per year estimated by using multilevel modeling
[2] p value is result from multilevel modeling
PCS - Physical Component Summary
MCS - Mental Component Summery

Table 3
Determination of baseline health related quality of life values for the individual patients

	RAND-36 PCS	RAND-36 MCS	EuroQOL EQ-5D	EuroQol EQ-VAS
Constant	61.48 ($p<0.0001$)	55.81 ($p<0.0001$)	0.982 ($p<0.0001$)	85.23 ($p<0.0001$)
Married/ cohabiting	- 2.880 ($p=0.034$)			
Duration of disease (in years/ diagnosis to baseline)	- 0.111 ($p=0.007$)			
Frequency of self monitoring per week	- 0.129 ($p<0.001$)			
Hyperglycaemia	- 2.492 ($p=0.003$)	- 4.960 ($p<0.0001$)	- 0.072 ($p<0.0001$)	- 9.223 ($p<0.0001$)
Neuropathy	- 2.869 ($p=0.028$)			
Retinopathy			- 0.048 ($p=0.004$)	
Intermittent claudication	- 10.030 ($p=0.002$)			
Comorbidity	- 1.919 ($p=0.022$)	- 2.150 ($p=0.018$)	- 0.061 ($p<0.0002$)	

PCS - Physical Component Summary
MCS - Mental Component Summary
EQ-5D - EuroQol Utility Index
EQ-VAS - EuroQol Visual Analogue Scale

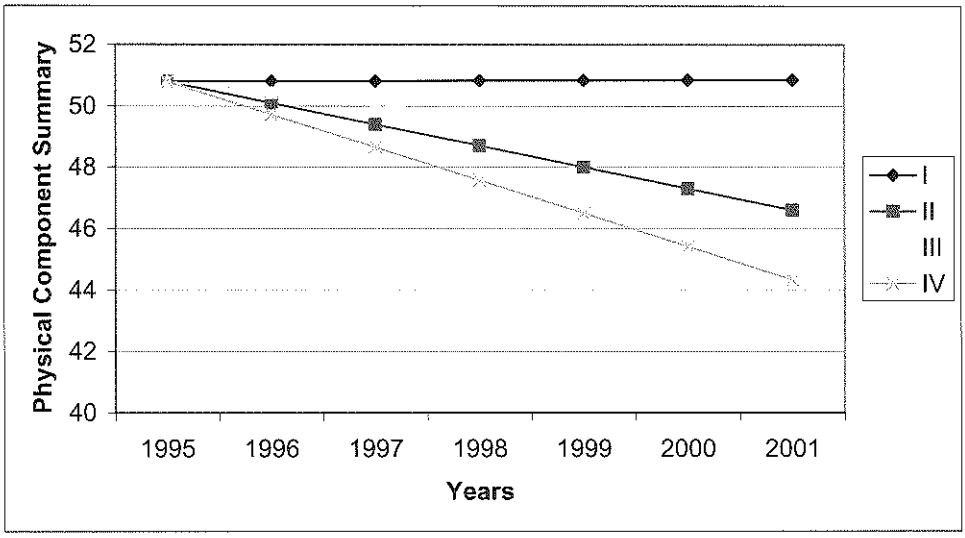
Table 4 shows the socio-demographic and diabetes-specific factors associated with changes in HRQOL over time. A higher baseline diastolic blood pressure in 1995 was associated with a faster decrease in PCS over time. The presence of nephropathy (in 1995) was also associated with a faster decrease in PCS over time.

Table 4
Factors predicting change in health related quality of life

	RAND-36 PCS	RAND-36 MCS	EuroQoL EQ-5D	EuroQol EQ-VAS
Time since baseline in years (T)	2.01 (p = 0.0345)	-2.14 (p = 0.003)	-0.007 (p = 0.0007)	- 1.817 (p < 0.0001)
Predictors				
T* diastolic blood pressure	- 0.025 (p = 0.020)			
T* nephropathy	- 0.711 (p = 0.002)			
T* systolic blood pressure		0.015 (p = 0.0034)		
T* intermittent claudication			-0.051 (p = 0.004)	
T* married/ cohabiting				1.021 (p = 0.036)
T* macrovascular complications				- 1.678 (p = 0.016)

PCS - physical component summary
MCS - mental component summary
EQ-5D - EuroQol Utility Index
EQ-VAS - EuroQol Visual Analogue Scale
T - time since baseline in years
T*covariate - multiplication of time by covariate

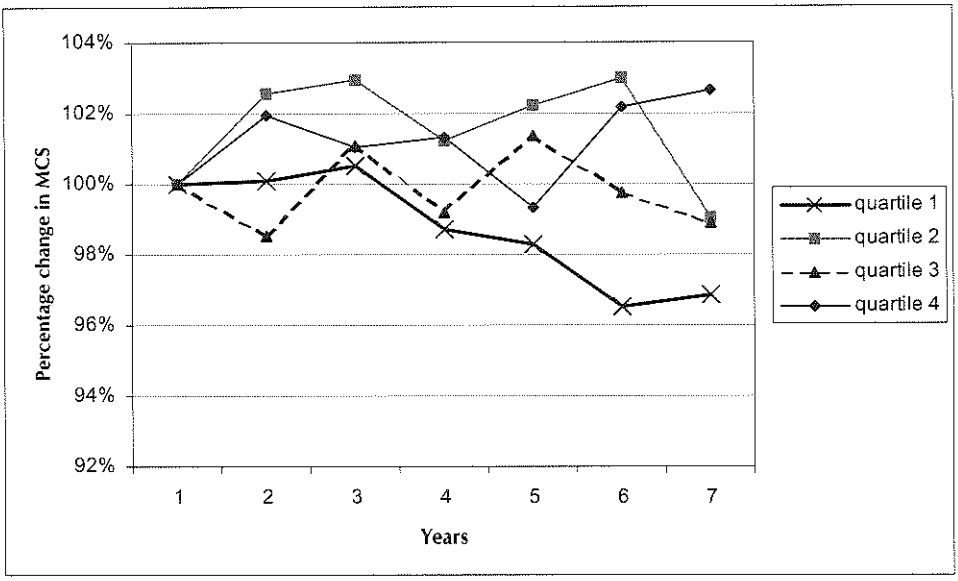
Figure 1 shows the predicted change in PCS over time for patients, divided into four subgroups on the basis of diastolic blood pressure and nephropathy in 1995. Patients with a higher diastolic blood pressure and with nephropathy showed the fastest decrease in PCS.



I - Patients with a diastolic blood pressure of 80 mm Hg and without nephropathy
II - Patients with a diastolic blood pressure of 80 mm Hg and with nephropathy
III - Patients with a diastolic blood pressure of 95 mm Hg and without nephropathy
IV - Patients with a diastolic blood pressure of 95 mm Hg and with nephropathy

Figure 1
Physical Component Summary changes predicted according to the model

A higher systolic blood pressure (in 1995) was associated with a slower decrease in MCS over time. Figure 2 shows that patients within the three highest systolic blood pressure quartiles seem to maintain their MCS level over time, in comparison with the faster decrease in MCS of the patients within the lowest quartile.



Quartile 1	< 126	mm Hg
Quartile 2	126-137.9	mm Hg
Quartile 3	138-147.9	mm Hg
Quartile 4	> 148	mm Hg

Figure 2
Percentage change observed in Mental Component Summary scores, in subgroups of patients based on baseline systolic blood pressure

Patients with intermittent claudication in 1995 experienced a faster decrease in EQ-5D than patients without intermittent claudication. Patients with macrovascular complications showed a faster decrease in EQ-VAS than patients without macrovascular complications. Married patients showed a slower decrease in EQ-VAS over time than unmarried patients.

Since we expected that patients with a baseline diastolic blood pressure greater than the mean value in 1995 had, and will develop, more diabetic complications, we investigated the complication status of these patients. In 1995 these patients already had a somewhat higher prevalence of microvascular complications (51.5 vs. 41.1%, $p=0.08$). In 2001 the same was true (76.2 vs. 56.7%, $p=0.004$) and in that year they also tended to have more macrovascular complications (12.4 vs. 7.8%, $p=0.173$).

Patients with a baseline systolic blood pressure higher than the mean value (138.9 mm Hg) reported hyperglycaemic complaints more frequently at baseline (57.3 vs. 49.6%, $p=0.151$) and already had an increased prevalence of microvascular complications (59.1 vs. 33.3%, $p<0.001$) and somewhat higher prevalence of macrovascular complications (5.3 vs. 3.3%, $p=0.343$) and comorbidity (62.7 vs.

53.8%, p=0.108). They reported lower baseline PCS scores (51.3 vs. 53.8, p=0.007) and baseline EQ-5D scores (0.86 vs. 0.92, p=0.006).

Discussion and conclusion

In this longitudinal study, a cohort of 234 adult patients with DMT1 was followed for six years. These patients showed a statistically significant decrease per year for almost all of the HRQOL outcomes we studied. Moreover, patients who left the study had a lower HRQOL at baseline, which might have caused an underestimation of the annual decrease in HRQOL, since these patients might have lost HRQOL even faster.

Cross-sectionally the presence of hyperglycaemic complaints, a higher frequency of self-monitoring blood glucose (SMBG), diabetic complications and comorbidity had the most profound negative association with HRQOL.

Remarkably, the frequency of self-monitoring blood glucose and presence of hyperglycaemic complaints were not associated with changes in HRQOL over time. This might possibly be explained by the use of generic instruments in this study.

Longitudinally, higher diastolic blood pressure and macrovascular complications showed the most negative influence on changes in HRQOL.

Patients with a higher baseline diastolic blood pressure had in 2001 a PCS score lower than the PCS scores seen in other patients. We might explain this by the fact that high blood pressures are a risk factor for the development of cardiovascular disease. Patients with, in this case, a higher diastolic blood pressure in 1995 are more at risk to develop macro- and microvascular complications in the future, which are known to be associated with a lower HRQOL (6, 24-26).

Indeed, the United Kingdom Prospective Diabetes Study Group (UKPDS) showed that in patients with diabetes mellitus type II (DMT2), tight blood pressure control achieved a clinically important reduction of diabetic complications (27). Moreover, in patients with DMT2, complications affected HRQOL, whereas therapeutic policies shown to reduce the risk of complications, i.e. improving blood glucose or blood pressure, had no direct effect on HRQOL (28).

In our study, patients with a higher baseline diastolic blood pressure, had indeed a higher prevalence of chronic complications in 2001, which can explain their loss in HRQOL compared with patients with a lower diastolic blood pressure.

However, a higher systolic blood pressure was associated with a slower decrease in MCS. We cannot explain this finding. It might be possible that, where others experience a faster decrease over time, this specific category of patients might recover from an earlier loss of MCS by their higher prevalence of hyperglycaemic complaints and comorbidity in 1995.

Moreover, these patients reported a significant lower PCS in 1995 too. This lower baseline physical health will also inevitably reduce their mental health and be responsible for a lower baseline MCS. We cannot confirm this hypothesis. This is inherent to the choice of the use of orthogonally rotated summary scores, resulting in uncorrelated summary scores (9, 29).

Whereas we formulated possible explanations for the predictive value of higher systolic blood pressures, we still cannot explain this finding and further investigations concerning this item are necessary. A change association is one possible explanation.
The lower PCS in 2001 for patients with nephropathy in 1995 can be explained by the fact that these patients have a higher risk to develop cardiovascular disease in the future, which will negatively influence their PCS in 2001 (30-34).
The fact that patients with complications in 1995, i.e. nephropathy [PCS], claudication [EQ-5D] and macrovascular complications [EQ-VAS] show a faster decrease in HRQOL than patients without these complications confirms our hypothesis that patients with late complications at study entry will lose HRQOL faster than other patients. The late complications, already present in 1995, will be increased in severity several years later. Further progression of these complications will likely become symptomatic in 2001 and will impair their daily functioning and thereby reduce their HRQOL (5).
Married patients reported a lower PCS in 1995, but showed a slower decrease in EQ-VAS than unmarried patients. Many studies have reported the positive influence of having a partner on HRQOL (25, 26, 35-38). It is possible that patients with poorer physical health, i.e. lower PCS scores in 1995, needed and searched for more social and marital support, and were therefore more often married than other patients. The presence of a partner probably will support patients with the handling of their chronic disease. Trief et al. even showed that the quality of marriage prospectively predicted the diabetes related HRQOL in patients with DMT1; less diabetes-related distress was predicted by better marital adjustment at baseline (39).
Conclusion
This study shows that patients with DMT1 report a statistically significant decrease in HRQOL over time. Cross-sectionally, the symptoms of the disease (hyperglycaemic complaints) and its therapy (e.g. self-monitoring blood glucose) were negatively associated with HRQOL. Longitudinally, higher diastolic blood pressure and late diabetic complications were negatively associated with HRQOL. This study identified patients who were at risk for a faster decrease in HRQOL.

References

1. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15(3):205-18.
2. Bradley C. Measuring quality of life in diabetes. The Diabetes Annual 1996;10:207-224.
3. Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res 2003;12(8):1089-1097.
4. Hart HE, Redekop WK, Bilo HJG, Berg M, Meyboom-de Jong B. Change in health related quality of life over time in patients with type I diabetes mellitus. Qual Life Res 2004;In press.
5. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.
6. Hahl J, Hamalainen H, Sintonen H, Simell T, Arinen S, Simell O. Health related quality of life in type I diabetes without or with symptoms of long-term complications. Qual Life Res 2002;11:427-436.
7. Zee vdKI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding [Measuring general state of health with the RAND-36. A guide]. Groningen: University of Groningen; 1993.
8. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. Health Econ 1993;2:217-227.
9. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33(4 Suppl):AS264-79.
10. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.
11. Zee vdKI, Sanderman R, Heyink J, Haes dH. The psychometric qualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-122.
12. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
13. Dolan P. Modeling valuations for EuroQol Health States. Med Care 1997;35(11):1095-108.
14. Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol-questionnaire. Health Econ 1993;2(3):237-46.
15. Dutch Advisory on Health Research. Advice on chronic diseases: priorities for research. 's Gravenhage, the Netherlands; 1991.
16. de Jong PTVM. Screening op diabetische retinopathie [Screening for diabetic retinopathy]. Ned Tijdschr Geneeskd 1993;137(34):1701-1705.
17. Holewski JJ, Stess RM, Graf PM, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. J Rehabil Res Dev 1988;25(2):1-10.
18. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329(5):304-9.

19. EURODIAB. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994;37(3):278-85.
20. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Nederlandse Diabetes Federatie. Diabetische retinopathie, diabetische nefropathie, diabetische voet, hart- en vaatziekten bij diabetes mellitus [Diabetic retinopathy, diabetic nephropathy, diabetic foot, cardiac and vascular pathology in diabetes mellitus]. Utrecht: Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing; 1998.
21. Singer J. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. J. Educ Behav Stat 1998;24(4):323-355.
22. Crosby R, Kolotkin R, Williams G. Defining clinically meaningful change in health-related quality of life. J. Clin Epidemiol 2003;56:395-407.
23. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GEH, Niessen LW. Health related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care 2002;25(3):458-463.
24. Haider A, Larson M, Franklin S, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2003;138(1):10-6.
25. Aalto AM, Uutela A, Aro AR. Health related quality of life among insulin-dependent diabetics: disease-related and psychosocial correlates. Patient Educ Couns 1997;30(3):215-25.
26. Bott U, Muhlhauser I, Overmann H, Berger M. Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes Care 1998;21(5):757-69.
27. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes:UKPDS 38. BMJ 1998;317:703-13.
28. U.K. Prospective Diabetes Study Group. Quality of life in Type 2 Diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999;22(7):1125-1136.
29. Ware JE, Kosinki M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10:405-413.
30. Jensen T. Micro-albuminuria and large vessel disease in diabetes. J Hypertens Suppl 1992;10(1):S21-4.
31. Jensen T, Deckert T. Diabetic retinopathy, nephropathy and neuropathy. Generalized vascular damage in insulin-dependent diabetic patients. Horm Metab Res Suppl 1992;26:68-70.
32. Jensen T. Pathogenesis of diabetic vascular disease: evidence for the role of reduced heparan sulfate proteoglycan. Diabetes 1997;46 Suppl 2:S98-100.
33. Jensen T, Bjerre-Knudsen J, Feldt-Rasmussen B, Deckert T. Features of endothelial dysfunction in early diabetic nephropathy. Lancet 1989;1(8636):461-3.
34. Tuomilehto J, Borch-Johnson K, Molarius A, Forsen T, Rastenyte D, Sarti C, et al. Incidence of cardiovascular disease in Type 1 (insulin dependent) diabetic subjects with and without diabetic nephropathy in Finland. Diabetologia 1998;41(7):784-90.
35. Hanestad BR. Self-reported quality of life and the effect of different clinical and demographic characteristics in people with type 1 diabetes. Diabetes Res Clin Pract 1993;19(2):139-49.
36. Parkerson GR, Jr., Connis RT, Broadhead WE, Patrick DL, Taylor TR, Tse CK. Disease-specific versus generic measurement of health-related quality of life in insulin-dependent diabetic patients. Med Care 1993;31(7):629-39.
37. Lloyd CE, Orchard TJ. Physical and psychological well-being in adults with Type 1 diabetes. Diabetes Res Clin Pract 1999;44(1):9-19.

