Insulin therapy in poorly controlled type 2 diabetic patients: does it affect quality of life?

W J C de Grauw, E H van de Lisdonk, W H E M van Gerwen, H J M van den Hoogen and C van Weel

SUMMARY

Background: *Strict glycaemic control in type 2 diabetic patients is recommended in a number of treatment protocols. However, although better glycaemic control prevents or postpones chronic diabetic complications, it remains uncertain how this affects quality of life in the short and long term.*

Aim: *To study the impact of insulin therapy on glycaemic control and quality of life in type 2 diabetic patients, with secondary failure on maximal oral medication.*

Design of study: *Two separate sets of analyses were performed: a longitudinal analysis of those patients converted to insulin therapy and a comparison of 12-week outcomes between the two randomisation groups.*

Setting: *Ten general practices, participating in the Nijmegen Monitoring Project.*

Method: *Patients, poorly controlled on maximal oral therapy, were stratified with respect to age and sex, and randomly allocated to insulin therapy in two different schedules: (a) after a 12-week period with enhanced compliance to diet and oral therapy; or (b) as soon as secondary failure was established. Patients were referred to a diabetologist to start insulin therapy and were referred back to their general practitioner (GP) as soon as glycaemic control was stable. We assessed fasting blood glucose, $HbA1_c$, functional health, and quality of life (Sickness Impact Profile, COOP/WONCA charts, Diabetes Symptom Checklist) at baseline, after the patient was referred back to the GP, and nine months later.*

Results: *Of the 38 included patients, three patients dropped out and seven patients were not switched over to insulin therapy. In patients starting insulin therapy, mean $HbA1_c$ and fasting blood glucose level decreased from 9.5% to 7.6%, and from 12.0 mmol to 8.4 mmol, respectively ($P < 0.001$). The better control was accompanied by a decrease in hyperglycaemic complaints ($P = 0.01$). No increase in hypoglycaemic complaints was found. There were no statistically significant changes in quality-of-life parameters. After 12 weeks, patients directly referred to insulin therapy showed a statistically significant improvement in $HbA1_c$ and fasting glucose level, in contrast to patients with enhanced compliance. Quality-of-life scores did not significantly differ statistically.*

Conclusion: *Insulin therapy in poorly controlled type 2 diabetic patients from general practice resulted in a significant clinical improvement of glycaemic control, accompanied by a reduction of hyperglycaemic complaints, without an increase in hypoglycaemic complaints or an adverse influence on quality of life.*

Keywords: *insulin therapy; type 2 diabetes; quality of life.*

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Introduction

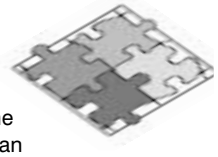
THE life expectancy and quality of life of type 2 diabetic patients is reduced by the long term complications of this chronic disease, in particular cardiovascular morbidity.[1,2] The United Kingdom prospective diabetes study showed that tight blood glucose control in newly diagnosed type 2 diabetes patients resulted in a 25% risk reduction in microvascular endpoints, but did not result in a statistically significant reduction in cardiovascular morbidity and mortality.[3] Nevertheless, many studies of type 2 diabetes have shown a positive relation between a higher blood glucose level and higher mortality, suggesting that lower indices of blood glucose control are associated with longer life.[4,5] As a consequence, strict glycaemic control is recommended in a number of treatment protocols.[6,8]

However, although better glycaemic control prevents or postpones chronic diabetic complications, it remains uncertain how this affects quality of life in the short and long term. In some studies, well controlled type 2 diabetic patients experience fewer symptoms and better quality of life, compared with less well controlled patients.[9,10] In other studies better glycaemic control was not associated with a better quality of life.[11-13]

These results seem to reflect the experience from daily practice that hyperglycaemia can give rise to symptoms but that measures to reach strict glycaemic control may interfere with patients' lifestyle and may cause side effects. Both elements may be present in the case of poor metabolic control, in spite of maximum oral medication. When insulin is considered in this situation, patients and even general practitioners (GPs) often hesitate.[14-16] Patients are afraid of the daily insulin injections, self-monitoring of blood glucose, and hypoglycaemic episodes. General practitioners largely do not feel familiar with insulin therapy and do not have access to a specialist diabetic nurse to arrange the necessary education.[16] So in cases of insulin therapy, patients have to be referred and that may cause discomfort, especially for the older patient. This is the circumstantial evidence that the expected negative impact of insulin therapy on daily functioning and quality of life may cause the patient and/or the GP to delay the start of a therapy that has a proven benefit on clinical outcomes.[15]

