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On Severe Hypoglycaemia in Children and Adolescents with Type 1 Diabetes

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To young people with diabetes and their families

List of papers

This thesis is based on the following studies which will be referred to by their Roman numerals:

I

Nordfeldt S, Jonsson D, Ludvigsson J. Increasing response rate in data registration and follow-up of type 1 diabetes children and adolescents. A prospective population study 1992-97.

Practical Diabetes International 1999;16:101-6.

II

Nordfeldt S, Ludvigsson J. Severe hypoglycemia in children with IDDM. A prospective population study, 1992-1994.

Diabetes Care 1997;20:497-503.

III

Nordfeldt S, Ludvigsson J. Adverse events in intensively treated children and adolescents with type 1 diabetes.

Acta Paediatr 1999;88:1184-93.

IV

Nordfeldt S, Ludvigsson J. Seasonal variation of HbA1c in intensive treatment of children with type 1 diabetes.

J Pediatr Endocrinol Metab 2000;13:529-35.

V

Nordfeldt S, Jonsson D. Short-term effects of severe hypoglycaemia in children and adolescents with type 1 diabetes. A cost-of-illness study.

Acta Paediatr 2001;90:137-42.

VI

Nordfeldt S, Ludvigsson J. Self-study material to prevent severe hypoglycaemia in a type 1 diabetes population.

Submitted.

Contents

Abstract

Background
For people with type 1 diabetes, there is no alternative to treatment with insulin. The major side effect of insulin is severe hypoglycaemia (SH), when the patient needs help or even becomes unconscious.
Material
We have studied a geographic population of yearly 130-140 unselected type 1 diabetes patients aged 1-18 years during 1992-1999. They were intensively treated with 87-96% on 4-7 daily insulin doses, combined with active self-control, psychosocial support and problem-based education from onset. Average HbA1c was 6.5 with Mono-S standard (1.15% below DCCT level).
Methods
We evaluated use of a prospective patient questionnaire for continuous long-term registration of treatment and outcome data and analysed HbA1c, SH and other variables. Over years, 95-100% response rate was achieved. We used also temporary questionnaires.
Results
We found SH with unconsciusness reported from on average 11% of patients yearly, SH without unconsciousness but needing assistance from on average 36% yearly and weak associations to HbA1c, such as a relative risk of SH 1.24 for yearly mean HbA1c <7.0% compared to ≥7.0%. There was a seasonal variation in HbA1c ($p=0.023$) and incidence of SH. The strongest predictor for SH was SH during the previous year ($r=0.38$, $p<0.0001$).
The impact from SH showed great variation, and 20-30% of events led to practical disturbancies for parents and/or other people. Hospital visits took place only at 5% and hospitalisations at 3% of events. Social activities for patients were cancelled after 10% of events. Increased worry for patients was reported after 8% of events, bad sleep after 7%. We estimated the average socio-economic cost for SH at EURO 239 per event of SH with unconsciousness, and EURO 63 per event of SH without unconsciousness but needing assistance.
Mass-distributed self-study material (brochures and videos) aimed at the prevention of SH without compromising metabolic control reached high dissemination and was widely appreciated by patients. The material copy cost was only EURO 7 per patient. It also seems to have contributed to a decrease in SH with unconsciousness from yearly 13% of patients before to 9% after intervention (3-years average), but controlled studies are needed.
Conclusions
We conclude that SH remains a very serious problem of multifactorial aethiology. It causes considerable discomfort and costs. Systematic patient education might reduce the incidence. Interventions using mass-distribution of high quality self-study material such as videos and brochures seem to have a potential to be cost-effective. There is a great patient/consumer interest in high quality- and advanced information/education materials.

Abbreviations

ADA	American Diabetes Association
ANOVA	Statistical method for analysis of variance in multiple comparisons
CNS	Central nervous system
CV	Coefficient of variation
DCA	Diagnostic chemistry analyser
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
EEG	Electroencephalography
EQUALIS	External Quality Assurance In Laboratory medicine In Sweden
EURO	European currency
HbA1c	Glycosylated haemoglobin of type A1c, higher level predicts higher risk of long-term complications
HPLC	High-performance liquid chromatography
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
ISPAD	International Society for Pediatric and Adolescent Diabetes
NU	Severe hypoglycaemia without unconsciousness but needing the assistance of another person
SD	Standard deviation
U	Severe hypoglycaemia with unconsciousness
VAS	Visual Analogue Scale
WHO	World Health Organisation

Review of the literature

Background

Type 1 diabetes

The ancient words diabetes mellitus described ”the flowing over of sweet urine”. Diabetes mellitus is a state of absolute or relative insulin deficiency causing the body to lose its ability to utilise carbohydrates as fuel. As a result, glucose levels are elevated in the blood and spill into the urine, and fat and proteins are utilised to supply the body’s energy. The spilling of glucose in the urine causes the classical symptoms frequent increased urination, consequent thirst and frequent drinking.

For the increasing numbers of young people with type 1 diabetes (earlier called insulin-dependent diabetes mellitus, IDDM), *there is no alternative to treatment with insulin*. If untreated, dehydration and acidosis will lead to coma and death. Suboptimal insulin replacement will lead to growth retardation and delayed puberty, irreversible long-term complications on the microvascular and organ level, and severely reduced life expectancy (Bojestig, Arnqvist et al. 1994).

The first clinically suitable insulin preparation became available in 1921, following the discoveries of Banting and Best (Joslin, Gray et al. 1922). Today, a broad range of different insulin preparations with different action profiles offers the possibility of individually tailored treatment (ISPAD 2000).