38. Wikblad K, Leksell J, Wibell L. Health-related quality of life in relation to metabolic control and late complications in patients with insulin dependent diabetes mellitus. Qual Life Res 1996;5(1):123-30.
39. Trief M, Wade M, Britton K, Weinstock R. A prospective analysis of marital relationship factors and quality of life in diabetes. Diabetes Care 2002;25(7):1154-8.

Chapter 7

The use of utilities in a cohort of patients with Diabetes Mellitus Type I

Hart HE, Redekop WK, Dikkeschei LD, Berg M, Meyboom-de Jong B, Bilo HJG. The use of utilities in a cohort of patients with diabetes mellitus type I. 2004; submitted.

Abstract

Objective

The objective of this study was to investigate the suitability of two generic utilities and their Quality Adjusted Life Years (QALYs) in patients with diabetes mellitus type I (DMT1). We wanted to investigate whether these utilities are sensitive to changes over time and can provide information about associations of diabetes-specific factors with health related quality of life (HRQOL), expressed in utilities and QALYs, in patients with DMT1.

Research design and methods

The HRQOL in a Dutch cohort of 234 patients with DMT1 was assessed annually for 6 years using the utilities of the Short Form- 36 (SF-6D) and the EuroQol (EQ-5D). QALYs were calculated for two three-year periods. We performed stepwise multivariate regression analysis to investigate associations between QALYs and several socio-demographic (sex, age, marital status, level of education) and diabetes-specific variables (e.g. HbA1c, therapy, hyper-/ hypoglycaemic complaints, diabetic complications).

Results

Both utilities assessed changes over time; the declines in SF-6D and EQ-5D were statistically significant ($p=0.001$ and $p=0.004$). The utilities assessed associations of diabetes-specifc factors with HRQOL. Hyperglycaemic complaints, macrovascular complications and comorbidity had the most negative association with the QALYs.

Conclusion

The generic utilities SF-6D and EQ-5D were responsive to changes in HRQOL over time and measured associations between QALYs and diabetes-specific variables, already known to be associated with HRQOL. Both generic utilities offer possibilities for survival analyses and health economic studies in patients with DMT1.

Introduction

In past decades, many studies have been performed concerning health related quality of life (HRQOL) in patients with diabetes mellitus. In these studies, generic as well as diabetes specific questionnaires have been used (1, 2). Both types of instruments have their possibilities and limitations and each measure may be valuable for certain purposes (3). Diabetes specific instruments are said to be more sensitive to changes over time in patients with diabetes, while generic instruments allow comparisons with patients with other diseases and persons form the general population (4, 5). Different health states, provided by some generic questionnaires, have been given a value by the general public (6-8). These values, or utilities, are put on a scale on which 0 expresses worst health/ death and 1 expresses perfect health (7-9). These utilities, based on generic instruments, offer possiblities for health economic studies.

Quality-adjusted life-years (QALYs) are the multiplication of the utility score by the number of years (e.g. until death) and describes the amount of years lived adjusted for HRQOL.

For patients with diabetes mellitus type I (DMT1) few studies have used empirically derived utilities (10, 11). These studies examined indirectly assessed utilities based on generic instruments. Wu et al. calculated Quality of Well-Being Index (QWB) scores, derived from SF-36 scores, from which they calculated a utility score (10). Coffey et al. used the Self-Administered Quality of Well Being index (QWB-SA) to calculate a utility score (11). For patients with diabetes mellitus type II, the EuroQol has been applied to calculate a utility score (12, 13).

In the present study, we applied the QALY method to describe the HRQOL over time in a Dutch cohort of patients with DMT1. We calculated QALYs using two different utility scales, derived from the generic Short Form-36 and from the EuroQol, to compare the results between them, and to investigate the usefulness of these utilities in DMT1 studies.

Furthermore we examined associations of patient characteristics with QALYs, and investigated whether these associations with QALYs persisted over time and whether the use of different utility scales led to the same or different associations. The possible use of QALYs can facilitate cost-effectiveness studies to determine best diabetes treatment strategies.

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 this study. A group of 281 patients agreed to participate and were included in the study. DMT1 was defined as starting insulin therapy within six 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 Ethics Committee. All patients gave informed consent. This cohort was followed for six years (1995-2001).

Health Related Quality of Life

HRQOL was assessed using two generic instruments: the Short Form-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. When attending the next outpatient appointment, the patients returned the completed questionnaires to the diabetes specialist nurse. Patients who did not return the completed questionnaires when visiting the clinic were asked to send their completed questionnaires afterwards.

A six-dimensional health state classification (SF-6D) has been derived by using a subset of 11 items of the SF-36 questionnaire: physical functioning, role limitations, social functioning, pain, mental health and vitality (14). A sample of states, defined by these six dimensions, has been valued by a representative sample of the UK general population, using the standard gamble method. The values, or utilities, are put on a scale on which 0 is the value of death and 1 is the value of perfect health (14). The instrument has been translated into Dutch and validated for the Dutch population (15). The SF-36 is seen as an appropriate measure of HRQOL in patients with DMTI (3, 10, 16). Since the SF-36 questionnaire was completed yearly from 1995-2001, SF-6D scores could be calculated for all years.

The EuroQol, a simple generic measure, consists of two parts (EQ-5D and EQ-VAS) (7). For the EQ-5D part, there are five questions covering the areas of 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 U.K. general public, using time trade-off. The values, or utilities, are scaled on a scale on which -0.594 is even worse than death, 0 is the value of death and 1 is the value of perfect health (17).The EuroQol has been validated for the Dutch situation (18) and was completed yearly between 1995 and 1998 and in 2001.

Clinical data

One trained physician examined all patients according to a standardised protocol at the entry of the study. Demographic data (age, sex, married/ having a partner, level of education) and data concerning therapy (frequency of insulin injection, frequency of self monitoring of blood glucose) were recorded yearly. Patients recorded all *hypoglycaemic events* ('did you have a hypo in the past three months?') during the three months preceding the outpatient visit and were asked to report whether they had one or more of six different *hyperglycaemic complaints* during the last three months (yes/ no): tiredness, weight loss, pruritus, thirst, polyuria and polydipsia.

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 (19).
Macrovascular complications
The physician recorded the presence, or absence, of macrovascular complications in 1995 and 2001. Macrovascular complications were not recorded in 1998. Macrovascular complications comprised angina pectoris, myocardial infarction, intermittent claudication, transient ischaemic attack (TIA), and cerebrovascular accident (CVA).
Microvascular complications
The presence of the different microvascular complications was recorded yearly. 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 de Jong (20): 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 (21). At five dorsal and plantar sites on the feet sensitivity was tested using six different monofilaments. When the monofilament 5.07 was not felt at one of the ten test sites, patients were diagnosed as having neuropathy.
Nephropathy
The 24-hour urinary excretion of albumin (UAER) was measured yearly. UAER was considered abnormal when it was ≥ 30mg/ 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 (22-24). At the time of start of the study (1995) patients with a micro-albuminuria >100 mg/ 24 hour 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
We calculated Quality Adjusted Life Years (QALYs) from the SF-6D and EQ-5D. We performed repeated measures analyses to measure change in HRQOL over time.
We defined two three-year periods: 1995-1998 and 1998-2001.
Since the EuroQol was not assessed in 1999 and 2000, we calculated three QALY values for each patient: SF-6D (1995-1998), SF-6D (1998-2001) and EQ-5D (1995-1998). The QALYs were essentially a weighted average of HRQOL scores over a

given time period. For example, the SF-6D QALY (1995-1998) was calculated using the following formula:
½* SF-6D (1995) + SF-6D (1996) + SF-6D (1997) + ½* SF-6D (1998).
To investigate whether these utitilies can provide information about associations of diabetes-specific factors we performed a multivariate stepwise regression analysis, once for each of the three QALY scores as a dependent variable. For the first three-year period (1995-1998) the patient and diabetes-specific characteristics in 1995 were the independent variables, for the second three-year period (1998-2001) the characteristics in 1998 were the independent variables, with the exception of the macrovascular complications. For the second three-year period we added the factor 'macrovascular complications in 1995' in the regression analysis since the macrovascular complications were not recorded in 1998.
We compared the adjusted R^2 of the models to compare the percentage explained variance in HRQOL.
Furthermore we determined Spearman rank order correlations between the QALYs derived from the SF-6D and the EQ-5D.
Data were analysed using the statistical computer package SPSS for Windows version 10.0. We considered changes statistically significant when p-values less than or equal to 0.05 were observed.

Results

A total of 281 adult patients with diabetes mellitus type I entered the study in 1995. The dropout rate over these six years was 16.7% (n=47); 234 patients completed the study period of six years. Patients who withdrew from the study were more frequently female (59.6% vs. 42.7%, p=0.04), were patients with a longer disease duration (20.6 vs.16.5 years, p=0.05), were more often single (24.0 vs. 9.2%, p=0.01), had a higher HbA1c (9.0 vs. 8.1%, p=0.007), and had a statistically lower baseline HRQOL than the patients continuing the study.
Personal and disease-specific characteristics of the patients who completed the entire study period of six years are shown in table 1. At the start of the study mean age was 38.2 years and 57.3% were men. At that time, one quarter of the patients used a pump (26.9%). Almost half of the patients had microvascular complications (45.8%), whereas only 4.3 % had macrovascular complications (mainly angina pectoris and intermittent claudication). A majority of those patients with comorbidity had one or two other chronic medical conditions besides their diabetes (mean 1.2, range 0-7).
In 1998, after three years of follow-up, the percentage of patients using a subcutaneous pump (26.9% to 32.6%, p=0.016), the body mass index (24.8 to 25.6 kg/m^2, p<0.001) and the percentage of patients with microvascular complications (45.8% to 58.1%, p=0.005) increased. The HbA1c declined significantly (8.1% to 7.9 %, p=0.016).
Both utility indices declined over six years: the SF-6D declined from 0.83 (0.12) to 0.80 (0.13) (p=0.001) and the EQ-5D declined from 0.90 (0.15) to 0.85 (0.19) (p=0.004) (table 2).

The percentage of patients reporting the best possible EQ-5D health state (value 1) varied from 51.5 – 59.0% across the follow-up period, whereas this was only 5.0-15.3% for the SF-6D.

The SF QALYs for the first three-year period were 2.50 (SD=0.31), for the second three-year period 2.46 (SD=0.36). EQ-QALYs for the first three-year period were 2.64 (SD=0.40) (table 2). The difference between the SF QALYs and EQ QALYs was 0.137 (95% CI: 0.100-0.174, $p<0.001$).

Multivariate regression analysis, with patient characteristics in 1995, showed that in the first three-year period a longer disease duration, a higher frequency of self-monitoring blood glucose and the presence of hyperglycaemic complaints, macrovascular complications and comorbidity (in 1995) were associated with lower SF QALYs (table 3).

The negative influence of a higher frequency of self-monitoring blood glucose and the presence of hyperglycaemic complaints and comorbidity (in 1998) remained statistically significant in the second period. The presence of microvascular complications was associated with lower SF QALYs.

The presence of hyperglycaemic complaints, retinopathy and comorbidity was associated with lower EQ QALYs (table 3).

Patient characteristics (sex, age, marital status, level of education), HbA1c, body mass index, diastolic and systolic blood pressure, frequency of insulin injection and the presence of hypoglycaemic complaints were not associated with either of the QALYs.

The SF QALY (1995-1998) scores correlated strongly with SF QALY (1998-2001) scores (Spearman rank correlation coefficient 0.807, $p<0.001$), as well with the EQ (1995-1998) QALY scores (Spearman rank correlation coefficient 0.759, $p<0.001$).

Table1
Personal and disease-specific characteristics of the study population (n = 234)

	1995		1998		
Gender (men)	134	(57.3%)	134	(57.3%)	
Age (years)	38.2	(11.5)	41.2	(11.5)	
Duration of diabetes (years)	16.5	(10.1)	19.5	(10.1)	
Married/ cohabiting	207	(90.8%)	194	(89.4%)	
High level of education	76	(33.6%)	72	(34.0%)	
Systolic blood pressure (mm Hg)	138.9	(17.8)	131.1	(19.4)	**< 0.001**[1]
Diastolic blood pressure (mm Hg)	83.0	(8.4)	79.4	(10.2)	**< 0.001**[1]
Pulse pressure	55.9	(15.2)	51.6	(15.9)	**< 0.001**[1]
Ratio cholesterol/HDL	3.8	(1.2)	3.6	(1.3)	**0.031**[1]
Body mass index (kg/m^2)	24.8	(3.2)	25.6	(3.6)	**< 0.001**[1]
Hba1c (%)	8.1	(1.9)	7.9	(1.3)	**0.016**[1]
Insulin pump	63	(26.9%)	76	(32.6%)	**0.016**[2]
Nr. of control measurements/week	12.0	(11.3)	18.2	(14.4)	**< 0.001**[1]
Number of patients with:					
hypoglycaemic events	185	(80.8%)	180	(84.9%)	0.110[2]
hyperglycaemic complaints	122	(53.2%)	105	(50.5%)	1.000[2]
Prevalence of diabetic complications					
Microvascular	104	(45.8%)	111	(58.1%)	**0.005**[2]
Retinopathy	79	(34.6%)	88	(44.9%)	**0.007**[2]
Nephropathy	43	(18.4%)	33	(16.7%)	0.210[2]
Neuropathy	24	(10.7%)	32	(15.2%)	**0.004**[2]
Macrovascular	10	(4.3%)	[3]		
Comorbidity	133	(58.1%)	130	(62.5%)	0.212[2]

Values are number of patients or means with valid percentage or standard deviation between parentheses
[1] P values are result of paired samples T-test
[2] P values are result of Mc Nemar test
[3] Not recorded

Table 2
Health Related Quality of Life over time in patients with diabetes mellitus type I (n = 234)

	SF-6D			EQ-5D		
	Mean	SD	Range	Mean	SD	Range
1995	0.83	0.12	0.45-1.00	0.90	0.15	0.17–1.00
1996	0.84	0.12	0.50-1.00	0.88	0.16	0.10–1.00
1997	0.83	0.12	0.50-1.00	0.87	0.17	-0.07–1.00
1998	0.83	0.13	0.33-1.00	0.87	0.18	-0.23–1.00
1999	0.82	0.14	0.40-1.00	[1]	[1]	
2000	0.82	0.14	0.40-1.00	[1]	[1]	
2001	0.80	0.13	0.40-1.00	0.85	0.19	-0.17–1.00
p value [2]	0.001			0.004		

	QALYs		QALYs	
	Mean	SD	Mean	SD
1995-1998	2.50	0.31	2.64	0.40
1998-2001	2.46	0.37		

SF-6D - Short Form utility index
EQ-5D - EuroQol utility index
QALYs - Quality Adjusted Life Years
SD - standard deviation
[1] EuroQol was not assessed in 1999 and 2000.
[2] P values are result of repeated measure analysis

Table 3
Results of the multivariate regression analysis of the Quality Adjusted Life Years

	SF- QALYs 1995-1998	SF- QALYs 1998-2001	EQ-QALYs 1995-1998
	R^2 = 0.290 (n = 174) Characteristics 1995	R^2 = 0.318 (n = 157) Characteristics 1998	R^2 = 0.194 (n = 209) Characteristics 1995
Intercept	2.821	2.856	2.911
Diabetes duration	-0.006 (p = 0.008) *(-0.01, -0.002)*		
Selfmonitoring a week	-0.005 (p = 0.008) *(-0.009, -0.001)*	-0.005 (p = 0.012) (-0.009, -0.001)	
Hyperglycaemic complaints	-0.179 (p < 0.001) *(-0.267, -0.091)*	-0.249 (p < 0.001) *(-0.351, -0.147)*	- 0.228 (p < 0.001) *(-0.328, - 0.128)*
Microvascular complications (and specifically retino-/ neuro-/nephropathy)		-0.096 (p = 0.052) *(-0.192, 0)*	Retinopathy: -0.146 (p = 0.006) *(-0.246, - 0.046)*
Macrovascular complications	-0.257 (p = 0.011) *(-0.447, -0.067)*		
Comorbidity	-0.116 (p = 0.008) *(-0.196, - 0.036)*	-0.202 (p < 0.001) *(-0.305, -0.097)*	-0.172 (p = 0.001) *(-0.272, -0.072)*

Between parentheses the p value and the 95% confidence interval
SF QALYs - Quality adjusted life years based on the utility of the Short Form-36
EQ QALYs - Quality adjusted life years based on the utility of the EuroQol

Discussion and conclusion

In this study, 234 patients with DMT1 were followed for six years. This is the first study in which the utilities of both the SF-36 and the EuroQol have been used in a population of patients with DMT1. Although the SF-36 and the EuroQol are generic HRQOL instruments, their utilities, based on respectively only 11 and 5 items, measured changes in HRQOL over time in patients with DMT1. Diabetes-specific instruments are considered to be more sensitive to changes in HRQOL than generic instruments, since the disease-specific items of these instruments predominantly concern aspects of HRQOL, which are important for patients with that specific disease (4). Since in this study generic utilities were able to discern changes in HRQOL in patients with DMT1, this might undermine the presumed added value of diabetes-specific instruments.

