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A. Sämann · I. Mühlhauser · R. Bender · Ch. Kloos · U. A. Müller

Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study

Abstract *Aims/hypothesis:* The aim of this study was to evaluate the implementation of a course teaching flexible, intensive insulin therapy on glycaemic control and severe hypoglycaemia in routine care. *Methods:* This is a continuous quality-assurance project involving hospital diabetes centres. Every third year each centre re-examines 50 consecutive patients (evaluation sample) 1 year after participation in the course. Ninety-six diabetes centres in Germany participated and 9,583 patients with type 1 diabetes (190 evaluation samples) were re-examined between 1992 and 2004. The intervention was a 5-day inpatient course for groups of up to ten patients with a fixed curriculum of education and training for dietary flexibility and insulin adjustment. The main outcome measures were HbA_1c and severe hypoglycaemia. *Results:* Mean baseline HbA_1c was 8.1%, and had decreased to 7.3% at follow-up; incidence of severe hypoglycaemia was 0.37 events per patient per year prior to intervention and 0.14 after intervention. In mixed-effects models adjusted for effects of centres, age and diabetes duration, the mean difference was −0.7% (95% CI −0.9 to −0.6%, $p<0.0001$) for HbA_1c and −0.21 events per patient per year (95% CI −0.32 to −0.11, $p=0.0001$) for severe hypoglycaemia, with similar results for evaluation samples, with a maximum of 10% of patients lost to follow-up. Before intervention, the incidence of severe hypoglycaemia was three-fold higher in the lowest quartile than in the highest quartile of HbA_1c, whereas the risk was comparable across the range of HbA_1c values after intervention. *Conclusions/interpretation:* Implemented as part of a continuous quality-assurance programme the self-management programme is effective and safe in routine care. Improvement of glycaemic control can be achieved without increasing the risk of severe hypoglycaemia.

Keywords Clinical routine care · Diabetes mellitus type 1 · Diet therapy · HbA_1c · Hypoglycaemia · Implementation study · Insulin therapy · Multicentre study · Patient education · Self-management

Abbreviations DAFNE: Dose Adjustment for Normal Eating Trial · DTTP: Diabetes Treatment and Teaching Programme

A. Sämann (✉) · C. Kloos · U. A. Müller
Department of Internal Medicine III,
Friedrich Schiller University,
Erlanger Allee 101,
D-07740 Jena, Germany
e-mail: alexander.saemann@med.uni-jena.de
Tel.: +49-3641-9324632
Fax: +49-3641-9326422

I. Mühlhauser
Unit of Health Sciences and Education,
University of Hamburg,
Hamburg, Germany

R. Bender
Institute for Quality and Economic Efficiency in Health Care,
Cologne, Germany

Introduction

Strict glycaemic control reduces microvascular complications in type 1 diabetes [1]. However, in the DCCT intensive insulin therapy was associated with a three-fold increase in severe hypoglycaemia and there was a strong inverse exponential association between the incidence of severe hypoglycaemia and HbA_1c levels [1]. Iatrogenic hypoglycaemia may limit the use of intensive insulin therapy in routine care.

However, there is increasing evidence that intensive insulin therapy is not necessarily associated with a high risk of severe hypoglycaemia [2–7]. In the DAFNE trial (Dose Adjustment for Normal Eating), a UK multicentre randomised controlled study, the incidence of severe hypoglycaemia remained unchanged while HbA_1c and quality of life improved [6]. The intervention was an outpatient

self-management training course adopted from the Düsseldorf University diabetes centre. The Düsseldorf Diabetes Treatment and Teaching Programme (DTTP) was first introduced in 1978 [8]. It consists of a 5-day structured inpatient training course for intensive insulin therapy. Patients are taught to match insulin doses to their food choices, while keeping blood glucose close to normal. In several controlled clinical trials the programme has shown sustained improvements in glycaemic control without increasing the risk of severe hypoglycaemia [2–5, 7]. The DTTP has become the standard treatment approach for individuals with type 1 diabetes in Germany.

