Improved Biomedical and Psychological Outcomes 1 Year After Structured Education in Flexible Insulin Therapy for People With Type 1 Diabetes

The U.K. DAFNE experience

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OBJECTIVE—DAFNE (Dose Adjustment For Normal Eating), a structured education program in flexible insulin therapy, has been widely adopted in the U.K. after validation in a randomized trial. To determine benefits in routine practice, we collected biomedical and psychological data from all participants attending during a 12-month period.

RESEARCH DESIGN AND METHODS—HbA_{1c}, weight, self-reported hypoglycemia awareness, severe hypoglycemia frequency, PAID (Problem Areas In Diabetes), HADS (Hospital Anxiety and Depression Scale), and EuroQol Group 5-Dimension Self-Report Questionnaire scores were recorded prior to DAFNE and after 1 year.

RESULTS—Complete baseline and follow-up HbA_{1c} data were available for 639 (54.9%) of 1,163 attendees. HbA_{1c} fell from 8.51 ± 1.41 (mean ± SD) to 8.24 ± 1.29% (difference 0.27 [95% CI 0.16–0.38]; $P < 0.001$), with a greater mean fall of 0.44% from baseline HbA_{1c} >8.5%. Severe hypoglycemia rate fell from 1.7 ± 8.5 to 0.6 ± 3.7 episodes per person per year (1.1 [0.7–1.4]) and hypoglycemia recognition improved in 43% of those reporting unawareness. Baseline psychological distress was evident, with a PAID score of 25.2 and HADS scores of 5.3 (anxiety) and 4.8 (depression), falling to 16.7 (8.5 [6.6–10.4]), 4.6 (0.7 [0.4–1.0]), and 4.2 (0.6 [0.3–0.8]), respectively (all $P < 0.001$ at 1 year). Clinically relevant anxiety and depression (HADS ≥8) fell from 24.4 to 18.0% and 20.9 to 15.5%, respectively.

CONCLUSIONS—A structured education program delivered in routine clinical practice not only improves HbA_{1c} while reducing severe hypoglycemia rate and restoring hypoglycemia awareness but also reduces psychological distress and improves perceived well-being.

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Structured education on flexible insulin treatment has been shown to result in improved glycemic control, with lower glycated hemoglobin (HbA_{1c}) and less severe hypoglycemia 3–6 years later (1,2). The U.K.-based DAFNE (Dose Adjustment For Normal Eating) program is a 5-day course for adults with type 1 diabetes, focusing on adjustment of insulin according to carbohydrate intake and reflective use of home blood glucose monitoring data, derived from principles pioneered in the successful German language program developed in Düsseldorf and widely used in Germany and Austria (1,2). After initial developmental work, the U.K. program was tested in a three-center randomized controlled trial (RCT) in which DAFNE training was associated with clinically relevant improvements in HbA_{1c} and in aspects of quality of life specific to diabetes (3).

After completion of this trial, DAFNE has been adapted as part of routine clinical practice in >60 centers in the U.K. and the Republic of Ireland. The rollout of the program has occurred gradually, with seven centers starting DAFNE in 2002 and more centers joining each year since. Expansion has been accompanied by a quality assurance program, including collection of participant data on various biomedical and psychological parameters in a central audit database prior to course enrollment and at annual follow-up visits.

To determine whether the benefits of DAFNE training observed in the trial setting translate into routine clinical practice, we have conducted a retrospective audit of biomedical and psychological outcomes at baseline (enrollment in the program) and at 1 year posttraining, including all participants who attended DAFNE courses in one 12-month period. The primary purpose of the study was to test the hypothesis that DAFNE education delivered in routine care would be associated with similar improvements in biomedical and psychological outcomes to those seen in the RCT.

