

# Insulin therapy and quality of life. A review

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## Summary

Three central goals in the treatment of diabetes mellitus are (1) the avoidance of hyperglycaemia to prevent the development or progression of diabetes complications over time, (2) the avoidance of hypoglycaemia and (3) the maintenance or achievement of good quality of life. Insulin is the most powerful agent that can be used to control blood glucose levels. This article reviews the studies that have investigated the effects of different types of insulin and insulin delivery techniques on quality of life of patients with type 1 or type 2 diabetes. First, the concept of 'quality of life' (QoL) is defined and different ways of measuring QoL are explained. Secondly, the effects of different aspects of insulin therapy on QoL are reviewed: (1) the phenomenon of 'psychological insulin resistance'; (2) the effects of different types of insulin: regular insulin *versus* short-acting insulin analogues, long-acting insulin analogues or biphasic mixtures; (3) multiple daily injections *versus* pump therapy.

Having multiple complications of diabetes is clearly associated with decreased QoL. Results from large studies such as the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) suggest that intensive treatment itself does not impair QoL. Recent findings further suggest that pump therapy, compared to multiple daily injections, has beneficial effects on QoL. The fact that multiple tools are used to assess QoL makes it difficult to draw conclusions regarding the effects of different types of insulin on QoL. More work on the standardization of the assessment of QoL in diabetes is urgently needed. Copyright © 2009 John Wiley & Sons, Ltd.

**Keywords** Diabetes mellitus; insulin; NPH; long-acting; quality of life; insulin infusion systems; review

## Introduction

During the past few years, interest in the associations between diabetes and quality of life (QoL) has grown considerably. A Medline search showed that in the 1970s, just 13 studies mentioned the words 'diabetes' and 'quality of life' in their abstracts (Figure 1). This number became 10 times higher in the 1980s (132), and almost another 10 times higher in the 1990s. Between 1 January 2000 and 31 August 2008, 2960 studies were published on diabetes and QoL.

It is now common knowledge that diabetes mellitus (type 1 or type 2) is a chronic disease with burdensome long-term complications. These long-term co-morbid health problems include cardiovascular disease, retinopathy, nephropathy, neuropathy and depression [1–5]. The presence of multiple complications is one of the most important determinants of impaired QoL in people with diabetes mellitus [3–5].

Received: October 15 2008

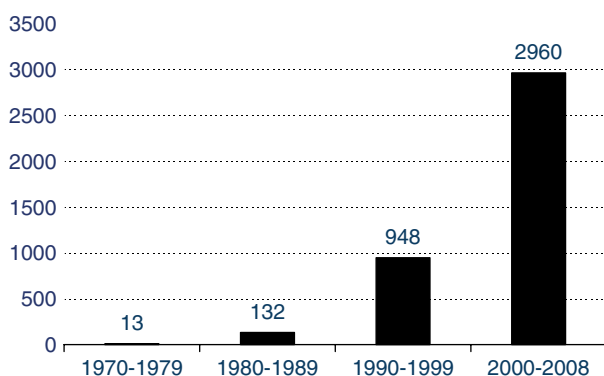


Figure 1. Number of publications with the words 'diabetes' and 'quality of life' in their abstract in the 1970s, 1980s, 1990s and between January 2000 and 31 August 2008

Insulin therapy is an efficient tool to improve glycaemic control and prevent the development of long-term complications of diabetes in both types of diabetes. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) convincingly showed the benefits of good glycaemic control in patients with type 1 or type 2 diabetes mellitus in delaying the onset of microvascular complications of diabetes [1,2]. Short-term complications of diabetes such as high blood glucose levels can also have a negative impact on the mood of patients [6] and optimized glycaemic control was found to improve health-related QoL [7]. However, treatments that elevate insulin concentrations in the blood independent of the ambient glucose variability inevitably carry the risk of intermittent hypoglycaemia, another short-term complication of diabetes [8]. Episodes of hypoglycaemia are often distressing. It is therefore important that regimens of insulin therapy are designed not only to aim at near-normoglycaemia but also to minimize the risk of hypoglycaemia [8,9].