Modern treatment and complications

The Diabetes Control and Complications Trial (DCCT) showed that the onset, progression rate and severity of long-term complications of type 1 diabetes are exponentially related to blood glucose levels that are elevated on a long-term basis as reflected by mean glycosylated haemoglobin HbA1c levels (DCCT 1993). This evidence has led to more or less intensified treatment of type 1 diabetes in children and adolescents throughout the world, though not to the extent aimed for in the St. Vincent and Kos declarations (WHO and IDF 1990; Weber, Brink et al. 1995), and later in the national guidelines (Berne and Agardh 1997).

Since the 1980s, treatment has become increasingly physiological, aiming at near normal blood glucose and HbA1c levels. A combination of multiple pre-meal doses of short-acting or direct-acting insulin and an intermediate-acting night dose is frequently used. There is also a need for regularity concerning what is eaten and when it is eaten, physical exercise and other habits. This intensive treatment is complex and difficult for the patient, the family and the diabetes team. New technologies such as more physiological direct-acting and slow-acting insulin analogues, improved infusion pumps and forthcoming glucose sensor systems continue to offer new options (Bolli, Di Marchi et al. 1999).

However, severe hypoglycaemia has been the major acute complication since the first dose of the life-saving insulin treatment was given to a boy in Canada in 1922 (Joslin, Gray et al. 1922). And this is still the case, even when the most modern treatments are used. Intensive treatment in the DCCT also led to an increase in severe hypoglycaemia (DCCT 1991) (fig. 1).

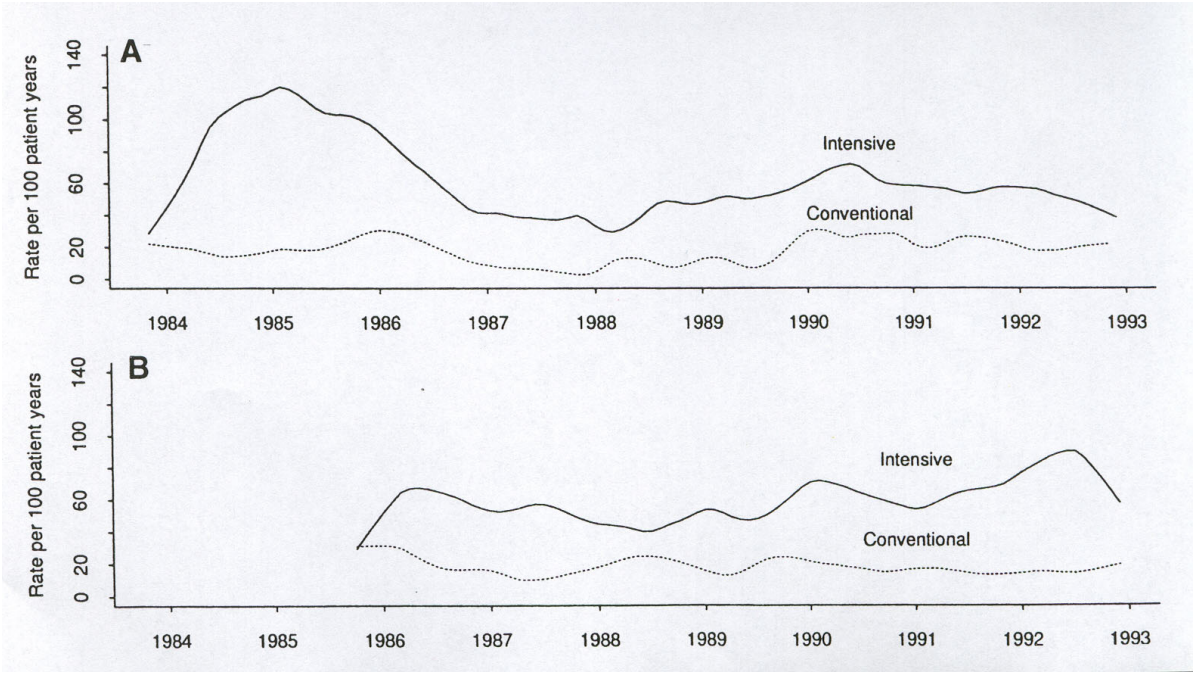


Fig. 1. Incidences of severe hypoglycaemia in the DCCT, intensive and conventional treatment groups. A feasibility phase n=278, B=full scale trial n=1163. With permission from the American Diabetes Association (DCCT 1997).

From this perspective, severe hypoglycaemia has been considered to set the limits for modern diabetes treatment (Cryer 1994). Home blood glucose monitoring often shows levels outside of the target range (fig. 2-3).

