TILBURG ◆ UNIVERSITY

Tilburg University

Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes

de Vries, J.H.; Eskes, S.A.; Snoek, F.J.; Pouwer, F.; van Ballegooie, E.; Spijker, A.J.; Kostense, P.J.; Seubert, M.; Heine, R.J.

Published in:
Diabetic Medicine: Journal of Diabetes UK

Publication date:
2002

Link to publication in Tilburg University Research Portal

Citation for published version (APA):
de Vries, J. H., Eskes, S. A., Snoek, F. J., Pouwer, F., van Ballegooie, E., Spijker, A. J., Kostense, P. J., Seubert, M., & Heine, R. J. (2002). Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: Favourable effects on glycaemic control and hospital stay. *Diabetic Medicine: Journal of Diabetes UK*, *19*(6), 496-501.

DM

Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: favourable effects on glycaemic control and hospital stay

J. H. DeVries, S. A. Eskes, F. J. Snoek*, F. Pouwer*, E. van Ballegooie†, A. J. Spijker‡, P. J. Kostense§, M. Seubert and R. J. Heine

Abstract

Aims To evaluate the effects of continuous intraperitoneal insulin infusion (CIPII) using implantable pumps on glycaemic control and duration of hospital stay in poorly controlled 'brittle' Dutch diabetes patients, and to assess their current quality of life.

Methods Thirty-three patients were included. Glycaemic control was retrospectively assessed with HbA_{1c} levels acquired before implantation, 1 year later and at long-term follow up of 58 months. Duration of hospital stay the year before and the year following first implantation was extracted from hospital records. Determinants of long-term glycaemic response were sought. Self-report questionnaires were administered at 58 months follow-up only, to assess current psychopathology and quality of life.

Results Mean HbA_{1c} decreased from $10.0 \pm 2.3\%$ to $9.0 \pm 1.8\%$ ($P = 0.039$) 1 year after implantation and stabilized at $9.0 \pm 1.6\%$ ($P = 0.023$) during long-term follow-up. Median number of hospital days in the 20 patients suffering from hospital admission before implantation decreased from 45 the year before implantation to 13 the year after ($P = 0.005$). Patients with a higher baseline HbA_{1c} showed a larger long-term response ($P < 0.001$). Relatively low levels for quality of life were found, as well as a higher than expected number of patients with psychiatric symptoms.

Conclusions CIPII proved effective in complex patients with a history of poor control and hospital admission. Despite a substantial long-term improvement in glycaemic control and diminished hospital stay, normal levels of glycaemic control and quality of life were not attained.

Diabet. Med. 19, 496–501 (2002)

Keywords continuous intraperitoneal insulin infusion, insulin infusion systems, quality of life

Abbreviations CIPII, continuous intraperitoneal insulin infusion; DCCT, Diabetes Control and Complications Trial; SCL-90, Symptom Checklist 90; SF-36, Medical Outcome Study 36-Item Short Form Survey; DQOL, diabetes quality of life measure; PAID, problem areas in diabetes

Correspondence to: Dr J. Hans DeVries, Department of Endocrinology 1 OBU 42, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands. E-mail: hans.devries@vumc.nl

Introduction

Despite its application for almost 20 years, no agreement has been reached on the indications for continuous intraperitoneal

insulin infusion using implantable pumps (CIPII). CIPII is mostly used in France, where the initial research focused on its feasibility and safety aspects. Currently, compliant patients in reasonably good glycaemic control qualify for this form of therapy [1]. The main demonstrable benefit of CIPII has been the low number of severe hypoglycaemic events: at a mean HbA_{1c} level of 6.8%, the number of severe hypoglycaemic episodes was 2.5 per 100 patient years [2]. This compares favourably with the intensively treated group of the Diabetes Control and Complications Trial (DCCT), where this rate was 62 per 100 patient years, at a similar level of glycaemic control [3]. A modest benefit in terms of glycaemic control was reported in the French study of 224 patients, with an HbA_{1c} decrement of 0.5% after 1 year on CIPII treatment. Other studies included patients in fairly good glycaemic control [4–10] or exluded patients who had suffered from recurrent severe hypoglycaemia or significant long-term diabetic complications [11–13].