Many clinicians now view diabetic patients themselves as primarily responsible for the daily management of their disease [10]. Insulin self-management can be burdensome, as patients must deal with their diabetes all day and every day, by self-monitoring of the blood glucose, taking insulin and making (sometimes complex) decisions about insulin dosage in relation to physical activity and diet.

This article reviews the studies that have investigated the effects of different types of insulin and insulin delivery techniques on QoL of patients with type 1 or type 2 diabetes. Firstly, the concept of 'quality of life' will be defined and different ways of measuring QoL will be explained. Secondly, the effects of the following aspects of insulin therapy on QoL will be reviewed: (1) psychological insulin resistance; (2) the effects of different types of insulin on QoL: regular insulin *versus* short-acting insulin analogues, long-acting insulin analogues or biphasic mixtures; and (3) multiple daily injections *versus* pump therapy.

## Definition of QoL

QoL is commonly recognized as a multidimensional concept including not only the domains of physical health and functioning, mental health and different aspects of social functioning, but also concerns about the future. The perception of a situation, such as having diabetes, is strongly influenced by a person's values, norms, personality and coping skills. The same circumstances can be experienced in a totally different way by different persons [3,7]. Because QoL is a subjective phenomenon, the best way to measure it is by means of self-report. At the moment, researchers and clinicians can choose between three types of measures: generic measures of QoL, diabetes-specific measures of QoL, and measures assessing one or more specific elements of QoL [3,7].

## Measurement of quality of life: generic *versus* diabetes-specific measures

Direct observations, face-to-face interviews and telephone interviews are used to assess QoL, but this construct is most commonly measured with a self-report questionnaire. An important distinction is made between 'quality of life in general' and 'diabetes-specific quality of life.' Generic QoL instruments are suitable for the general population, but also for specific populations to assess a wide range of domains applicable to a variety of health states, conditions and diseases. Generic measures can therefore be used to compare the QoL between patients with diabetes, cancer or multiple sclerosis and healthy controls. The Sickness Impact profile [11], the Nottingham Health profile [12] and the Medical Outcome Study Short Form-36 (SF-36) and its shorter form SF-12 [13] and the EuroQoL (EQ5D) [14] are well-known examples of generic QoL instruments. The UKPDS [15], for example, used the EQ5D to assess generic QoL. The EQ5D consists of five questions about mobility, self-care, usual activities, pain and anxiety [14]. In addition to this generic questionnaire, the UKPDS assessed mood using the Profile of Mood State [16], cognitive failures using the Cognitive Failures Questionnaire [17], work satisfaction, support from relatives and symptoms [15].

In addition to generic measures of QoL, many diabetes-specific measures of QoL have been developed. Such instruments inquire about problems or symptoms or other elements of QoL that are specifically relevant for patients with diabetes: for example, long-term complications that can hamper physical functioning, such as vision problems, kidney damage, cardiovascular disease, erection problems, chronic pain or problems with bladder function as a result of neuropathy, foot problems and difficulties with walking. Disease-specific questionnaires are therefore also regarded as more sensitive than generic measures to capture the impact of short-term complications, such as frequent

hyperglycaemia or hypoglycaemia or 'brittle diabetes.' Chronically elevated blood glucose levels are often accompanied by fatigue, sleep problems and more frequent infections. On the other hand, tight glycaemic control may lead to unwanted weight gain, more frequent hypoglycaemia and/or loss of hypoglycaemic warning signs [18]. The diabetes therapy can also interfere with the life style of the patient and influence QoL. For example, when patients feel forced to limit certain activities in order to manage their diabetes effectively, QoL is likely to be affected in a negative way. Examples include not going to the swimming pool because one is on pump therapy and hesitant to show this to others, or declining sports activities to avoid hypoglycaemia or even losing one's driving license due to frequent and severe hypoglycaemia. Another more physical example is lypohypertrophy resulting from repeated insulin injections. Several instruments have been developed to measure diabetes-specific QoL, for example the DSQOLS, the ADDQoL, D-39 or the D-QoL, which was the QoL measure used in the DCCT study [19]. For adolescents with diabetes, the PedsQL and the KINDL-R appear to be suitable measures to assess QoL [20].