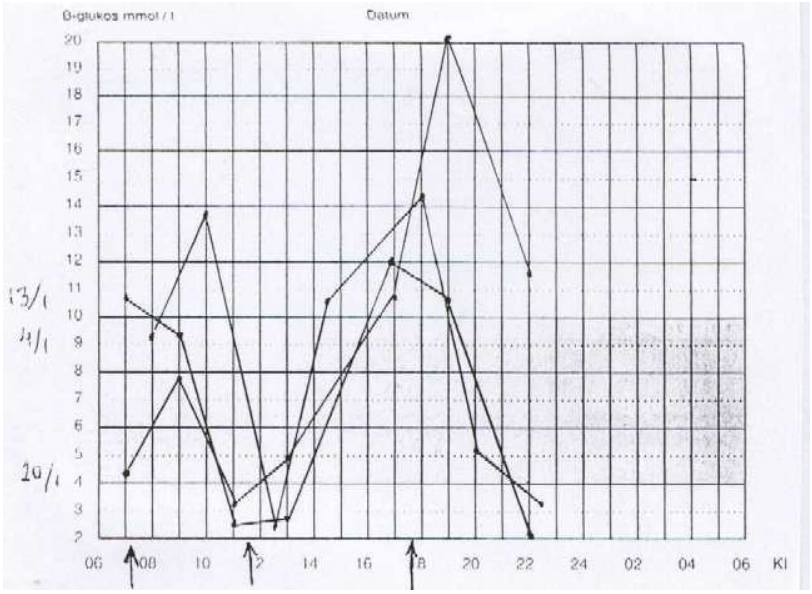


Fig. 2. Three home blood glucose profiles from 6-year-old boy. Shows informative pattern of fluctuations, useful for adjustment of treatment. Determinations during the night are lacking. Target interval for random blood glucose is 4-10 mmol/L.

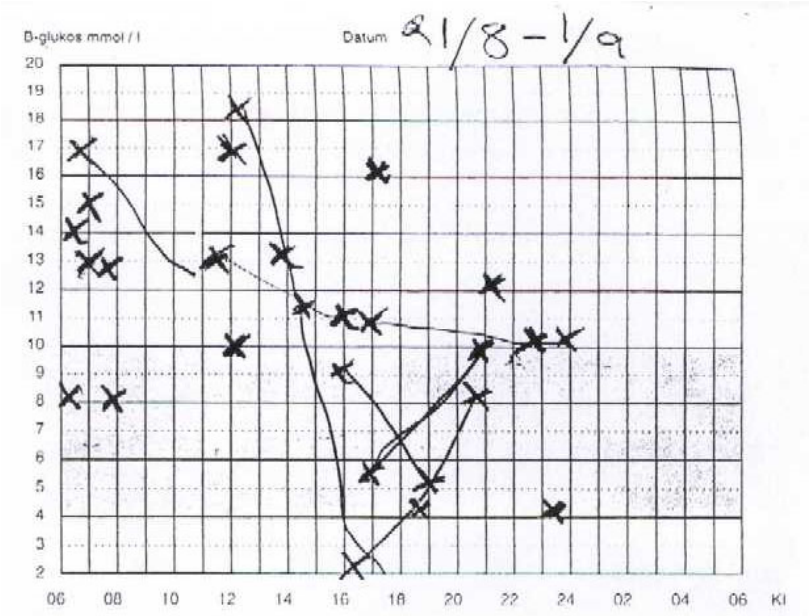


Fig. 3. Home blood glucose determinations from 18-year-old girl. Shows incomplete profiles and single values at different levels. Target interval for random blood glucose is 4-10 mmol/L.

Intra-individual variation in blood glucose may be considerable even during hospitalisation (Simell, Simell et al. 1993). In addition, many fluctuations that occur in between blood glucose readings are undetected (Bolinder, Hagstrom-Toft et al. 1997). There are also discrepancies between tissue glucose and blood glucose levels, especially when fast changes occur.

Some well-controlled patients may function surprisingly well in mild or moderate hypoglycaemia, but in others cognitive function may already be disrupted in mild hypoglycaemia (Cox, Gonder-Frederick et al. 2000). There are regional differences in cerebral blood flow and glucose utilisation (Cranston, Marsden et al. 1998). Certain parts of the central nervous system (CNS) may adapt to some extent to severe hypoglycaemia by using other fuels like ketone bodies (Evans and Amiel 1998).

Treatment goals

Absence of acute as well as long-term complications in combination with a high quality of life are major goals for the treatment of type 1 diabetes according to Swedish and international guidelines (Berne and Agardh 1997; ISPAD 2000). Thus for patients treated with insulin, the reported number of events of severe hypoglycaemia is an important outcome to monitor. However, studies of such continuous registration in paediatric practice have been lacking.

Severe hypoglycaemia

Typical examples

A person on insulin treatment is irritated and has a headache before a delayed meal, but takes no fast-acting carbohydrates. After a period of time CNS function is further disrupted, and increasing confusion leads to severe hypoglycaemia, when help from another person is needed, with or without unconsciousness.

A person on insulin treatment engages in extra exercise such as sports, going to a disco or simply a very long day spent outdoors, eats regularly, takes insulin as usual, but forgets to compensate for the extra exercise by increasing the size of

meals and/or taking less insulin. During the night or early morning, this person may experience severe hypoglycaemia.

Definitions

There is a lack of consensus concerning the definition of severe hypoglycaemia. Incongruent definitions of severe hypoglycaemia have been used in different studies, making comparisons difficult.

In the DCCT, severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the patient required the assistance of another person and which was associated with a blood glucose level below 2.8 mmol/L or prompt recovery after oral carbohydrates, iv glucose or Glucagon administration (DCCT 1991).

However, cognitive dysfunction may also occur at blood glucose levels of 3-4 mmol/L (Cox, Gonder-Frederick et al. 2000). A more conservative, physiological definition would be a blood glucose level <4 mmol/l (Bolli 1999). Moreover, it is sometimes the case that patients rely only on patterns of symptoms without blood-glucose determinations or other documentation (Pramming, Thorsteinsson et al. 1991).

There has been an absence of studies with definitions that are more useful for hypoglycaemia registration in clinical practice.