The implementation of the DTTP into routine care was linked with a national continuous quality-assurance project using a central database [9]. Since 1992 a total of 96 hospital-based diabetes centres have collected outcome data on glycaemic control and severe hypoglycaemia of 9,583 patients with type 1 diabetes. We have used this database to analyse the association between HbA_1c levels and severe hypoglycaemia. We hypothesised firstly that the DTTP would be followed by both better HbA_1c and fewer severe events of hypoglycaemia, and secondly that the strong inverse association between HbA_1c and severe hypoglycaemia found in the DCCT would disappear following patient participation in the DTTP.

Subjects and methods

The DTTP

Detailed descriptions of the DTTP have been published [4, 10, 11]. In short, the standard DTTP is carried out as a 5-day inpatient course of 20 h. Objectives are to enable participants to improve glycaemic control, to decrease the risk of hypoglycaemia and to enable dietary and lifestyle freedom. Patients are advised to measure blood glucose before main meals and at bedtime and to adjust insulin to actual blood glucose levels and their desired carbohydrate intake on a meal-by-meal basis. Standard insulin therapy consists of multiple injection therapy with NPH insulin in the morning and at bedtime and regular insulin before main meals. The DTTP courses are conducted by specially trained nurse educators and dieticians based on a written curriculum including explicit learning objectives in a group setting with up to ten patients.

Patients are referred by their family physicians or diabetologists. A history of repeated or unexplained severe hypoglycaemia or hypoglycaemia unawareness are indications for participation in the DTTP rather than exclusion criteria. After discharge, patients are primarily followed up by their family physicians.

The continuous quality-assurance project

Details of the project have been published [12]. Long-term implementation of the DTTP on a national basis and quality assessment has been accomplished by the creation of a working group of hospital-based diabetes centres dedicated to this approach. This voluntary and non-profit organisation accredits diabetes clinics, which undergo periodic evaluations of structure, process and outcome quality of their programmes [12]. This includes a re-examination of consecutively referred patients 1 year after participation in the DTTP. Patients were invited for re-examination in the chronological order that they entered the DTTP. In addition, visiting observers, physicians and educators exchange experience on educational methods during regular supervision visits. Results are publicly presented and discussed at annual meetings. Accreditation does not depend on the outcome quality of a programme but rather on the accomplishment of the evaluation procedures.

Data collection in a central database is supervised and audited by two of the present authors, U. A. Müller and A. Sämann, at Jena University. Each evaluation sample had to pass the following procedure before it became accepted: (1) primary data analysis to check for completeness and plausibility of each documented item; (2) cluster analysis of age, diabetes duration, HbA_1c and severe hypoglycaemia to detect study centres with doubtful data collection; and (3) comparison of statistics of each evaluation sample with those of the whole dataset. Unusual or impossible data had to be revised or explained by the study centres [12].

Participants and outcome measures

Data were recorded between 1992 and 2004 in 96 hospital diabetes clinics all over Germany (83 general hospitals with 8,100 patients, 13 university hospitals with 1,483 patients, Table 1). For evaluation of outcome quality, every centre was asked to re-examine at least 50 consecutive patients (at least 30 patients since 2002) 1 year after participation in the DTTP (evaluation sample). This was to be repeated every 3 years. The rate of patients who were lost to follow-up was not to exceed 10%. Patient characteristics such as age, diabetes duration, date of participation in the DTTP, and date of re-examination were documented.

Immediately before participation in the DTTP, and again after 1 year, two outcome measures are assessed. First, HbA_1c levels are analysed at the local hospital laboratories by using HPLC. Local HbA_1c values are adjusted to DCCT standards with an evaluated standardisation procedure [12] using local reference ranges by calculation of relative HbA_1c by dividing measured absolute HbA_1c by the local mean of healthy subjects and calculation of DCCT-adjusted absolute HbA_1c by multiplying relative HbA_1c values by 5.05%. Consequently, the mean relative HbA_1c of healthy subjects would be 1.0, the mean DCCT-adjusted absolute HbA_1c of healthy subjects 5.05%. Secondly, episodes of severe hypoglycaemia are assessed by an interview for the preceding year. Severe hypoglycaemia is defined as a condition treated by i.v. glucose or glucagon injection [12].