Many diabetes-specific measures partly assess QoL by addressing one or more key elements of QoL. One well-known example is the Problem Areas in Diabetes (PAID) Survey, which captures emotional problems which are specifically related to diabetes, such as worries about diabetes complications, uncomfortable social interactions around diabetes, worries about hypoglycemia or worries about food [21]. Other measures assess issues specifically related to the diabetes therapy, such as the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [22], the Insulin Treatment Appraisal Scale (ITAS) [23], the Insulin Treatment Experience Questionnaire (ITEQ) [24] or the Diabetes Fear of Injecting and Self-testing Questionnaire (D-FISQ) [25], or assess diabetes-symptom distress such as the Diabetes Symptom Checklist [26,27].

If researchers aim to study the specific effects of different types of insulin on QoL, they need questionnaires that are sensitive enough to measure differences caused by the use of different types of insulin or by using different insulin delivery devices. Generally, diabetes-specific measures are more sensitive for differences caused by insulin therapy. This is well illustrated by findings of Kohlman and Mook, who compared patients

on insulin glargine ( $n = 982$ ) with a group of patients treated with NPH insulin ( $n = 620$ ) who participated in the LIVE-DE Study [24]. They used the SF-12 as a generic measure of QoL, the DTSQ and ITEQ to assess treatment satisfaction and the PAID to measure diabetes-specific emotional distress. As illustrated in Table 1, they found that particularly the ITEQ items and the ITEQ total scale were sensitive for differences between both insulin therapies [23]. If one's hypothesis is that a certain insulin therapy will result in less frequent hypoglycaemic episodes and as a result less worries about serious hypos, one could consider using the Fear of Hypoglycaemia Survey [28]. Other elements of QoL that can be affected by a change in insulin therapy are, for example, impact on leisure activities, the extend to which the patient feels in control of diabetes, weight issues, flexibility in eating behaviours or quality of sleep, which can be assessed with measures like the ITEQ.

## Psychological insulin resistance

Only a few studies have reported results regarding the prevalence of negative appraisals of insulin, or 'psychological insulin resistance.' For example, in the UKPDS, 27% of the patients randomized to insulin therapy initially refused insulin, compared to 7% in the glibenclamide group and 13% in the chlorpropamide group [2]. A study by Polonsky *et al.* had comparable results, showing that about 28% of insulin-naive patients with diabetes reported to be unwilling to begin insulin if prescribed [25]. Hence, these results suggest that considerably strong, negative appraisals regarding insulin therapy exist in about one-third of the insulin-naive patients. Recent studies have shown that the patients' reasons for disliking insulin therapy clearly extend beyond fear of injections alone. Other factors, such as worries about gaining weight, the impact of insulin therapy on the social environment or feelings that insulin therapy signifies that one has failed to manage diabetes with diet/tablets, also appear to play a role [24,27]. However, results from the UKPDS showed that commencement of insulin therapy did not impair QoL (EQ5D, and measures of work satisfaction, mood state, symptoms and cognitive mistakes) [15].

**Table 1.** Comparing the effects that two different types of insulin have on QoL, using three different scales that assess different dimensions of QoL. The measures used in a study by Kohlman *et al.* [24] are used as an example

Dimension	Measurement	Overlap with overall quality of life	Sensitivity to differences caused by different types of insulin (NPH vs glargine)
Satisfaction with diabetes treatment	Insulin treatment experience questionnaire (ITEQ)	Low	High
Diabetes-related distress	Problem areas in diabetes (PAID)	Medium	Low
Generic quality of life measure	Mental health (SF12 health survey)	High	Low

## Different types of insulin and QoL

Plank *et al.* have recently conducted a systematic review and meta-analysis of 42 studies comparing the effect of treatment with regular insulin *versus* short-acting insulin analogues [29]. The authors describe that 11 trials reported data on QoL and they conclude that objective interpretation of the results was not possible due to the various instruments used and their open study design. A recent interesting study by Ashwell *et al.*, not included in the meta-analysis of Plank *et al.*, involved a 32-week two-way crossover trial in 56 individuals with type 1 diabetes randomized to evening insulin glargine plus mealtime insulin lispro or to NPH insulin (once or twice daily) plus mealtime unmodified human insulin [30]. Insulin glargine plus insulin lispro improved treatment satisfaction and reduced the negative impact of diabetes on QoL, and improved QoL in comparison with NPH insulin plus unmodified human insulin in type 1 diabetes [30].