Occurrence

The subcategory with hypoglycaemic coma and/or seizures may be a category that is more reliable for making comparisons, as such events are easier to recognise and are normally quickly reported by the parents to the diabetes team. This category of events has previously been described as occurring in children and adolescents 0.1-0.2 times on average per patient year, mostly in those studies with conventional treatment and rather unsatisfactory metabolic control (Soltesz 1993). Incidences were higher with intensive treatment, with 0.27 events per patient year in selected adolescents and young adults (DCCT 1997). A cross-sectional international multicenter study of children mainly on conventional treatment reported 0.22 events yearly per patient (Mortensen, Robertson et al. 1998), but only 70% of patients participated.

One might expect a higher incidence in a complete geographic population of children and adolescents which includes patients with all kinds of psychosocial problems, etc. However, the incidence of severe hypoglycaemia in such real-world populations receiving modern intensive treatment from the onset of their diabetes has previously been unknown.

Symptoms

Studies in healthy adults have shown that a low or a rapidly falling glucose level normally causes hormonal counter-regulation with immediate stress-symptoms from the autonomic nervous system. In type 1 diabetes, these symptoms are also *warning symptoms* to the hypoglycaemic person (Cryer 1997). If hypoglycaemia persists, it also results in reversible *neuroglycopenic symptoms*, mainly from the central nervous system (CNS), causing restorable cognitive dysfunction (table 1) (Lindgren, Eckert et al. 1996).

Hypoglycaemic symptoms may vary from time to time as well as from person to person. The level for onset of warning symptoms may be lower after

Table 1. Autonomic (warning symptoms), neuroglycopenic and nonspecific symptoms and signs of hypoglycaemia (Åman and Wranne 1988; McCrimmon, Gold et al. 1995).

Autonomic	Neuroglycopenic	Nonspecific
Sweating	Fatigue	Nausea
Pallor	Dizziness	Headache
Hunger	Irritability	Abdominal pain
Palpitations	Reduced concentration	Weakness in legs
Tremor	Odd behaviour	Tearfulness
	Blurred vision	
	Slurred speech	
	Paresthesia	
	Confusion	
	Coma	
	Seizures	

preceding low blood glucose levels (Dagogo-Jack, Craft et al. 1993). In addition, the capability of correctly judging a risk based on disrupted performance may vary (Clarke, Cox et al. 1999).

In the treatment of children it is important to recognise that *unspecific symptoms and behavioural changes* related to neuroglycopenia are more common, and classical autonomic symptoms may be less prominent than in adults (McCrimmon, Gold et al. 1995; Tupola and Rajantie 1998).

Treatment

Early and adequate self-treatment is needed to prevent mild or moderate hypoglycaemia from resulting in severe hypoglycaemia requiring the assistance of another person. A quick blood glucose determination will confirm the level of hypoglycaemia, and together with symptoms, the actual blood glucose level should be noted in the logbook accordingly.

Hypoglycaemic symptoms or signs need to be immediately treated with fast-acting carbohydrates like *glucose tablets taken with liquid and 10-15 minutes of rest* until the treatment has taken effect. The glucose tablets should be carried as a medicine reserved for only this purpose (Hanås 1998). Overtreatment should be avoided, and therefore the patient/family must be aware of the appropriate dose of glucose tablets. As a guideline, 0.15 g of glucose tablets per kg body weight will be adequate to elevate blood glucose by 2 mmol/L, and this should be repeated after 15 minutes if the effect is insufficient (Wiethop and Cryer 1993). The patient/family can investigate this by doing blood glucose determinations before and 30 minutes after treatment of several episodes of hypoglycaemia.

Juice or other sweet drinks, fruit or other fast-acting carbohydrates may be used if glucose tablets are not available. Sandwiches, milk, chocolate, etc., should not be recommended for the initial treatment of hypoglycaemia, because the uptake of fatty foods is slower than that of fast-acting carbohydrates (Hanås 1998).

However, glucose tablets are short-acting, and a snack may also be needed if the next meal will not occur for more than 1.5 hours (Wiethop and Cryer 1993).
Finally, severe hypoglycaemia with loss of consciousness is most safely and rapidly reversed with the intramuscular injection of Glucagon 0.1-0.2 mg/10 kg bodyweight by a trained relative or staff member (Aman and Wranne 1988; ISPAD 2000).

Causes of severe hypoglycaemia

Predictors

Earlier workers have pointed out the multifactorial aetiology of severe hypoglycaemia (Cryer, Fisher et al. 1994). The role of the HbA1c level has been highlighted by some (Egger, Davey Smith et al. 1997). But in a DCCT model, the strongest predictors, including HbA1c, explained only 8.5% of the episodes. These predictors were history of hypoglycaemia, longer duration of type 1 diabetes (9-12 years), higher baseline HbA1c, recent lower HbA1c, and higher baseline insulin dose (DCCT 1991). Some adult studies suggest that behavioural variables related to the recognition and self-treatment of hypoglycaemia may be of predictive value (Cox, Gonder-Frederick et al. 1999).
However, up until now little has been known about the relationship between HbA1c and severe hypoglycaemia in geographic populations of children receiving intensive treatment from the onset of their diabetes.

Seasonal variation

Seasonal variations in plasma glucose levels and HbA1c appear in healthy subjects (Suarez and Barrett-Connor 1982; MacDonald, Liston et al. 1987). Similar variations have been observed in conventionally treated type 1 diabetes children (Mortensen, Vestermark et al. 1982). Severe hypoglycaemia may also vary with the seasons, with higher risk in the spring and summer (Daneman, Frank et al. 1989). There has been a lack of studies of seasonal variations in HbA1c and severe hypoglycaemia in children with intensive treatment.