The participants gave their informed consent to participate in the study. The investigation was carried out in accordance with the Declaration of Helsinki as revised in 2000.

Table 1 Descriptive data of hospital diabetes clinics between 1993 and 2004

Year	Evaluation samples (*n*)	Patients lost to follow-up (%)	Patients (*n*)	Mean age (years)	Mean duration of diabetes (years)	Mean HbA$_1$c before DTTP (%)	Mean HbA$_1$c after DTTP (%)	Incidence of severe hypoglycaemia before DTTP (events per patient per year)	Incidence of severe hypoglycaemia after DTTP (events per patient per year)
1993	1	0	94	36	14.8	9.5	7.7	0.27	0.23
1996	1	0	59	33	10.9	9.0	8.1	0.24	0.24
1997	12	17	524	n.d.	n.d.	8.4	7.6	0.46	0.23
1998	32	17	1,789	36	12.9	8.1	7.4	0.46	0.19
1999	21	21	1,125	36	13.2	7.8	7.2	0.31	0.13
2000	32	13	1,704	39	13.2	8.3	7.4	0.36	0.11
2001	29	15	1,493	39	13.2	7.9	7.4	0.29	0.12
2002	19	19	986	40	13.5	8.1	7.2	0.49	0.19
2003	23	15	963	40	14.2	7.8	7.2	0.29	0.09
2004	20	8	846	39	14.3	7.8	7.3	0.35	0.14
Total	190	15	9,583	38	13.4	8.1	7.3	0.37	0.14

n.d. no data recorded

Statistical analyses

For descriptive statistical analysis means, SD, absolute and relative frequencies were calculated. For descriptive purposes, patients were divided into deciles and into quartiles according to HbA$_1$c at intervention (first quartile: ≤6.67%, second quartile >6.67% and ≤7.68%, third quartile >7.68% and ≤8.99%, fourth quartile >8.99%). For statistical analysis of differences between follow-up and intervention regarding HbA$_1$c and incidence of severe hypoglycaemia, mixed-effects models were used with 'centre' as a random effect and 'age' and 'diabetes duration' as fixed effects. In order to assess the possible bias due to missing values, analyses were repeated by considering only subjects of those evaluation samples with a maximum of 10% of patients lost to follow-up. $p<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 10.0 (SPSS, Chicago, IL, USA) and SAS 8.02 (SAS Institute, Inc., Cary, NC, USA).

Results

At the annual meetings of the working group between 1993 and 2004, the 96 diabetes centres had provided data of 190 evaluation samples including a total of 9,583 participants. There were 92 evaluation samples containing a total of 4,648 patients with a maximum of 10% of patients lost to follow-up.

For the 9,583 participants, mean age at enrolment was 38 (SD 14) years, and mean duration of diabetes was 13.4 (SD 10.9) years. Mean HbA$_1$c was 8.1% (SD 2.0) at baseline and 7.3% (SD 1.5) at follow-up (Fig. 1). For the year before the DTTP, 15% of patients reported at least one severe hypoglycaemia (incidence 0.37 events per patient per

year), whereas during the year after the DTTP 7.7% had at least one severe hypoglycaemia (incidence 0.14 events per patient per year).