The SF (1995-1998) QALYs were significantly lower than the EQ-5D (1995-1998) QALYs (difference 0.14 QALYs over 3 years). This can possibly be explained by the fact that the SF-6D is derived from 11 items, whereas the EQ-5D is derived from only 5 items. Moreover the SF-6D items have more answer possibilities than the EQ-5D. This offers the SF-6D the possibility of a more detailed assessment of HRQOL, and a further differentiation in various HRQOL levels. The high percentage of patients reporting the best EQ-5D health state, a ceiling effect, has been noted previously (25, 26). This ceiling effect probably makes the EQ-5D less suitable than the SF-6D, when relatively small changes in the highest ranges are expected in patients with DMT1.

This new finding, that the utility of the SF-36 is sensitive to changes in HRQOL in DMT1 over time, should reassure investigators that if they have employed the SF-36, they can retrieve a utility score which is sensitive and can perform fairly well in patients with DMT1. It provides health planners with a useful tool to compare alternative treatment strategies for patients with DMT1 and supports subsequent decision making.

The three most pronounced negative influences on QALYs were the presence of hyperglycaemic complaints, macrovascular complications and comorbidity. This negative influence on QALYs can be explained by the fact that these factors will likely cause symptoms experienced by the patients. In turn, these symptoms will influence a patient's physical, mental and social functioning in daily life, and will thereby influence a patient's HRQOL (27). The associations we found, correspond with prior knowledge (10, 11, 13, 28). This comparison supports the validity of these utilities in measuring HRQOL in DMT1.

The inclusion of several socio-demographic and diabetes-specific variables in the regression analysis only led to a 22-30% percentage of explained variance of patient's HRQOL, meaning that a rather large percentage of variance in HRQOL remained unexplained (70-78%). A patient's personality, social environment and life events will to a large extent explain a person's perception of symptoms and functioning and in this way influence a patient's HRQOL (27). Indeed, Rose et al developed a model that explained 62% of variance of HRQOL, patient's

psychological characteristics being the most significant determinant of HRQOL (mostly measures of psychological condition) (27, 29, 30).
Most of the above-mentioned characteristics were diabetes-specific factors. Nevertheless, the utilities of the generic SF-36 and EuroQol, which are not focused on aspects of special interest for patients with DMT1, apparently are sensitive enough to reveal associations between these diabetes-specific factors and QALYs. The explained percentage of variance in QALYs was higher with the SF QALY than the EQ QALY regression analysis. This might - again - be explained by the more detailed descriptive system of the SF-6D compared to the EQ-5D.
The EuroQol and the SF-36 both are generic and approach HRQOL as broadly as possible. Utilities of both instruments suggested a negative association between hyperglycaemic complaints and comorbidity and QALYs. This finding supports the validity of the two utilities and the robustness of these associations. However, this study showed that these two instruments can nevertheless give slightly different results. For example, the EQ-5D did not show an influence of macrovascular complications on EQ-QALYs, whereas the SF-6D did. The less detailed descriptive system of the EQ-5D can possibly explain this finding. However retinopathy showed a negative influence on EQ-QALYs, but no association with the SF-QALYs. We do not have an explanation for this finding.
The negative influence of a high frequency of self-monitoring blood glucose, hyperglycaemia and comorbidity on HRQOL was assessed in both three-year periods, suggestive of a persisting influence over time. This finding can possibly support not only the robustness of this negative influence but also the consistency of the instruments used.
This study also showed that different moments can reveal different associations with HRQOL. Socio-demographic and particularly diabetes-specific variables change over time, which can probably explain this finding. For example, in the second three-year period microvascular and not macrovascular complications had a negative influence on SF-QALYs. In this later phase of the study, the severity of microvascular complications might be greater and more frequently accompanied by symptoms, which in turn will influence patient's functioning. Coffey et al. showed a growing negative influence of microvascular complications with increased severity (11). In the case of macrovascular events, however, Clarke et al. showed in the UKPDS study that in patients with diabetes mellitus type 2 the negative influence on the EQ-5D of some complications, e.g. ischaemic heart disease and myocardial infarction, appeared to be less in the years subsequent to the year of the event (26). In our study, the macrovascular events registered in 1995 were events that had taken place in 1995 or earlier, which thus might explain a diminishing influence on a patient's HRQOL.

Conclusion

This is the first study in which SF-36 and EuroQol utilities and QALYs were calculated in patients with DMT1. This study showed a statistically significant decline in SF-6D and EQ-5D over time in a Dutch cohort of 234 patients with DMT1, an indication that both generic utilities were able to reveal changes in HRQOL over time and offer possibilities for cost effectiveness studies in patients with DMT1.

Presence of hyperglycaemic complaints, macrovascular complications, and comorbidity had the most profound negative association with QALYs. Both instruments were able to measure these associations between diabetes-specific factors and QALYs, associations already known to be associated with HRQOL, and thus showing the robustness and the validity of these utilities in patients with DMT1.

It should be emphasized, however, that the choice of the instrument and the moment of assessment of HRQOL can lead to partly different results. The SF-6D is more responsive to small changes in the highest ranges of HRQOL in patients with DMT1.

References

1. Garratt AM, Schmidt L, Fitzpatrick R. Patient-assessed health outcome for measures for diabetes: a structured review. Diabet Med 2002;19:1-11.
2. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15(3):205-18.
3. Bradley C. Measuring quality of life in diabetes. The Diabetes Annual 1996;10:207-224.
4. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993;118(8):622-9.
5. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27(3 Suppl):S217-32.
6. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. J Clin Epidemiol 1998;51(11):1115-1128.
7. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
8. Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems: Health Utility Index. Pharmacoeconomics 1995;7:490-502.
9. Kaplan RM, Ganiats TG, Rosen P, Sieber W, Anderson JP. Development of a self administered Quality of Well-Being scale (QWB-SA). Qual Life Res 1995;4:443.
10. Wu SY, Sainfort F, Tomar RH, Tollios JL, Fryback DG, Klein R, et al. Development and application of a model to estimate the impact of type 1 diabetes on health-related quality of life. Diabetes Care 1998;21(5):725-31.
11. Coffey J, Brandle M, Zhou H, Marriott D, Burke R, Tabaei B, et al. Valuing health-related quality of life in diabetes. Diabetes Care 2002;25(12):2238-2243.
12. U.K. Prospective Diabetes Study Group. Quality of life in Type 2 Diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999;22(7):1125-1136.
13. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GEH, Niessen LW. Health related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care 2002;25(3):458-463.
14. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271-292.
15. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.
16. Parkerson GR, Jr., Connis RT, Broadhead WE, Patrick DL, Taylor TR, Tse CK. Disease-specific versus generic measurement of health-related quality of life in insulin-dependent diabetic patients. Med Care 1993;31(7):629-39.
17. Dolan P. Modeling valuations for EuroQol Health States. Med Care 1997;35(11):1095-108.
18. Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol-questionnaire. Health Econ 1993;2(3):237-46.
19. Dutch Advisory on Health Research. Advice on chronic diseases: priorities for research. 's Gravenhage, the Netherlands; 1991.
20. de Jong PTVM. Screening op diabetische retinopathie [Screening for diabetic retinopathy]. Ned Tijdschr Geneeskd 1993;137(34):1701-1705.

21. Holewski JJ, Stess RM, Graf PM, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. J Rehabil Res Dev 1988;25(2):1-10.
22. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329(5):304-9.
23. EURODIAB. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994;37(3):278-85.
24. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Nederlandse Diabetes Federatie. Diabetische retinopathie, diabetische nefropathie, diabetische voet, hart- en vaatziekten bij diabetes mellitus [Diabetic retinopathy, diabetic nephropathy, diabetic foot, cardiac and vascular pathology in diabetes mellitus]. Utrecht: Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing; 1998.
25. Jenkinson C, Gray A, Doll H, Lawrence K, Keoghane S, Layte R. Evaluation of index and profile measures of health status in a randomized controlled trial. Comparison of the Medical Outcomes Study 36-Item Short Form Health Survey, EuroQol, and disease specific measures. Med Care 1997;35(11):1109-18.
26. Clarke P. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002:340-349.
27. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.
28. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes:UKPDS 38. BMJ 1998;317:703-13.
29. Rose M, Burkert U, Scholler G, Schirop T, Danzer G, Klapp BF. Determinants of the quality of life of patients with diabetes under intensified insulin therapy. Diabetes Care 1998;21(11):1876-85.
30. Rose M, Fliege H, Hildebrandt M, Schirop T, Klapp BF. The network of psychological variables in patients with diabetes and their importance for quality of life and metabolic control. Diabetes Care 2002;25(1):35-42.

Chapter 8

Health Related Quality of Life in patients with Diabetes Mellitus Type I: generic and disease-specific measurement

Hart HE, Redekop WK, Bilo HJG, Meyboom-de Jong B, Berg M. Health related quality of life in patients with type I diabetes mellitus: generic and disease-specific measurement. 2004;submitted.

Abstract

Background
An ideal instrument for the assessment of Health Related Quality of Life (HRQOL) in patients with diabetes mellitus type I (DMT1) should incorporate the benefits of both generic and disease-specific instruments. The objective of this study was to investigate the responsiveness and the ability to provide information about diabetes-specific associations with HRQOL, of two generic instruments, in comparison with two diabetes-specific instruments, in patients with DMT1.
Methods
In a Dutch cohort of 234 patients with DMT1 we longitudinally assessed HRQOL using both generic and diabetes-specific instruments. We investigated the responsiveness, the associations with diabetes-specific variables and the identification of specific patients by the instruments used.
Results
The generic RAND-36 was able to detect statistically significant and clinically relevant changes in HRQOL over time. Moreover, the RAND-36 was associated with (changes in) diabetes-specific variables. The generic and diabetes-specific instruments partly identified different patients with lowest HRQOL.
Conclusions
The RAND-36 was highly responsive to changes in HRQOL in patients with DMT1 and revealed diabetes-specific associations with HRQOL. A low correlation between the generic and diabetes-specific instruments and partly different identification of patients with lower HRQOL support the complementary use of these instruments in patients with DMT1.

Introduction

Diabetes mellitus type I (DMT1) will permanently change a person's life. Patient's self care, consisting of daily insulin injections and self-monitoring of blood glucose, has an impact on health related quality of life (HRQOL). Moreover, the acute and long-term complications which might develop will also affect a person's HRQOL (1).

However, only in recent years has attention been paid to HRQOL in patients with DMT1 (2). Many different instruments have been developed to measure the physical, psychological and social aspects of HRQOL (3-7). One can distinguish between generic and disease-specific HRQOL instruments (8, 9). *Generic instruments* are applicable to healthy people as well as to persons with diseases, and thereby enable comparisons to be made between various groups of patients and general population samples. Moreover, the general public has valued different health states, provided by some generic questionnaires, which makes economic evaluations possible (10-12). *Disease-specific instruments* focus on a population with a specific disease and are expected to be more sensitive to treatment effects and changes over time than generic instruments (8, 9). The limitation of these instruments, however, is that the scores such instruments generate remain specific for the affliction studied.

Many cross-sectional studies, using many different instruments of both types, have been performed in DMT1, and have shown that older and female patients, patients without a partner, patient with a lower education, and patients with complications are at risk for a decrease in HRQOL (13-29).

An ideal instrument for the assessment of HRQOL in DMT1 should incorporate the benefits of both generic and diabetes-specific instruments. This instrument should be sensitive for changes, should provide information about diabetes-specific associations with HRQOL, should enable comparisons between various groups of patients or general population samples and should make economic evaluations possible.

The aim of this study was to investigate these properties of two generic instruments in the assessment of HRQOL in DMT1. Moreover, we wanted to investigate the feasibility of these instruments and the clinical relevance of their results.

We therefore examined whether the generic instruments used in our study are capable of measuring (clinically relevant) changes in HRQOL in patients with DMT1 (1) and whether these generic instruments can identify diabetes-specific associations with HRQOL (2). An additional aim was to examine whether diabetes-specific and generic instruments identify the same patients, when low HRQOL scores are assessed (3).

Methods

Patients

In 1995 a series of 293 consecutive DMT1 patients seen at the outpatient clinic of the Isala Clinics in Zwolle, the Netherlands, was invited to participate in the study. A group of 281 patients agreed and was investigated from 1995 onwards on a yearly basis. DMT1 was defined as starting insulin therapy within six months after the first signs of diabetes mellitus and before the age of 30 years, or the absence of C-peptide secretion. Ethics committee approval was obtained from the Hospital Scientific and Ethics Committee. All patients gave their informed consent.

Health Related Quality of Life (HRQOL)

We used two different, frequently applied generic instruments, the RAND-36 and the EuroQol, which have both been translated and validated for the Dutch situation. In addition we used two different diabetes-specific instruments (Problem Areas In Diabetes, Fear of Hypoglycamia Scale) to measure some diabetes-specific aspects of HRQOL and to make comparisons possible with the generic assessments (10, 30-32).

These four instruments were sent to the patient's home address in one package. Patients were asked to fill in the questionnaires at home. At the next visit to the outpatient clinic the patients returned the completed questionnaires to the diabetes-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, generic questionnaire containing 36 items involving eight different subscales. For each subscale, scores are transformed to a scale from 0 (worst health) to 100 (best health) (31, 33). In addition, physical and mental component summary scores can be determined (PCS/ MCS) (34). The questionnaire takes about ten minutes to complete. The instrument has been translated into Dutch (35) and validated for the Dutch population (36). The RAND-36 was assessed yearly.

The Euroqol (EQ)

The EuroQol was developed by a multidisciplinary group of researchers from 5 European countries to describe and value health states (10). It is a generic, multidimensional measure, consisting of two parts, and takes about 2 minutes to complete by the patient.

The first part consists of five questions covering 5 dimensions (EQ-5D). Each dimension is divided into 3 levels: 'no problem', 'some/ moderate problems' and 'extreme/ unable to'. A respondent's health state is defined by combining one level from each of the 5 dimensions. A total of 243 possible health states can be defined in this way. Valuations of these health states have been made, by the U.K. general public, using time trade-off (37). The set of possible values has a range of -0.594 to 1, where 1 is the value of perfect health, 0 is the value of death and –0.594 indicates the worst possible health state, which is viewed by the general public as considerably worse than death.

The second part, a single overall score, can be gained from a "thermometer": a self-rated health status using a graduated (0-100) visual analogue scale (EQ-VAS), in which 0 indicates worst HRQOL and 100 best possible HRQOL. The EuroQol has been validated for the Dutch situation (38). The EQ was assessed in 1995 through 1998, and in 2001.

The Problem Areas in Diabetes Survey (PAID)

The PAID was developed as a new measure of psychosocial adjustment to diabetes. It is a diabetes-specific, unidimensional instrument. The instrument can be scored quickly, in 3-5 minutes, by the patient. Its primary aim is to tap the breadth of emotional responses to diabetes (32, 39). The PAID is a 20-item questionnaire in which each item represents a unique area of diabetes-related psychosocial distress. The items are divided over four areas. A total score, hypothesised to reflect the overall level of diabetes-related emotional distress, is computed by summing the 20 item responses. It is scored on a scale of 0 to 100, with higher PAID scores indicating greater emotional distress. Reliability and validity are good (32, 39) and the PAID has been validated for the Dutch situation (40). The PAID was assessed in 1998 and 2001.

The Fear of Hypoglycaemia Scale (FHS)

The FHS was developed as a research and clinical tool measuring the degree of fear experienced with respect to hypoglycaemia (30). Worries about hypoglycaemia as well as behaviour designed to avoid hypoglycaemia are examined. It is a diabetes-specific, unidimensional measure. The scale consists of 23 items: 13 items concerning worry and fear and 10 items concerning behaviour or avoidance. The 13 worry items can be summed to a Worry subscale, while the 10 behaviour items can be summed to a Behaviour subscale. Together, the two subscales can be summed to create the total FHS-score, a higher score indicating greater fear for hypoglycaemia (41). Various studies support the validity and the reliability of the FHS (30, 41). We only used the Worry subscale, since at the time of the study the validity of the behaviour subscale was discussed (41, 42). The Worry subscale was assessed in 1997 and 2001.

Clinical data

Socio-demographic data including sex, age, marital status and level of education were recorded. *Therapy-specific data* were recorded and included pen-/ pump use, frequency of insulin injections and number of blood glucose control measurements per week. *Metabolic control* was assessed by measuring glycosylated haemoglobin A1c (HbA1c). The *acute complications* of the therapy were also recorded; patients recorded all *hypoglycaemic events* during the three months preceding the outpatient visit. Patients were asked to report whether they had one or more of six different *hyperglycaemic complaints* during the previous three months (yes/ no): tiredness, weight loss, pruritus, thirst, polyuria and polydipsia.