Other causes

The insulin secretion from the beta cells of the pancreas in healthy subjects is a rather immediate and accurate response to elevated blood glucose (Olsson, Arnqvist et al. 1988). It is difficult to provide a substitute for this by means of subcutaneous injections, and irregularities in insulin absorption and action are therefore common (Polak, Beregszaszi et al. 1996; Hanås 1998). Accidental mismatch between energy intake, physical activity and insulin administration may alter metabolic balance and cause mild or moderate hypoglycaemia (ISPAD 2000). Many temporary factors such as delayed or missed meals, irregular contents of meals, increased physical activity, stress, infections, alcohol, and various mistakes and difficulties in self-control and insulin dosage may alter the balance (Cryer 1997).

If self-treatment of mild or moderate hypoglycaemia is delayed or inadequate, the progression to neurological dysfunction and severe hypoglycaemia without or with unconsciousness may be rapid. Training in readiness for early corrective action when the initial hypoglycaemic symptoms occur may be a crucial step in prevention (Cox, Gonder-Frederick et al. 1999).

The adolescent

In adolescence, the endocrine system goes into a period of imbalance related to rapid growth, puberty and emotional lability (Ludvigsson 1991). Forgetting doses and/or self-control may be common, and parents may underestimate this problem (Weissberg-Benchell, Glasgow et al. 1995). Irregularities in physical activity, meals and treatment compliance may lead to instability and complications (Bryden, Neil et al. 1999).

Increased growth hormone secretion during puberty contributes in both sexes to a decreased peripheral insulin-sensitivity or a so-called insulin resistance, resulting in a greater insulin need (Amiel, Sherwin et al. 1986).

An increase in the prevalence of overweight has been observed in girls during puberty but not in boys (Domargard, Sarnblad et al. 1999). The fear of weight gain may lead some young women to omit insulin doses and/or to disordered eating behaviours, causing instability and a tendency for the less common acute complication of diabetic ketoacidosis (Brink 1997; Smith, Firth et al. 1998).

Also smoking may increase insulin resistance and needs to be avoided for this and other strong reasons (Attvall, Fowelin et al. 1993; Eliasson, Attvall et al. 1997).

Finally, at the end-stage of puberty a down-regulation of insulin doses is crucial to avoid excess weight gain and prevent severe hypoglycaemia.

The small child

Insulin treatment of the small child is especially difficult because of the fact that on top of rapid growth and frequent infections there are also unpredictable variations in food intake and in physical activity. In practice, parents sometimes need to give the meal-dose of insulin after the meal, when the amount of food eaten is known. Direct-acting insulin may be more suitable for this (Hanås 1998).

As in older patients, increased physical activity leads to an increased risk for hypoglycaemia and may need to be compensated for by an increase in energy intake and a decrease in the nightly insulin dose.

Great caution is required when treating children younger than 8 years of age with regard to this vulnerable phase of growth and development (Amiel 1996; Brink 1997). An individualised glycaemic target is needed and a somewhat higher mean blood glucose level may have to be accepted to prevent severe hypoglycaemia in pre-school children (Brink 1997; ADA 1998).

Defective counter-regulation

In normal subjects, hormonal counter-regulation will result in autonomic symptoms and the release of glucose if the blood glucose level is falling or is below normal (Cryer 1997). These effects are primarily mediated by the rapid glucagon response and, when needed, also by epinephrine secretory responses

and, to a lesser and slower extent, by the cortisol and growth hormone responses (fig. 4).

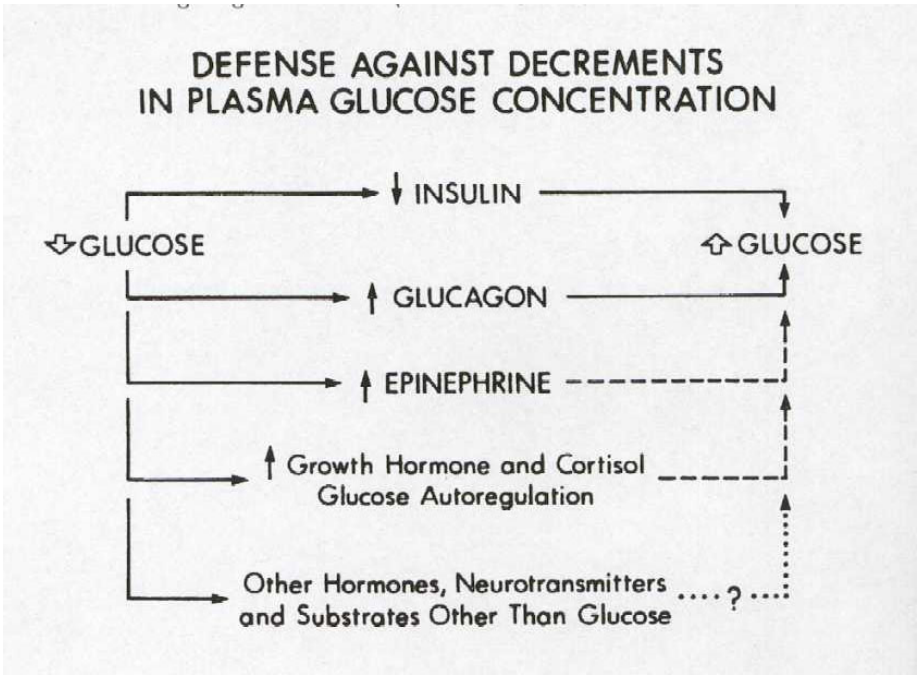


Fig. 4. Glucose counter-regulation in healthy humans. From Cryer PE, ”Hypoglycemia. Pathophysiology, diagnosis and treatment”, with permission from Oxford University Press (Cryer 1997).

