Appropriate Insulin Regimes for Type 2 Diabetes

A multicenter randomized crossover study

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OBJECTIVE — To directly compare the rate of hypoglycemia and metabolic control achieved on once-daily ultralente insulin administration with twice-daily NPH insulin administration in patients with type 2 diabetes. Patient treatment satisfaction and quality of life were also examined before and during each treatment.

RESEARCH DESIGN AND METHODS — A crossover study was performed involving five centers and 79 patients with type 2 diabetes (fasting blood glucose >8 mmol/l) with a 2-month run-in followed by two 6-month periods of either NPH or ultralente insulin administration. Patients were managed by a specialist nurse using a dosage adjustment protocol.

RESULTS — HbA1c was lower with NPH insulin therapy during each of the 6-month periods (9.7 ± 0.2 vs. 9.1 ± 0.3 and 9.8 ± 0.2 vs. 9.0 ± 0.3 mmol/l, both P < 0.01). The difference was accounted for by higher evening glucose levels with ultralente insulin (fasting 8.2 ± 0.3 vs. 8.2 ± 0.3 mmol/l, 6:00 p.m. 11.5 ± 0.4 vs. 10.6 ± 0.4 mmol/l). Despite worse control, the total number of hypoglycemic episodes was greater with ultralente insulin (220 vs. 171), and hypoglycemic episodes requiring third-party assistance occurred almost entirely with ultralente (14 vs. 1). Treatment satisfaction scores increased more with NPH insulin compared with ultralente insulin and rose further upon changing to NPH insulin, but fell upon changing to ultralente insulin. These changes were highly significant (P < 0.001). Diabetes quality of life improved on both regimens.

CONCLUSIONS — These data clearly demonstrate the lower hypoglycemia rate, better glucose control, and greater treatment satisfaction accompanying therapy for type 2 diabetes with twice daily NPH compared with once daily ultralente insulin.

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Abbreviations: DCCT, Diabetes Control and Complications Trial; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
Study design

This study was designed to reflect everyday clinical practice; hence, routine management and adjustment of insulin dose was conducted by diabetes specialist nurses in each center. They saw the patients at frequent intervals and advised on adjustment of insulin dosage according to a predetermined protocol. They also administered the psychometric tests under standard conditions. Meetings of the specialist nurses were held at intervals to ensure as similar an approach as possible in each center.

After recruitment, all patients were assessed by a dietitian to optimize dietary therapy. This was followed by a 2-month run-in phase to ensure that blood glucose control was not improved by the study itself. Thereafter, subjects were randomized to one of two groups, provided that fasting blood glucose remained >8.5 mmol/l. One group received twice-daily NPH insulin (Insulatard; Novo Nordisk, Copenhagen, Denmark) for 6 months followed by once-daily ultralente insulin (Ultratard; Novo Nordisk) for a further 6 months. The other group received ultralente first and then NPH insulin.

Insulin therapy was commenced at a dosage of 0.3 U·kg\(^{-1}\)·day\(^{-1}\), with administration of NPH insulin divided equally between pre-breakfast and pre-dinner doses and ultralente insulin given in a single pre-dinner dose. During the first 4 weeks, the insulin dose was increased by a maximum of 4 U/day until fasting and 6:00 P.M. blood glucose was <8 mmol/l, with the rate of increase at the clinical discretion of the diabetes specialist nurse. From 4 weeks onward, the target blood glucose range was 4–7 mmol/l. To minimize risk of hypoglycemia, the total daily dose at the time of crossover was decreased by 20% when changing from ultralente to NPH insulin and was left constant when changing from NPH to ultralente insulin because of relative bioavailability.

Hypoglycemic episodes were recorded by patients in their monitoring diary using the Diabetes Control and Complications Trial (DCCT) classification system (12). The definitions of each grade were printed in the diaries. These data were recorded by the specialist nurse at each visit (4, 13, 22, and 26 weeks into each treatment period). Additionally, on each occasion, the patient’s spouse or partner was questioned in person or by telephone using four defined questions to establish whether hypoglycemia unreported by the patient had occurred. Blood glucose control was monitored using Companion 2 blood glucose meters (Abbott Laboratories), and this information was downloaded at each visit using Sensorlink (Abbott Laboratories). Tests were carried out before meals and before an evening snack (i.e., four per day) on 2 days per week. In addition, seven-point profiles (at 4:00 A.M., 8:00 A.M., 10:00 A.M., noon, 2:00 P.M., 6:00 P.M., and 10:00 P.M.) were performed once weekly during the final 4 weeks of each treatment period. HbA\(_{1c}\) was measured at each visit to assess overall blood glucose control.

