Research: Educational and Psychological Issues

Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with Type 1 diabetes

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Abstract

Aims   To determine the impact of structured education promoting flexible intensive insulin therapy on rates of diabetic ketoacidosis, and the costs associated with emergency treatment for severe hypoglycaemia and ketoacidosis in adults with Type 1 diabetes.

Methods   Using the Dose Adjustment For Normal Eating research database we compared the rates of ketoacidosis and severe hypoglycaemia during the 12 months preceding Dose Adjustment For Normal Eating training with the rates during the 12-month follow-up after this training. Emergency treatment costs were calculated for associated paramedic assistance, Accident and Emergency department attendance and hospital admissions.

Results   Complete baseline and 1-year data were available for 939/1651 participants (57%). The risk of ketoacidosis in the 12 months after Dose Adjustment For Normal Eating training, compared with that before training, was 0.39 (95% CI: 0.23 to 0.65, $P < 0.001$), reduced from 0.07 to 0.03 episodes/patient/year. For every 1 mmol/mol unit increase in HbA_{1c} concentration, the risk of a ketoacidosis episode increased by 6% (95% CI: 5 to 7%; 88% for a 1% increase), and for each 5-year increase in diabetes duration, the relative risk reduced by 20% (95% CI: 19 to 22%). The number of emergency treatments decreased for ketoacidosis ($P < 0.001$), and also for severe hypoglycaemia, including paramedic assistance ($P < 0.001$), Accident and Emergency department attendance ($P = 0.029$) and hospital admission ($P = 0.001$). In the study cohort, the combined cost of emergency treatment for ketoacidosis and severe hypoglycaemia fell by 64%, from £119,470 to £42,948.

Conclusions   Structured training in flexible intensive insulin therapy is associated with a 61% reduction in the risk of ketoacidosis and with 64% lower emergency treatment costs for ketoacidosis and severe hypoglycaemia.

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Introduction

Individuals with Type 1 diabetes are vulnerable to ketoacidosis if exogenous insulin is relatively deficient and to

severe hypoglycaemia if insulin is delivered in relative excess. Both acute complications are, at least, disabling and, at worst, can be fatal. Whilst the number of deaths as a result of ketoacidosis or severe hypoglycaemia is lower than for cardiovascular disease in people with Type 1 diabetes, these acute metabolic decompensations cause 9–13% of deaths in adults [1,2], with a higher proportion of 20–44% of deaths in children and young adults (excluding ketoacidosis at diagnosis) [1–5]. In addition to the detrimental personal impact of ketoacidosis and severe hypoglycaemia,

What's new?

• Diabetic ketoacidosis is a common but potentially fatal medical emergency. Among people with Type 1 diabetes there are ~6000 episodes per year in the UK but, until now, few interventions to reduce episodes have been reported. Both ketoacidosis and severe hypoglycaemia have a major impact on quality of life and attract considerable emergency treatment costs.

• Our data suggest that structured training in insulin self-management reduces both the rates of ketoacidosis and severe hypoglycaemia requiring emergency treatment, and their associated costs. This study reinforces the importance of making high-quality structured education more readily available to people with Type 1 diabetes.

the financial cost to healthcare providers of treating these acute complications is considerable [6]. The frequency of ketoacidosis in adults with Type 1 diabetes is estimated to be 0.8 to 8.6 events per 100 patient-years in the USA, Europe and Israel [7–9]. Figures from the recently published National Diabetes Audit [10] in the UK show that 6141 people with Type 1 diabetes were admitted to hospital once or more with ketoacidosis over a 12-month period, which is equivalent to an incidence of 3.32%. Each episode of ketoacidosis costs on average ~£900 [6], equating to a total of ~£5.5 m per year. It has been estimated that the incidence rate for emergency treatment of severe hypoglycaemia in people with Type 1 diabetes is ~11.5 per 100 patients-years [11]. In that study, the associated cost was estimated to be ~£6.5 m across the UK. More recently, in 2010, the estimated costs of severe hypoglycaemia were calculated at £13.6 m for England, although in that study no differentiation was made between Type 1 and Type 2 diabetes [12].