For reasons that are unknown, the glucagon response to hypoglycaemia is often lost in type 1 diabetes, but this is compensated for by the rapid epinephrine response (Bolli 1999). However, in periods of therapeutic insulin excess causing frequent low blood glucose levels, the onset level of the epinephrine response may be shifted towards lower blood glucose levels (Dagogo-Jack, Craft et al. 1993). When the epinephrine response to falling blood glucose is also lacking and therefore glucose is not released at a critical blood glucose level, *the syndrome of defective glucose counter-regulation* is established (fig 5). *The physiological defence* against hypoglycaemia is then compromised. Furthermore, counter-regulation in children and adolescents is reduced during sleep (Jones, Porter et al. 1998; Matyka, Crowne et al. 1999).

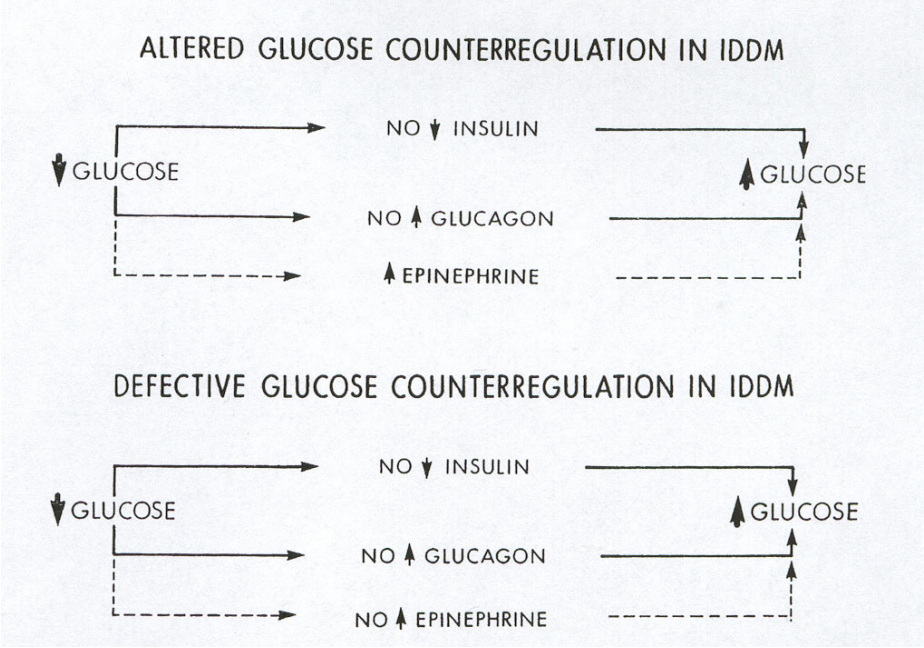


Fig. 5. Glucose counter-regulation in type 1 diabetes (IDDM): altered and defective regulation. From Cryer PE, "Hypoglycemia. Pathophysiology, diagnosis and treatment", with permission from Oxford University Press (Cryer 1997).

Hypoglycaemia unawareness

If the threshold for the epinephrine response to low blood glucose is lowered, the subject may not experience autonomic warning symptoms early enough before neuroglucopenic behavioural symptoms make severe hypoglycaemia inevitable. Thus, *the syndrome of hypoglycaemia unawareness* is established and the *behavioural defence* against hypoglycaemia is compromised (Cryer 1997; Bolli 1999).

Recurrent hypoglycaemia

These maladaptive mechanisms causing impairment of the physiological and behavioural defences against severe hypoglycaemia may lead to a vicious cycle of recurrent hypoglycaemia (fig 6) (Cryer, Fisher et al. 1994; Bolli 1999). Fortunately, the epinephrine response may be more or less restored in a few days or weeks by highly intensive self-control, carefully avoiding hypoglycaemia (Fanelli, Epifano et al. 1993; Amiel 1996).

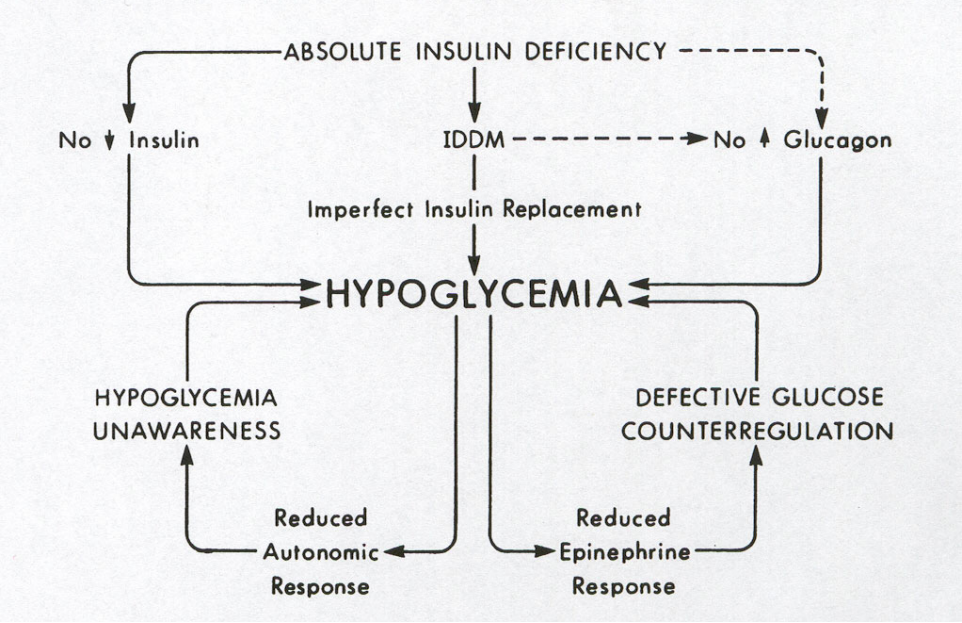


Fig. 6. Mechanisms leading to vicious cycle of recurrent severe hypoglycaemia in type 1 diabetes (IDDM). From Cryer PE, ”Hypoglycemia. Pathophysiology, diagnosis and treatment”, with permission from Oxford University Press and the American Diabetes Association (Cryer 1997).