RESEARCH DESIGN AND METHODS—This study was a retrospective audit of data collected prior to attendance at a DAFNE course and at follow-up 1 year later. Regulatory approval for data collection and audit was obtained from the Newcastle and North Tyneside Health Authority Joint Ethics Committee. Demographic and biomedical data collected comprised age, sex, duration of diabetes, height, weight, blood pressure, HbA_{1c}, serum creatinine, and

lipid profile. Self-reported frequency of severe hypoglycemia was recorded based on the number of times an individual had required assistance from another person to treat hypoglycemia as a result of incapacity in the year before attendance at a DAFNE course. In addition, subjects were asked to rate their perceived awareness of hypoglycemia by stating whether they usually recognized that they were hypoglycemic at a blood glucose concentration ≥ 3 mmol/L, <3 mmol/L, or not at all.

Psychological assessment included three well-validated measures of psychological well-being relevant to diabetes: the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), a generic measure of quality of life (4); the Hospital Anxiety and Depression Scale (HADS), a screening tool for evidence of anxiety and depression (5); and Problem Areas In Diabetes (PAID), a specific measure developed to evaluate the impact of diabetes on psychological well-being (6). Scores >8 on HADS and ≥ 40 for PAID were used to define clinically relevant psychological distress. EQ-5D health states were determined using an algorithm based on the U.K. population.

For this study, baseline data were extracted for all participants attending DAFNE courses during a 12-month period (from 1 January to 31 December 2005), together with linked follow-up data obtained between 300 and 420 days postattendance at DAFNE. Data from all centers participating in DAFNE were pooled for analysis. Statistical comparisons between baseline and follow-up data were made using a population-averaged linear model with robust SEs and exchangeable correlation structure to allow for clustering by center for biochemical and physical parameters and psychological measures. A negative binomial model with a coefficient for before versus after DAFNE with a population-averaged exchangeable correlation and robust SEs to allow for clustering on center were used for hypoglycemia data. To avoid error due to regression to the mean, the change in HbA_{1c} percentage was regressed on the mean of the HbA_{1c} percentage on the two occasions (7). All data are presented as mean and SD or range.

RESULTS

Demographics and data quality
In the audit year, 31 DAFNE centers were active and 1,163 individuals attended courses. Complete baseline and follow-up HbA_{1c} data were available for 639 (54.9%) subjects at 29 centers. The mean interval between baseline and follow-up was 380 ± 62 days. Compared with those with follow-up data, those with only baseline data available were younger (mean age 38.8 ± 12.8 vs. 41.5 ± 13.7 years) with shorter duration of diabetes (15.8 ± 12 vs. 18.0 ± 12.1 years) and higher mean HbA_{1c} (8.7 ± 1.6 vs. $8.5 \pm 1.4\%$).

There was a wide distribution in baseline HbA_{1c} within the cohort (range 5.2–15.3%, lower quartile 7.6%, upper quartile 9.3%) with 21.0% of subjects having a baseline HbA_{1c} of $<7.5\%$, the cutoff used for exclusion from the original DAFNE RCT.

Changes in HbA_{1c}, lipids, weight, and blood pressure
Data on changes in biomedical parameters for the 639 subjects with follow-up data are shown in Table 1. Over the course of the year post-DAFNE, mean HbA_{1c} fell by 0.27% (95% CI 0.17–0.38; $P < 0.001$), with no accompanying changes in weight, blood pressure, or lipid profile. The regression slope of the mean pre- and post-DAFNE HbA_{1c} plotted against the difference (post- minus pre-DAFNE) was 0.092% ($P = 0.015$), indicating a greater fall in HbA_{1c} for those with higher mean HbA_{1c}, with mean fall in HbA_{1c} of 0.44% for those with baseline $HbA_{1c} > 8.5\%$.

Frequency of severe hypoglycemia
Baseline and follow-up data on hypoglycemia frequency were available for 501 subjects. Of these, 125 (25%) had suffered at least one severe hypoglycemic event in the year preceding DAFNE, with 80 (16%) having had more than one episode during the preceding year. After DAFNE, 62% of those who had experienced severe hypoglycemia remained free of further episodes at follow-up, while 10% of those who had been free of severe hypoglycemia in the preceding year experienced one or more episodes. The overall mean severe hypoglycemia rate for the cohort fell from 1.93 (range 0–99) to 0.61 (0–70) episodes/person/year after DAFNE (difference 1.15 [95% CI 0.73–1.57]; $P < 0.001$).