Among people with established Type 1 diabetes, ketoacidosis and severe hypoglycaemia are potentially avoidable if exogenous insulin is administered appropriately. As Type 1 diabetes is a long-term condition requiring intensive daily self-management, high-quality education and training are essential. The Dose Adjustment For Normal Eating (DAFNE) [13] structured education programme has now been delivered to > 28 000 adults with Type 1 diabetes in the UK. It was primarily designed to increase dietary freedom and improve blood glucose control and, thereby, reduce the risk of long-term microvascular complications. An earlier observational study reported a reduced incidence of severe hypoglycaemia and improved awareness of hypoglycaemic symptoms after DAFNE training [14]. The German model [15] on which DAFNE is based has also previously reported a reduction in the incidence of both ketoacidosis and severe hypoglycaemia (defined as a reduction in hypoglycaemic coma or the need for intravenous glucose) in a high-risk cohort [16].

As the financial costs of ketoacidosis and severe hypoglycaemia are substantial, we undertook a detailed retrospective analysis among a large cohort of adults with Type 1 diabetes attending a DAFNE course. Our aim was to determine the impact of DAFNE training on the incidence of emergency treatment of both acute complications, and to calculate the associated costs to the healthcare system based on the level of healthcare input required and the length of hospital stay. In addition, we examined the relationship between HbA$_{1c}$ and the incidence of ketoacidosis.

Patients and Methods

The DAFNE research database was created as part of a programme of research supported by the UK National Institute of Health Research. Biomedical and psychosocial data are collected from participants attending DAFNE courses from selected secondary care diabetes units (21 in total) as part of their routine clinical care. HbA$_{1c}$ concentration was measured at local Diabetes Control and Complications Trial (DCCT)-aligned laboratories, with a normal range considered to be 35–48 mmol/mol. Patients participating in DAFNE training at these centres are invited to give consent for their yearly biomedical and psychosocial data to be stored anonymously on the database. Clinical staff contact participants directly and examine medical records to gather retrospective biomedical data, specifically enquiring about any episodes of ketoacidosis or severe hypoglycaemia, the level of healthcare input required, and, if admitted, the length of stay. Severe hypoglycaemia is defined as an episode requiring the assistance of a third party in order to recover [17,18]. Ketoacidosis is defined as a physician-diagnosed episode requiring admission to hospital. All records of participants recruited between December 2008 and June 2011 were included in the present study. Emergency treatment costs were calculated for paramedic assistance, Accident and Emergency department attendance and hospital admissions (based on age and length of stay), using NSRC1 NHS Trust reference cost schedule 2010–2011 [6].

Ethics approval for this research database was approved by the Trent Research Ethics Committee, 10/10/08, Rec No. 08/H0405/48, and participants are required to give written informed consent.

Statistical analyses

We constructed negative binomial models with a fixed factor for before vs after DAFNE training and a population-averaged exchangeable correlation to allow for clustering by centre. This allows modelling of variables which are over-dispersed relative to a Poisson model. We assumed that rates for individuals came from a distribution with a fixed, but non-zero variance. These models produce relative risks, 95% CIs and *P* values. A second negative binomial model

with an interaction between the covariate for duration of diabetes and the fixed factor for before vs after DAFNE training was fitted to see if the relationship between ketoacidosis and duration of diabetes was different after the training course. In the same manner, a model with HbA_{1c} as the covariate was used to determine if the relationship between ketoacidosis and HbA_{1c} was altered before and after DAFNE training.

For binary data, logistic models with a fixed factor for before vs after DAFNE with a population-averaged exchangeable correlation to allow for clustering on centre were used. These models produce odds ratios, 95% CIs and P values. Models were fitted using SPSS version 19, and the plots were performed in R (http://cran.r-project.org/). For both types of data, a P value <0.05 was considered to indicate statistical significance.