Therefore, we studied the impact of insulin therapy on daily functioning and quality of life in type II diabetic patients with secondary failure on maximal oral medication. Patients were referred to a diabetologist for initiation of insulin therapy and were referred back to their GP as soon as glycaemic control was stable. A second aim was to assess the effect on glycaemic control and quality of life of a strict control regi-

HOW THIS FITS IN



What do we know?
Strict glycaemic control in type 2 diabetic patients can prevent or postpone diabetic complications. Insulin therapy can improve glycaemic control in type 2 diabetic patients with secondary failure; poor glycaemic control despite maximum oral medication.

What does this paper add?
Better glycaemic control, obtained by insulin therapy started in a shared care model, can be maintained and even further improved after the patient is referred back to the GP. Insulin therapy in type 2 diabetic patients in general practice with secondary failure does not have adverse influences on quality of life. The reluctance to begin insulin therapy by some GPs and patients may be based on a prejudice towards presumed consequences of treatment, rather than on actual side-effects.

men by the GP, with enhanced compliance to diet and oral therapy before starting insulin therapy.

Method

Setting and study population

Patients were selected from the Nijmegen Monitoring Project (NMP). In this project, a longitudinal registration of chronic diseases in 10 general practices has been in progress since 1985. The extensive design and purpose of the NMP were presented earlier.[17,18] The management of diabetes mellitus in the NMP is based on the guidelines of the Dutch College of General Practitioners.[19]

This study included type 2 diabetic patients with secondary failure: poor glycaemic control in spite of maximum oral medication. Poor glycaemic control was defined as age-dependent, too high fasting blood glucose levels on average over the past 12 months (less than 60 years: ≥8.0 mmol, 60–70 years: ≤ 9.0 mmol, more than 70 years: ≥11.0 mmol[20]) or a $HbA1_c$ level ≥8.0%. Maximum oral medication was defined as the use of sulphonyl-ureum and biguanide in maximal oral dosages. The study was approved by the scientific and ethical committee of Nijmegen University. Written informed consent was requested from all participating patients.

Study design

To evaluate the possible bias, introduced through the specific setting and high attention related to the start of insulin therapy (among others referral to a diabetologist and diabetic nurse), patients were stratified with respect to age (under and over 70 years) and sex, and randomly allocated to insulin therapy in two different schedules (Table 1):

1. study group A — insulin was started if poor control remained after a 12-week period, wherein a final attempt was undertaken by the GP to enhance compliance to diet and oral therapy; during this period patients were seen monthly by the GP and dietician; and
2. study group B — insulin therapy was started after secondary failure was established.

Endpoints were glycaemic control and functional health. These endpoints were compared in two separate sets of analyses. First, a longitudinal analysis of all patients converted to insulin therapy (group A and group B) over a period of nine months. Secondly, a comparison of 12-week outcomes between patients randomised to continuing oral medication with enhanced compliance and patients randomised to insulin therapy (group A versus group B).

Intervention: insulin therapy

Patients were switched over to insulin therapy in a shared care model. A diabetologist initialised insulin therapy in an outpatient department setting. After 12 weeks, or as soon as glycaemic control was sufficiently improved and considered stable, patients were referred back to their GP.

At the outpatient department, all patients visited a diabetes specialist nurse first. The diabetes nurse provided information and education that included general knowledge of diabetes and self-monitoring of blood glucose. Next, all oral hypoglycaemic medication was stopped and two daily injections, before breakfast and dinner, of a combination of short-acting and intermediate-acting insulin (Mixtard 30: 30% dissolved insulin and 70% isophane insulin, Novo Nordisk A/S Denmark) was started.

Physical examination, medical history, and laboratory investigation

All patients were examined by the GP according to a standard protocol including physical examination, medical history, blood samples at baseline, blood samples at referral for insulin therapy (for half of the patients this was also their baseline measurement — Table 1), after the patient was referred back, and six months later. For medical history, a standardised questionnaire was used containing questions about cardiovascular risk factors, cardiovascular morbidity, diabetes complications, and comorbidity. A blood sample was analysed for $HbA1_c$, total serum cholesterol, HDL-cholesterol, triglycerides, and serum creatinine.

