Hidden Gems

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Contributing Editor

Shining a light into the past for the articles that continue to shape our diabetes clinical practice today

This issue: Mühlhauser I, Jörgens V, Berger M et al (1983) Bicentric evaluation of a teaching and treatment programme for type 1 (insulin-dependent) diabetic patients: improvement of metabolic control and other measures of diabetes care for up to 22 months. *Diabetologia* 25:470–6

The origins of DAFNE

Structured education is one of the more evidence-based interventions supporting modern type 1 diabetes management. The approach now known as "Dose Adjustment for Normal Eating" (DAFNE) has its roots in the diabetes clinics of Germany and Austria during the 1970s. In this seminal study by Mülhauser et al (1983), an intensive insulin therapy teaching programme was found to be effective at reducing HbA_{1c} and reducing hospital admissions without increasing risk of severe hypoglycaemia. This led on to later studies that would confirm the benefit of tight glycaemic control on long-term complications, and refine the educational approach in line with the development of modern insulin formulations.

The decades following the discovery and mass production of insulin saw a focus of research effort on its purification and an expansion in the formulations available. This led to the development of genetically engineered human insulin (first available in 1982) and later, insulin analogues. Prior to 1982, animal insulins extracted from the pancreatic tissue of cows and pigs were the only formulations available. There are still preferred by some patients today. During the 1970s, the range of insulin options was relatively limited and included soluble insulin, acting relatively quickly, and those with delayed action due to the inclusion of either zinc or protamine. The development of products acting over different time-scales supported the move to reproduce physiological insulin profiles through multiple injections. The availability of short- and longer-acting insulins enabled a distinction to be made between the basal insulin requirement (to be met through the longer-acting formulations) and the bolus requirement covering carbohydrate ingestion at mealtimes. The basal requirement was relatively constant day to day but the bolus component needed to be varied according to meal content.

However, at this time, people with type 1 diabetes tended to have their insulin doses optimised initially during a hospital admission and later through a review as outpatients. Self-monitoring technology was still in its infancy, and so the process was inevitably doctor centred. The doctor clearly could not be present continuously during everyday life, so the approach to achieving stability was through constancy and regularity of both insulin dosage and carbohydrate intake.

The situation changed partly through the invention of convenient self-monitoring devices, which would enable individuals to adjust insulin doses themselves, according to variations in requirement. What was then needed was an effective training programme that would enable and empower the individual to take control of insulin dose adjustment flexibly, particularly the short-acting component, according to their own perception of hour-to-hour requirement.

The hidden gem

Mülhauser et al discuss the background to their study, in which prior educational programmes had lacked structure and had continued to rely on strict dietary regimens and clinicians advising patients rather than patients taking decisions themselves. Results were conflicting and in some cases, disappointing. Their new programme, based in an inpatient setting over a 5-day period, was structured, and broke with the prevailing requirement for strict dietary discipline.

Eighty-eight consecutive, conventionally treated insulin-dependent individuals were recruited to the study. The programme included 17 hours of theoretical and practical sessions over the course of a week. It was delivered to groups of 6–12 people at a time by a diabetes nurse, a dietitian and a laboratory technician under the guidance of medical staff.

The participants were aged between

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18 and 36, had durations of diabetes ranging from 4 to 16 years and all had a normal BMI. Despite the participants' relatively young age, 38 (43%) had late complications of diabetes and had spent an average of 10 days in hospital per year since their diagnosis. In 71 cases (81%), the insulin regimen was by twice-daily injection, while 12 were taking just one injection and five were taking three per day. Follow-up data were available for 78 of the originally enrolled 88 patients.

The programme departed significantly from the standard approach of the time, as it moved the responsibility for management decisions away from the clinical staff and towards the patient and family. The authors describe how "patients were to attempt (near-) normoglycaemia and handle minor metabolic derangements without contacting a doctor. They should gain a certain 'liberalisation' of life style with respect to exercise and eating schedules, and their relatives would administer glucagon in the case of severe hypoglycaemia." This change in approach was particularly significant because the investigators decided not to exclude people with low intellect or low educational achievement.

The programme recognised that optimisation of control depended upon rapid correction of glycaemic excursions, and that this was only possible using regimens including a short-acting component. Unless using one of them already, all patients were, therefore, started on a combination of either Monotard® MC and Actrapid® MC, or Insulatard® and Velosulin®.