Results

Records from 1651 patients [49.6% women, baseline mean (SD) age 39.4 (13.7) years, mean (range) duration of diabetes 16.5 (0–65) years] were identified and, of these, 939 (57%) had paired HbA_{1c} concentration and severe hypoglycaemia data at baseline and at first annual follow-up. In order to exclude any episodes of ketoacidosis experienced at diagnosis, only participants with a duration of diabetes of ≥2 years at baseline were included in the ketoacidosis analyses ($n = 864$). The mean (SD) time to collection of first follow-up data was 388 (48) days. At this follow-up, the mean (SD) HbA_{1c} concentration had decreased from 71 (17) mmol/mol [8.7 (1.5)%] to 69 (16) mmol/mol [8.4 (1.5)%], mean (SD) difference of -3 (-0.2), (95% CI: -3 [-0.3] to -2 [-0.2], $P < 0.001$). The participants excluded because of insufficient data at follow-up were slightly younger, and had shorter diabetes duration, higher HbA_{1c} concentrations and more episodes of severe hypoglycaemia and ketoacidosis. Similar proportions of those included/excluded were women (Table 1).

The number and type of events requiring emergency treatment with healthcare input in the 12 months before and after DAFNE training are summarized in Table 2. In the year before DAFNE training, 41 participants (4.7%) with paired data experienced a total of 57 episodes of ketoacidosis requiring admission to hospital, compared with 18 participants (2.1%) reporting 22 episodes in the year after DAFNE training. This represents a 56% reduction in the number of people experiencing ketoacidosis over the course of 1 year (odds ratio=0.42, 95% CI: 0.25 to 0.71, $P = 0.001$). The number of individuals with multiple episodes of ketoacidosis also decreased by 73% from 11 (1.3%) to 3 (0.3%; odds ratio =0.28, 95% CI: 0.10 to 0.79, $P = 0.017$). The estimated relative risk for ketoacidosis before vs after DAFNE was 0.39 (95% CI: 0.23 to 0.65), $P < 0.001$, reduced from 0.07 to 0.03 episodes per patient per year; therefore, participants had a 61% reduced risk of an episode of ketoacidosis after DAFNE training compared with before the training.

In participants with paired data, at baseline, those with a history of ketoacidosis requiring admission within the preceding 12 months, when compared with those without an episode, were younger [34.4 (SD 11.6) vs 41.7 (SD 13.7) years, difference of -7.2 (95% CI: -11.5 to -3.0), $P = 0.001$] and had a shorter duration of diabetes [12.3 (SD 7.7) vs 19.2 (SD 13.1) years, difference -6.8 (95% CI: -10.9 to -2.8), $P = 0.001$], but there was no gender difference between the two groups [56.1 vs 50.9% female, difference 5.2% (95% CI: -10.8 to 21.2), $P = 0.517$]. Using a negative binomial model, the relative risk of ketoacidosis in those with at least one ketoacidosis episode at baseline compared with those with no ketoacidosis at baseline was estimated as 9.35 (95% CI: 2.75 to 31.75). Individuals experiencing ketoacidosis in the 12 months before DAFNE training had a significantly higher HbA_{1c} concentration compared with the remainder of the cohort: mean (SD) 88 (22) mmol/mol [10.3 (2.0)%] vs 71 (16) mmol/mol [8.6 (1.4)%], mean (SD) difference 18 [(1.6); 95% CI: 13 (1.2) to 23 (2.1), $P < 0.001$]. Likewise, when the whole baseline dataset was analysed, those individuals with a history of ketoacidosis within the previous 12 months had significantly higher HbA_{1c} concentrations: mean (SD) 87 (20) mmol/mol [10.1 (1.8)%] vs 72 (17) mmol/mol [8.7 (1.5)%], difference 15 [(1.4); 95% CI: 11 (1.1) to 19 (1.7); $P < 0.001$].