At recruitment and at the end of each treatment period, the Diabetes Treatment Satisfaction Questionnaire (13) and the Diabetes Quality of Life Questionnaire (14) were administered under standard conditions by the specialist nurse. All analyses were performed in a central laboratory (Clinical Biochemistry Laboratory, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.). HbA\(_{1c}\) was measured monthly by BioRad high-performance liquid chromatography (coefficient of variation 1.3% at mean HbA\(_{1c}\) of 10.0% and 1.9% at mean HbA\(_{1c}\) of 5.8%). The HbA\(_{1c}\) assay was standardized based on that used in the DCCT central laboratory at the University of Minnesota, with an upper limit of normal of 6.1% (15). Serum samples were stored at −40°C until assay. Serum total cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic methods using a DAX-72 analyzer (Bayer, Basingstoke, U.K.). Fasting serum insulin

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**Table 1—Patient characteristics at study entry**

<table>
<thead>
<tr>
<th></th>
<th>Ultralente insulin first</th>
<th>NPH insulin first</th>
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<tbody>
<tr>
<td><strong>Personal characteristics</strong></td>
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<tr>
<td>Age (years)</td>
<td>59.6 ± 9.9</td>
<td>59.4 ± 9.0</td>
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<tr>
<td>Sex (M/F)</td>
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<td>Weight (kg)</td>
<td>81.9 ± 14.6</td>
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<td>Height (cm)</td>
<td>168.3 ± 8.7</td>
<td>169.0 ± 9.7</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td>145 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85 ± 11</td>
<td>84 ± 12</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
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<td>10.3 ± 4.7</td>
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</tr>
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<td>13</td>
</tr>
<tr>
<td>Paternal second degree</td>
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<td>12</td>
</tr>
<tr>
<td>Asthma/chronic bronchitis</td>
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</table>

Data are means ± SD or n.
was assayed in batches using an enzyme-linked immunosorbent assay kit (Dako). Fasting C-peptide was assayed by radioimmunoassay (Novo Nordisk).

Statistical methods
The projected sample size required (n = 80) was based on assumption of the previously reported rate of hypoglycemia on ultralente insulin (10). The power calculation indicated that a true difference in number of hypoglycemic episodes of 25% would be detected with a power of 80%. Results at the end of each treatment period were summarized by sequence and treatment and were analyzed using analysis of variance appropriate to the trial design. For comparisons of group data appropriate to the crossover design, analysis of variance and Gart’s test were used.

RESULTS

Protocol compliance
A total of 79 patients were entered into the study, 6 of whom were not randomized (3 because of noncompliance with treatment, 2 because of improvement of blood glucose control during the run-in phase, and 1 for unspecified reasons). Of those patients randomized to have ultralente insulin followed by NPH, 7 were withdrawn, and of those randomized to receive NPH insulin followed by ultralente, 6 were withdrawn. Of these 13 patients, 1 was noncompliant, 6 found the treatment ineffective, 3 suffered intercurrent medical problems, and 3 withdrew for unspecified reasons. A total of 60 patients completed the study.