Using a list of 26 chronic diseases/ diagnoses the patients could indicate which other diseases they had besides diabetes (43). When they indicated one or more chronic diseases, apart from diabetes mellitus, they were scored as having *comorbidity*.

Chronic complications of the disease were recorded (micro-/ macrovascular complications).

Microvascular complications

Patients with retinopathy, neuropathy or nephropathy were categorised 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 de Jong (44): 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 (45). At five dorsal and plantar sites on the foot (left and right) sensibility was tested with six different monofilaments. When the monofilament 5.07 was not felt at one of the ten test sites, patients were considered to have neuropathy.

Nephropathy

The 24-hour urinary excretion of albumin (UAER) was measured annually. UAER was considered abnormal when it was ≥ 30mg/ 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 (46-48). At the Isala clinics, patients with a micro-albuminuria >100 mg/ 24 hour received an angiotensin converting enzyme inhibitor (ACE-inhibitor) in 1995. We included ace-inhibitor users, even with normalbuminuria, as having nephropathy, when treatment was initiated for micro-albuminuria at an earlier stage.

Macrovascular complications

The clinician recorded the status of 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).

Analysis

We investigated the responsiveness of the RAND-36 and the EuroQol in patients with DMT1, in order to answer the question whether these generic instruments are sensitive for changes in HRQOL in patients with DMT1. Although responsiveness is considered to be an essential property of an evaluative instrument, the methodology of assessing reponsiveness tends to be less well understood (49).

In this study we applied three methods to investigate responsiveness of the generic instruments used in our cohort. Firstly, we investigated the ability to detect, longitudinally, statistically significant changes in HRQOL over time (1998 – 2001) using paired sample T-tests. Since the diabetes-specific instruments were assessed only in 1998 and 2001 we used this time interval.

Secondly, we investigated whether the observed changes were also clinically relevant. The developers of the RAND-36 and the EuroQol do not provide cut-off points for clinically important changes in HRQOL scores. However, changes of > 2-5 points for the RAND-subscales and > 1 point for the RAND summary scores are sometimes considered as the smallest clinically significant changes (33, 50, 51). For the EQ-5D and the EQ-VAS, 0.05 points and five points can be used as a rough guide although formally the EuroQol Group has not published any minimally significant values.
Finally, we investigated whether the generic instruments assessed changes in HRQOL when changes were expected on the basis of changes in diabetes-specific clinical characteristics. We expected a decrease in HRQOL for the patients who developed microvascular complications between 1998 and 2001 and compared the means of the patients who did develop microvascular complications and of the patients who did not (using the Mann Whitney test).
To investigate whether the generic instruments can provide information about diabetes-specific influences on HRQOL, we performed multivariate stepwise regression analyses to investigate cross-sectional associations of HRQOL scores with several demographic and disease-specific patient characteristics (in 2001). The different HRQOL scales were the dependent variables and all the personal and disease specific variables (see table 1) were the independent variables. We used the adjusted R^2 (result of the multivariate regression analysis) to describe the degree of variance in HRQOL explained by the model.
To investigate whether diabetes-specific and generic instruments identify the same patients, we calculated correlations between the different instruments using Spearman rank correlation coefficients. Moreover, for each instrument the 10% lowest scores (in 2001) were defined and the patients, thus identified by the different instruments, were compared.
Finally, we described several feasibility characteristics of the instruments, to provide practical information for the use of these instruments.
Relationships were considered statistically significant when p-values ≤ 0.05 were reached. Data were analysed using SPSS for Windows, version 10.0.

Results

A total of 281 adult patients with type I diabetes mellitus entered the study in 1995. The dropout rate over these six years was 16.7% (n=47). Dropouts were more frequently women (59.6% vs. 42.7%, p=0.04), more often single (24% vs. 9.2%, p=0.01), had a longer disease-duration (20.6 vs.16.5 years, p=0.05), and a higher HbA1c (9.0 vs. 8.1, p=0.007) and reported a lower baseline HRQOL.

Table 1
Personal and disease-specific characteristics of the study population (n = 234)

	1995		1998		2001	
Gender (men)	134	(57.3%)	134	(57.3%)	134	(57.3%)
Age (years)	38.2	(11.5)	41.2	(11.5)	44.2	(11.5)
Duration of diabetes (years)	16.5	(10.1)	19.5	(10.1)	22.5	(10.1)
Married/ cohabitinh	207	(90.8%)	194	(89.4%)	189	(87.9%)
High level of education	76	(33.6%)	72	(34.0%)	76	(35.5%)
Systolic blood pressure	138.9	(17.8)	131.1	(19.4)	131.5	(19.2)
Diastolic blood pressure	83.0	(8.4)	79.4	(10.2)	77.8	(10.4)
Body mass index (kg/m^2)	24.8	(3.2)	25.6	(3.6)	26.1	(4.0)
Hba1c (%)	8.1	(1.9)	7.9	(1.3)	7.6	(1.1)
Insulin pump	63	(26.9%)	76	(32.6%)	102	(43.6%)
Insulin pen	171	(73.1%)	157	(67.4%)	132	(56.4%)
Frequency of insulin pen injections (per day)						
1-3	24	(14.0%)	22	(14.0%)	19	(14.4%)
4	147	(86.0%)	128	(81.5%)	108	(81.8%)
>4	0	(0.0%)	7	(4.5%)	5	(3.8%)
Number of control measurements (per week)	12.0	(11.3)	18.2	(14.4)	20.0	(15.2)
Patients with:						
hypoglycaemic events last 3 months	185	(80.8%)	180	(84.9%)	173	(87.4%)
hyperglycaemic complaints last three months	122	(53.3%)	105	(50.5%)	116	(58.3%)
Comorbidity (at least one comorbid condition)	133	(58.1%)	130	(62.5%)	107	(52.7%)
Patients with diabetic complications						
Microvascular	104	(45.8%)	111	(58.1%)	119	(65.7%)
Retinopathy	79	(34.6%)	88	(44.9%)	99	(48.5%)
Nephropathy	43	(18.4%)	33	(16.7%)	45	(23.0%)
Neuropathy	24	(10.4%)	32	(15.2%)	23	(12.2%)
Macrovascular	10	(4.3%)	-	-	23	(9.8%)

Values are number of patients (with valid percentages between parentheses) or means (with standard deviation between parentheses)

Personal and disease-specific characteristics of the patients who completed the study period of six years are shown in table 1 (n=234). Data are shown for the years 1995, 1998 and 2001. Mean age at entry was 38.2 years, and 57.3% were men. The percentage of patients using a pump increased from 26.9% in 1995 to 32.6 % in 1998 ($p=0.002$) to 43.6% in 2001 ($p<0.001$). The therapy was intensified over the six-year study period. An increased number of control measurements per week, a lower HbA1c and a rise in body mass index were observed over this period. The percentage patients with hypoglycaemic events did not increase statistically significantly between 1995 and 2001 ($p=0.096$). The percentage of patients with microvascular complications increased from 45.8% in 1995 to 58.1% in 1998 ($p=0.005$) and later to 65.7% in 2001 ($p=0.248$). In 1995 the percentage of patients with macrovascular complications was 4.3% and in 2001 9.8% ($p<0.001$).

Ability to detect change in HRQOL over time

Table 2 shows the HRQOL over time for the different instruments.

RAND-36. Five subscales of the RAND-36 and the PCS showed a statistically significant decrease in HRQOL over time. The subscales role physical and social functioning and the Mental Component Summary tended to decrease, whereas the subscale role emotional remained stable between 1998 and 2001. Seven RAND-subscales and the PCS showed a clinically relevant change over time within this study period. The subscale role emotional and the MCS did not show a clinically relevant change in HRQOL over time.

EuroQoL. The EQ-5D as well as the EQ-VAS tended to decline between 1998 and 2001. This decline was not statistically significant and/ or clinically relevant however. In both years the percentage of patients with the highest possible EQ-5D score was high (52.3% and 46.6% respectively).

PAID. The problems related to treatment increased after 3 years follow-up ($p=0.03$). The diabetes related problems and the total score tended to increase, whereas the problems related to food and social support remained stable over time.

Hypoglycaemia Fear. The degree of worry was not increased after the 3-year period.

Ability to detect real changes in the concept being measured

The patients, who developed microvascular complication(s) between 1998 and 2001 reported a faster decrease in MCS and EQ-5D than the patients without new microvascular complication(s) [MCS -4.85 vs. +0.26, $p=0.006$ and EQ-5D −0.09 vs. +0.02, $p=0.013$)].

Table 2
Health related quality of life in 1998 versus 2001

	1998		2001		p value
RAND-36					
Physical functioning	91.0	(15.8)	87.3	(19.0)	**0.004**
Role physical	81.2	(33.3)	76.2	(37.8)	0.070
Bodily pain	87.5	(19.9)	83.6	(20.2)	**0.016**
General health	66.8	(18.9)	64.4	(20.3)	**0.015**
Vitality	68.3	(19.8)	61.6	(20.0)	**<0.001**
Social functioning	86.5	(18.6)	84.2	(20.3)	0.086
Role emotional	83.0	(35.5)	83.5	(32.6)	0.913
Mental health	79.9	(15.9)	77.1	(16.1)	**0.004**
Physical summary score	51.5	(7.6)	49.8	(9.1)	**0.006**
Mental summary score	51.7	(9.5)	50.9	(9.3)	0.176
EuroQol					
EQ-5D	0.87	(0.18)	0.85	(0.19)	0.191
EQ-VAS	77.1	(14.4)	76.0	(13.5)	0.054
PAID					
Diabetes related	13.8	(11.8)	14.9	(12.0)	0.073
Treatment related	1.7	(2.7)	2.2	(2.9)	**0.030**
Food related	2.5	(2.7)	2.4	(2.6)	0.862
Social support related	1.1	(1.9)	1.1	(1.8)	0.808
Total Score	19.5	(17.2)	20.5	(17.5)	0.254
Hypoglycaemia Fear					
Worry subscale	10.9	(8.4)[1]	10.7	(8.0)	1.000

Values are means with standard deviations between parentheses
p-values are based on paired sample T-Tests
HRQOL data in this table are based on 213-220 patients, resulting in 204-213 paired samples
[1] Worry subscale was assessed in 1997

EQ-5D - EuroQol utility index
EQ-VAS - EuroQol Visual Analogue Scale
PAID - Problem Areas in Diabetes

Ability to provide information about diabetes-specific associations with HRQOL
Table 3 shows the results of the multivariate stepwise regression analyses. The explained variance in HRQOL varied from 3.8% (Worry scale) to 24.3% (PCS). Only four characteristics showed a statistically significant association with a HRQOL scale; the presence of hyperglycaemic complaints, comorbidity and

macrovascular complications were all negatively associated with HRQOL. A lower HbA1c was associated with more worries about hypoglycaemia.

Table 3
Results of the multivariate regression analysis of health related quality of life scores in 2001

	PCS	MCS	EQ-5D	EQ-VAS	PAID-total	Worry subscale
R^2	0.243 (n=180)	0.075 (n=192)	0.180 (n=177)	0.157 (n=177)	0.083 (n=184)	0.038 (n=201)
Intercept	55.4	54.6	0.96	82.9	14.4	19.77
HbA1c						-1.29 (p=0.014)
Hyper-glycaemia	- 4.71 (p<0.001)	-5.03 (p<0.001)	-0.09 (p<0.001)	-6.80 (p<0.001)	10.85 (p<0.001)	
Comorbidity	- 2.78 (p=0.018)		-0.05 (p=0.033)			
Macrovascular complications	-10.03 (p<0.001)		-0.135 (p=0.002)	-11.6 (p=0.001)		

R^2 - Adjusted R square
Intercept - Mean value of the population
PCS - Physical component summary
MCS - Mental component summary
EQ-5D - EuroQol utility index
EQ-VAS - EuroQol Visual Analogue Scale
PAID - Problem Areas in Diabetes

The presence of macrovascular complications had the most pronounced negative association with HRQOL; these patients reported a lower PCS, EQ-5D, EQ-VAS. Patients with hyperglycaemic complaints also had a lower HRQOL (PCS, MCS, EQ-5D, EQ-VAS) and reported more diabetes related emotional distress (PAID).
A lower HbA1c was associated with more worries about hypoglycaemia (p=0.014).
Both generic instruments revealed a negative association between the presence of comorbidity and HRQOL (PCS and EQ-5D).

Identification of specific patients
Table 4 shows the Spearman rank order correlations between the different instruments.

Table 4
Spearman rank order correlations between the different quality of life scales

	PCS	MCS	EQ-5D	EQ-VAS	PAID-total	Worry subscale
PCS	-					
MCS	0.071 p=0.303	-				
EQ-5D	0.643 p<0.001	0.409 p<0.001	-			
EQ-VAS	0.531 p<0.001	0.557 p<0.001	0.613 p<0.001	-		
PAID	-0.263 p<0.001	-0.457 p<0.001	-0.293 p<0.001	-0.432 p<0.001	-	
Worry subscale	-0.219 p=0.002	-0.402 p<0.001	-0.281 p<0.001	-0.296 p<0.001	0.627 p<0.001	-

PCS - Physical component summary
MCS - Mental component summary
EQ-5D - EuroQol utility index
EQ-VAS - EuroQol Visual Analogue Scale
PAID - Problem Areas in Diabetes

Generic / generic – the PCS showed a strong correlation with the EQ-5D and a moderate correlation with the EQ-VAS. The MCS was moderately correlated with the EuroQol scales.
The PCS and MCS were uncorrelated, inherent to the method we chose to calculate the summary scores (34).
Diabetes-specific / diabetes-specific – the PAID was strongly correlated with the Worry subscale.
Generic / diabetes-specific – The PCS and EQ-5D correlated only weakly with the more psychological health scales (i.e., the PAID and the Worry subscale), whereas the MCS correlated moderately with the PAID and the Worry scale. The EQ-VAS correlated moderately with the PAID.

Table 5 shows the extent to which the instruments identified the same patients within the 10% lowest HRQOL range. The percentage of agreement was highest between the PCS, the EQ-5D and EQ-VAS. For example, of the patients with the 10% lowest PCS scores, 60% reported lowest EQ-VAS scores. Of the patients with the highest hypoglycaemia worry scores, only a quarter was found in the lowest MCS-score category (26.1%). Patients reporting most diabetes-related emotional distress had in 42.1% lowest MCS scores.

Table 5
Percentage of patients with 10 % lowest HRQOL identified by both instruments

	PCS	MCS	EQ-5D	EQ-VAS	PAID-total	Worry subscale
PCS	-	9.5%	50.0%	60.0%	19.1%	20.0%
MCS	9.5%	-	33.3%	38.9%	42.1%	30.0%
EQ-5D	58.8%	29.4%	-	72.2%	23.5%	25.0%
EQ-VAS	41.4%	24.1%	46.4%	-	26.7%	21.4%
PAID	21.1%	42.1%	33.3%	47.1%	-	55.6%
Worry subscale	17.4%	26.1%	21.1%	28.6%	43.5%	-

PCS - Physical component summary
MCS - Mental component summary
EQ-5D - EuroQol utility index
EQ-VAS - EuroQol Visual Analogue Scale
PAID - Problem Areas in Diabetes

Feasibility Table 6 shows several feasibility data of the instruments used in our cohort. All four instruments led to very high percentages of valid scores.

Table 6
Several feasibility data of the different instruments used in the cohort

	Number of subscales	Number of items	Total score	Completion time in minutes	Suitable for self assessment	Valid scores (1998)
RAND-36	8	36	Yes	10	Yes	92.3-93.6%
EuroQol	5	6	Yes	2	Yes	93.2-93.6%
PAID	4	20	Yes	3-5	Yes	89.7-92.7%
HFS	2	23	Yes	3	Yes	92.7% [1]

PAID - Problem Areas in Diabetes
HFS - Hypoglycaemic Fear Survey
[1] - Based on Worry subscale

Discussion and conclusion

In our study we followed a Dutch cohort of 234 patients with DMT1 for three years. We used both generic and diabetes-specific HRQOL instruments to assess HRQOL.

A central question was how well the generic RAND-36 and EuroQol capture changes in HRQOL in patients with DMT1 and whether they provide information about diabetes-specific associations with HRQOL. Moreover we examined the feasibility and the clinical relevance of their results. Could these generic instruments replace the diabetes-specific instruments in the assessment of HRQOL in DMT1?

The responsiveness of the generic RAND-36 was good: it was sensitive to changes in HRQOL over three years and the changes could also be considered clinically relevant. Moreover, the RAND mental summary score (MCS) was associated with a change in a diabetes-specific characteristic. The onset of microvascular complications was associated with a decrease in MCS, which we can explain by the fact that the knowledge of having a microvascular complication will negatively influence mental health. Very likely the PCS will be influenced negatively later, when the severity of the microvascular complications is increased, and the complications become symptomatic. These symptoms will influence patient's functioning and thereby HRQOL indirectly (52).