Horvath *et al.* [31] have recently published their meta-analysis assessing the effects of long-term treatment with long-acting insulin analogues (glargine and detemir) compared to NPH insulin in patients with type 2 diabetes mellitus. Studies were included if they had a randomized controlled trial design and a duration of at least 24 weeks. Six studies comparing insulin glargine to NPH insulin and two studies comparing insulin detemir to NPH insulin were identified. Effects on glycaemic control and adverse effects did not differ between both types of insulin therapy: no statistically significant difference for severe hypoglycaemia rates was shown in any of the trials. However, the rate of symptomatic, overall and nocturnal hypoglycaemia was significantly lower in patients treated with either insulin glargine or detemir. No evidence for a beneficial effect of long-acting analogues on mortality, morbidity, QoL or costs was found [31].

Holman *et al.* [32] described the results of an open-label controlled multi-centre trial comparing three insulin regimens: basal insulin detemir (twice/day if needed), prandial insulin aspart (three times/day) or biphasic insulin aspart (twice daily), in a sample of 708 patients with type 2 diabetes, who were receiving maximally tolerated doses of metformin and sulfonylurea and were in suboptimal glycaemic control (HbA<sub>1c</sub> 7–10%). At 1-year follow-up, the patients in the basal insulin group had a higher mean HbA<sub>1c</sub> level (0.3–0.4%), but a lower number of hypoglycaemic events (2) and lower weight gain (+2 kg) compared to the biphasic group (6 hypos and +5 kg) and the prandial insulin group (12 hypos +6 kg). So, addition of mixed insulin or rapid-acting insulin analogues resulted in better glycaemic control than basal long-acting insulin detemir, at the expense of an increased risk for hypoglycaemia and weight gain [32].

A study by Bretzel *et al.* [33] compared the combination of basal insulin therapy with insulin glargine and oral antidiabetic agents with a combination of thrice-daily prandial insulin lispro. There was an equivalent

impact on glycaemic control of both regimens, whereas patients treated with the combination of basal insulin and oral agents reported significantly less hypoglycaemic events than patients treated with thrice-daily prandial insulin injections and oral agents. Interestingly, treatment satisfaction was significantly more improved in the combination using basal insulin and oral agents. Thus it seems that simpler insulin regimes seem to be preferred by patients if they have an equivalent impact on glycaemic control [33].

## Multiple daily injections (MDI) *versus* continuous subcutaneous insulin infusion (CSII)

Barnard *et al.* [34] studied, by means of a systematic literature review, whether CSII provides any QoL benefits compared to MDI. They identified 17 relevant articles, conducted over the past 20 years, including 5 randomized controlled trials. Three trials reported mixed results, one trial reported QoL benefits of CSII over MDI and one trial found no evidence of QoL benefits of CSII [34]. Most studies that were included in the systematic review of Barnard *et al.* suffered from several methodological problems. For example, many different tools were used to assess QoL, making comparisons between studies difficult or even impossible [34,35]. The DQOL has been a popular choice for assessing QoL in studies comparing pump therapy and MDI, but this instrument may not be sensitive enough to capture differences in QoL resulting from both treatments [34,35]. Another limitation was that it was unclear what measurements were used to identify patients who started in pump therapy but subsequently discontinued its use [35].