Changes in self-reported hypoglycemia awareness
For the purposes of this analysis, those reporting symptom onset <3 mmol/L or not at all were considered to have impaired awareness of hypoglycemia, and those recognizing hypoglycemia symptoms at a glucose of ≥ 3 mmol/L were considered hypoglycemia aware. Baseline data from this question were available for 539 subjects, of whom 324 (60%) were hypoglycemia aware and 215 (40%) had impaired awareness. Frequency of severe hypoglycemia in the year preceding DAFNE was more than threefold higher among subjects reporting impaired awareness (Table 2).

At follow-up, 43% of those with impaired awareness at enrollment reported restoration of the ability to detect hypoglycemia at a blood glucose >3 mmol/L. The rate of severe hypoglycemia fell significantly in both groups (Table 2).

Psychological data
Complete pre- and postcourse psychological data were available for 459 subjects (EQ-5D), 484 subjects (PAID), and 484 subjects (HADS). Mean baseline and follow-up data derived from these measures are presented in Table 3. At baseline, the majority of subjects showed no impairment in any of the domains of the

Table 1—Biochemical and physical parameters pre- and post-DAFNE

Parameter	Pre-DAFNE		1 year post-DAFNE	
	Mean	SD	Mean	SD
HbA_{1c} (%)	8.51	1.41	8.24*	1.29
Serum creatinine (mol/L)	80.3	20.1	82.2	22.8
Total cholesterol (mmol/L)	4.7	0.9	4.7	2.0
Triglyceride (mmol/L)	1.1	0.8	1.1	1.3
HDL cholesterol (mmol/L)	1.6	0.5	1.7	0.5
Weight (kg)	75.1	13.8	75.1	14.4
Systolic blood pressure (mmHg)	129	17.2	129	16.6
Diastolic blood pressure (mmHg)	75	9.7	75	9.9

*$P < 0.001$ for comparison of pre- and post-DAFNE mean values. There were no significant differences between pre- and post-DAFNE means for other parameters.

Table 2—Hypoglycemia awareness status and severe hypoglycemia rates at enrollment and 1 year post-DAFNE

		Status at 1 year			SH pre-DAFNE		SH post-DAFNE	
Baseline	n	Aware	Impaired	No data	Mean	SD	Mean	SD
Aware	324	202 (62)	81 (25)	41 (13)	0.87	3.99	0.35*	1.63
Impaired awareness	215	92 (43)	97 (45)	26 (12)	3.6	13.6	1.3*	5.9
All	539	294 (54)	178 (33)	67 (12)	1.7	8.5	0.6*	3.7

Data are n (%) of people in each category at baseline and follow-up, together with self-reported mean number of severe hypoglycemic (SH) episodes per subject for the year preceding DAFNE attendance and for 1st year post-DAFNE. *$P < 0.05$ for comparison of pre- and post-DAFNE mean data.

EQ-5D, and no changes were observed during follow-up. However, there was a small but statistically significant improvement in subjects' overall well-being as rated on the visual analog scale (VAS) element of the EQ-5D.

The cohort did demonstrate a high prevalence of baseline psychological distress as indicated by the HADS and PAID results. For the former, 24.4 (anxiety) and 20.5% (depression) of subjects scored ≥8, and 21.2% of subjects scored ≥40 on the PAID questionnaire.

At follow-up, there were statistically significant falls in the mean scores for all three of these measures (Table 3). In addition, there were falls in the prevalence of scores of ≥8 on both HADS component scales (for anxiety, from 24.4 to 18.0%; for depression, from 20.5 to 15.5%) and a fall in the prevalence of subjects with PAID scores of ≥40 (from 20.5 to 9.9%).