Quality of life

'Quality of life' was operationalised as functional health status: the impact of a disease on an individual's daily functioning[21] and measured with two questionnaires — the Sickness Impact Profile (SIP) and the COOP/WONCA charts.[22-24] As the intervention aimed to achieve improved glycaemic control, we expected a decrease of hyperglycaemic complaints and eventually an increase in hypoglycaemic complaints. Therefore, we also employed a disease-specific instrument; the Diabetes Symptom Checklist (DSC-2).[25] Dutch validated versions were available for all instruments used in the study.[24-26]

The SIP consists of 136 questions on daily functioning in relation to health and illness. These questions are grouped into 12 different categories. The calculation of the SIP-scores is described in detail elsewhere.[22]

The Dartmouth COOP functional status assessment charts/WONCA (COOP/WONCA) assess six domains of functional health: physical activities, feelings, daily activities, social activities, change in health, and overall health. Each

Table 1. Study design.

Time in weeks	0	12	24	40	52
Group A[a]					
Intervention	Enhanced compliance	Start insulin	Referred back to GP		End of study
Standard medical examination by GP[c]	X	●	■		◀
Quality of life/functional health assessment[d]	X	●	■		◀
$HbA1_c$, lipid profile	X	●	■		◀
Group B[b]					
Intervention	Start insulin	Referred back to GP		End of study	
Standard medical examination by GP[c]	●	■		◀	
Quality of life/functional health assessment[d]	●	■		◀	
$HbA1_c$, lipid profile	●	■		◀	

[a]Study group A: insulin was started if poor control remained after a 12-week period, wherein a final attempt was undertaken by the GP to enhance compliance to diet and oral therapy. [b]Study group B: insulin therapy was started as soon as secondary failure was confirmed. [c]According to a standard protocol including physical examination and medical history. [d]The Sickness Impact Profile (SIP), the COOP/WONCA charts, and the Diabetes Symptom Checklist (DSC-2).

domain is covered by a single question supported by a pictograph representing the options.[24]

The DSC-2 has been specially developed to assess the frequency and severity of diabetes mellitus-related symptoms in type 2 diabetes. It includes 34 questions covering six symptom categories: hyperglycaemic; hypoglycaemic; cardiovascular; polyneuropathic, sensory, and pain; psychological fatigue and cognitive distress; and ophthalmological. The calculation of the DSC-2 scores is described in detail elsewhere.[25] The SIP was completed by interview, the COOP/WONCA charts and DSC-2 were given to the patients for self-completion.

Statistical analyses

Baseline clinical characteristics in patients who had or had not switched over to insulin therapy were compared with χ^2, unpaired *t*-test (two-tailed) or Mann–Whitney U-test. To compare differences in baseline, follow-up (referred back to GP), and final results, with respect to clinical characteristics and quality of life questionnaires, repeated measurement analysis was used. To compare differences in baseline and final results, paired analysis was accomplished using the Wilcoxon scores or *t*-tests when appropriate. The Statistical Analysis System (version 6.12, SAS Institute) was used for data analysis.

Results

In 38 patients secondary failure was established. These patients were randomised according to age and sex: 18 patients started with a 12-week period of enhanced compliance to diet and oral medication (group A) and 20 patients were referred directly for insulin therapy (group B). Three of these patients dropped out: one patient withdrew her informed consent and in two patients the protocol was no longer followed after referral to a diabetologist. As a consequence, from both these patients no follow-up data were available. So, there were 35 patients remaining: 17 patients in group A and 18 patients in group B.

Seven patients were not switched over to insulin therapy: five patients from group A were no longer poorly controlled after 12 weeks of enhanced compliance; and in two patients of group B the diabetologist did not start insulin therapy as a consequence of markedly improved glycaemic control after education by the diabetes nurse and initiating self-monitoring of blood glucose by the patient. The rate of not starting insulin therapy (29% versus 11%) was not statistically different between the two study groups. Patients not switched over to insulin had a statistically significant lower fasting glucose level ($P = 0.002$) and a higher body mass index ($P = 0.008$) at baseline, compared with patients that were started on insulin therapy (Table 2).

Twenty-eight patients switched over to insulin therapy. The baseline characteristics of these patients are shown in Table 2. One patient on insulin therapy was withdrawn by the GP from further follow-up, after an attempted suicide during the period in which he was under supervision by the diabetologist.