The Equality Study group has recently published results of their large case-control study comparing patients using CSII with those on MDI. Using the DSQOLS as a diabetes-specific measure of QoL, these researchers found that patients on CSII reported more life style flexibility, less fears about hypoglycaemia, less diet restrictions and less daily hassles than those treated with NPH-based MDI [36]. These findings are in line with results of a large randomized controlled trial in 11 European centres, comparing CSII with MDI with NPH insulin, showing that patients with type 1 diabetes who are being treated with CSII feel less limited in the aspects related to diet and everyday activities [37]. In this study, CSII resulted in a somewhat better glycaemic control in the CSII group (HbA<sub>1c</sub> 7.5 vs 7.7% in the MDI group). Importantly, there was a marked reduction in the frequency of hypoglycaemic events using CSII compared with NPH-based MDI, with an incidence ratio of 1.12 [95% confidence interval (CI): 1.08–1.17] and 2.61 (95% CI: 1.59–4.29) for mild and severe hypoglycaemia, respectively [37]. Pańkowska *et al.* have recently published their systematic review and meta-analysis, aiming to investigate the effects of CSII *versus*

MDI on glycaemic control and QoL in children with type 1 diabetes [38]. The results from this meta-analysis were based on data from six randomized controlled trials involving 165 children with type 1 diabetes, showing that CSII, compared with MDI, was associated with a significant reduction in the level of HbA<sub>1c</sub> (−0.24%). No differences in the incidences of ketoacidosis and severe hypoglycemic events were found. QoL and satisfaction with treatment were assessed in four trials ( $n = 98$ ): in one trial, no differences were found between those treated with CSII and with MDI on the Paediatric Diabetes QoL questionnaire [38]. One study found a higher level of treatment satisfaction in the CSII group. Another study showed that those on CSII had larger improvements on treatment satisfaction compared to MDI; however, an important limitation is that the authors of that study did not compare both groups at the end of the observation period [38]. Two studies were not yet included in the meta-analysis by Pankowska *et al.* Opipari-Arrigan *et al.* [39] conducted a randomized controlled trial in 16 children aged 3–5 years with type 1 diabetes, comparing medical, nutritional and psychosocial outcomes of CSII and MDI. Parents of the children in the CSII group reported a significant decrease in diabetes-related worry, while parents of the patients in the MDI group reported an increased frequency of stress associated with their child's medical care. Mean HbA<sub>1c</sub> levels remained stable in both groups, and no differences were found for hypo- or hyperglycaemic events [39]. Nuboer *et al.* [40] have conducted a small ( $n = 39$ ) study to test the effects of CSII *versus* four times daily injections on glycaemic control, hypoglycaemia and QoL, using an open, parallel, randomized controlled study in 38 children with type 1 diabetes, aged 4–16 years. Only one child stopped participation in the study. Treatment with an insulin pump resulted in a small decrease in HbA<sub>1c</sub> after a run-in period (0.22% reduction) and a decrease in symptomatic hypoglycaemias, compared to MDI.

## Discussion

Approximately 80 years after the discovery of insulin by Banting and Best, insulin therapy has markedly improved, though we are still striving to find ways to mimic the natural insulin response of non-diabetic persons. The main aim of this study was to determine whether different aspects of insulin therapy influenced the QoL of patients with diabetes.

Firstly, the development of long-term complications of diabetes is generally regarded as the largest threat to the QoL of patients with diabetes [3]. Both the DCCT and the UKPDS showed that the onset of these long-term complications can be prevented or delayed by strict glycaemic control, often with the use of insulin therapy. We can therefore infer that insulin has a beneficial impact on QoL in general via the prevention of long-term diabetes complications.

Secondly, a considerable number of insulin-naive patients with diabetes nevertheless have negative appraisals of insulin therapy. Some patients fear injecting insulin, whereas others have worries about gaining weight when using insulin, or worry about the impact of insulin therapy on the social environment. Some patients have the idea that insulin therapy signifies one's failure to manage diabetes. Delay of insulin therapy that is based on unrealistic ideas should be avoided. Only a few cross-sectional studies have been conducted into the negative appraisals of insulin therapy. Longitudinal research into the determinants of negative appraisals of insulin therapy is now urgently needed. Studies could, for example, focus on the question of whether emotional factors such as depression are associated with negative appraisals of insulin therapy, subsequent delay of initiating insulin therapy and poor glycaemic control [41].