In contrast, in The Netherlands, CIPII has been used since 1986 as a 'last resort' treatment, i.e. when multiple injection and/or subcutaneous pump therapy has failed. Predominantly, so called 'brittle' patients in very poor glycaemic control and often following long and/or recurrent hospital admissions have received an implant. To date, the efficacy of CIPII using this Dutch approach has not been described. We report here on glycaemic results, length of hospital stay and perceived health-related quality of life in patients treated with CIPII in The Netherlands. Furthermore, we sought potential determinants of glycaemic response to CIPII.

Patients and methods

The protocol was approved by the respective institutional Ethics Committees.

Patients

At the time of inclusion, a total of 41 patients was treated with CIPII in The Netherlands. Thirty-four were treated in one of the three centres caring for more than three patients. These 34 patients were asked to participate by their treating physician. Thirty-three patients (Zwolle $n = 20$, Amsterdam $n = 7$ and Roermond $n = 6$) gave informed consent, one patient refused to participate. Two patients, in whom an implantable pump was explanted, were not included in the investigation. In one patient suffering from Werner's syndrome, characterized by the absence of subcutaneous fat, the pump was explanted because of a pump pocket infection. Another pump was explanted, a few weeks following implantation, on the patient's request because of local complaints and psychological problems.

Biomedical measures

Glycaemic control and hospital stay were assessed retrospectively from hospital records. HbA_{1c} values (ion-exchange high-performance liquid chromatography, reference value 4.3–6.1%) were measured prior to pump implantation (mean

of all values in the year before implantation, median 1 (25–75th%: 1–2) measurement per patient), 1 year after implantation (mean of all values measured from 9 to 15 months after the first implantation, median 2 (25–75th%: 1–2) measurements per patient) and at the time of the investigation (mean of all values measured in the 6 months before completing the questionnaires, after a mean follow-up of 58 months on CIPII, median 1 (25–75th%: 1–2) measurement per patient). In patients who were admitted to the hospital in the year before implantation because of 'brittle' diabetes ($n = 20$), the number of hospital days in the year before implantation was compared with the number of days in the first year following implantation, starting 2 days before implantation. The following diabetic complications were classified on the basis of the patients' medical records: retinopathy (background or proliferative/lasered), clinically manifest polyneuropathy and nephropathy (microalbuminuria, i.e. urinary albumin 30–300 mg/24 h, or proteinuria, i.e. urinary albumin > 300 mg/24 h and/or serum creatinine > 150 µmol/l).

Psychosocial measures

Data on demographic and medical background, on psychological dysfunction and on health-related quality of life were gathered only at the time of the investigation, after a mean of 58 months on CIPII. No baseline measures before starting CIPII were taken. Self-report questionnaires were introduced to the patient by a diabetes nurse specialist and filled out by the patient during an out-patient clinic visit.

The questionnaire on demographic and medical background contained questions covering ethnic background, marriage status, educational level, disablement (i.e. legally only partly capable of work), comorbidity, psychiatric history, and frequency of self-monitoring of blood glucose. Results were compared with means obtained in a large survey of Dutch diabetes patients ($n = 1472$, 51% Type 1 diabetes patients, 49% female) [14].

The Symptom Checklist 90 (SCL-90) is a widely used 90-item questionnaire, that provides a global severity index of psychological dysfunction, comprising eight major subscales: depression, anxiety, phobic anxiety, hostility, somatization, interpersonal sensitivity, insufficiency of thought or behaviour (compulsive–obsessive behaviour) and sleeping problems. The percentage of patients scoring ≥ 80th percentile (i.e. the high or very high range, as defined in the SCL-90 manual, and differentiated to sex) was compared with the expected 20% found in a normal reference population [15]. The global severity index was compared with reference values from a Dutch population-based sample of 907 subjects [16].

The following instruments were used to assess health related quality of life;
- Medical Outcome Study 36-Item Short Form Survey (SF-36) [17]. The generic SF-36 measures eight health concepts: physical functioning, physical role functioning, social functioning, bodily pain, mental health, emotional role functioning, vitality, and general health perceptions. We compared the mean scores with mean scores of two reference groups: patients with complicated diabetes or complicated coronary artery disease ($n = 144$), and patients with both depressive symptoms and complicated medical conditions ($n = 43$) [18].