In the remaining 27 patients, mean $HbA1_c$ and fasting blood glucose level decreased significantly from 9.5% to 7.6% and from 12.0 mmol to 8.4 mmol, respectively

Table 2. Baseline characteristics.

	Switched over to insulin (n = 28)	Not switched over to insulin (n = 7)	P-value
Man/woman	11 (39%)/17 (61%)	4 (57%)/3 (43%)	0.43
Mean age (years)	60.3 (SD = 11.5)	59.9 (SD = 9.7)	0.93
Duration of diabetes (years)	8.7 (SD = 3.1)	7.5 (SD = 5.0)	0.42
Glycaemic control			
$HbA1_c$ (%)	9.4 (SD = 2.2)	8.4 (SD = 2.2)	0.32
Patients with $HbA1_c$ >8%	18 (64%)	3 (43%)	0.40
Glucose level (mmol)	11.7 (SD = 2.1)	8.9 (SD = 1.4)	0.002
Body mass index (kg/m^2)	28.9 (SD = 6.2)	37.2 (SD = 9.6)	0.008
Waist-to-hip ratio			
Male	0.95	1.03	0.13
Female	0.94	0.88	0.36
Current smokers	8 (29%)	1 (14%)	0.64
Comorbidity			
Hypertension	6 (21%)	3 (43%)	0.34
Cardiovascular morbidity	9 (32%)	1 (14%)	0.64
Locomotory morbidity	6 (21%)	1 (14%)	1.00
Pulmonary morbidity	5 (18%)	0	0.55
Psychosocial morbidity	3 (11%)	1 (14%)	1.00

Table 3. Changes in clinical features in type 2 diabetic patients, with poor glycaemic control in spite of maximum oral medication, switched over for insulin therapy.

	At referral for insulin therapy (SD)	Referred back to GP (SD)	Six months' control by GP (SD)	P-value
$HbA1_c$ (%)	9.5 (2.2)	8.2 (1.9)	7.6 (1.9)	<0.001
Fasting blood glucose (mmol)	12.0 (2.1)	9.0 (2.8)	8.4 (2.1)	<0.001
Lipids				
Cholesterol (mmol)	6.2 (1.6)	6.1 (1.2)	5.7 (1.5)	0.14
HDL cholesterol (mmol)	1.0 (0.3)	1.3 (0.5)	1.1 (0.3)	0.001
Triglycerides (mmol)	4.2 (6.6)	2.5 (2.9)	3.2 (3.5)	0.18
Blood pressure				
Systolic (mmHg)	148 (21)	143 (24)	146 (26)	0.57
Diastolic (mmHg)	84 (12)	80 (11)	78 (11)	0.02
Body mass index (kg/m^2)	28.6 (6.3)	29.2 (6.0)	29.8 (5.9)	<0.001
Weight (kg)	79.1 (20.2)	80.6 (19.2)	82.5 (18.6)	0.001

(P<0.001, Table 3). In 19 patients $HbA1_c$ decreased by 1% in only three patients the $HbA1_c$ value at the end of the study was higher than at baseline (0.4%–1.5%). The better control was accompanied by a statistically significant decrease in hyperglycaemic complaints (P = 0.01). This decrease was most notable in the first 12 weeks of insulin therapy (Table 4). No hypoglycaemic event occurred that required professional medical intervention and no increase in hypoglycaemic complaints was found. The mean weight increased by 3.4 kg (P = 0.001), resulting in a mean increase in body mass index of 1.3 kg/m^2 (P<0.001). Blood pressure and lipid profiles showed an improved trend (Table 3). Diastolic blood pressure also improved, from 84 mmHg to 78 mmHg (P = 0.02), as did HDL cholesterol (from 1.0 mmol to 1.1 mmol, P = 0.001).

Although the SIP total score showed a small decrease, none of the sub-dimensions of the SIP (data not shown) or the physical or psychosocial sub-scores showed any significant change (Table 4). Functional health, expressed with the COOP/WONCA charts, showed a similar pattern, with the exception of the dimension change in health (P = 0.006) which showed some improvement.

$HbA1_c$ levels and quality of life scores showed no statistically significant differences between baseline and the end of study in patients from group A and B.