Table 1 Demographics of participants included in the analysis, compared with those excluded as lost to follow-up

	Mean (SD) baseline values				
	Subjects included: $n = 939$	Subjects excluded: $n = 712$	Difference (SD)	95% CI	P value of the difference
HbA_{1c} concentration, mmol/mol	71 (17)	75 (19)	3 (0.3)	2, 5	<0.001
HbA_{1c} concentration,%	8.7 (1.5)	9.0 (1.7)	(2 (0.2), 5 (0.5)	0.2, 0.5	
Age, years	41.0 (13.6)	37.7 (13.3)	-3.2	-4.5, -1.9	<0.001
Gender, % female	47.2	51.4	4.2	-0.7, 9.1	0.087
Duration of diabetes, years	17.4 (13.4)	15.5 (11.6)	-1.9	-3.1, -0.7	0.002
Rate of severe hypoglycaemia/ patient/year	0.82	1.25	1.53*	1.39, 1.69	<0.001
Rate of ketoacidosis/patient/year	0.07	0.12	1.80*	1.29, 2.52	0.001

*Relative risk.

Table 2 Number of episodes of severe hypoglycaemia and ketoacidosis in the 12 months before compared with the 12 months after Dose Adjustment For Normal Eating training

	Before DAFNE training (baseline)			12 months after DAFNE training			Absolute risk	*Relative risk (95% CI)	P value of the difference
	Total	Range	Rate	Total	Range	Rate			
Admissions for ketoacidosis	57	0–3	0.07	22	0–3	0.03	−0.04	0.39 (0.23, 0.65)	<0.001
Nights spent in hospital as a result of ketoacidosis	210	0–17	0.24	67	0–9	0.08	−0.16	0.32 (0.19, 0.54)	<0.001
Admissions for severe hypoglycaemia	30	0–2	0.03	10	0–2	0.01	−0.02	0.33 (0.17, 0.64)	0.001
Nights spent in hospital as a result of hypoglycaemia	80	0–21	0.09	21	0–8	0.02	−0.07	0.32 (0.20, 0.54)	<0.001
Episodes requiring paramedics	167	0–6	0.18	51	0–5	0.05	−0.13	0.30 (0.19, 0.46)	<0.001
Episodes requiring Accident and Emergency department attendance	53	0–5	0.06	20	0–3	0.02	−0.04	0.37 (0.15, 0.90)	0.029
Episodes requiring both paramedics and Accident and Emergency department attendance	52	0–5	0.06	18	0–3	0.02	−0.04	0.34 (0.13, 0.89)	0.028

DAFNE, Dose Adjustment For Normal Eating.
*Negative binomial models with a fixed factor for before vs after DAFNE with a population-averaged exchangeable correlation to allow for clustering on centre were used for data which are counts. These models produce relative risks, 95% CIs and P values.

Within our cohort, the estimated relative annual risk of an episode of ketoacidosis for a 1-mmol/mol increase in HbA_{1c} concentration was 1.06 (1.88 for a 1% increase [95% CI: 1.05 (1.65) to 1.07 (2.13); $P < 0.001$]; therefore for every 1-mmol/mol unit increase in HbA_{1c} concentration, the risk of a ketoacidosis episode increased by 6% (88% for a 1% increase). In our model, the equations for an episode of ketoacidosis dependent on HbA_{1c} before DAFNE training, equation 1, and after DAFNE training, equation 2, are shown below, where HbA_{1c} is expressed in mmol/mol. This is shown graphically in Fig. 1 (shaded areas indicate 95% CI bands).

- Equation 1 = $\exp(-7.385 + 0.058 \times HbA_{1c})$

- Equation 2 = $\exp(-8.178 + 0.058 \times HbA_{1c})$

The interaction between the fixed factor for before vs after DAFNE training and the covariate for HbA_{1c} was not significant ($P = 0.483$); therefore, the increase in risk of ketoacidosis with increased HbA_{1c} concentration was the same before and after DAFNE.