One important finding from the literature comes from the systematic review and meta-analysis of 42 studies comparing the effect of treatment with regular insulin *versus* short-acting insulin analogues [29]. The authors mentioned an important barrier that exist: they reported that it was impossible to draw conclusions about the effects of short-acting insulin analogues because of the aforementioned problem with different measurement scales of QoL [29]. Another meta-analysis assessed that the long-term treatment with long-acting insulin analogues (glargine and detemir) compared to NPH insulin in patients with type 2 diabetes mellitus was more successful. It appeared that the effects on glycaemic control and adverse effects did not differ between both types of insulin therapy. Though the overall and nocturnal hypoglycaemia rates were lower in patients treated with either insulin glargine or detemir, no evidence for the beneficial effects of long-acting analogues on mortality and morbidity as well as the overall QoL or costs was found [31].

Another landmark publication came from Barnard *et al.* [34], who conducted a systematic literature review to study whether CSII provides any quality of life benefits compare to MDI. These authors too had to deal with the problem that many different tools were used to assess QoL in eligible studies, making comparisons between studies difficult or even impossible. Recent results from larger studies, though, suggest that patients on CSII experience more life style flexibility, less fears about hypoglycaemia, less diet restrictions and less daily hassles than those treated with NPH-based MDI [36]. These findings are in line with results of a large randomized controlled trial in 11 European centres, comparing CSII with MDI with NPH insulin, showing that patients of type 1 diabetes who are being treated with CSII feel less limited in the aspects related to diet and everyday activities [37]. A recent study comparing CSII and MDI in children suggests that parents of the children in the CSII group reported a significant decrease in diabetes-related worry, while parents of the patients in the MDI group reported an increased frequency of stress associated with their child's medical care. Mean HbA<sub>1c</sub> levels remained stable in

both groups, and no differences were found for hypo- or hyperglycaemic events.

The key message of the present review is the value of standardization of disease-specific measures of QoL, which is an important patient-reported outcome [42]. Generic measures of QoL are less sensitive and often not suitable at all to detect potential benefits of new types of insulin or new insulin delivery devices [3,34,35]. An important limitation is that the studies that investigated the associations between different aspects of insulin therapy and QoL used many different measures to assess QoL. As a result, it is difficult to compare results of different studies and to determine the relative effects that different forms of insulin therapy have on QoL. It is clear that standardization of the assessment of QoL in people with diabetes is urgently needed. In their Editorial [35], Speight and Shaw make an interesting comparison with the assessment of glycaemic control before the DCCT study and the way QoL is currently assessed in people with diabetes:

*“Before the Diabetes Control and Complications Trial, there were several widely used assays of blood glucose control, which made extrapolating from one study to another incredibly difficult. Following the DCCT, diabetes clinicians and researchers recognized the importance of adopting one standardized approach to the assessment of blood glucose control. Despite some efforts to standardize the assessment of psychological well-being in diabetes, e.g. in the St Vincent Declaration, there has been no equivalent attempt with regard to the assessment of the impact of diabetes on QoL. This is urgently needed [35].”*

Our review explored the associations between insulin therapy and QoL. Based on the results in the literature, we conclude that insulin therapy can indirectly contribute to good QoL via the prevention of diabetes complications. A considerable number of patients have negative appraisals of insulin therapy before they actually start using insulin, although results from the UKPDS showed that a switch to insulin therapy probably does not impact on QoL. Recent findings comparing MDI with CSII suggest that CSII therapy can help to improve QoL.

The final key message of our review is that the measurement of QoL related to insulin therapy should comprise the following levels: (1) generic aspects of QoL and (2) diabetes-specific and treatment-specific aspects of perceived QoL. A better standardization of the assessment tools that are being used to measure these different aspects of QoL in people with diabetes is urgently needed, in order to facilitate comparisons between studies.

## Conflict of interest

FP has received an unrestricted grant from Novo Nordisk to study the associations between depression and negative appraisals of insulin therapy; NH is a member of the Global Diabetes Educator Advisory Board for Eli Lilly, and he has received speaker fees and research support from Elli Lilly,

Berlin Chemie, Sanofi Aventis, Roche Diagnostics and Menarini diagnostics.

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