The effects on glycaemic control and quality of life of 12 weeks with enhanced compliance to oral medication and diet (group A), compared with direct switching to insulin therapy (group B) are presented in Table 5. There were no statistically significant differences at baseline, with respect to any of the characteristics shown in Table 2 and with respect to the scores for quality of life between both groups. The differences for body mass index (P = 0.04) and scores on hypoglycaemic complaints (P = 0.03) may be considered as insignificant as we have made multiple comparisons, in which case probabilities are significant at the 1% level. Patients directly referred for insulin therapy showed a clinically and statistically significant improvement in $HbA1_c$ and fasting glucose level after 12 weeks of insulin therapy. This was not the case in patients after 12 weeks with enhanced compliance. The change in scores on SIP, COOP/WONCA (not shown) or DSC-2 were not statistically significant between the two study groups.

Table 4. Changes in quality of life scores of type 2 diabetic patients, with poor glycaemic control in spite of maximum oral medication, switched over for insulin therapy.

	At referral for insulin therapy (SD)	Referred back to GP (SD)	Six months control by GP (SD)	*P*-value
Sickness Impact Profile[a]				
Physical	4.6 (6.3)	4.5 (7.5)	4.8 (9.3)	0.9
Psychosocial	4.4 (6.8)	4.3 (9.9)	2.9 (5.2)	0.7
Total	6.2 (6.4)	6.1 (9.2)	5.5 (8.2)	0.9
COOP/WONCA charts[b]				
Physical fitness	3.4 (1.1)	3.4 (1.3)	3.5 (1.2)	0.9
Feelings	1.6 (0.8)	1.6 (0.9)	1.6 (0.7)	1.0
Daily activities	2.0 (1.1)	1.8 (1.2)	1.8 (1.2)	0.8
Social activities	1.4 (0.6)	1.4 (1.0)	1.4 (0.9)	0.9
Change in health	2.9 (0.7)	2.2 (0.9)	2.6 (0.8)	0.006
Overall health	3.1 (0.9)	2.6 (0.9)	3.0 (0.8)	0.07
DSC-2[c]				
Hyperglycaemic complaints	3.8 (2.9)	2.0 (2.7)	2.6 (2.5)	0.01
Hypoglycaemic complaints	1.1 (1.7)	0.8 (1.5)	0.7 (1.3)	0.40
Total	2.3 (1.6)	1.4 (1.5)	1.7 (1.4)	0.02

[a]A higher score reflects worse functional health. [b]Scores range from 1 ('not limited at all') to 5 ('severely limited'). The change in health chart ranges from 1 ('much better') to 5 ('much worse'). [c]A higher score reflects more complaints.

Table 5. Changes in glycaemic control and quality-of-life parameters[a] after 12 weeks with enhanced compliance, compared with insulin therapy. Figures in brackets are standard deviations unless otherwise indicated.

	Group A 12 weeks with enhanced compliance (n = 17)		Group B directly referred for insulin therapy (n = 18)		*P*-value (Difference T1–T0)
Quality-of-life parameter	Start (T0)	After 12 weeks (T1)	Start (T0)	After 12 weeks (T1)	
$HbA1_c$ (%)	8.7 (1.7)	9.0 (2.4)	9.7 (2.6)	8.0 (1.9)	0.002
Fasting blood glucose (mmol)	10.3 (2.3)	10.7 (2.6)	11.9 (2.0)	8.6 (3.0)	<0.001
Patients switched to insulin		12 (71%)		16 (89%)	0.21
SIP Physical	3.4 (5.3)	4.4 (4.9)	4.5 (6.6)	5.0 (8.0)	0.24
SIP Psychosocial	3.5 (4.9)	3.0 (3.8)	6.7 (9.8)	7.0 (13.0)	0.63
SIP Total	5.2 (6.3)	6.0 (4.7)	6.8 (7.0)	7.6 (10.2	0.44
DSC-2 Hyperglycaemic	4.0 (3.4)	1.6 (2.5)	4.2 (3.3)	2.2 (2.4)	0.49
DSC-2 Fatigue	2.9 (2.9)	3.2 (3.0)	3.9 (3.7)	3.1 (2.8)	0.81
DSC-2 Cognitive	1.6 (2.5)	1.5 (2.4)	1.7 (2.2)	1.7 (2.3)	0.69
DSC-2 Hypoglycaemic	0.5 (1.7)	0.5 (1.4)	1.5 (1.7)[b]	1.5 (1.7)	0.67
DSC-2 Total	2.1 (1.4)	1.9 (1.4)	2.3 (1.7)	1.7 (1.8)	0.96

[a]Data of COOP/WONCA charts not shown, at baseline and after 12 weeks no differences between the two study groups. [b]Hypoglycaemic complaints were statistically different at baseline between group A and group B (P = 0.04).