The responsiveness of the EQ was limited. The mean observed changes in EQ between 1998 and 2001 were neither statistically significant nor clinically relevant. Moreover, this instrument showed a considerable ceiling effect, in that half of the patients reported the best possible HRQOL. This inability of the EQ to differentiate between small differences in the highest HRQOL ranges has previously been described (53, 54). Nevertheless, the EQ-5D decreased when microvascular complications developed.

Patients reported more treatment related problems in 2001 than in 1998. Earlier studies provided support for the responsiveness for changes of the PAID (55). Indeed therapy was intensified during that period. Nevertheless, no associations were found between PAID scores and objective factors of intensified therapy (i.e. pump use/ more than 4 times daily pen injection, higher frequency of self monitoring blood glucose, lower HbA1c) or the possible side effects of an intensified therapy (weight gain and more hypoglycaemic events) and PAID scores. The PAID scores purely reflected patient's subjective self-report and evaluation of problems concerning treatment.

The Worry subscale did not show changes over time. Although the HbA1c declined significantly, the number of patients that reported hypoglycaemic events did not increase significantly, which might explain this result.

We conclude that the generic RAND-36 was highly responsive to changes in HRQOL over time and to changes in a diabetes-specific variable.

Both the RAND-36 and the EuroQol provided information about diabetes-specific influences on HRQOL. Hyperglycaemia and the presence of macrovascular complications were associated with a lower HRQOL. The generic instruments

showed a lowered HRQOL in the presence of non-diabetic morbidity (comorbidity), whereas the diabetes-specific instruments did not. Woodcock et al reported in a general practice DMT2 population the negative influence of comorbidity on generic measured HRQOL and used this finding to support the complementary use of generic and disease-specific instruments (56).

Although the PCS is a generic measure, the model used to explain variance in PCS resulted in the largest percentage explained variance (i.e. 24.3%). This percentage was much lower for the MCS, the EuroQol, the Worry subscale of the HFS and the PAID. This suggests that it is easier to explain variance in the more physical aspects than in the more mental aspects of HRQOL. The RAND-36 is multidimensional and approaches HRQOL as broadly as possible, including physical, psychological and social aspects. In contrast, the HFS worry scale and the PAID are uni-dimensional and focus on a small though important portion of the concept HRQOL of patients with DMT1 (57).

We can state that the generic RAND-36, and the EQ in a less degree, gave information about diabetes-specific influences on HRQOL. This information was partly different from that provided by the diabetes-specific, uni-dimensional instruments used in our study (3, 5, 39, 57, 58).

The low correlations between the generic and diabetes-specific instruments used in our study suggest that these instruments measure different aspects of health. Indeed, rather different aspects, ranging from problems with one's job ('did you have any problem with your work as result of your physical health?' RAND-36) to fear for hypoglycaemia ('do you worry about passing out in public?' HFS) are assessed (3). When instruments have a low correlation, a complementary use of these instruments can give additional information.

The generic and diabetes-specific instruments in our study only partly identified the same patients with the lowest HRQOL. When a clinician wishes to identify and select patients who are at greatest risk of a worsening in HRQOL, the choice of the instrument will influence which patients will be identified. For example, for patients showing poor glycaemic control, a clinician can wonder whether these patients are more afraid of hypoglycaemic events than others, since this fear can lead to non-compliance and poor glycaemic control. This specific question should lead to a carefully considered choice of instrument, and in this case, the HFS would be the most appropriate choice.

Although the RAND-36 questionnaire consists of more items and takes longer to complete than other instruments, this did not lead to a lower response rate or a lower percentage of valid scores. Apparently, the length of this instrument and the longer completion time were not a problem in this group of patients.

Conclusion

The generic RAND-36 appears to be very sensitive to changes in HRQOL in a cohort of patients with DMT1. Although the RAND-36 is a generic instrument, it provides information about diabetes-specific associations with HRQOL. The generic and diabetes-specific instruments show low correlations and identify for the most part different patients with the lowest HRQOL.

We recommend the use of the RAND-36 for assessing HRQOL in patients with DMT1. The complementary use of a diabetes-specific measure like the PAID and

the HFS will give additional information about the psychological status of patients with DM.

References

1. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15(3):205-18.
2. Anonymous. Diabetes care and research in Europe: the Saint Vincent Declaration. Diabet Med 1990;7(4):360.
3. Bradley C. Measuring quality of life in diabetes. The Diabetes Annual 1996;10:207-224.
4. Coons SJ, Rao S, Keininger DL, Hays RD. A Comparative Review of Quality-of-Life Instruments. Pharmacoeconomics 2000;17(1):13-35.
5. Garratt AM, Schmidt L, Fitzpatrick R. Patient-assessed health outcome for measures for diabetes: a structured review. Diabet Med 2002;19:1-11.
6. Hirsch A, Bartholomae C, Volmer T. Dimensions of quality of life in people with non-insulin-dependent diabetes. Qual Life Res 2000;9:207-218.
7. Luscombe FA. Health-related Quality of Measurement in Type 2 Diabetes. Value in Health 2000;3(Supplement 1):15-28.
8. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993;118(8):622-9.
9. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27(3 Suppl):S217-32.
10. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
11. Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems: Health Utility Index. Pharmacoeconomics 1995;7:490-502.
12. Kaplan RM, Ganiats TG, Rosen P, Sieber W, Anderson JP. Development of a self administered Quality of Well-Being scale (QWB-SA). Qual Life Res 1995;4:443.
13. Aalto AM, Uutela A, Kangas T. Health behaviour, social integration, perceived health and dysfunction. A comparison between patients with type I and II diabetes and controls. Scand J Soc Med 1996;24(4):272-81.
14. Aalto AM, Uutela A, Aro AR. Health related quality of life among insulin-dependent diabetics: disease-related and psychosocial correlates. Patient Educ Couns 1997;30(3):215-25.
15. Bardsley MJ, Astell S, McCallum A, Home PD. The performance of three measures of health status in an outpatient diabetes population. Diabet Med 1993;10(7):619-26.
16. Bott U, Muhlhauser I, Overmann H, Berger M. Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes Care 1998;21(5):757-69.
17. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L. Quality of life and associated characteristics in a large national sample of adults with diabetes. Diabetes Care 1997;20(4):562-7.
18. Hanestad BR. Self-reported quality of life and the effect of different clinical and demographic characteristics in people with type 1 diabetes. Diabetes Res Clin Pract 1993;19(2):139-49.
19. Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res 2003;12(8):1089-1097.
20. Jacobson AM, de Groot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. Diabetes Care 1994;17(4):267-74.

21. Jacobson AM, de Groot M, Samson JA. The effects of psychiatric disorders and symptoms on quality of life in patients with type I and type II diabetes mellitus. Qual Life Res 1997;6(1):11-20.
22. Hahl J, Hamalainen H, Sintonen H, Simell T, Arinen S, Simell O. Health related quality of life in type I diabetes without or with symptoms of long-term complications. Qual Life Res 2002;11:427-436.
23. Kent LA, Gill GV, Williams G. Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis. Lancet 1994;344(8925):778-81.
24. Muhlhauser I, Overmann H, Bender R, Bott U, Jorgens V, Trautner C, et al. Social status and the quality of care for adult people with type I (insulin-dependent) diabetes mellitus--a population-based study. Diabetologia 1998;41(10):1139-50.
25. Parkerson GR, Jr., Connis RT, Broadhead WE, Patrick DL, Taylor TR, Tse CK. Disease-specific versus generic measurement of health-related quality of life in insulin-dependent diabetic patients. Med Care 1993;31(7):629-39.
26. Reviriego J, Millan MD, Millan M. Evaluation of the diabetes quality-of-life questionnaire in a Spanish population. An experience of translation and reliability. Pharmacoeconomics 1996;10(6):614-22.
27. Wandell PE, Brorsson B, Aberg H. Quality of life among diabetic patients in Swedish primary health care and in the general population: comparison between 1992 and 1995. Qual Life Res 1998;7(8):751-60.
28. Wikblad K, Leksell J, Wibell L. Health-related quality of life in relation to metabolic control and late complications in patients with insulin dependent diabetes mellitus. Qual Life Res 1996;5(1):123-30.
29. Wu SY, Sainfort F, Tomar RH, Tollios JL, Fryback DG, Klein R, et al. Development and application of a model to estimate the impact of type 1 diabetes on health-related quality of life. Diabetes Care 1998;21(5):725-31.
30. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care 1987;10(5):617-21.
31. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. Health Econ 1993;2:217-227.
32. Welch GW, Jacobson AM, Polonsky WH. The Problem Areas in Diabetes Scale. An evaluation of its clinical utility. Diabetes Care 1997;20(5):760-6.
33. Hays RD, Morales LS. The RAND-36 measure of health related quality of life. Ann Med 2001;33:350-357.
34. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33(4 Suppl):AS264-79.
35. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.
36. Zee vdKl, Sanderman R, Heyink J, Haes dH. The psychometric qualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-122.
37. Dolan P. Modeling valuations for EuroQol Health States. Med Care 1997;35(11):1095-108.
38. Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol-questionnaire. Health Econ 1993;2(3):237-46.
39. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, et al. Assessment of diabetes-related distress. Diabetes Care 1995;18(6):754-60.

40. Snoek FJ, Pouwer F, Welch GW, Polonsky WH. Diabetes-related emotional distress in Dutch and U.S. diabetic patients: cross-cultural validity of the problem areas in diabetes scale]. Diabetes Care 2000;23(9):1305-9.
41. Irvine A, Cox D, Gonder-Frederick L. The fear of hypoglycaemia scale (HFS). In: Bradley C, editor. Handbook of Psychology of Diabetes: A guide to psychological measurement in diabetes research and practice. Chur, Switserland: Hardwood Academic Publishers; 1994. p. 133-155.
42. Snoek F, Pouwer F, Mollema E, Heine R. The Dutch version of the Hypoglycaemia Fear Survey; Internal consistency and validity. Gedrag & Gezondheid 1996;24(5):287-292.
43. Dutch Advisory on Health Research. Advice on chronic diseases: priorities for research. 's Gravenhage, the Netherlands; 1991.
44. de Jong PTVM. Screening op diabetische retinopathie [Screening for diabetic retinopathy]. Ned Tijdschr Geneeskd 1993;137(34):1701-1705.
45. Holewski JJ, Stess RM, Graf PM, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. J Rehabil Res Dev 1988;25(2):1-10.
46. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329(5):304-9.
47. EURODIAB. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994;37(3):278-85.
48. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Nederlandse Diabetes Federatie. Diabetische retinopathie, diabetische nefropathie, diabetische voet, hart- en vaatziekten bij diabetes mellitus [Diabetic retinopathy, diabetic nephropathy, diabetic foot, cardiac and vascular pathology in diabetes mellitus]. Utrecht: Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing; 1998.
49. Terwee C, Dekker F, Wiersinga W, Prummel M, Bossuyt P. On assessing responsiveness of health-related quality of life instruments: Guidelines for instrument evaluation. Qual Life Res 2003;12:349-362.
50. Brook RH, Ware JE, Rogers WH, Keeler EB, Davies AR, Donald CA, et al. Does free care improve adults' health? Results from a Randomized Controlled Trial. N Engl J Med 1983;309(23):1426-1434.
51. Ware JE, Kosinki M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10:405-413.
52. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.
53. Clarke P. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002:340-349.
54. Jenkinson C, Gray A, Doll H, Lawrence K, Keoghane S, Layte R. Evaluation of index and profile measures of health status in a randomized controlled trial. Comparison of the Medical Outcomes Study 36-Item Short Form Health Survey, EuroQol, and disease specific measures. Med Care 1997;35(11):1109-18.
55. Welch G, Weinger K, Anderson B, Polonsky WH. Responsiveness of the Problem Areas in Diabetes (PAID) questionnaire. Diabetic Medicine 2003;20:69-72.
56. Woodcock A, Julious SA, Kinmouth AL, Campbell MJ. Problems with the performance of the SF-36 among people with type 2 diabetes in general practice. Qual Life Res 2001;10:661-670.
57. Polonsky WH. Understanding and assessing diabetes-specific quality of life. Diabetes Spectrum 2000;13:36-45.

58. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. Qual Life Res 1999;8(1-2):79-91.

Chapter 9

General discussion

Introduction

The main aim of this thesis was to investigate the *Health Related Quality of Life* (HRQOL) in patients with *Diabetes Mellitus Type I* (DMT1) and to investigate the possibility of providing recommendations for the assessment of the HRQOL in patients with DMT1. To this purpose a long-term clinical follow-up of a cohort of patients with DMT1 was performed.
We were interested in the HRQOL of patients with DMT1 compared to that of persons of comparable age in the general population, and which factors are associated with their HRQOL. To explain associations between several demographic and diabetes-specific characteristics and HRQOL the model of Wilson and Cleary was followed. We hypothesized, that when disease symptoms are present and when the more severe complications of DMT1 will lead to symptoms, these symptoms will serve as important determinants of a person's functioning. Such impaired functioning will be associated with changes in HRQOL (1).
We also investigated HRQOL during the first year after diagnosis. One year after diagnosis we compared HRQOL, with the HRQOL of persons from the general population. Furthermore, changes in HRQOL over time, in the six-year study period, were assessed, and compared to changes in the general population. Even more interesting was the question whether the changes in HRQOL are predictable allowing for the possibility of anticipating and preventing decreases in HRQOL.
In our effort to provide recommendations for the assessment of HRQOL in patients with DMT1 several generic and disease-specific HRQOL questionnaires were used to assess possibilities and limitations seen with both types of questionnaires. We investigated whether utilities of generic instruments in patients with DMT1 can be used to allow cost-effectiveness studies, when taking their HRQOL into account.
Follow-up of patients with DMT1 was possible in a cohort of patients with DMT1 in the Isala Clinics in Zwolle, the Netherlands, from 1995 through 2001.
In this general discussion (chapter 9) the main findings of this study will be presented and discussed. Recommendations for the future will be formulated. First, the cohort is described, followed by the main topic of the study, HRQOL in patients with DMT1. The chapter closes with conclusions and recommendations.

A cohort of patients with DMT1

Background
DMT1 is characterized by the inability to regulate blood glucose levels due to the lack of insulin production, resulting in hyperglycaemia and the eventual development of micro- and macrovascular complications. These complications associated with diabetes predominantly define the degree of morbidity in this group of patients. Therefore the primary goal in treating patients with DMT1, is to normalize blood glucose levels as much as possible in an effort to prevent or delay the onset and progression of complications, while at the same time optimizing the patient's HRQOL.

Major findings and discussion

A cohort of 281 patients with DMT1 entered the study in 1995; 234 of these patients were followed for the entire duration of the six-year study. Therapy was intensified during the study period. The percentage of patients using an external or internal insulin pump increased significantly during these six years, from 26.9% in 1995 up to 43.6% in 2001. Of the patients using the insulin pen, 85.6% injected $\geq$ 4 times per day. Thus, 93.2% of the study population was treated intensively by the end of the study period. As a result the mean HbA1c dropped statistically significantly from 8.1% to 7.6%. There also was a significant increase in body mass index from 24.8 in 1995 to 26.1 kg/m^2 in 2001, which may be associated with the intensified insulin therapy. A consequence of the intensified insulin therapy was a significant increase in the number of control measurements of blood glucose level per week (from 12.0 in 1995 to 20.0 per week in 2001), (chapter 2). Despite this intensive therapy, the percentage of patients that reported hypoglycemic events during the study period, did not increase significantly. A possible explanation for this finding might be that severe hypoglycaemia can be reduced as much as 4-fold by insulin pump use, compared with multiple daily pen injections (2).

The increase in the percentage of patients with micro- and macrovascular complications in our cohort was statistically significant, from 45.8% in 1995 to 65.7% in 2001 for microvascular and from 4.3% in 1995 to 9.8% in 2001 for macrovascular complications (chapter 2).

The Diabetes Control and Complications Trial (DCCT) showed that an intensified therapy delays the onset and progression of microvascular complications (3). Moreover, a reduction in some risk factors for cardiovascular disease suggested a potential beneficial effect of intensive therapy on macrovascular disease in DMT1 (4). Despite the intensified therapy in our cohort, a significantly increased percentage of patients with micro- and macrovascular complications was observed over the six-year study period.

Whereas in the DCCT an unusually supportive network of professionals was present, patients in our cohort seemed to be able to regulate and monitor their blood glucose levels adequately under standard diabetes care.

Limitations of our study

- *Dropouts*

The number of dropouts in this study was not high (n=46), but unfortunately we were not able to follow up them adequately. At study entry these patients had a higher HbA1c (9.0 vs. 8.1%, p=0.007) and a longer disease duration (20.6 vs. 16.5 years, p=0.05), factors which are known to be negatively associated with the development of diabetic complications. The dropouts were more often single, more frequently female, and reported a lower level of HRQOL at study entry.

Dropout of these patients may have led to lower percentages of patients with diabetic complications in 2001, higher levels of HRQOL at baseline and less decrease in HRQOL over time.