In the mixed-effects models taking effects of 'centre', 'age' and 'duration of diabetes' into account, the mean difference between follow-up and intervention was −0.7% (95% CI −0.9 to −0.6%, $p<0.0001$) for HbA$_1$c and −0.21
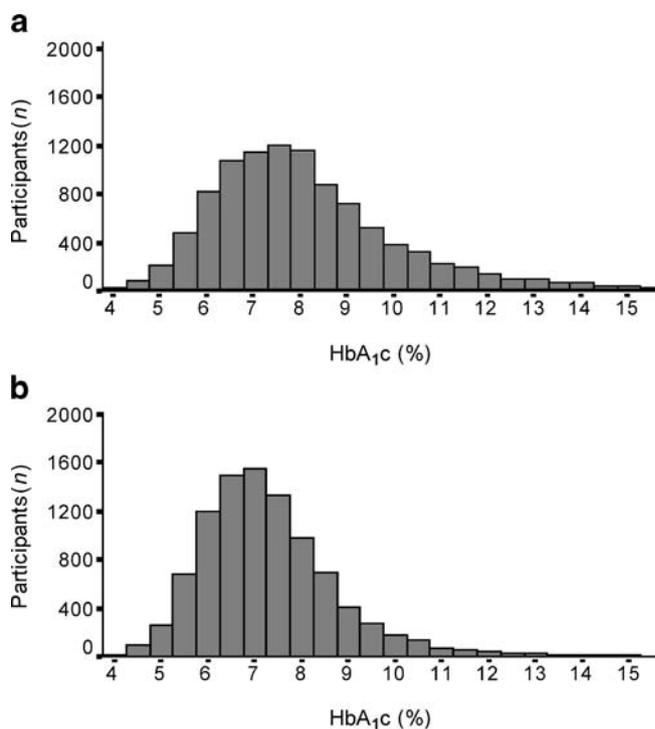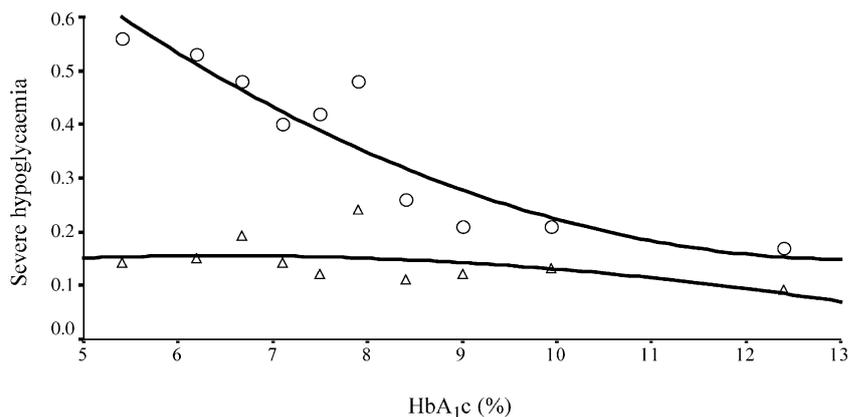

Fig. 1 Distribution of HbA$_1$c values before (**a**) and 1 year after intervention (**b**)

Fig. 2 Incidence of severe hypoglycaemia (events per patient per year) 1 year before (*circles*) and after intervention (*triangles*) across centiles of HbA$_1$c. Curves were fitted using polynomials of order 3

events per patient per year (95% CI −0.32 to −0.11, p=0.0001) for the incidence of severe hypoglycaemia. Considering only evaluation samples with a maximum drop-out rate of 10%, the mean difference for HbA$_1$c was −0.6% (95% CI −0.8 to −0.4%, p<0.0001) and for severe hypoglycaemia −0.29 events per patient per year (95% CI −0.41 to −0.16, p<0.0001).

Analyses of associations between HbA$_1$c and severe hypoglycaemia are shown in Fig. 2 and Table 2. Subgroups of patients (quartile grouping according to HbA$_1$c at baseline) had different benefits from participation in the DTTP: participants with high HbA$_1$c levels at baseline (10.8%) improved glycaemic control substantially (8.4% after 1 year) without increasing the risk of severe hypoglycaemia (0.18 vs 0.11 events per patient per year). In patients with tight glycaemic control and a high initial rate of severe hypoglycaemia, HbA$_1$c remained stable (6.0 vs 6.3%) while severe hypoglycaemia decreased significantly (0.54 vs 0.16 events per patient per year).

Discussion

The present analyses confirm that structured self-management programmes for intensive insulin therapy can improve glycaemic control without increasing the risk of severe hypoglycaemia. In addition, for the first time it could be shown that the inverse association between HbA$_1$c and severe hypoglycaemia can be prevented during intensive insulin therapy. Before intervention, the incidence of severe hypoglycaemia was three times higher in the lowest compared with the highest quartile of HbA$_1$c, whereas the risk was almost identical across HbA$_1$c ranges during the year after the DTTP. Although we did not measure quality of life, there is good evidence from the DAFNE study and other trials that participants benefit from introducing dietary freedom [2, 3, 6, 10, 13], which was a primary goal of the courses.