The estimated relative risk of ketoacidosis for a 1-year increase in diabetes duration was 0.96, (95% CI: 0.94 to 0.98); therefore, for every 1-year increase in duration, the risk of a ketoacidosis hospital admission decreased by 4% and, for every 5-year increase in duration, the risk of a ketoacidosis hospital admission decreased by 20%. In our model, the equation for a ketoacidosis hospital admission dependent on duration of diabetes before DAFNE training is shown as equation 3, and after DAFNE training, as equation 4, below. This is shown graphically in Fig. 2 (shaded areas indicate 95% CI bands).

- Equation 3 = $\exp(-2.006 − 0.045 \times \text{duration})$

- Equation 4 = $\exp(-2.952 − 0.045 \times \text{duration})$
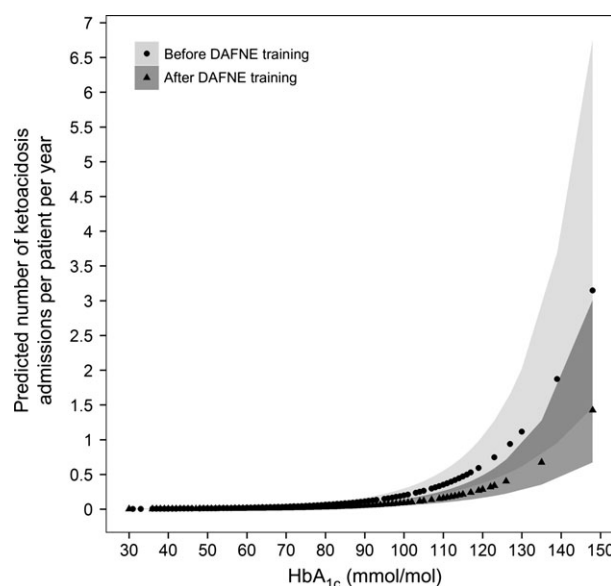

FIGURE 1 Effect of HbA_{1c} concentration on rates of ketoacidosis admissions before and after Dose Adjustment For Normal Eating training.

The total number of nights spent in hospital as a result of ketoacidosis was 210 in the 12 months before DAFNE training and 67 in the following 12 months, (relative risk 0.32 (95% CI: 0.19 to 0.54) $P < 0.001$). The number of patients admitted with hypoglycaemia ($P < 0.001$), requiring paramedic assistance ($P < 0.001$), and/or requiring Accident and Emergency department attendance ($P = 0.029$) were all significantly reduced. Likewise, the total number of nights spent in hospital as a result of hypoglycaemia fell from 80 to 21 ($P < 0.001$). Within this cohort there were no deaths

attributable to ketoacidosis or hypoglycaemia. The costs of all diabetes emergency care are shown in Table 3. In the 12 months before DAFNE training, the total cost of emergency treatments for ketoacidosis and severe hypoglycaemia in this cohort was £119,470, compared with £42,947 in the 12 months after DAFNE training. This represents a 64% reduction in costs and a saving of £81 per participant over 1 year.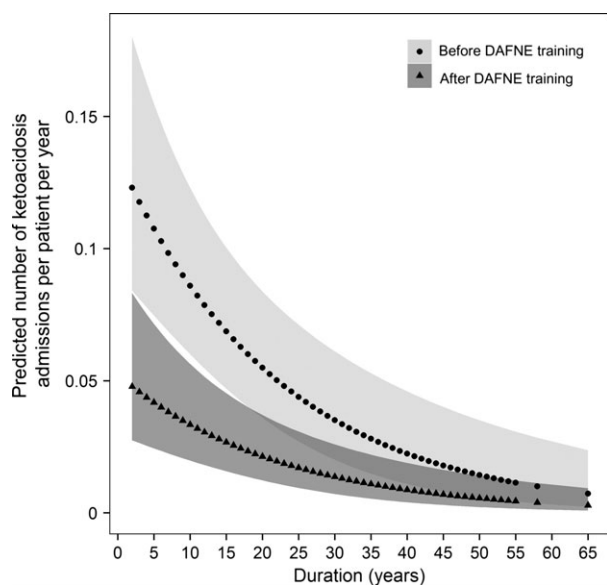 For comparison, the cost of a DAFNE course is on average £359 per participant [19]. Just over half the savings (51%) were as a result of fewer ketoacidosis admissions, and the remainder were attributable to the combination of treatments for severe hypoglycaemia.