- *Missing data*

During the study the percentage of missing clinical data increased. Patients were asked to complete a list consisting of diabetes-specific questions concerning

therapy, hypoglycemia, hyperglycemia and comorbidity every year. They also completed several HRQOL questionnaires. It is certainly possible that some of the patients were no longer motivated to complete the same questionnaires from 1995 to 2001. Logistic reasons account in part for other missing data, such as the absence of a podiatrist in the clinic for the assessment of neuropathy at some follow-up visits.
Since the number missing clinical data increased during the study period, fewer patients could be included for some of the multivariate regression analyses, e.g. when investigating associations between HRQOL and diabetes-specific factors, for which a complete dataset is required. Despite the sometimes limited patient numbers in some of the regression analyses, it was still possible to assess statistical significance of associations. When comparing the profiles of the patients excluded from the analysis with the profiles of the included patients, they did not differ significantly.
- *Onset of complications*
When the degree of complications becomes more severe it will lead to symptoms. We hypothesized that when these symptoms are present, HRQOL will be negatively influenced. Whereas early stages of microvascular complications will probably not give any symptoms, it might be the onset and just the fact of knowing about the presence of a microvascular complication that influences mentally HRQOL. However, it was impossible to assess HRQOL just at the moment of onset of complications.
- *Control group*
The prevalence of complications might have been even higher, when therapy would not have been intensified. Unfortunately we were not able to compare our data with data in a control group.

Novel developments
Recent studies emphasize the multifactorial genesis of vascular damage in diabetes mellitus. In the Epidemiology of Diabetes Interventions and Complications Study (EDIC), Nathan et al. showed that an increase in carotid intima-media thickness was associated with age as well as systolic blood pressure, smoking, the ratio of low-density lipoprotein to high-density lipoprotein and urinary albumin excretion (5, 6). Perkins et al showed that a glycosylated hemoglobin of less than 8 percent and low levels of both cholesterol and triglycerides were independently associated with the regression of microalbuminuria (7). In the Pittsburgh Epidemiology of Diabetes complications study, Orchard et al. demonstrated that insulin resistance related factors, and not glycemia, predicted coronary artery disease in DMT1 (8). Some weight gain (increased body mass index) is one of the side effects of intensive therapy. This often results in an increased central obesity, and may therefore contribute to the emergence of the insulin resistance syndrome (9).
The EURODIAB IDDM Complications Study Group showed that cardiovascular disease is presaged by dyslipidemia, hypertension and increased body mass index, but not by elevated HbA1c levels (9, 10).
These new insights offer possibilities for further delay and even prevention of onset and progression of diabetic complications. Indeed, and by analogy, the Steno-2 Study showed that a long-term (mean 7.8 years) intensified intervention involving

multiple risk factors, including behavior modification and pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidemia and microalbuminuria, as well as secondary prevention of cardiovascular disease with low dose acetylsalicylic acid, reduced the risk of cardiovascular and microvascular events by about 50 percent in patients with diabetes mellitus type 2 and microalbuminuaria (11).
The UK Prospective Diabetes Study Group showed that tight blood pressure control in patients with hypertension and type 2 diabetes resulted in a clinically important reduction in the risk of mortality related to diabetes (two thirds of which were cardiovascular disease), complications related to diabetes, progression of diabetic retinopathy and deterioration in visual acuity (12). They also showed that quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (13).

Health related quality of life in patients with DMT1

Background
HRQOL in patients with DMT1 refers to the patient's perception of the way diabetes mellitus affects physical, psychological and social functioning in daily life. It reflects the perceived burden of living with DMT1.

Major findings and discussion
Level of HRQOL in comparison with general population sample
Most aspects of HRQOL in patients with DMT1 are comparable with HRQOL in persons of comparable age in the general population. Patients with DMT1 judge their physical, psychological and social functioning in daily life predominantly equal to persons of comparable age in the general population (chapter 3) (14).
On the other hand, when we asked them 'How good or bad is your own health state today?' (EQ-VAS) or 'How is your health generally?' (Aspect of General Health subscale) they reported a lower HRQOL than the general population sample (chapter 3).
Socio-demographic associations
Older patients reported a lower, predominantly physical, HRQOL (PCS, EQ-5D), patients with a higher education level reported a lower EQ-VAS. Married or cohabiting patients reported a higher mental HRQOL (MCS) (chapter 3).
In this study we did not investigate the personality (patient's character) and the personal environment (family relationships, social support, life events) of the patients. It is likely that such factors will to a large extent explain a person's perception of symptoms and functioning, and will, in this way, be associated with the person's HRQOL. For example, Rose et al showed that patients with a more optimistic attitude reported a higher HRQOL (15, 16).
Diabetes-related associations
The presence of hyperglycaemic complaints and macrovascular complications showed the most profound negative association with HRQOL (chapter 3).

Hyperglycaemia and macrovascular events produce symptoms in the patients to such a degree as to impair daily functioning. These findings confirmed our hypothesis that when symptoms are present patients will experience a lower HRQOL.
A higher frequency of self-monitoring blood glucose (SMBG) testing each week was also negatively associated with HRQOL. These tests, which are done by the self administration of a finger prick, are painful, and result, in accordance with our model, in a negative influence on HRQOL. New methods for self-administered glucose blood monitoring are under development, which will likely cause less discomfort for the patient. Courses in intensive insulin management might be helpful for patients learning and improving skills necessary in diabetes care and management. The dose adjustment for normal eating (DAFNE) study group showed that skills promoting dietary freedom improved quality of life and glycaemic control in patients with DMT1 without worsening the risk for severe hypoglycaemia or cardiovascular risk (17).
No prior studies have reported either the negative association of a high frequency of SMBG or the presence of hyperglycaemic symptoms with HRQOL.
Whereas others found a negative association of the presence of hypoglycaemic events with HRQOL, our study did not confirm this (18). De Vries et al compared pump use with multi-daily pen injection (MDI) and reported that, although the number of mild hypoglycaemic episodes was higher in the pump group, higher scores were measured for the general health and mental health subscales after starting the pump than for patients starting MDI (19). During our study period the percentage of patients using an insulin pump increased significantly, which might explain why we did not find a decreased HRQOL by hypoglycaemia.
Newly diagnosed diabetes mellitus
In a small group of patients with newly diagnosed DMT1 (n=15) HRQOL improved during the first six months after diagnosis. As expected HbA1c decreased, as did the number of patients that reported hyperglycaemic complaints (20). One year after diagnosis HRQOL of the study group was comparable to that of a general population sample (chapter 4). Three months after diagnosis, HbA1c levels did not show any further significant decrease. One might expect the percentage of patients reporting hyperglycaemic complaints to decrease and the HRQOL to normalize within these first three months after diagnosis. Unfortunately, the time parameters for the assessment of HRQOL and the presence of hyperglycaemic complaints used in this study were six and twelve months after diagnosis and we were therefore unable to address this question. Although the number of patients in this part of the study was small, we nevertheless found statistically significant changes over time. The results are in agreement with those found in our cross-sectional study (chapter 3) and also confirm the hypothesis in our model, which states that, when symptoms are present, HRQOL will be impaired (chapter 1). Both findings strengthen our opinion that these study results are representative.
Change in HRQOL in DMT1 over time
Patients with DMT1 have a clinically relevant loss of, predominantly physical, HRQOL over time. Additionally, these patients have a faster decrease in HRQOL over time, as measured on most subscales, when compared to age matched

persons from the general population (chapter 5) (21, 22). The mental subscales remained more or less stable over time. The subjects who dropped out of the study had a lower HRQOL, predominantly mental, than the patients who continued with the study. Loosing the dropouts may partly explain the fact that the subscales role emotional and mental health and the MCS did not show a significant change over time (chapter 2). The possibility that many patients have learned to cope with a demanding disease like DMT1 might also positively influence their mental health, and will protect them from a decrease in mental HRQOL over time.
The faster decline of the patients with DMT1 in predominantly physical HRQOL is probably due to the development of chronic complications related to diabetes. These complications will cause symptoms, which will influence the patient's functioning and result in a decrease in HRQOL.
Unfortunately, we did not have longitudinal HRQOL population data with which to compare our cohort; we therefore estimated the change per year in the population sample. Despite this limitation we consider our data are representative, since it confirms prior knowledge and our own cross-sectional data (chapter 1 and 3).

Predicting change in HRQOL over time

It was possible to identify factors which act as predictors for change in HRQOL. The presence of diabetic complications in 1995 predicted a lower HRQOL in 2001 (chapter 6). This finding can be explained by the assumption that late complications already present in 1995 will be more severe in 2001, will lead to symptoms and will in this way negatively influence HRQOL (chapter 1). Moreover, we found that a high diastolic blood pressure, a risk factor for the development and progression of complications, was predictive for a decrease in HRQOL (chapter 6). This is the first study, which identifies patients who are at risk for a faster decrease in HRQOL.

The assessment of HRQOL in DMT1

Background

Generic and disease-specific HRQOL questionnaires both have their possibilities and limitations. Diabetes-specific instruments are said to be more sensitive to changes over time in patients with DMT1 and should be more suitable to assess diabetes-specific associations with HRQOL, whereas generic instruments allow comparisons with subjects in the general population and with patients with other diseases, looking at the relative burden of diseases (23, 24). Furthermore, 'utilities' derived from several of the generic instruments make cost-effectiveness studies possible (25-27). An ideal instrument for the assessment of HRQOL in DMT1 would incorporate the benefits of both generic and disease-specific instruments.
In our study, we investigated the use of two generic questionnaires, the RAND-36 and the EuroQol (EQ), and two diabetes-specific instruments, the Problem Areas In Diabetes (PAID) and the Hypoglycaemia Fear Scale (HFS) for the assessment of HRQOL (28-30).

Major findings and discussion

Responsiveness

We showed that generic instruments can assess changes over time in DMT1. Several subscales and the Physical Summary Scale of the RAND-36 showed a change over time which was statistically significant (chapter 5 and 8). Most changes were also clinically relevant as perceived by patients and clinicians. The RAND-36 was also able to detect changes in HRQOL when patients developed microvascular complications. Changes over time when using the generic EuroQol were not statistically significant and clinically relevant between 1998 and 2001 (chapter 8). During the total study period (1995-2001) however, the changes were statistically significant (chapter 5), although they remained clinically not relevant. 'Utilities', derived from the RAND-36 and the EuroQol, revealed changes in HRQOL over time in patients with DMT1 as well (chapter 7).

Associations with diabetes-specific variables

The RAND-36 and the EQ, and their utilities as well, assessed associations between diabetes-specific factors and HRQOL (chapter 3, 7 + 8). These generic instruments can provide information about associations of diabetes-specific variables and HRQOL.

Redundancy of diabetes-specific instruments

The question arises whether the application of diabetes-specific instruments may become redundant in the assessment of HRQOL in patients with DMT1. Whereas the RAND-36 and EQ were indeed responsive to changes over time and provided information about associations of diabetes-specific factors with HRQOL in patients with DMT1, they only partially identified the same patient group when compared with diabetes-specific instruments. The diabetes-specific instruments used in our study focus partly on different aspects of living and coping with DMT1. The complementary use of a diabetes-specific measure like the PAID and the HFS can give additional information about the (psychological) status of patients with DMT1.

RAND-36 versus EuroQol

The higher number of varied items of the RAND-36 will lead to a more detailed description of the different physical, psychological and social aspects of a patient's HRQOL than is assessed by the EQ. The RAND-36 is more responsive to changes over time than the EQ. Furthermore, the percentage patients reporting highest EQ-5D health was almost 60%. This 'ceiling effect' probably makes the EQ less suitable when relatively small changes in the highest ranges of HRQOL are expected (chapter 8). The larger number of items of the RAND-36 did not result in a lower response rate or a higher percentage of missing values compared to the EQ.

RAND-36 versus Short Form-36 (SF-36)

In this study we used the RAND-36 (28-31). The RAND-36 includes the same 36 items as those in the SF-36, but the recommended subscale scoring method is somewhat different from that of the SF-36 (31-34). Scoring differences exist only for the subscales Bodily pain and General health. RAND Bodily pain scores are somewhat higher and RAND General health scores are somewhat lower than the SF-36 scores (31). Despite these scoring differences, correlations of 0.99 were obtained in the Medical Outcomes Studies (MOS) panel sample when responses were scored using the RAND-36 versus the SF-36 scoring method (31).

The use of SF-36 summary scores from RAND-36 subscales
The use of summary scores reduces the number of statistical comparisons, thereby reducing the role of chance, but should not lead to a substantial loss of information. This appeared to be the case when the SF-36 summary scores were used (35). The SF-36 summary scores are described and tested extensively and applied more frequently than the RAND-36 summary scores (31, 35, 36). We chose to calculate SF-36 summary scales based on RAND-36 subscales.
Results partly depend on moment of assessment and choice of instrument
The attentive reader of this thesis will possibly have noted that different chapters sometimes give varying results. These differences are not mistakes, but instead show the problems associated with assessing HRQOL in patients with DMT1.
As time goes by, the severity of complications will increase and will lead to symptoms and problems which will have an impact on the patient's functional capacity from day to day. However, something as a myocardial infarction or a Transient Ischaemic Attack (TIA) a week before an assessment of HRQOL will certainly have a negative influence on the HRQOL scores. When no symptoms or problems remain after the acute phase of the incident, this does not necessarily lead to a decreased HRQOL several years later. Furthermore, microvascular complications at an early stage can be controlled of even reversed by the implementation of intensive treatment policies (7, 12).
The results of each multivariate regression concern a changing number and different selection of patients, since inclusion in this analysis is only possible with a complete data set. Finally, using a different HRQOL instrument can give varying results through the aggregation of information pertaining to quite different questions.

Conclusions

It is feasible, under standard diabetes care, to intensify the insulin regime in a Dutch cohort of patients with DMT1, resulting in a mean HbA1c of 7.6%. Despite this reasonable HbA1c, the number of patients with micro- and macrovascular complications still increased over the six-year period. HRQOL does not decrease with intensive treatment, whereas the consequences of a less strict control of blood glucose are associated with a decrease in HRQOL. However, higher frequencies of SMBG per week are associated with decreased HRQOL scores.
HRQOL in patients with DMT1 is comparable with that of persons from the general population. In the first half-year after diagnosis, patients recover from a decreased HRQOL at diagnosis, and one year after diagnosis their HRQOL is comparable with that of persons from the general population.
Patients with DMT1 have a clinically relevant loss of, predominantly physical, HRQOL over time. They experience a faster decrease in HRQOL over time than persons from the general population. This is likely due to the development of complications. Furthermore, high diastolic blood pressure and the presence of complications specific to diabetes are predictive factors for a faster decrease in HRQOL.

The generic RAND-36 appears to be very sensitive to changes in HRQOL over time in patients with DMT1, and can provide information about diabetes-specific associations with HRQOL. The complementary use of a diabetes-specific measure like the PAID and the HFS can give additional information about the (psychological) status of patients with DMT1, which can be very useful.

Recommendations

Studies with a multifactorial interventionist focus, promoting, for example, physical activity, cessation of smoking and a diet with a reduction in saturated fat, should be of value in achieving lower prevalences of chronic diabetic complications in patients with DMT1.

In daily clinical practice a multifactorial approach, emphasizing factors like smoking habits, physical activity and nutrition, might lower the eventual prevalence of complications in patients with DMT1. Nurses and other caregivers specialized in diabetes could play an important role in the combined and sustained efforts to reach these goals. They should pay attention to these lifestyle factors in an effort to achieve this goal. A lower prevalence of complications will help keep HRQOL as normal as possible and will prevent a decrease in HRQOL in patients with DMT1.

Since higher frequencies of self monitoring blood glucoses are associated with lower HRQOL, attention should be paid to this frequency. Clinicians should strive for a minimal frequency of SMBG, sufficient for reaching adequate metabolic control. New techniques in SMBG may also alleviate this problem.

The RAND-36 can be recommended for the assessment of the HRQOL in patients with DMT1. For clinical studies and cost-effectiveness studies the RAND-36 is also a good choice. Clinicians who suspect a decreased HRQOL in a specific patient, or who wonder why a specific patient's blood glucose levels remain poorly controlled can, besides the RAND-36, also administer the PAID and the HFS to obtain additional insight into the specific problems of such a patient, in order to identify further possibilities to support the individual patient and thus improve control.