This was a "before–after" observational study rather than a randomised trial. However, the improvement in metabolic control was very definite and clearly attributable to the educational intervention. The primary outcome was the HbA_{1c}, a relatively new test at the time that was still measured in different ways by different laboratories. For this reason the investigators chose to use the difference between the level and the locally established upper limit of normal, rather than the level itself. This difference reduced from a mean of 2.6% at baseline to 1.0% after 12 months, and 1.5% after 22 months.

Numerous other variables were measured reflecting adequacy of metabolic control and response to the educational programme. Whilst not increased, severe hypoglycaemia was still a problem and occurred on 33 occasions in 11 individuals during the first 12 months. Four patients experienced 76% of these episodes, and the authors speculate that this was due to excessive insulin dosage, alcohol excess, pregnancy and renal failure. But despite this, risk of admission to hospital reduced from an initial mean of 10 days per year to a median of 1 day per year following the programme. Presumably, this was a direct consequence of the new ability of the participants to self manage both hypo- and hyperglycaemic episodes, and there was no evidence reported of harm resulting from failure to seek medical advice. The percentage that received emergency glucagon administered by a relative rose from 12% to 73%. At the 12-month follow-up, 87% of people were still using the regimen including soluble insulin. Perhaps predictably, the best outcomes were seen in the more compliant individuals who kept their log books with them and had emergency carbohydrate available, but there was no association between response to the programme and intelligence quotient.

Why it shines today

This study is seminal because it demonstrated that even before the advent of modern insulin formulations, which have greatly increased the potential for flexible insulin dosing, improvement could be made in type 1 diabetes control simply by frequent self-monitoring combined with patient-centred education.

Today's type 1 diabetes management typically involves a basal–bolus approach, particularly for younger people more likely to expect and benefit from flexibility in lifestyle. The basal insulin may be an older NPH insulin (usually given twice daily), a modern long-acting analogue or a continuous infusion of a rapid-acting analogue delivered through a pump. The bolus component is usually one of these very rapidly absorbed analogues such as insulin aspart (Novorapid®), insulin glulisine (Apidra®) or insulin lispro (Humalog®). The rapid-onset analogue more closely mimics physiological insulin release at mealtimes, and the short duration of action reduces the risk of overlap between doses given with adjacent meals. These characteristics are perfectly suited to the role of this insulin as the flexible, adjustable component of the regimen.

The distinction between the "conventional" approach (in which insulin doses and carbohydrate intake and timing were kept constant day to day) and the flexible, dose-adjusting approach was later used to define the two trial populations of the DCCT (Diabetes Control and Complications Trial), reported in 1993. This confirmed the benefits, particularly on microvascular complications, of tight glycaemic control in type 1 diabetes. It would not have been possible without the development of successful intensive insulin management approaches, of which this Mülhauser study gives an early example.

The following decade saw the publication of the DAFNE trial (2002). This developed the German-style approach to deliver a similar educational programme for optimising control, and has become a widely available intervention for people with type 1 diabetes. In contrast to the intensive

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arm intervention of the DCCT study, the DAFNE approach is much more patient-centred and less supervised. It demonstrated improvements in HbA_{1c} as well as quality of life using a randomised controlled trial design, and has led on to many further studies with huge impact on type 1 diabetes management (see www.dafne.uk.com).

Flexible bolus insulin dosing has become much easier using modern rapid-acting insulin analogues. However, it is interesting that for the basal component, the older NPH insulin used in the DAFNE trial is associated with better outcomes than once-daily basal replacement, and a twice-daily NPH approach is still recommended by the DAFNE group for the basal insulin (Hopkinson, 2013).

Diabetes care is an area of medicine often celebrated for the victory of patient autonomy over medical paternalism. This paternalism arose inevitably at a time when self-monitoring technology did not exist and patients who did not stick to the prescribed schedule could easily become seriously unstable. Even those who did adhere to the schedule were sometimes living close to hospital admission. Some individuals were unable to take decisions themselves, or preferred not to, and this remains the case. But the gradual handing over of responsibility from clinician to patient was a process that most patients welcomed, and most doctors eventually felt comfortable with. This article by Mülhauser is a gem because it describes the seeds of this handover process, germinating in Dusseldorf and Vienna in the late 1970s. ■

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Hopkinson H (2013) *Background Insulin in DAFNE.* DAFNE, Tyne and Wear. Available at: http://bit.ly/1erXiid (accessed 26.05.15)

The DCCT Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* **329**: 977–86