Table 1 Clinical characteristics of the study population

n	33
Male/female	9/24
Age (years)	42.6 ± 13.3
Type 1 diabetes (*n*; %)	28 (84.8)
Diabetes duration (years)	20.5 ± 8.4
Retinopathy	
Background retinopathy (*n*; %)	19 (57.6)
Proliferative retinopathy (*n*; %)	7 (21.2)
Nephropathy	
Microalbuminuria (*n*; %)	7 (21.2)
Proteinuria (*n*; %)	3 (9.1)
Creatinine > 150 μmol/l	2 (6.1)
Neuropathy	19 (57.6)

Data are presented as means ± SD, *n* or *n* (%).

- The Diabetes Quality of Life Measure (DQOL) has four scales: satisfaction with current mode of therapy, impact of diabetes and treatment on living, social/vocational worry, and diabetes worry [19]. Mean scores were compared with those found in 684 intensively treated Type 1 patients of the DCCT study [20].
- The 20-item Problem Areas In Diabetes (PAID) scale measures diabetes-related distress [21]. Results were compared with scores obtained in a sample (*n* = 739) of Dutch Type 1 diabetes patients [22].

Statistical analysis

HbA_{1c} levels and length of hospital stay were analysed using paired samples *t*-test and the Wilcoxon signed rank test, respectively. Independent samples *t*-test was used to test for differences between mean scores of our patients and reference groups. A difference in long-term glycaemic response (the difference between HbA_{1c} at 58 months of CIPII and baseline) was sought between those with an HbA_{1c} before implantation above or below the group mean, using the Mann–Whitney test. In order to identify characteristics of those patients without any, or on the contrary a large improvement in glycaemic control, we used univariate linear regression analysis to explore the following possible determinants of long-term glycaemic response: sex, age at first implant, type of diabetes, frequency of self monitoring of blood glucose, duration of hospital stay in the year before implantation, presence of a psychiatric history, and the global severity index and depression subscale of the SCL-90. *P*-values < 0.05 were considered statistically significant. Data are presented as means ± SD or median (25%, 75%). Analyses were performed using the SPSS 9.0 [23] and confidence interval analysis [24].

Results

Clinical features, glycaemic control and hospital stay

Clinical characteristics of the 33 patients are shown in Table 1. Before CIPII, all patients had been treated with intensive insulin therapy. Intensification of insulin injection treatment and/or continuous subcutaneous insulin infusion had been attempted in all patients, before a pump was implanted. Mean HbA_{1c} decreased significantly during the first year on CIPII from 10.0 ± 2.3% before to 9.0 ± 1.8% after 1 year, *P* = 0.039. This improvement persisted, with a long-term mean HbA_{1c} at 58 ± 27 months follow-up of 9.0 ± 1.6%, *P* = 0.023 compared with before implantation. In the 20 patients who had hospital admission before implantation, the median duration of hospital stay was significantly reduced from 45 (19 to 114) days in the year before implantation to 13 (9–25) days in the year after (*P* = 0.005), the latter mostly due to the admission for implantation. At the time of the investigation, all patients were treated with a Minimed device (Minimed; Sylmar, CA, USA), although two had begun on an Infusaid device (Norwood, MA, USA).

Demographic and background clinical data

All patients were born in The Netherlands. Twenty-two (66.7%) patients were married or cohabiting with a partner. Twenty-seven patients (81.8%) had high school as their highest completed educational level, six patients (18.2%) completed college or university. These frequencies are similar to those found in a large survey of Dutch diabetes patients: 77.9% and 22.1%, respectively [14]. Disablement existed in 17 (52%) patients. Complete disablement existed in 12 (36%) of these patients. Twenty-six (79%) patients reported one or more comorbid conditions: hypertension (*n* = 11, 33.3%), chronic gastrointestinal disorders (*n* = 11, 33.3%) and chronic fatigue (*n* = 9, 27.3%). Four patients (12%) were currently under treatment of a psychologist or psychiatrist. Patients reported a mean frequency of home blood glucose measurements during CIPII of four times a day.