Discussion

This study showed that insulin therapy in poorly controlled type II diabetic patients from general practice resulted in a clinically significant[3] improvement of glycaemic control, accompanied by a statistically significant reduction of hyperglycaemic complaints without an increase in hypoglycaemic complaints. In the short term (nine months), insulin therapy had no adverse influence on quality of life. Better glycaemic control was maintained and even further improved after the patient was referred back to the GP.

As functional health will largely depend on existing comorbidity,[2,27] it can be argued that improvement of functional health by better glycaemic control was not to be expected. Moreover, the standard deviations for most items of the quality of life instruments were large as a consequence of the small number of patients and the specific properties of such instruments. Change in scores in our study will not easily reach statistical significance, as is the case in the trend to improvement found in the psychosocial dimension and total scores of the SIP.

A common problem in studies comparing the effect of insulin therapy is that, since they cannot be double-blind, bias may be introduced through the attitude of those prescribing the treatment, as well as the specific setting, with a high attention to therapy consequences (for example, referral to a specialist nurse). This may be especially true for quality-of-life aspects. To evaluate this eventual bias we randomised patients in two different schedules for insulin therapy. As we found no differences on quality-of-life scores between patients from group A and B, neither after 12 weeks nor at the end of study, the effect on quality of life scores seems not to be influenced by the period of enhanced compliance by GP in group A. Nevertheless, after 12 weeks, five of the 17 patients in group A insulin therapy could be postponed and hyperglycaemic complaints improved in a similar way to those patients switched to insulin therapy.

There are few studies concerning the effect of insulin therapy on quality of life in patients failing to respond adequately to oral therapy. These studies show that initiation of insulin therapy improves glycaemic control effectively and, although insulin therapy is experienced as more demanding, this therapy does not adversely influence quality of life.[12,13,28,29] Moreover, these studies show that quality-of-life scores are not associated to $HbA1_c$ levels or the achievement of an objectively better control.[13,28,30]

Our study, based in general practice, underlines the fact that insulin therapy in type 2 diabetic patients with secondary failure results in an improvement of glycaemic control without adverse influences on quality of life. Therefore, the reluctance to start insulin therapy by some GPs and patients may be based on a prejudice towards presumed consequences of the treatment, rather than on actual effects.[15] On the other hand, the case reports of diabetologists, pointing at a marked improvement in well being after starting insulin therapy, are not supported either by our study or by the literature.