Discussion

In a large-scale cohort of participants in DAFNE training, we have shown that the relative risk of ketoacidosis was reduced by 61% in the year after DAFNE training compared with the year before. This compares favourably with a study reporting the German experience, in which the incidence fell by 55% [16], particularly as that study was conducted in individuals at high risk of ketoacidosis, who had experienced two or more episodes in the year before training. Second to a history of ketoacidosis, the most important reported factor predicting ketoacidosis is higher HbA_{1c} concentration [8,9,20]. In the present cohort, those experiencing an episode of ketoacidosis did have significantly higher HbA_{1c} concentrations than the remainder of the cohort. We calculated that for every 1-mmol/mol unit increase in HbA_{1c}, there was a 6% increased risk of an episode of ketoacidosis (88% for a 1% increase). This relationship was unchanged by the impact of DAFNE training, although the overall incidence was markedly reduced. The substantial reduction in risk of ketoacidosis occurred despite only a modest fall in overall HbA_{1c} concentration. The improvement in ketoacidosis incidence may be attributable to greater participant understanding of the pathogenesis of ketoacidosis and its management, as this is an integral component of the curriculum. For example, training in relation to sickness management includes guid-

FIGURE 2 Effect of duration of diabetes on rates of ketoacidosis admissions before and after Dose Adjustment For Normal Eating training.

Table 3 Costs of emergency treatment in the 12 months before and after attendance of a Dose Adjustment For Normal Eating training course

	Number of episodes		Unit cost of emergency treatment	Total emergency treatments costs	
	12 months before DAFNE	12 months after DAFNE		12 months before DAFNE	12 months after DAFNE
Emergency treatment for ketoacidosis					
Length of stay = 1 night	8	5	£405.57*	£3,244.56	£2,027.85
Length of stay >1 night	49	17	£1,176.53*	£57,649.97	£20,001.01
Total cost of ketoacidosis treatments				£60,894.53	£22,028.86
Hypoglycaemia in patients <70 years of age					
Length of stay = 1 night	16	5	£385.00	£6,160.00	£1,925.00
Length of stay >1 night	7	3	£1,177.00	£8,239.00	£3,351.00
Hypoglycaemia in patients >70 years of age					
Length of stay =1 night	0	1	£418.00	£0.00	£418.00
Length of stay >1 night	1	1	£1,657.00	£1,657.00	£1,657.00
Hypoglycaemia requiring:					
Paramedic assistance	167	51	£222.48	£37,154.13	£11,346.47
Accident and Emergency department attendance and no admission	24	10	£110.85	£2,660.36	£1,108.48
Accident and Emergency department attendance and admission	29	10	£93.28	£2,705.04	£932.77
Total cost of hypoglycaemia treatments				£58,575.53	£20,918.72
Total cost of emergency treatments				£119,470.06	£42,947.58
Mean cost of emergency treatments / patient				£127.23	£45.74

DAFNE, Dose Adjustment For Normal Eating.
*All episodes occurred in patients <70 years of age.

ance on when to take supplemental insulin doses at 10 or 20% of usual total daily insulin dose, based on blood glucose and blood or urine ketone levels. In addition, our data confirm that those with a longer duration of diabetes are less likely to experience an episode of ketoacidosis; in this cohort, for each 5-year increase in duration, the risk of ketoacidosis was reduced by 20%. We excluded episodes of ketoacidosis at presentation of newly diagnosed Type 1 diabetes.