Psychological dysfuntion (see Table 2)

On the SCL-90, the percentage of patients scoring ≥ 80th percentile of the scores in the normal reference population was 51.6% on the subscale somatization, 48.3% on the subscale insufficiency of thought or behaviour, and 42.4% on the depression subscale. On the other subscales, the percentage was around the expected 20% (data not shown).

Health-related quality of life measures (see Table 2 and Fig. 1)

Generic health-related quality of life (Fig. 1)
Mean scores on the subscales of the SF-36 Health Survey for physical functioning and mental health were similar to the reference values for patients with serious complicated diabetes or coronary artery disease (57.1 ± 30.5 vs. 57.4 ± 28.1, *P* = NS and 71.4 ± 22.0 vs. 77.6 ± 15.8, *P* = NS, respectively). Mean scores were in the psychiatric range for the subscales general health, pain and social functioning (40.1 ± 22.6 vs. 39.9 ± 15.1, *P* = NS; 50.6 ± 30.0 vs. 50.2 ± 23.1, *P* = NS; and 59.9 ± 32.6 vs. 65.1 ± 22.6, *P* = NS, respectively).

Table 2 Mean scores on the questionnaires in the study population and various reference groups

Questionnaire (range) Subscale	Dutch CIPII patients ($n = 33$)	Reference groups
SCL-90 (0–450, highest psychological dysfunction)		Normal population
Global Severity Index	140.6 ± 41.1	125.0 ± 30.3*
DQOL (0–100, highest quality of life)		DCCT cohort
Impact of diabetes	61.8 ± 13.4	75 ± 8*
Satisfaction	64.5 ± 17.0	74 ± 3*
Social worry	68.2 ± 25.4	78 ± 16*
Diabetes worry	70.3 ± 17.6	81 ± 13*
		Dutch Type 1 patients
PAID (0–100, highest distress)	28.6 ± 19.0	24.6 ± 18.7

Data are presented as means ± SD.
*P-value ≤ 0.05.
CIPII, Continuous intraperitoneal insulin infusion; SCL-90, Symptom Check List-90; DQOL, diabetes quality of life measure; DCCT, Diabetes Control and Complications Trial; PAID, problem areas in diabetes.
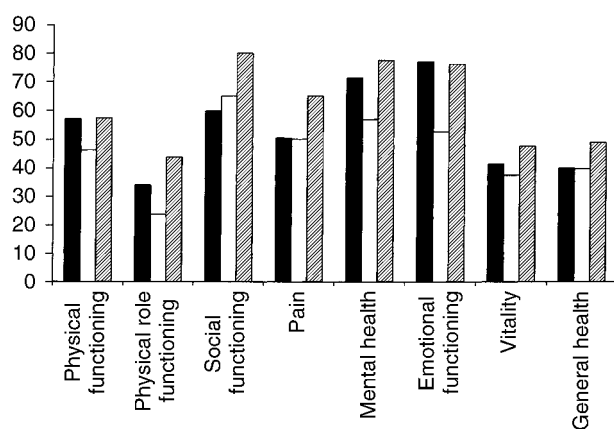
Figure 1 SF-36 scores of our study population (■) compared with two SF-36 reference groups: a group of 43 depressive patients with a serious chronic medical condition (□) and a group of 144 non-depressive patients with complicated diabetes or coronary artery disease (hatched).

Diabetes-specific health-related quality of life

For all four subscales of the Diabetes Quality of Life Measurement (DQOL), the patients reported a poor quality of life compared with the patients in the DCCT cohort. As measured using the Problem Areas In Diabetes (PAID) scale, our patients did not report significantly different levels of diabetes-related emotional distress, compared with those found earlier in Dutch diabetes patients.

Determinants of long-term glycaemic response

The long-term glycaemic response in those with an HbA_{1c} before implantation above the group mean (> 10.0%) was larger than in those below the group mean (< 10.0%): median 2.30% (0.8%, 4.70%) vs. 0.2% (−1.0%, 0.71%), respectively ($P < 0.001$). At univariate linear regression analyses, to identify characteristics of patients who reacted very well or not at all to CIPII, sex, age at first implant, type of diabetes, frequency of self monitoring of blood glucose, duration of hospital stay the year before implantation, presence of a psychiatric history, and the global severity index and depression subscale of the SCL-90 were not found to be significant determinants of long-term glycaemic response (data not shown).