HbA$_{1c}$
In the study as a whole, there was a highly significant difference in achieved HbA$_{1c}$ between the two treatments (P < 0.001 by analysis of variance). The group that started NPH insulin therapy first had, by chance, a higher HbA$_{1c}$ at the end of run-in (11.4 ± 0.3 vs. 10.6 ± 0.2 mmol/l), but this fell more on treatment than was the case in the ultralente insulin group. This difference in change of HbA$_{1c}$ was significant (P < 0.001) (Fig. 1). After the first 6 months of NPH insulin therapy, HbA$_{1c}$ decreased from 11.4 ± 0.3 to 9.0 ± 0.3 mmol/l (P < 0.001), whereas after the first 6 months of ultralente insulin therapy, HbA$_{1c}$ decreased from 10.6 ± 0.2 to 9.7 ± 0.2 mmol/l (P < 0.001). The better blood glucose control during therapy with NPH insulin was demonstrated by a significant difference in HbA$_{1c}$ between the groups at the end of the first 6 months (P < 0.001). After crossover from NPH to ultralente insulin, there was a deterioration in blood glucose control (HbA$_{1c}$ from 9.0 ± 0.3 to 9.7 ± 0.3%; P < 0.002). Conversely, after changeover from ultralente to NPH insulin, there was an improvement in control (HbA$_{1c}$ from 9.7 ± 0.2 to 9.0 ± 0.3; P < 0.03). During therapy with NPH and ultralente insulin, mean HbA$_{1c}$ was identical in the two treatment groups; on combining the groups, the overall HbA$_{1c}$ with ultralente insulin was 9.7 ± 0.2% and with NPH insulin, 9.0 ± 0.2% (P < 0.001). In the study as a whole, there was a substantial improvement in control when changing to insulin therapy of either type (mean HbA$_{1c}$ before insulin 11.0 ± 0.2%).

Diurnal blood glucose profiles
Figure 2 shows blood glucose measured throughout the 24-h period. Fasting blood glucose during the last 4 weeks of each treatment period was similar in each treatment group. It became clear during the study that this was the factor that prevented further dosage increase in the ultralente insulin group, with morning hypoglycemia being a potential risk. This is reflected in the analysis of the twice-weekly four-point blood glucose profiles that were used to adjust insulin dosage. These profiles showed fasting blood glucose levels of 8.3, 8.4, and 8.4 mmol/l at

![Figure 1](image1.png)

*P < 0.05; **P < 0.01; ***P < 0.001.

![Figure 2](image2.png)

For each patient, the mean of each weekly profile was analyzed. *P < 0.02, ***P < 0.001.
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striking that only four readings from 16 patients studied in one center, it was in the last 4 weeks of each treatment period), point blood glucose profiles (all performed ultralente and NPH insulin, respectively.

rates of 6.0 and 4.7 per patient-year for indicated overall reported hypoglycemia (220 vs. 171), but this did not reach statisti-

there were more hypoglycemic episodes on NPH insulin. Overall, of these hypoglycemic episodes was 0.38 per

of 1% in HbA1c was associated with a significant relationship from baseline to 13 weeks of treatment (P < 0.005). A decrease of 1% in HbA1c was associated with a weight gain of 0.44 kg.

Changes in lipid profile

After initiation of insulin therapy, plasma triglyceride levels fell in both groups (from 2.48 ± 0.33 to 2.22 ± 0.35 mmol/l on ultralente insulin and from 2.59 ± 0.19 to 2.28 ± 0.21 mmol/l on NPH insulin; P < 0.001 for both groups, P = 0.98 ultralente vs. NPH). The decrease in plasma triglyceride levels continued when blood glucose control was further improved upon changing from ultralente to NPH insulin (from 2.22 ± 0.35 to 1.92 ± 0.24 mmol/l). Even though HbA1c deteriorated upon changing from NPH to ultralente insulin, the previous improvement in plasma triglyceride levels was maintained (from 2.28 ± 0.21 to 2.32 ± 0.17 mmol/l; P < 0.001 for baseline to end of study).

Total and LDL cholesterol levels fell to a small extent, and HDL cholesterol rose to a small extent on commencing insulin ther-

Figure 3—Mean ± SEM body weight in the two groups throughout the study. - - - - , ultralente insulin first (ultralente insulin from weeks 0 to 26 and NPH insulin from weeks 26 to 52); — — , NPH insulin first (NPH insulin from weeks 0 to 26 and ultralente insulin from weeks 26 to 52). The arrow indicates time of crossover between insulin regimens.

Figure 4—Mean ± SEM treatment satisfaction scores in the two groups at the end of run-in and at the end of each 6-month treatment period. A: NPH insulin first; B: ultralente insulin first. IT, Insulatard (NPH insulin); UT, Ultratard (ultralente insulin).