The most likely explanation for the observed effects is that the DTTP improves self-management skills, which is essential for successful treatment of type 1 diabetes. The DTTP gives patients the opportunity to define individual treatment goals and to balance favourable HbA$_1$c levels and an unacceptable risk of severe hypoglycaemia, whereas the DCCT primarily aimed at normalisation of HbA$_1$c values. The DTTP enables patients to adjust insulin to suit, instead of adapting their lifestyle to match prescribed doses of insulin. Patients become more competent in both recognition and management of critical situations involving increased risk for severe hypoglycaemia. Insulin therapy and patient education were not standardised in the DCCT. The DCCT approach required frequent outpatient visits with close supervision of insulin dose adjustment, and did not consider dietary freedom an objective.

Table 2 HbA$_1$c and incidence of severe hypoglycaemia for quartiles of baseline HbA$_1$c

Quartiles of baseline HbA$_1$c	Patients (*n*)	Mean HbA$_1$c before DTTP SD)	Mean HbA$_1$c after DTTP (SD)	Incidence of severe hypoglycaemia before DTTP (events per patient per year)	Incidence of severe hypoglycaemia after DTTP (events per patient per year)
First	2,413	6.0 (0.5)	6.3 (1.0)	0.54	0.16
Second	2,352	7.2 (0.3)	7.0 (1.0)	0.42	0.14
Third	2,422	8.3 (0.4)	7.6 (1.2)	0.35	0.16
Fourth	2,396	10.8 (1.7)	8.4 (1.9)	0.18	0.11

Since the present implementation study does not include a control group, at least part of the observed changes may be due to the phenomenon of regression to the mean. However, the DTTP has been extensively studied including randomised controlled trials with follow-up periods between 6 months [6] and 2 years [5, 11]. In study groups with poor glycaemic control at baseline, HbA$_1$c values decreased by up to 3% at stable risks of severe hypoglycaemia [5, 7]. In several long-term cohort studies in Germany and Austria, where patients had lower initial HbA$_1$c values and higher rates of severe hypoglycaemia, the DTTP was consistently followed by significant decreases in the risk of severe hypoglycaemia and sustained but less-pronounced improvements of glycaemic control [2, 3, 11, 14].

Overestimation of the benefits may also result from a biased data collection. Follow-up examination of patients by the members of the diabetes care team and the agreement to present outcome data in public at annual meetings may lead to framing of the data. Yet with the regular supervisional visits by peers and open discussions of results with the common mutual aim of improving the DTTP, this problem should be minimised. In addition, accreditation was not dependent on outcome quality.

Particularly in the early years of the project most participating institutions had little experience with collection of outcome data, possibly leading to overoptimistic results due to follow-up bias. However, the sub-analyses including only evaluation samples with a maximum of 10% of patients lost to follow-up showed similar effects for HbA$_1$c and severe hypoglycaemia as compared with the total sample.

Comparison of our data with DCCT data may be limited by the different definitions of severe hypoglycaemia and different patient characteristics. Although similar definitions for severe hypoglycaemia have been used in the DCCT feasibility study and the present study, in the DCCT hypoglycaemia requiring assistance from another person was included in the definition of severe hypoglycaemia [15]. However, there is no evidence that the association between severe hypoglycaemia and HbA$_1$c changes with the definition of severe hypoglycaemia [2, 16]. In addition, the DCCT patients were younger and probably had less residual beta-cell function than patients with type 1 diabetes treated under routine care conditions. A lack of beta-cell responsiveness contributes to instability of glycaemic control [17, 18]. However, it has already been shown that neither residual beta-cell function nor a history of severe hypoglycaemia influences the extent and nature of the association between glycaemic control and the risk of severe hypoglycaemia [2].

In conclusion, we have shown that a structured diabetes treatment and teaching programme for intensified insulin therapy in type 1 diabetes is effective and safe in routine care if implemented as part of a nationwide continuous quality-assurance project. Improvements of metabolic control can be achieved without increasing the risk of severe hypoglycaemia.

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