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References

1. de Grauw WJC, van de Lisdonk EH, van den Hoogen HJM, van Weel C. Cardiovascular morbidity and mortality in type II diabetic patients: a 22-year historical cohort study in Dutch general practice. *Diabetic Med* 1995; **12:** 117-122.
2. de Grauw WJC, van de Lisdonk EH, Behr RA, *et al*. The impact of type II diabetes mellitus on daily functioning. *Fam Pract* 1999; **16:** 133-139.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type II diabetes mellitus (UKPDS 33). *Lancet* 1998; **352:** 837-853.
4. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995; **18:** 258-268.
5. Groeneveld Y, Petri H, Hermans J, Spinger MP. Relationship between blood glucose level and mortality in type II diabetes mellitus: a systematic review. *Diabetic Med* 1999; **16:** 2-13.
6. European Diabetes Policy Group. A desktop guide to type II diabetes mellitus. *Diabetic Med* 1999; **16:** 716-730.
7. Zimmerman BR (Ed.) *Medical management of type II diabetes*. 4th edition. Alexandria, VA: American Diabetes Association, 1998.
8. Rutten GEHM, Verhoeven S, Heine RJ, *et al*. NHG standaard diabetes mellitus type II (eerste herziening, in Dutch). *Huisarts Wet* 1999; **42:** 67-84.
9. Wolffenbuttel BHR, Weber RFA, van Koetsveld PM, Verschoor L. A randomised crossover study of sulfonylurea and insulin treatment in patients with type II diabetes poorly controlled on dietary therapy. *Diabetic Med* 1989; **6:** 520-525.
10. van der Does FEE, de Neeling JND, Snoek FJ, *et al*. Symptoms and well-being in relation to glycemic control in type II diabetes. *Diabetes Care* 1996; **19:** 204-210.
11. Weinberger M, Kirkman MS, Samsa GP, *et al*. The relationship between glycemic control and health-related quality of life in patients with non-insulin-dependent diabetes mellitus. *Med Care* 1994; **29:** 1173-1181.
12. de Sonnaville JJ, Snoek FJ, Colly LP, *et al*. Well-being and symptoms in relation to insulin therapy in type II diabetes. *Diabetes Care* 1998; **21:** 919-924.
13. Goddijn PPM, Bilo HJG, Feskens EJM, *et al*. Longitudinal study on glycaemic control and quality of life in patients with type II diabetes mellitus referred for intensified control. *Diabetic Med* 1999; **16:** 23-30.
14. Peacock I, Tattersall RB. The difficult choice of treatment for poorly controlled maturity onset diabetes: tablets or insulin? *BMJ* 1984; **288:** 1956-1959.
15. Taylor R. Insulin for the non-insulin-dependent. *BMJ* 1988; **296:** 1015.
16. Miedema K, Veltmaat LJ, Reenders K. Switching to insulin therapy in NIDDM patients. A study of inhibiting factors in family practice. *Huisarts Wet* 1995; **38:** 614-617.
17. de Grauw WJC, van de Lisdonk EH, van den Hoogen HJM, van Weel C. Monitoring of non-insulin dependent diabetes mellitus in general practice. *Diab Nutr Metab* 1991; **4:** 67-71.
18. van Weel C, Smith H, Beasley JW. Family practice research networks: experience from three countries. *J Fam Pract* 2000; **49:** 938-943.
19. Nederlands Huisarts Genootschap. Standaard Diabetes Mellitus Type II. *Huisarts Wet* 1989; **32:** 15-18.
20. Van Ballegooie E, De Boer JGJ, Lemmens JHMP, Verhoeven S. *Diabetes mellitus type II. Guidelines for control and treatment according to the 'Zwollse Protocol'.* (In Dutch.) Zwolle: De Weezenlanden, 1987.
21. van Weel C. Functional health status in primary care: COOP/WONCA charts. *Disability Rehabilitation* 1993; **15:** 96-101.
22. Berger M, Bobbitt RA, Carter WB. The Sickness Impact Profile: development and final testing of a health status measure. *Med Care* 1981; **19:** 787-805.
23. Nelson EC, Wasson J, Kirk J, *et al*. Assessment of function in routine clinical practice; description of the COOP chart method and preliminary findings. *J Chron Dis* 1987; **40(suppl 1):** 55S-64S.
24. van Weel C, König-Zahn C, Touw-Otten FWMM, *et al*. *Measuring functional health with the COOP/WONCA charts: a manual.* Groningen: Northern Centre of Health Care Research, 1995.
25. Grootenhuis PA, Snoek FJ, Hiene RJ, Bouter LM. Development of a type II diabetes symptom checklist: a measure of symptom severity. *Diabetic Med* 1994; **11:** 253-261.
26. Jacobs HM, Luttik A, Touw-Otten FWMM, de Melker RA. The sickness impact profile; results of a validation of the Dutch version. [De 'Sickness Impact Profile'; resultaten van een valideringsonderzoek van de Nederlandse versie] *Ned Tijdschr Geneesk* 1990; **134:** 1950-1954.
27. UK Prospective Diabetes Study Group. Quality of life in type II 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:** 1125-1136.
28. Peacock I, Tattersall RB. The difficult choice of treatment for poorly controlled maturity onset diabetes: tablets or insulin? *BMJ* 1984; **288:** 1956-1959.
29. Barnett AH, Bowen Jones D, Janes JM, *et al*. Multicentre study to assess quality of life and glycaemic control of type II diabetic patients treated with insulin compared with oral hypoglycaemic agents. *Practical Diabetes International* 1996; **13:** 179-183.
30. Johansen J, Claudi T, Holtedahl K. Insulin treatment for poorly regulated diabetic patients in general practice. *Scand J Prim Health Care* 1999; **17:** 244-249.