Discussion

We found a substantial improvement in glycaemic control (1% reduction of HbA_{1c}) following implantation of an insulin pump in 'brittle' patients in poor control. Although the mean HbA_{1c} level on CIPII remained unsatisfactorily high at 9.0%, this difference, sustained over 5 years, will have reduced long-term diabetic complication rates. Furthermore, a large decline in duration of hospital stay was seen following the start of CIPII.

Also, after almost 5 years on CIPII, we found relatively low levels of quality of life, as well as a higher than expected number of patients with psychiatric symptoms in our group. Low quality of life in diabetes patients has been shown to be related to psychiatric symptoms [25] as well as the presence of long-term diabetic complications [26]. Both were present in our group. A relationship between poor glycaemic control and low health-related quality of life has been denied by both the DCCT investigators and others [20,27]. In the DCCT, the conventionally treated group showed a much better health-related quality of life, measured with the same instruments we used, at a comparable level of glycaemic control as in our patients. We therefore hypothesize that our patients had pre-existing low coping abilities and social functioning. When they were affected by diabetes they were not able to cope with the demands imposed by this chronic disease and fared poorly, but their burden of disease was partially relieved by CIPII.

Earlier studies have reported improved health-related quality of life following start of CIPII [6,10]. It is likely that health-related quality of life improved in our group, certainly in those who suffered from hospital admissions before implantation, but a limitation of our quality of life data is the absence

500   CIPII in poorly controlled patients • J. H. DeVries et al.

DMI

of a baseline measurement. Therefore the quality of life data can serve only to illustrate the major impact of disease in this group, and that normalization of scores was not attained.

For a group of 'brittle' patients, who regularly skip insulin injections [28], CIPII may be an acceptable mode of treatment. Using this instrument, a more secure insulin delivery can probably be established. This may result in a more stable and improved glycaemic control, but may not improve psychosocial stress.

Since CIPII is relatively expensive and laborious, the identification of predictors for successful application would be of great value. The glycaemic response was larger in those with higher baseline HbA_{1c}. Therefore, CIPII is not contraindicated in these patients, as one might have predicted. No other factors predicting a positive or negative glycaemic effect could be identified. This suggests that intuitive contraindications for CIPII, e.g. presence of a history of psychiatric treatment, do not necessarily prevent better glycaemic control. Overall, for patients in persistent poor control, suffering frequent hospitalization, CIPII seems a reasonable option. However, good glycaemic control and quality of life can be reached only in a minority.

The predominance of female subjects in our group is striking. The burden of diabetes may be larger in women [29], and most 'brittle' diabetes patients in other reported series are female [30]; nine of our female patients received their first implant before the age of 30 years.

We did not gather any information on technical complications, as our retrospective data would not have added to the prospective data of the French registry [31]. Following the introduction of a more stable insulin, with less tendency to aggregate, catheter obstruction, the most frequent complication, is rarely seen [32].

A limitation of French, US and Dutch studies on CIPII is the absence of large-scale controlled trials. When applied as a last resort, a control group is not appropriate. However, prospective controlled trials should be carried out, for those with both good and poor control, and should measure cost-effectiveness.

In conclusion, this 'Dutch experience' suggests that very poor glycaemic control and repeated hospital admissions due to diabetes are reasonable indications for CIPII.

Acknowledgements

References

1 Pinget M, Jeandidier N. Long term safety and efficacy of intraperitoneal insulin infusion by means of implantable pumps. *Horm Metab Res* 1998; **30**: 475–486.

2 Broussole C, Jeandidier N, Hanaire-Broutin H, the EVADIAC Study Group. French multicenter experience of implantable insulin pumps. *Lancet* 1994; **343**: 514–515.

3 DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.

4 Point Study Group. One-year trial of a remote-controlled implantable insulin infusion system in type I diabetic patients. *Lancet* 1988; **2**: 866–869.

5 Irsigler K, Hutter R, Kritz H, Abrahamian H, Lochli S, Hagmuller G et al. Evaluation of long-term treatment with implanted insulin infusion devices (1981-1988). *Diab Nutr Metab* 1990; **3**: 191–201.

6 Selam JL, Micossi P, Dunn FL, Nathan DM. Clinical trial of programmable implantable insulin pump for type I diabetes. *Diabetes Care* 1992; **15**: 877–885.