Effects from severe hypoglycaemia

Long-term effects on cognitive function

A proportion of patients may experience repeated episodes of severe hypoglycaemia over a longer period of time (Oskarsson, Adamson et al. 1999). Especially prolonged and recurrent severe hypoglycaemia in children may cause irreversible alterations in cognitive functions (Ryan and Becker 1999), but in some studies no such effects were found (Deary and Frier 1996; Austin and Deary 1999). In some reports impaired neuropsychological function was found more frequently in diabetic children with early onset than in those with later onset of their diabetes, possibly related to a larger number of severe hypoglycaemia events at a vulnerable age (Ryan, Vega et al. 1985; Bjorgaas, Gimse et al. 1997).

Neurophysiology and radiology

A number of authors have described neurophysiological abnormalities related to a history of severe hypoglycaemia among diabetic children (Haumont, Dorchy et al. 1979; Soltesz 1993; Bjorgaas, Sand et al. 1996; Seidl, Birnbacher

et al. 1996). Some reported that abnormal EEGs were more often found among younger children and/or those with earlier onset (Soltesz and Acsadi 1989). Neuroradiological abnormalities have also been found to be related to a history of severe hypoglycaemia (Perros, Deary et al. 1997).

Morbidity and mortality

An excess early mortality has been found is type 1 diabetes patients (Joner and Patrick 1991). Accidents, disablement, and even premature deaths are caused by severe hypoglycaemia. In some epidemiological studies, severe hypoglycaemia was estimated to have caused approximately one "dead in bed" death per 3746 patient years in patients aged 0-30 years (Sartor and Dahlquist 1995), one death per 749 patient years in patients aged 15-34 years (Nystrom, Ostman et al. 1992), and 7% of deaths in patients aged 7-40 years (Thordarson and Sovik 1995). Many cases showed no obvious brain damage, but cardiac arrhythmias have been suggested as a possible cause of death (Eckert and Agardh 1998; Weston and Gill 1999). Physical injury may result from severe hypoglycaemia as often as in 4 events per year in a population of 100 adult patients (MacLeod, Hepburn et al. 1993).

Traffic risk

A large number of studies have focused on driving and diabetes. Good evidence exists that, on the one hand, average crash rates in drivers with diabetes are not higher than in the general population but, on the other hand, a history of severe hypoglycaemia may increase the individual risk dramatically (Lave, Songer et al. 1993; MacLeod 1999). Performance of critical tasks may be impaired in type 1 diabetes even with mild hypoglycaemia, and patients often wait too long in critical situations like driving before taking corrective action (Cox, Gonder-Frederick et al. 2000). Thus, improved prevention of severe hypoglycaemia might reduce crash rates further.

Quality of Life

Fear of severe hypoglycaemia (table 2) may be common and may to some extent be related to personality (Hepburn, Deary et al. 1994). Some found increased

anxiety and decreased experienced happiness in adult patients prone to severe hypoglycaemia (Wredling, Theorell et al. 1992).

Table 2. Severe hypoglycaemia – examples of possible fears. After (Cryer 1997), (Irvine, Cox et al. 1994) and a lecture in Sep 2000 of Maria de Alva, IDF President.

Possible fear
❑ Not recognising hypoglycaemia
❑ Unpleasant symptoms
❑ Neurological dysfunction
❑ Dysfunctional behaviour
❑ Embarrassing behaviour
❑ Appearing stupid or drunk
❑ Passing out in public
❑ No one to help
❑ Feeling dizzy
❑ Difficulty thinking clearly
❑ Making mistakes
❑ Hypoglycaemia when driving
❑ Causing an accident
❑ Losing control of treatment
❑ Hypoglycaemia in front of ones children
❑ As a parent being unable to care for ones children at a critical moment
❑ “Glucose won’t ever rise again” during event
❑ Unwanted hospitalisation
❑ Hypoglycaemia at night
❑ Hypoglycaemia at long meeting
❑ Hypoglycaemia at party
❑ Too much exercise when blood glucose is low
❑ Too high insulin dosage
❑ Not having glucose available
❑ Being alone when blood glucose is low
❑ Brain damage, being disabled
❑ Premature death - dead in bed

Severe hypoglycaemia may cause just as much anxiety as the late complications of type 1 diabetes (Pramming, Thorsteinsson et al. 1991). Hypoglycaemia fear measurement instruments have been validated (Irvine, Cox et al. 1994). Also close relatives may experience fear and sleeping disturbances after severe hypoglycaemia (Gonder-Frederick, Cox et al. 1997; Clarke, Gonder-Frederick et al. 1998).

Severe hypoglycaemia can be distracting, embarrassing and result in social limitations or even employment discrimination. It can be mistaken for alcohol intoxication or drug abuse, and alterations in judgement and behaviour may lead to abusive or illegal acts (Cryer 1997).

Effects on factors such as emotional status, quality of life and relationships have received little attention (Gonder-Frederick, Clarke et al. 1997). There has also been a lack of data regarding various disturbances, practical problems and cancelled activities for patients, families, teachers and other people.