References

1. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.
2. Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion. A comprehensive review of insulin pump therapy. Arch Intern Med 2001;161(oct 22):2293-2300.
3. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.
4. DCCT. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75(14):894-903.
5. Ritz ER. Albuminuria and vascular damage - The Vicious Twins. N Engl J Med 2003;348:2349-2352.
6. DCCT. Intensive Diabetes Therapy and Carotid Intima-Media Thickness in Type 1 Diabetes mellitus. N Engl J Med 2003;348:2294-303.
7. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of Microalbuminuria in Type I diabetes. N Engl J Med 2003;348(23):2285-2292.
8. Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline Kinder L, et al. Insulin Resistance-Related Factors, but not Glycemia, Predict Coronary Artery Disease in Type 1 Diabetes. Diabetes Care 2003;26:1374-1379.
9. Sobel B. Coronary Disease in Type I Diabetes. Diabetes Care 2003;26:1629-1630.
10. Koivisto VA, Stevens LK, Mattock M, Ebeling P, Muggeo M, Stephenson J, et al. Cardiovascular disease and its risk factors in IDDM in Europe. EURODIAB IDDM Complications Study Group. Diabetes Care 1996;19(7):689-697.
11. Gaede PH, Vedel P, Larsen N, Jensen G, Parving HH, Pederson OB. Multifactorial Intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348(5):383-459.
12. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes:UKPDS 38. BMJ 1998;317:703-13.
13. U.K. Prospective Diabetes Study Group. Quality of life in Type 2 Diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999;22(7):1125-1136.
14. Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res 2003;12(8):1089-1097.
15. Rose M, Burkert U, Scholler G, Schirop T, Danzer G, Klapp BF. Determinants of the quality of life of patients with diabetes under intensified insulin therapy. Diabetes Care 1998;21(11):1876-85.
16. Rose M, Fliege H, Hildebrandt M, Schirop T, Klapp BF. The network of psychological variables in patients with diabetes and their importance for quality of life and metabolic control. Diabetes Care 2002;25(1):35-42.
17. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type I diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002;325:746-9.
18. Wikblad K, Leksell J, Wibell L. Health-related quality of life in relation to metabolic control and late complications in patients with insulin dependent diabetes mellitus. Qual Life Res 1996;5(1):123-30.

19. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ. A randomized trial of continuous subcutaneous insulin infusion and intensive therapy in type I diabetes for patients with long-standing poor glycemic control. Diabetes Care 2002;25(11):2074-80.
20. Hart HE, Redekop WK, Assink JH, Meyboom-de Jong B, Bilo HJG. Health-Related Quality of Life in Patients with Newly Diagnosed Type I Diabetes. Diabetes Care 2003;26(4):1319-1320.
21. Hart HE, Redekop WK, Bilo HJG, Busschbach vJJ, Casparie AF. Quality of life over time in a cohort of patients with type I diabetes mellitus measured with the Euroqol and the SF-36. Pamplona, Spain: EuroQol Group; 2001.
22. Hart HE, Redekop WK, Bilo HJG, Berg M, Meyboom-de Jong B. Change in health related quality of life over time in patients with type I diabetes mellitus. Qual Life Res 2004;In press.
23. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993;118(8):622-9.
24. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27(3 Suppl):S217-32.
25. EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
26. Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems: Health Utility Index. Pharmacoeconomics 1995;7:490-502.
27. Kaplan RM, Ganiats TG, Rosen P, Sieber W, Anderson JP. Development of a self administered Quality of Well-Being scale (QWB-SA). Qual Life Res 1995;4:443.
28. Hays RD, Morales LS. The RAND-36 measure of health related quality of life. Ann Med 2001;33:350-357.
29. Irvine A, Cox D, Gonder-Frederick L. The fear of hypoglycaemia scale (HFS). In: Bradley C, editor. Handbook of Psychology of Diabetes: A guide to psychological measurement in diabetes research and practice. Chur, Switserland: Hardwood Academic Publishers; 1994. p. 133-155.
30. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, et al. Assessment of diabetes-related distress. Diabetes Care 1995;18(6):754-60.
31. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. Health Econ 1993;2:217-227.
32. Moorer P, Suurmeijer T, Foets M, Molenaar I. Psychometric properties of the RAND-36 among three chronic diseases (multiple sclerosis, rheumatic diseases and COPD) in the Netherlands. Qual Life Res 2001;10:637-645.
33. Zee vdKI, Sanderman R, Heyink J, Haes dH. The psychometric qualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-122.
34. Zee vdKI, Sanderman R, Heyink J. A comparison of two multidimensional measures of health status: the Nottingham Health Profile and the RAND 36-Item Health Survey 1.0. Qual Life Res 1996;5(1):165-74.
35. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33(4 Suppl):AS264-79.
36. Ware JE, Kosinki M. Interpreting SF-36 summary health measures: A response. Qual Life Res 2001;10:405-413.

Chapter 10

Summary

Chapter 1 describes the aims of this study and the model used in this thesis.
The main aim of this thesis was to investigate the health related quality of life (HRQOL) in patients with diabetes mellitus type I (DMT1). A secondary aim was to investigate the possibility of providing recommendations for the assessment of HRQOL in patients with DMT1.
To achieve these aims a Dutch cohort of patients with DMT1 is followed for six years (1995-2001) and several socio-demographic and diabetes-specific characteristics are recorded whilst assessing HRQOL in this cohort yearly.

In chapter 2 the longterm clinical follow-up of the cohort is described. A total of 234 patients with DMT1 could be followed for the total study period of six years (1995-2001) all treated at the outpatient department of the Isala Clinics, location Weezenlanden, in Zwolle, The Netherlands. During the study period therapy was intensified. The percentage of patients using an internal or external insulin pump increased from 26.9 % in 1995 to 43.6 % in 2001. The mean HbA1c decreased from 8.1 to 7.6%. The body mass index increased and the percentage of patients reporting hypoglycaemic events tended to increase, probably both as a consequence of the more intensive treatment. The frequency of self-monitoring blood-glucose levels increased as well. Despite the intensified treatment, the percentage of patients with microvascular and macrovascular complications increased during the study period.

Chapter 3 describes the HRQOL of patients with DMT1 in comparison with a sample of the general population. HRQOL was assessed using two generic instruments, the RAND-36, consisting of eight subscales and two summary scales (physical and mental), and the EuroQol, consisting of the utility (EQ-5D) and a Visual Analogue Scale (EQ-VAS). Most of the RAND-36 subscales were comparable between the cohort of patients with DMT1 and the general population sample. In the cohort, the EQ-5D was comparable and the EQ-VAS was lower than those of subjects of comparable age from a UK general population sample.
Multivariate regression analysis for the RAND-36 and the EQ showed that the presence of macrovascular complications had the most pronounced negative association with HRQOL in patients with DMT1. The presence of comorbidity and hyperglycaemic complaints and a higher frequency of self-monitoring blood-glucose per week also had a negative association with HRQOL. Whereas HRQOL did not decrease with a more intensive treatment, the consequences of a less strict blood glucose control were associated with a decrease in HRQOL.

In chapter 4 the follow-up of fifteen patients during the first year following their diagnosis of DMT1 is described. In the first six months after diagnosis mean HbA1c decreased from 14.3% to 5.9% ($p<0.001$). The percentage of patients with hyperglycaemic complaints also decreased, from 93% to 53% ($p=0.014$). Body mass index increased significantly during the first six months from 22.2 to 23.9 kg/m^2 ($p=0.001$). All the subscales of the RAND-36, both the summary scores and the EQ-scores, showed an increase during the first six months after diagnosis.
One year after diagnosis, HRQOL of the study population was comparable with that of a sample drawn from the general population.

Chapter 5 describes the changes in HRQOL over time in the cohort. The patients reported a statistically significant decrease per year, for six of the eight RAND-36 subscales and for the PCS. The EQ-5D and the EQ-VAS showed a statistically significant decrease per year as well. Changes over time in the RAND subcale scores could be seen as clinically relevant too, after two to four years time. The EQ-5D did not show a clinically relevant decline in HRQOL over these six years, whereas the EQ-VAS showed this only after six years. The decline in HRQOL was steeper than in a general population sample. The steeper decline in diabetes patients might be due to the development of diabetic complications.

In Chapter 6 a multilevel model, developed to identify factors predicting the degree of change in HRQOL over time, is described.
Higher diastolic blood pressures in 1995 and the presence of diabetic complications in 1995 were predictive for a faster decline in HRQOL.
The progression of complications already present in 1995 will give symptoms to the patients, will impair their functioning in daily life and will thus negatively influence their HRQOL.

Chapter 7 describes the use of utilities, derived from generic instruments, in patients with DMT1. The SF-6D, derived from 11 items of the SF-36, and the EQ-5D, based on the 5 EQ items, both measured changes over time in this group of patients. The SF-6D Quality Adjusted Life Years (QALYs) were significantly lower than the EQ-5D QALYs possibly by the fact that the SF-6D is based on more items, allowing for a more detailed assessment of HRQOL. Furthermore, a large percentage of patients (51.5 up to 59.0%) reported the best possible EQ-5D health: a ceiling effect.
The three most pronounced negative associations with HRQOL were the presence of hyperglycaemic complaints, macrovascular complications and comorbidity.
Both utilities offer possibilities for cost-effectiveness studies in patients with DMT1.

Chapter 8 describes the study in which we assessed HRQOL in patients with DMT1 using two different generic instruments and two different diabetes-specific instruments, to compare the two types of instruments. The RAND-36 appeared to be responsive to changes in HRQOL over three years. The EQ was not effective at measuring changes over such a time period. Both the RAND-36 and the EQ assessed associations between diabetes-specific variables and HRQOL. The generic and diabetes-specific instruments used in this study, only partially identified the same patients with the lowest HRQOL scores, because the instruments measured different aspects of HRQOL. When a clinician wishes to identify and select patients with a decreased HRQOL, instrument choice will determine patient identification. A complementary use of both types of instruments seems to be warranted.
In conclusion, we can recommend the RAND-36 for assessing HRQOL in patients with DMT1. The complementary use of a diabetes-specific measure will give additional information, particularly about the psychological status of patients with DMT1.

Chapter 9 presents the major findings of this study in the form of a general discussion. Conclusions and recommendadtions made on the basis of this thesis are:

The cohort

- Therapy was intensified during the six-year study period
- Under standard diabetes care it was possible to reach a mean HbA1c level of 7.6%
- Despite the intensified therapy the percentage of patients with microvascular and macrovascular complications increased over time.

Recommendation

Studies in patients with DMT1 focusing, next to the striving for a bloodglucose level close to normal, on lifestyle factors such as smoking cessation, stimulation of physical exercise, a diet with a reduction in saturated fat, might offer possibilities for further delay and even prevention of onset and progression of complications in patients with DMT1.

Health related quality of life

- Most aspects of HRQOL in patients with DMT1 are comparable with HRQOL of subjects of comparable age in the general population
- A higher frequency of self-monitoring of blood glucose, hyperglycaemic complaints, and diabetic complications are associated negatively with HRQOL
- HRQOL in newly diagnosed patients with DMT1 improves within the first six months after diagnosis. One year after diagnosis HRQOL is comparable with that of persons from the general population
- Patients with DMT1 can experience a clinically relevant loss of predominantly physical HRQOL within several years
- Patients with DMT1 have a faster decrease in HRQOL over time than comparably aged persons from the general population, probably due to the development of complications related to diabetes
- When symptoms of the disease are present, these will negatively influence daily functioning, and will in this way negatively influence HRQOL
- Higher diastolic blood pressure and the presence of diabetic complications are predictive for the degree of decrease in HRQOL over time.

Recommendation:

In consideration of the preservation of HRQOL, our results encourage intensive therapy to delay the onset and progression of diabetic complications.

The assessment of HRQOL in patients with DMT1

- The generic RAND-36 and EuroQol can assess changes in HRQOL over time in patients with DMT1
- The generic RAND-36 and EuroQol can assess associations between diabetes-specific factors and HRQOL in patients with DMT1

- We prefer the RAND-36 to the EuroQol in the assessment of HRQOL in patients with DMT1, since the more detailed description of the different physical, psychological and social aspects of patient's HRQOL, lead to a good differentiation at various HRQOL levels
- The RAND-36 and the EuroQol only partly identify the same patients as the PAID and the HFS. These diabetes-specific instruments can give, in relation to the generic RAND-36 and EQ, additional information about patients with DMT1
- The utility of the RAND-36, the SF-6D, offers possibilities for cost-effectiveness studies in patients with DMT1. The utility of the EuroQol, the EQ-5D, showed a large ceiling effect and makes it less suitable than the SF-6D.

Recommendation:
The generic RAND-36 is a suitable choice for the assessment of HRQOL in patients with DMT1. The assessment of HRQOL (generic and diabetes-specific) might offer new possibilities in the support of patients with DMT1 and in improving glycaemic control in modern diabetes care.

Chapter 11

Samenvatting

Hoofdstuk 1 beschrijft de doelstellingen van dit onderzoek en het model dat is gebruikt. De hoofddoelstelling van dit promotieonderzoek was het onderzoeken van de gezondheidsgerelateerde kwaliteit van leven (HRQOL) van patiënten met diabetes mellitus type I (DMT1). Daarnaast is onderzocht of het mogelijk was aanbevelingen te doen voor het meten van HRQOL van patiënten met DMT1. Om deze doelstellingen te bereiken is zes jaar lang (1995-2001) een Nederlands cohort van patiënten met DMT1 gevolgd. Naast het jaarlijks meten van de HRQOL werden diverse socio-demografische en diabetesspecifieke variabelen geregistreerd.

In hoofdstuk 2 wordt de lange termijn follow-up van het cohort beschreven. In totaal konden 234 patiënten met DMT1, van de polikliniek van de Isala Klinieken, lokatie Weezenlanden, te Zwolle (Nederland) gedurende de totale onderzoeksperiode van 6 jaar (1995-2001) worden vervolgd. Gedurende de onderzoeksperiode werd de therapie geïntensiveerd. Het percentage patiënten dat een interne of externe insuline pomp gebruikte nam toe van 26.9% in 1995 tot 43.6% in 2001. Het gemiddelde HbA1c nam af van 8.1 tot 7.6%. De bodymass index nam toe en het percentage patiënten dat hypoglycaemiëen rapporteerde liet een lichte stijging zien, beide waarschijnlijk het gevolg van de meer intensieve behandeling. De frequentie van het aantal keren zelfcontrole van het bloedglucose (per week) nam ook toe. Ondanks de toegenomen intensiviteit van de behandeling en het verbeterde HbA1c, nam het percentage patiënten met micro- en macrovasculaire complicaties toe tijdens de onderzoeksperiode.

Hoofdstuk 3 beschrijft de HRQOL van patiënten met DMT1 in vergelijking met een steekproef uit de algemene populatie. De HRQOL werd vastgelegd met twee generieke meetinstrumenten: de RAND-36, die uit acht subschalen en twee somscores (fysiek en mentaal) bestaat, en de EuroQol, die uit een utiliteit (EQ-5D) en een Visuele Analoge Schaal (EQ-VAS) bestaat. De meeste RAND-36 subschalen waren vergelijkbaar tussen het cohort en de steekproef uit de algemene populatie. In het cohort was de EQ-5D vergelijkbaar, en de EQ-VAS lager dan van mensen van vergelijkbare leeftijd uit een steekproef van de Engelse bevolking.
Multivariate regressie analyses voor de RAND-36 en de EQ lieten zien dat de aanwezigheid van macrovasculaire complicaties het meest uitgesproken negatieve verband met de HRQOL van patiënten met DMT1 had. De aanwezigheid van comorbiditeit, hyperglycaemische klachten, en een hogere frequentie van de zelfcontrole van het bloedglucose (per week) had ook een negatief verband met de HRQOL.
De HRQOL nam niet af bij een meer intensieve behandeling, maar juist de consequenties van een minder strikte bloedglucose controle lieten een verband zien met een afname van de HRQOL.

In hoofdstuk 4 wordt de follow-up van 15 patiënten in het eerste jaar direct na hun diagnose DMT1 beschreven. In de eerste zes maanden na de diagnose nam het gemiddelde HbA1c af van 14.3% tot 5.9% ($p<0.001$). Het percentage patiënten met hyperglycemische klachten nam ook af, van 93% tot 53% ($p=0.014$). De bodymass index steeg in de eerste zes maanden, van 22.2 tot 23.9 kg/m^2

(p=0.001). Alle subschalen van de RAND-36, beide somscores en de EQ scores, lieten in de eerste zes maanden na diagnose een verbetering zien. Eén jaar na diagnose, was de HRQOL van de studiepopulatie vergelijkbaar met die van een steekproef uit de algemene bevolking.

Hoofdstuk 5 beschrijft de veranderingen in HRQOL in verloop van de tijd. De patiënten rapporteerden een statistisch significante daling per jaar voor zes van de acht RAND-36 subschalen en de fysieke somscore. Ook de EQ-5D en de EQ-VAS lieten een statistisch significante daling per jaar zien. De veranderingen, vastgelegd met de RAND subschalen, konden ook, na twee tot vier jaar, als klinisch relevant worden beschouwd. De EQ-5D liet in deze zes jaar geen klinisch relevante afname zien, terwijl de EQ-VAS dit pas na zes jaar liet zien. De afname in HRQOL was steiler dan in een steekproef van de algemene bevolking. De steilere afname in patiënten met DMT1 kan waarschijnlijk worden toegeschreven aan de ontwikkeling van complicaties ten gevolge van diabetes.