In recent years in the UK, efforts have been made to improve the management of ketoacidosis by providing national guidelines [21] and by developing diabetes specialist inpatient teams to decrease lengths of stay and improve patient safety [22,23]. Detailed data on the incidence of ketoacidosis and the effect of these changes on admission rates are lacking. Structured diabetes education is now a national standard, although access remains patchy [24]. In researching the effectiveness of the DAFNE programme, we have attempted to follow the Medical Research Council guidance for the evaluation of complex interventions, and the present study was conducted as an evaluated roll-out [25]. The recently published National Diabetes Audit [10] states that 'there is an imperative to reduce ketoacidosis everywhere', but published reports of interventions designed to reduce episodes of ketoacidosis are relatively scarce. One strategy used in young adults in Australia, after-hours telephone support, reported a reduction in ketoacidosis admissions of one-third [20]. Amongst adolescents, intensive home-based family therapy has been shown to reduce ketoacidosis admissions in one centre in the USA, with some of the costs offset by reductions in admissions [26].

Based on the latest National Diabetes Audit data, the annual cost of ketoacidosis admissions is £5.5 m. As a result of reduced incidence of ketoacidosis in the present cohort, expenditure on ketoacidosis admissions was decreased by 64%; thus, the potential for cost saving across the UK is considerable. The cost of providing emergency care for severe hypoglycaemia to adults with Type 1 diabetes includes not only inpatient expenditure, but also paramedic and Accident and Emergency assistance costs. The total cost to the NHS for people with Type 1 diabetes is likely to be in the region of ~£6.5 m [11]. The number of paramedic call-outs, Accident and Emergency department attendances and hospital admissions for the treatment of severe hypoglycaemia were all significantly reduced in the year after DAFNE training, compared with the year before. We have also calculated that the total cost of emergency treatment of hypoglycaemia was reduced by 64% in this cohort, in the year after DAFNE training.

While this work has demonstrated significant reductions in episodes of ketoacidosis and hypoglycaemia, and associated costs, there are some important limitations. It is possible that those participants excluded from the analysis because of incomplete data collection at follow-up may not have fared so well, although at baseline they had higher rates of both ketoacidosis and severe hypoglycaemia. The data were collected retrospectively and so recording of events may have been incomplete. As with any observational study, in the absence of a control group we cannot assume that the benefits achieved were solely as a result of the DAFNE intervention. In addition, we do not know how representative this cohort is in comparison with the population of people with Type 1 diabetes as a whole within the UK, for example, in terms of socioeconomic status, physical and mental health. A strength of the present study is the large number of unselected patients in whom data was collected during routine clinical care. The annual rates of ketoacidosis and severe hypoglycaemia after DAFNE training may be overestimated by 6% as the mean follow-up was slightly longer than 1 year (388 as opposed to 365 days). In addition, at baseline we do not know the accuracy with which patients have recalled events over the preceding year; however, there is evidence to show that severe hypoglycaemic events are recalled accurately by patients up to 1 year [27], and both severe hypoglycaemia and ketoacidosis events were corroborated by review of medical notes. As follow-up data are collected annually, in the future we aim to determine whether the reductions in requirement for emergency treatment (and the cost savings) are sustained beyond the first year. It is noteworthy that we have only considered the direct emergency costs associated with ketoacidosis and severe hypoglycaemia. Other indirect costs, such as loss of work productivity and increased use of blood glucose monitoring strips, are associated both with severe hypoglycaemia and non-severe hypoglycaemia [28,29]; thus, the overall cost savings reported in the present paper are likely to be underestimates of the true costs of these adverse events as a whole.

In conclusion, admissions as a result of ketoacidosis and the frequency of severe hypoglycaemia requiring healthcare professional assistance are significantly reduced after DAFNE skills training. In routine clinical care, the benefits of structured training in flexible intensive insulin therapy include not only improvements in glycaemic control and quality of life [13,14,30] but also substantial reductions in episodes of ketoacidosis, severe hypoglycaemia and emergency treatment costs.

Competing interests

None declared.

approved by the local Research and Development departments of all participating centres. The views expressed in this presentation are those of the author(s) and not necessarily those of the NHS, the National Institute of Health Research, Sheffield Teaching Hospitals NHS Foundation Trust or the Department of Health.

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