0–13, 13–22, and 22–26 weeks on ultralente insulin, compared with 8.9, 8.0, and 8.2 mmol/l on NPH insulin. After breakfast at the end of the treatment periods, blood glucose was significantly higher in patients on the ultralente insulin regimen (11.7 ± 0.5 vs. 10.7 ± 0.5 mmol/l, P < 0.02), and this difference widened during the day. This significant difference was still present at 4:00 A.M. the following morning (11.4 ± 0.5 vs. 9.3 ± 0.5 mmol/l; P < 0.001).

Hypoglycemic episodes

Despite higher HbA1c during ultralente insulin therapy, there were more hypoglycemic episodes that required help from another person (14 vs. 1; P < 0.01). The rate of these hypoglycemic episodes was 0.38 per patient-year on ultralente insulin and 0.03 per patient-year on NPH insulin. Overall, there were more hypoglycemic episodes reported on ultralente than on NPH insulin (220 vs. 171), but this did not reach statistical significance (P = 0.08). The total episodes indicated overall reported hypoglycemia rates of 6.0 and 4.7 per patient-year for ultralente and NPH insulin, respectively.

When inspecting the individual seven-point glucose profiles (all performed in the last 4 weeks of each treatment period), from 16 patients studied in one center, it was striking that only four readings <3.0 mmol/l were obtained, and three of these readings were at 4:00 A.M. Hypoglycemic episodes that occurred after the insulin dose adjustment had achieved stable blood glucose control during each period were considered. During the final 13 weeks of each treatment period, between visits 4 and 5 and 7 and 8, only two hypoglycemic episodes requiring third-party help occurred—both in patients on ultralente insulin therapy.

Insulin dose

At the end of the first treatment period, the total daily insulin dose was 49.0 ± 4.6 U on ultralente insulin and 62.3 ± 5.0 U on NPH insulin. During the second treatment period, dose requirements were 72.2 ± 7.6 U on ultralente insulin and 60.6 ± 5.8 U on NPH insulin. The difference between the two treatments was significant (P < 0.01), but there was no effect of sequence (P = 0.085). At the end of the NPH insulin treatment period, the morning and evening doses were 35.0 ± 2.5 and 29.1 ± 2.2 U, respectively.

Weight change

The observed changes in weight mirrored the degree of improvement in HbA1c (Fig. 3). Thus, weight increased more rapidly on the NPH insulin regimen (81.4 ± 2.5, 82.5 ± 2.5, 85.6 ± 2.5, and 88.0 ± 2.5 kg at 0, 4, 13, and 26 weeks), but leveled out thereafter (88.2 kg at 52 weeks). On achieving worse HbA1c levels during ultralente insulin therapy, weight gain was less rapid (80.7 ± 2.9, 80.6 ± 2.8, 82.2 ± 2.8, and 84.0 ± 2.9 kg at 0, 4, 13, and 26 weeks) but became similar as HbA1c improved during NPH insulin therapy (86.7 ± 3.1 kg at 52 weeks). The mean weight gain in the study was 6.0 kg. The weight gain was largely restricted to the early months of insulin therapy.

The analysis of covariance of weight change against change in HbA1c showed a significant relationship from baseline to 13 weeks of treatment (P < 0.005). A decrease of 1% in HbA1c was associated with a weight gain of 0.44 kg.
apy (from 5.7 ± 0.2 to 5.4 ± 0.2, from 3.8 ± 0.2 to 3.6 ± 0.2, and from 1.21 ± 0.06 to 1.25 ± 0.05 mmol/l, respectively), and these changes were all significant on paired analysis (P < 0.001).

**Blood pressure**

There was no significant change in either systolic or diastolic blood pressure on commencing insulin therapy, nor was there any significant difference between the two treatments.

**Psychometric data**

The Treatment Satisfaction Questionnaire showed that for the group treated with NPH insulin first, there was a marked and significant increase in treatment satisfaction during the first 6 months (from 26.7 ± 1.1 to 30.7 ± 1.0; P < 0.001) (Fig. 4). In this analysis, the higher the score, the more satisfied the patient; after the change from a twice-daily to a once-daily regimen; however, satisfaction fell (from 30.7 ± 1.0 to 26.0 ± 1.6; P < 0.02). Conversely, there was a small rise in treatment satisfaction on starting once-daily ultralente insulin treatment, followed by a further rise upon changing to NPH insulin (27.9 ± 1.2, 30.9 ± 1.1, and 33.2 ± 0.6; P < 0.001 for each). In the crossover study as a whole, there was a highly significant difference in treatment satisfaction between the two insulin regimens (P < 0.001).