7 Jeandidier N, Pinget M, Keipes M, Louy S, Vetter A, Reville P. Comparison of intraperitoneal insulin infusion (using implantable pump) and subcutaneous insulin administration: preliminary results of a crossover study. *Transplant Proc* 1992; **24**: 948–949.

8 Olsen CL, Liu G, Iravani M, Nguyen S, Khourdadjian K, Turner DS et al. Long-term safety and efficacy of programmable implantable insulin delivery systems. *Int J Artif Organs* 1993; **16**: 847–854.

9 Haardt MJ, Selam JL, Slama G, Bethoux JP, Dorange C, Mace B et al. A cost-benefit comparison of intensive diabetes management with implantable pumps versus multiple subcutaneous injections in patients with type I diabetes. *Diabetes Care* 1994; **17**: 847–851.

10 Saudek CD, Duckworth WC, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE et al. Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. *JAMA* 1996; **276**: 1322–1327.

11 Saudek CD, Selam JL, Pitt HA, Waxman K, Rubio M, Jeandidier N et al. A preliminary trial of the programmable implantable medication system for insulin delivery. *N Engl J Med* 1989; **321**: 574–579.

12 Selam JL, Raccah D, Jean-Didier N, Lozano JL, Waxman K, Charles MA. Randomized comparison of metabolic control achieved by intraperitoneal insulin infusion with implantable pumps versus intensive subcutaneous insulin therapy in type I diabetic patients. *Diabetes Care* 1992; **15**: 53–58.

13 Pitt HA, Saudek CD, Zacur HA. Long-term intraperitoneal insulin delivery. *Ann Surg* 1992; **216**: 483–491.

14 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**: 2004–2010.

15 Derogatis LR. SCL-90: *Administration, Scoring and Procedures Manual-I for the R(evised) Version.* Baltimore: John Hopkins University School of Medicine, 1977.

16 Arrindell WA, Ettema JHM. Dimensionele structuur, betrouwbaarheid en validiteit van de Nederlandse bewerking van de Symptom Checklist (SCL-90): gegevens gebaseerd op een fobische en een 'normale' populatie. *Nederlands Tijdschrift Voor Psychologie* 1981; **36**: 77–108.

17 Medical Outcomes Trust. *How to Score the SF-36 Health Survey.* Boston: The Health Institute, 1994.

18 McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; **31**: 247–263.

19 DCCT Research Group. Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). *Diabetes Care* 1988; **11**: 725–732.

20 DCCT Research Group. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. *Diabetes Care* 1996; **19**: 195–203.

21 Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Schwartz CE et al. Assessment of diabetes-related distress. *Diabetes Care* 1995; **18**: 754–760.

22 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**: 1305–1309.

23 *SPSS BASE 9.0 Applications Guide*. Chicago: SPSS, 2000.

24 Gardner SB, Winter PD, Gardner MJ. *Statistics with Confidence*. London: British Medical Journal, 1989.

25 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**: 11–20.

26 Lloyd CE, Matthews KA, Wing RR, Orchard TJ. Psychosocial factors and complications of IDDM. The Pittsburgh Epidemiology of Diabetes Complications Study. VIII. *Diabetes Care* 1992; **15**: 166–172.

27 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**: 375–381.

28 Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med* 1997; **336**: 1849–1854.

29 Rubin RR, Peyrot M. Men and diabetes. Psychosocial and behavioral issues. *Diabetes Spectrum* 1998; **11**: 81–87.

30 Gill GV, Alberti KG. Outcome of brittle diabetes. *BMJ* 1991; **303**: 285–286.

31 Renard E, Baldet P, Picot MC, Jacques-Apostol D, Lauton D, Costalat G *et al*. Catheter complications associated with implantable systems for peritoneal insulin delivery. An analysis of frequency, predisposing factors, and obstructing materials. *Diabetes Care* 1995; **18**: 300–306.

32 Renard E, Souche C, Jacques-Apostol D, Lauton D, Gibert-Boulet F, Costalat G *et al*. Improved stability of insulin delivery from implanted pumps using a new preparation process for infused insulin. *Diabetes Care* 1999; **22**: 1371–1372.