In hoofdstuk 6 wordt een multilevel model beschreven, dat ontwikkeld werd om factoren te identificeren die de mate van verandering van de HRQOL in de tijd kunnen voorspellen. Een hogere diastolische bloeddruk in 1995 en de aanwezigheid van diabetische complicaties in 1995 waren voorspellend voor een snellere afname van HRQOL. De progressie van de complicaties, die in 1995 al aanwezig waren, zal symptomen veroorzaken bij de patiënten. Tevens zal hun dagelijks functioneren belemmerd worden. Dit alles zal de HRQOL negatief beïnvloeden.

Hoofdstuk 7 beschrijft het gebruik van utiliteiten, afgeleid van generieke meetinstrumenten, bij patiënten met DMT1. De SF-6D, afgeleid van 11 items van de SF-36, en de EQ-5D, gebaseerd op de 5 EQ items, maten allebei veranderingen in de tijd in deze groep patiënten. De SF-6D kwaliteitsgecorrigeerde levensjaren (QALYs) waren significant lager dan de EQ-5D QALYs. Dit zou verklaard kunnen worden door het feit dat de SF-6D op meer items is gebaseerd, wat een meer gedetailleerde vastlegging van de HRQOL mogelijk maakt. Voorts rapporteerde een groot percentage van de patiënten de best mogelijke EQ-5D gezondheidstoestand: een 'plafond effect'. De drie meest uitgesproken negatieve verbanden met HRQOL waren de aanwezigheid van hyperglycemische klachten, macrovasculaire complicaties en comorbiditeit. Beide utiliteiten bieden mogelijkheden voor kosteneffectiviteitonderzoek bij patiënten met DMT1.

Hoofdstuk 8 beschrijft twee verschillende generieke en twee verschillende diabetesspecifieke instrumenten, die werden gebruikt om de HRQOL te bepalen en om de instrumenten met elkaar te vergelijken. De RAND-36 was gevoelig voor veranderingen in HRQOL in drie jaar tijd. The EQ was niet geschikt om veranderingen te meten in dit tijdsbestek. Zowel de RAND-36 als de EQ legden verbanden vast tussen diabetesspecifieke variabelen en HRQOL. De generieke en diabetesspecifieke instrumenten, die in dit onderzoek werden gebruikt, identificeerden slechts voor een deel dezelfde patiënten met de laagste HRQOL, omdat de instrumenten verschillende aspecten van HRQOL vastlegden. Wanneer

een arts patiënten wil identificeren en selecteren met een afgenomen HRQOL, zal de keuze van het instrument bepalen welke patiënten hij/ zij zal identificeren. Een complementair gebruik van de verschillende instrumenten lijkt aanbevolen. Concluderend, de RAND-36 kan worden aanbevolen voor het vaststellen van de HRQOL van patiënten met DMT1. Het complementaire gebruik van een diabetesspecifiek instrument zal aanvullende informatie verschaffen, in het bijzonder over de psychologische status van patiënten met DMT1.

Hoofdstuk 9 presenteert de belangrijkste bevindingen uit dit onderzoek in de vorm van een algemene discussie. Onderstaande conclusies en aanbevelingen zijn gemaakt op basis van dit proefschrift:

Het cohort:

- Gedurende de zes jaar durende onderzoeksperiode werd de therapie geïntensiveerd
- Het was mogelijk, met standaard diabeteszorg, een gemiddeld HbA1c niveau van 7.6% te bereiken
- Ondanks de geïntensiveerde therapie steeg het percentage patiënten met micro- en macrovasculaire complicaties in de loop van de tijd

Aanbeveling:
Onderzoek bij patiënten met DMT1 dat zich, naast het streven naar een zo normaal mogelijk bloedglucose, richt op leefstijlfactoren, zoals het staken van roken, het stimuleren van lichamelijke inspanning, en een dieet met een beperkt gehalte aan verzadigde vetten, kan inzicht verschaffen in de mogelijkheden om het ontstaan en de progressie van complicaties bij patiënten met DMT1 te vertragen dan wel te voorkomen.

Gezondheid gerelateerde kwaliteit van leven:

- De meeste aspecten van HRQOL van patiënten met DMT1 zijn vergelijkbaar met personen, van vergelijkbare leeftijd, uit de algemene populatie
- Een hogere frequentie van zelfcontrole van bloedglucose, hyperglycemische klachten, en diabetische complicaties zijn negatief geassocieerd met HRQOL
- De HRQOL van patiënten waarbij net DMT1 is gediagnosticeerd verbetert in de eerste zes maanden na de diagnosestelling. Een jaar na de diagnosestelling is de HRQOL van de onderzoekspopulatie vergelijkbaar met die van een steekproef uit de algemene populatie
- Patiënten met DMT1 kunnen, binnen enkele jaren, een klinisch relevant verlies van, voornamelijk fysieke, HRQOL ervaren
- Patiënten met DMT1 hebben een snellere afname van HRQOL in de tijd, dan personen van vergelijkbare leeftijd uit de algemene populatie, waarschijnlijk ten gevolge van de ontwikkeling van complicaties die gerelateerd zijn aan DMT1
- Wanneer symptomen van de ziekte aanwezig zijn, zullen deze het dagelijks functioneren negatief beïnvloeden, en zullen zodoende de HRQOL negatief beïnvloeden.

- Een hogere diastolische bloeddruk en de aanwezigheid van diabetische complicaties zijn voorspellend voor de mate van afname van HRQOL in de tijd.

Aanbeveling:
Het is aan te bevelen, met het oog op het behoud van de HRQOL, patiënten met DMT1 intensief te behandelen.

Het meten van HRQOL van patiënten met DMT1:
- De generieke RAND-36 en EuroQol kunnen veranderingen van HRQOL in de tijd van patiënten met DMT1 vastleggen
- De generieke RAND-36 en EuroQol kunnen verbanden tussen diabetesspecifieke factoren en HRQOL van patiënten met DMT1 vastleggen
- Voor het meten van HRQOL van patiënten met DMT1, wordt de voorkeur aan de RAND-36 boven de EuroQol gegeven, omdat de meer gedetailleerde beschrijving van de verschillende fysieke, psychologische en sociale aspecten van de HRQOL van deze patiënten, leidt tot een goede differentiatie op verschillende HRQOL niveaus
- De RAND-36 en de EuroQol identificeren slechts ten dele dezelfde patenten als de PAID en de HFS. Deze diabetesspecifieke instrumenten kunnen, in relatie tot de generieke RAND-36 en EuroQol, aanvullende informatie geven over patiënten met DMT1
- De utiliteit van de RAND-36, de SF-6D, biedt mogelijkheden voor kosteneffectiviteitonderzoek bij patiënten met DMT1. De utiliteit van de EuroQol, de EQ-5D, liet een groot 'plafondeffect' zien, waardoor het minder geschikt is dan de SF-6D

Aanbeveling:
Voor het bepalen van de HRQOL bij patiënten met DMT1 is de generieke RAND-36 een geschikte keuze. Het vastleggen van HRQOL (generiek en diabetesspecifiek) kan nieuwe mogelijkheden bieden in de ondersteuning van patiënten met DMT1 en in het verbeteren van de bloedglucose controle in moderne diabetes zorg.

Dankwoord

Het proefschrift is klaar! Begin 1999 werd ik door Els Grijseels en Marc Bruijnzeels gebeld dat er bij het Instituut Beleid en Management Gezondheidszorg een vacature was voor een promotieonderzoek onder leiding van Prof. Dr. A. Casparie, die overigens kort daarna het instituut ging verlaten. Het betrof een 'package deal' met een onderwijsaanstelling voor de stage 'Het Primaire Proces'. Na rijp beraad besloot ik de stap te wagen.
Jan Assink had al veel klinische gegevens verzameld in de Isala Klinieken in Zwolle (lokatie Weezenlanden) bij een grote groep patiënten met diabetes mellitus type I, mogelijk gemaakt door het Praeventiefonds. Ik stort mij op een nieuw onderdeel van het onderzoek; de kwaliteit van leven van deze groep patiënten. Allereerst wil ik de 250 patiënten bedanken die zich zeven jaar lang de moeite hebben getroost vele lijsten in te vullen over hun kwaliteit van leven. Zonder hun trouwe inzet was dit onderzoek niet mogelijk geweest. Ook dank ik de diabetesverpleegkundigen en het secretariaat diabeteszorg. Zonder jullie waren al de onderzoeksgegevens nooit verzameld!
Het klinisch chemisch onderzoek is verricht onder leiding van Bert Dikkeschei. Jaarlijks werd bovendien door alle patiënten de podotherapeut en de oogarts bezocht voor de beoordeling van een eventuele neuropathie en/ of retinopathie. Graag wil ik Bert Dikkeschei, de podotherapeuten en de oogartsen bedanken voor het registreren van deze microvasculaire complicaties, een belangrijk onderdeel van mijn onderzoek. Alle overige medewerkers van de polikliniek Diabeteszorg en Inwendige Geneeskunde ben ik dank verschuldigd voor hun inzet om alles draaiende te houden. Deze 'carrousel' staat onder de bezielende leiding van de internisten Evert van Ballegooie en Henk Bilo.
Henk, jij hebt als copromotor van het begin tot het eind een belangrijke rol gespeeld! Alles is mogelijk geweest, een bezoekje in de kelders om de alleroudste data te checken, of een duik in een diepe voorraadkast om alle statussen nog eens onder de loep te nemen. Greetje Kroes maakte het mogelijk om jou rustig te kunnen spreken, ondanks je drukke bezigheden. Alle onderzoeksgegevens en manuscripten werden van opbouwend commentaar voorzien. Ook is het mede dankzij jou mogelijk geweest dat mijn aanstelling bij het Instituut Beleid en Management Gezondheidszorg tot tweemaal toe is verlengd, door gelden beschikbaar te stellen uit de Stichting Medisch Research Fonds Zwolle. Hierdoor heb ik het onderzoek af kunnen ronden in de vorm van een proefschrift. Heel veel dank voor al je ondersteuning.
Compleet en correct data verzamelen is één, het juist invoeren is een ander verhaal. Heidi Veltmaat heeft enorm veel data ingevoerd, in een razend tempo, én

met een perfecte kwaliteit. Dankzij de logistieke ondersteuning van haar zus Lielith is de klus in hoog tempo geklaard. Heidi, heel veel dank!
Zonder promotor geen promotie! Begin 2001 heeft Prof.dr. B. Meyboom-de Jong deze taak op zich genomen. Betty, wat heb ik geboft dat jij op mijn weg kwam! Zonder jouw geweldige inzet zou dit proefschrift er nooit gekomen zijn. Ik vond het heel prettig om met jou samen te werken; altijd doortastend, enthousiast en positief. Razendsnel kwam jouw onmisbare reactie op mijn werk. Zo is de vaart er in gebleven. Ik wens iedereen zo'n promotor toe! Heel erg veel dank voor alles wat je voor me gedaan hebt.
Ken Redekop was mij toebedacht om me 'wat methodologisch en statistisch' te helpen. Voor Ken een niet geringe klus: een huisarts die komt aanwaaien en van toeten nog blazen weet. Ken, wat heb jij een eindeloos geduld met me gehad. Ik waardeer het zeer dat je door bent gegaan, ook nadat er geen tijd meer is vrijgemaakt op mij te helpen. Terwijl het voor jou soms efficiënter was geweest de analyses zelf te doen, liet je het altijd aan mij over. Vooral voor dit laatste ben ik je, achteraf dan, dankbaar.
Kor Grit is gedurende de grootste periode van mijn aanstelling mijn kamergenoot geweest. Kor, jij hebt dan ook van dicht bij het wel en wee van mijn onderzoekstijd meegemaakt. Dat was waarschijnlijk niet altijd een voorrecht. Dank je voor de gezellige tijd.
Het is voor mij van belang geweest ook een Rotterdamse promotor te hebben. Prof. dr. M. Berg heeft deze taak op zich genomen. Beste Marc, het valt niet mee om ergens te starten en dan een promovendus in je schoenen geschoven te krijgen, waarvoor ten eerste geen gelden beschikbaar zijn gesteld, en dan ook nog met een onderwerp dat inhoudelijk niet in één van de onderzoekslijnen van je sectie past. Het is bewonderenswaardig dat ik nooit enige wanklank hierover heb gehoord! Je intervenieerde op de kritieke momenten, zodat het voor mij mogelijk is geworden het onderzoek voort te zetten en het proefschrift te voltooien. Heel veel dank voor je betrokkenheid.
Anne Starreveld heeft een aantal hoofdstukken voorzien van commentaar op de engelse taal, een niet overbodige luxe. Dank je wel.
Het is een voorrecht naast wetenschappelijk onderzoek in de praktijk te kunnen werken. Ruim twaalf jaar heb ik met veel plezier als huisarts in Schiedam gewerkt. In het bijzonder wil ik mijn collega Peter van Dijk bedanken, altijd loyaal en met een portie droge humor.
Mijn 'begeleidingscommissie' in Amersfoort. Lieve papa en mama, jullie staan nu al 45 jaar onvoorwaardelijk achter me, een onontbeerlijke steun. Papa, jij kwam vanaf de eerste fase van het onderzoek met recente artikelen aan, en bleef dit volhouden tot de verdediging. Uiteindelijk heb je het totale manuscript gescreend en eigenlijk had je dolgraag her en der inhoudelijk nog wat willen toevoegen.
Al dat werken kan natuurlijk alleen als het thuis goed loopt. Dat kon vooral dankzij Ali Mol, onze oppas. Ali, het is fantastisch dat we áltijd op je konden rekenen. Nooit was iets je te veel, altijd was je er, een rustpunt voor de kinderen, en daardoor ook voor mij. Dat was wel afkicken toen we vorig jaar naar Zeist verhuisden.

Yvonne Rijnveld was vele jaren huisgenoot in Utrecht en woonde daarna nog eens tien jaar bij me op de hoek. Yvon, ik bedank je voor al je gezelligheid en vertrouwdheid.
Mijn paranimfen Ienske Vecht–Hart en Sibylla Nooijen, trouwe vriendinnen vanaf 1961 en 1981! Ik ben blij dat jullie mijn paranimfen willen zijn, en daarbij dat jullie beiden arts zijn, zodat ik tijdens de verdediging met gerust hart lastige vragen aan jullie kan doorspelen!
Lieve Lodi, door jouw vertrouwen in mijn kunnen, heb je een grote bijdrage geleverd aan dit boek. Door het verzorgen van de lay-out, waarachtig geen geringe klus, is dit proefschrift ook een beetje van jou geworden! Michiel en Céline, volgens mij vonden jullie het allemaal wel best wat ik deed. Hoewel jij, Michiel, twee jaar terug verbaasd en enigszins hoopvol aan mij vroeg 'zijn er dan ook moeders die niet werken?' De mooie omslag van dit boek is van jou! En Céline, jij vroeg mij een half jaar terug, hoeveel bladzijden m'n boek nu heeft. Toen ik daar antwoord op gaf, zei je opgelucht 'oh, dan zal het wel bijna klaar zijn'. Nu, ik kan jullie gerust stellen, het is nu echt helemaal klaar!

Currucilum vitae

Bertien Hart was born on June 10, 1959 in Utrecht. She passed her secondary school exam (Gymnasium ß) in 1977 at the Johan van Oldenbarnevelt Gymnasium in Amersfoort.
For three years, fate denied her admission to medical school, as this is determined by a lottery system in The Netherlands. From 1977 to 1978 she studied Biology at the University of Utrecht. From 1978 to 1980 she studied physical therapy at the Paramedical Academy which is also located in Utrecht. In 1980, she was finally granted a position in medical school at the University of Utrecht, where she obtained her Medical Degree in 1987. In 1988 she worked for one year as a clinical research scientist for the pharmaceutical industry. In 1989 she entered the two-year vocational training program for general practitioners at the Erasmus University in Rotterdam. From 1991 to 2003 she worked as a general practitioner in Schiedam. From 1991 to 2003 she combined this work with a part-time appointment at the department of General Practice in Rotterdam. Here she developed a national course in cardiology for the two-year vocational training program for general practitioners and participated in several research projects till 1999.
In March 1999, as a researcher at the Department of Health Policy and Management, Erasmus Medical Centre Rotterdam, she started the study that resulted in this thesis.
She is married to Lodi Hennink. They have two children, Michiel and Céline.

List of abbrevations

CVA	Cerebrovascular accident
DMT1	Diabetes Mellitus Type I
EQ	EuroQol
EQ-5D	EuroQol 5 Dimensions
EQ-VAS	EuroQol Visual Analogue Scale
FHS	Fear of Hypoglycaemia Scale
HbA1c	Glycosylated Haemoglobin A1c
HRQOL	Health Related Quality of Life
MCS	Mental Component Summary
PAID	Problem Areas in Diabetes Survey
PCS	Physical Component Summary
QALY	Quality Adjusted Life Year
RAND-36	RAND-36 item Health Survey
SMBG	Self-monitoring blood glucose
SD	Standard Deviation
SF-36	Medical Outcomes Study (MOS) 36-item Short-Form Health Survey
TIA	Transient Ischaemic Attack