There are four domains in the Quality of Life Questionnaire (Fig. 5). The impact of going onto insulin was considerable in each group, but was not affected by the type of regimen. Satisfaction increased more on NPH insulin in each group, and this was significant between the insulin regimens (P < 0.002), confirming the independent data from the Treatment Satisfaction Questionnaire. Social and diabetes-related worry scores were not changed either by commencing insulin or by the type of insulin regimen. Overall, more people reported an excellent overall quality of life on NPH insulin therapy (10 vs. 3).

**CONCLUSIONS** — The study has demonstrated that HbA1c was significantly better in type 2 diabetic patients on therapy with twice-daily NPH insulin at 9.0%, compared with 9.7% on ultralente insulin therapy. In addition, hypoglycemic episodes requiring third-party help were less common on the NPH insulin regimen. Commencement of insulin therapy was associated with greater treatment satisfaction and better quality of life, and this improvement was maintained, especially in patients on NPH insulin therapy. Weight gain was not marked but was inversely proportional to HbA1c. Blood pressure was not affected by introduction of insulin therapy despite the weight gain, and plasma triglyceride levels fell in proportion to improvement in glucose control.

Concern about the risk of hypoglycemia has been an inhibitory factor for introduction of insulin therapy as soon as appropriate in type 2 diabetes (1,3,4). Elderly people appear to be at particular risk of hypoglycemia (4,5,16). The original UKPDS protocol described only use of once-daily ultralente insulin administered before the evening meal (8). This regimen has been reported to be associated with a relatively high rate of hypoglycemia (5.6–12.0 hypoglycemic episodes per patient-year [9,10]). In contrast, use of twice-daily intermediate-acting insulin under usual clinical conditions in a 6-month crossover design has been reported to be associated with only three hypoglycemic episodes per patient-year (4). Such comparisons between studies are unsatisfactory because the degree of blood glucose control achieved, the extent of education provided, and the impact of local care provision are likely to differ substantially and to directly affect the reported rates of hypoglycemia.
The present study is the first to report a direct comparison of twice-daily intermediate-acting insulin and once-daily long-acting insulin. The data suggest that when the former regimen is used to achieve HbA$_1c$ levels of $\sim 9.0\%$, the risk of hypoglycemia requiring help from another person is very small (0.03 per patient-year), and the risk of any hypoglycemic episode is 4.7 per patient-year. When the once-daily long-acting regimen is used to achieve HbA$_1c$ levels of $\sim 9.7\%$, however, the risk of third-party hypoglycemic episodes is 0.38 per patient-year and the risk of any hypoglycemic episode is 6.0 per patient-year. The difference in total number of reported hypoglycemic episodes did not reach statistical significance, but this could represent a type 2 statistical error because the total number of subjects completing the study was 25% less than that allowed for in the power calculation. Variability of absorption of different insulin preparations is likely to contribute to rates of hypoglycemia, and variability increases with length of absorption time. The coefficient of variation of absorption of ultralente insulin has been reported to be $\sim 40\%$ (17).

It is possible that true hypoglycemic episodes may be either over- or under-reported (18). Because of this, each patient’s spouse or partner was questioned by the diabetes specialist nurse about the possibility of unreported hypoglycemic episodes. On no occasion during the trial was an unreported hypoglycemic episode identified. Two episodes were reported during the 2-month run-in phase when ambient blood glucose levels were high. It is unlikely, therefore, that the observed rates of hypoglycemia in this study are underestimated.

The goals for glycemic control in this study were set in 1993 and reflect the clinical goal of relieving hyperglycemic malaise, as identified in our previous study (7). Recently, the UKPDS reported the levels of blood glucose control achieved when the goal of therapy was to keep fasting blood glucose $<6.0$ mmol/l. The achieved mean steady-state HbA$_1c$ levels of $-8.0\%$ are only 1.0% below those achieved in the NPH insulin arms of the present study. Ideally, blood glucose control should be as tight as can reasonably be achieved for any one individual. In practice, comorbidity and frailty frequently ensure individual control goals to be less stringent. This study is important in that it demonstrates that good control can be achieved without sacrificing safety in terms of hypoglycemic risk. The study should not be interpreted to mean that all people with type 2 diabetes requiring insulin should receive twice-daily intermediate-acting insulin. Especially for younger patients, who have the most lifetime during which to benefit from treatment, it is appropriate to consider additional treatment with metformin or short-acting insulin. Obese patients have clear benefits from continuing metformin therapy when insulin is commenced (19).