CONCLUSIONS—The U.K. DAFNE program was initiated in response to the success of an earlier program developed in Düsseldorf (1,2). This program was associated with a prolonged improvement in mean blood glucose control, as exemplified by reduction in HbA_{1c} concentration and a fall in severe hypoglycemia rate (8,9). In 1999, with the help of the Düsseldorf team, the program materials were translated into English (including replacement of some food images with pictures of foods more relevant to British culture), and the U.K. program was tested in an RCT setting. After the success of this trial (3), the DAFNE program has been widely adopted for the management of type 1 diabetes in the U.K. However, those now being enrolled into the program represent a broader demographic group than those who were included in the original study. Although subjects with an HbA_{1c} <7.5% were excluded from the RCT, 21% of this audit cohort had HbA_{1c} ≤7.5% and 25% had experienced severe hypoglycemia, with 16% having experienced recurrent episodes.

The high prevalence of subjects with HbA_{1c} close to target in the present cohort suggests that improving glycemic control may not be the main motivation for patients and health professionals to consider DAFNE and that other perceived benefits, including increased lifestyle flexibility, hypoglycemia avoidance, and the improvements in psychological well-being seen in the original RCT, may be factors in the decision to participate.

In terms of biomedical outcomes, these data show that attendance at a DAFNE course delivered in routine clinical practice is associated with a small but statistically significant improvement in HbA_{1c}

during a 12-month period, achieved without weight gain. The smaller magnitude of the change in HbA_{1c} compared with that achieved in the RCT may reflect the high proportion of individuals enrolled in the program with initial HbA_{1c} values at or close to target, with the mean HbA_{1c} of the cohort being considerably lower than the mean baseline value of 9.4% reported for the RCT. Indeed, excluding those whose HbA_{1c} was <7.5% from the current analysis reveals that the mean fall in HbA_{1c} for the remainder of the cohort with follow-up data was 0.46%, which is close to that seen at 12 months in the original RCT. The original German program reports greater falls in HbA_{1c}, and we may speculate on the reasons for this because the DAFNE program tried to be faithful to the concepts underpinning the Düsseldorf program. Differences in the health care culture may contribute, and it should be noted that DAFNE did not offer specific structured follow-up after the initial training.

In contrast to the DAFNE RCT, this evaluation demonstrates an association between DAFNE education and reduction in self-reported severe hypoglycemia with perceived improvement in hypoglycemia recognition among those who reported inability to detect hypoglycemia at enrollment. These data are encouraging and suggest that structured education on insulin dose adjustment for carbohydrate intake and exercise can be effective at preventing hypoglycemia and restoring hypoglycemia awareness. The documentation of improved hypoglycemia awareness status after participation in a training program focusing on flexible insulin therapy we believe to be novel. It should be recognized that a limitation of the data is that they are based on recollection and self-reporting of hypoglycemia experience, with no prospective collection of hypoglycemia data during the course of the year. Nevertheless, it seems clear that participating in DAFNE both reduces the occurrence of severe hypoglycemia and helps restore awareness where this has been lost, despite the improvement in overall glucose control that might have been expected to increase the severe hypoglycemia experience. The benefits seen may relate to reduced exposure to low blood glucose levels in general because there are robust data to show that antecedent hypoglycemia limits the stress response to subsequent episodes in a reversible way (10–12).

In the DAFNE RCT, positive psychological outcomes of the program were

Table 3—Changes in measures of psychological well-being/distress

	Baseline		1 year post-DAFNE		
	Mean	SD	Mean	SD	P value
EQ-5D	0.84	0.16	0.84	0.18	NS
EQ-5D VAS	71.2	20.8	75.1	18.4	0.002
PAID	25.2	17.4	16.7	14.1	<0.001
HADS (anxiety)	5.3	3.7	4.6	3.5	<0.001
HADS (depression)	4.8	3.2	4.2	3.1	<0.001

Mean scores for psychological parameters measured at pre-DAFNE visit and 1 year post-DAFNE, with P value for comparison of means.

demonstrated using the Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire. For the purpose of auditing the effects of DAFNE in clinical practice, this questionnaire was replaced by the use of one diabetes-specific measure, PAID, and two generic measures, HADS and EQ-5D. These three measures have been widely used for evaluation of changes in perceived health status and psychological distress after an intervention in studies involving diabetic subjects and are well validated (13).

As in previous studies, the main EQ-5D scale shows poor sensitivity for detection of changes in perceived health status in diabetes (14). This reflects the domain structure of the questionnaire, with questions on mobility, ability to self-care, performance of usual activities, pain, and anxiety or depression, the majority of which are not relevant to a healthy, ambulatory population. However, the EQ-5D also includes a VAS on which subjects are asked to rate their perceived health status, and this did show an improvement of almost 5% at 1 year post-DAFNE.

HADS comprises two separate scales designed to identify symptoms of anxiety and depression in ambulatory subjects and has been widely used in the study of mental health status in subjects with chronic diseases. The original authors of the scale recommended that a cutoff of 8 on each of the respective scales is consistent with clinically significant anxiety and depression of mild severity, with scores of ≥ 11 indicating moderate severity. The use of a cutoff value of 8 has been validated by subsequent work, with a sensitivity and specificity for identification of clinically relevant anxiety and depression ranging between 0.7 and 0.9 among published studies (15). For the purpose of this audit, we have used the cutoff of 8 to determine prevalence of mild severity for both dimensions. On this basis, we identified a prevalence of mild to moderate anxiety and depression of 24.4 and 20.5%, respectively, with mean baseline scores of 5.3 and 4.8. These figures compare with an overall prevalence of 19.8 and 7.6% respectively reported for a previous U.K. single-center cohort of 313 type 1 diabetic subjects (16), although a higher prevalence has been reported in a further U.K. cohort including both type 1 and type 2 diabetic patients (17). These data suggest a higher prevalence of significant psychological distress among patients being referred for DAFNE. Because the program does not specifically

address psychological issues, the fall in the prevalence of high scores on these scales after DAFNE suggests that much of the measured distress is related to diabetes and may be ameliorated by acquisition of new skills after participation in structured education.

This concept is supported by the changes seen in mean PAID scores and in the prevalence of PAID scores ≥ 40. The PAID scale is designed to identify psychosocial distress specific to diabetes and has been validated in both North American and European populations, and a cutoff of 40 has been proposed as defining subjects with significant psychological distress. The mean baseline score observed in this cohort is very similar to that reported for a large Dutch type 1 diabetic cohort (24.6 ± 18.7), but 1 year after the structured education, it had fallen to 16.7 + 14.1, a score considerably lower than any previously reported for unselected type 1 diabetic populations (18).

Taken together, these audit data suggest that the benefits of DAFNE training observed in the original DAFNE RCT are obtained in those undergoing DAFNE training in routine clinical practice, with significant improvements in glycemic control and psychological distress. In addition, these data indicate a positive impact of DAFNE on self-reported frequency of severe hypoglycemia and perceived hypoglycemia awareness.

The use of data collected in routine clinical practice is both a strength and a major limitation. Routine data clearly reflect the true clinical impact of an educational intervention when delivered outside the setting of a clinical trial. However, in the absence of specific resources to support data collection, it is challenging to collect complete datasets. As a consequence, data are incomplete, with only 55% ascertainment at follow-up. There is a risk that the beneficial effects observed may have been overestimated if a greater proportion of those who responded less well had defaulted follow-up and, thus, were not included in the data collection. However, review of follow-up rates in centers suggests that the problem was related to the difficulty of collecting audit data in routine practice rather than default, and it is likely that most individuals with missing data are continuing to use DAFNE principles and attending some follow-up.

In conclusion, the audit data reported here suggest that the benefits of DAFNE training observed in the original DAFNE RCT are obtained in routine clinical practice,

with significant improvements in HbA$_{1c}$ and psychological distress sustained to at least 1 year. Furthermore, these data indicate additional benefit in reducing rates of severe hypoglycemia and improving hypoglycemia awareness. These findings, coupled with previously published evidence confirming its cost-effectiveness, make a powerful case for routine provision of high-quality structured education programs for adults with type 1 diabetes.

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