Weight gain after commencing insulin therapy is a common finding despite prior warning and specific dietary advice, and previous studies have reported median weight gains of between 2 kg/year (20) and 4.2 kg/6 months (3). In some individuals, weight gain reflects the reversal of previous weight loss due to insulin deficiency, and it is noteworthy that the patients who gained $>8$ kg during a previous study had lost the most weight over the 12 months before the study (mean loss 4.9 $\pm$ 0.7 kg). The initial rate of weight gain tended to plateau in the present study, and this phenomenon is likely to underlie the observation of a greater rate of weight gain in shorter studies (e.g., $2.9 \pm 0.5$ kg over 3 months (21)). The factors underlying the achievement of a new steady-state body weight require further investigation. The possible effect of insulin as an appetite stimulator is noteworthy (22), although there was no relationship between fasting plasma insulin levels and rate of weight gain in the present study. Relationships with mean diurnal plasma insulin levels and insulin dose have been reported (23). During the period of ultralente insulin therapy as a second treatment, plasma free insulin levels were highest (56.7 $\pm$ 16.0 mU/l) and weight gain was lowest (0.2 kg over 6 months). Yki-Jarvinen et al. (21) noted that weight gain was directly related to improvement in blood glucose control, and this is corroborated by the present data. It would appear likely that weight gain is a consequence primarily of prevention of habitual calorie loss as urinary glucose and of maintenance of previous energy intake. In explaining the possibility of weight gain to patients about to commence insulin therapy, it is important to point out that not all weight gain is adipose tissue accumulation. One-third of the weight gain is muscle tissue and two-thirds is adipose tissue (24). It is common experience that a small minority of patients gain weight enormously on transfer to insulin therapy (5). This has been ascribed to a specific problem of appetite control (25), and it is important that the experience of such patients does not inhibit introduction of insulin therapy at an appropriate time for all other patients.

Hyperinsulinemia has been reported as a risk factor for atherosclerosis (26), and this inhibited early use of insulin in type 2 diabetes. The significant improvement in serum triglyceride levels and slight fall in total cholesterol reported in the present study has previously been observed on commencing insulin therapy in type 2 diabetes (7,21). Because plasma triglyceride level is an independent risk factor for coronary heart disease (27), it is likely to be a major contributory factor to the decrease in overall macrovascular disease progression in well-controlled type 2 diabetic patients (1). A further adverse macrovascular risk factor is that of hypertension. There are strong theoretical grounds for considering that elevation of plasma insulin levels could exacerbate any tendency to hypertension (28–30). However, both in the present study and in that presented by Yki-Jarvinen et al. (21), there was no increase in blood pressure despite a marked increase in plasma insulin levels. Moreover, blood pressure did not increase despite weight gain, a change that by itself would be expected to be a causative factor for hypertension.

The effect of insulin in relieving the tiredness and often unrecognized general malaise of poorly controlled type 2 diabetes has previously been quantified using psychometric tests (7,21,31). The present study is the first to assess both treatment satisfaction and quality of life using validated psychometric instruments. Although treatment satisfaction improved and the social worry score remained constant during insulin therapy, it should not be overlooked that the change to insulin therapy did have a distinct impact on daily life (Fig. 5). The significantly greater treatment satisfaction afforded by twice-daily injection of intermediate-acting insulin and compared with once-daily injections is noteworthy. Doctors and nurses tend to assume that once-daily therapy will be more acceptable to patients, and the present data clearly show that this is not the case.

In conclusion, this 14-month study demonstrates that twice-daily NPH insulin therapy allows both lower hypoglycemia rates and better diurnal blood glucose control compared with once-daily ultralente insulin therapy. Patients felt better on insulin treatment of either type and preferred twice-daily NPH insulin.
Appropriate insulin regimes in type 2 diabetes

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References