Socio-economic costs

Severe hypoglycaemia in children and adolescents results in extra healthcare expenditures for ambulances, extra visits and hospitalisations and probably to a large extent also for long-term effects of worsened metabolic control (Tupola, Rajantie et al. 1998; Cryer 1999). The costs due to production losses caused by severe hypoglycaemia have been unknown, as studies of direct and indirect socio-economic costs specifically due to severe hypoglycaemia have been lacking. Further, the costs for premature deaths, disablement and other person and property damage, such as due to traffic accidents, are unknown.

Surprisingly, as much as 75% of the total socio-economic costs for diabetes are attributed to the consequences of long-term complications and their treatment, whereas only 25% of the socio-economic costs go to primary management (Henriksson and Jonsson 1998). This remains the case despite the well-established knowledge that primary management including patient education and training has the potential to prevent complications (DCCT 1993).

Prevention of severe hypoglycaemia

There is a great need for severe hypoglycaemia prevention strategies (Cryer, Fisher et al. 1994). In large studies, centre to centre differences appeared in severe hypoglycaemia outcomes that were independent of HbA1c levels (DCCT 1995; Mortensen, Robertson et al. 1998). Some have suggested that the attitudes of the diabetes team and the quality and intensity of patient training in the prevention and early treatment of hypoglycaemia might have a causal relationship to such centre to centre differences (Bott, Bott et al. 1997; Fritsche, Stumvoll et al. 1998). Others have found that severe hypoglycaemia in adult patients was related to a lack of knowledge about different aspects of diabetes treatment irrespective of general educational level (Schiel, Ulbrich et al. 1998).

Even early workers in the field emphasised the importance of clear patient information with examples such as, *"A reaction should be treated by eating an orange or taking the carbohydrate portion of the next meal"* (Joslin, Gray et al. 1922). Others have stated that spending time with the patient is the most valuable way to decrease HbA1c and hypoglycaemia, but patients are many in number and real diabetologists are few (Bolli 1999). Indeed, information and education are essential elements in preventing severe hypoglycaemia (Schiel, Ulbrich et al. 1998; Cox, Gonder-Frederick et al. 1999).

The need for active self-control and other practical advice has been emphasised in the literature (Brink 1997; Gonder-Frederick, Cox et al. 1997; Tamborlane and Ahern 1997). Regular snacks in between meals are used to prevent hypoglycaemia in children and may also be effective in adults (Orre-Pettersson, Lindstrom et al. 1999). Taking long-acting carbohydrates at bedtime may prevent nightly hypoglycaemia (Kaufman, Halvorson et al. 1997; Detlofson, Kroon et al. 1999). The importance of always carrying fast-acting glucose, early recognition of symptoms, and early treatment have also been underlined (Cox, Gonder-Frederick et al. 1999). Some found a reduction of severe hypoglycaemia when direct-acting insulin was used, but data are less complete regarding populations of children and adolescents (Brunelle, Llewelyn et al. 1998). Furthermore,

seasonal trends in the risk for severe hypoglycaemia may need to be taken into account (Ludvigsson and Nordfeldt 1998).

The need for blood glucose control before driving, prophylactic treatment if needed, and early treatment when symptoms occur was recently highlighted (Weinger, Kinsley et al. 1999; Cox, Gonder-Frederick et al. 2000). Patients with insulin treatment should be educated to check their blood-glucose before driving, and even before bicycling in traffic. Prophylactic treatment has been suggested unless the blood glucose is >4-5 mmol/L (Weinger, Kinsley et al. 1999; Cox, Gonder-Frederick et al. 2000). Patients should also make it a routine to stop driving at once in order to treat any hypoglycaemic symptoms and to rest for 10-15 minutes until the treatment has taken effect.

In spite of all this growing evidence regarding prevention of severe hypoglycaemia, educational materials clearly aiming to prevent hypoglycaemia with few exceptions (Hanås 1998) have been lacking.

Summary

In conclusion, at the beginning of the 21st century severe hypoglycaemia is still a very serious problem on a number of different levels.

Organs may be damaged and premature deaths may even occur. Patients with diabetes and their families experience fear, worries and disturbances. Quality of life is compromised. Treatment control may be worsened with long-term complications as a result. Patients and third parties may suffer from physical injuries and property damage, e g traffic accidents.

A health-economics perspective regarding severe hypoglycaemia has been lacking, although severe hypoglycaemia is likely to result in considerable socio-economic costs. Further efforts are needed to evaluate clinically useful methods to systematically monitor and prevent severe hypoglycaemia.

Aims

With the aim of initiating a problem-solving process, we described and evaluated an instrument for continuous registration of treatment and outcome data for use in the clinical care of patients with chronic diseases.

Using this instrument, we studied the incidences of severe hypoglycaemia with modern treatment. To describe real-world data, we monitored a large sample of unselected patients in a long-term follow-up. We also studied regularly determined HbA1c levels, an outcome of great interest in diabetes treatment because higher levels predict a higher risk for long-term complications. Accordingly, we evaluated the role of lower HbA1c as a risk factor for severe hypoglycaemia with modern treatment, analysing long-term population data obtained with the instrument mentioned above.

To further clarify the magnitude of the problem, we estimated the socio-economic costs and other effects from severe hypoglycaemia. The aim here was also to suggest a reasonable amount of resources for allocation to specific interventions aimed at the prevention of severe hypoglycaemia.

To continue the problem-solving process on a clinically applicable level, we produced high quality self-study material aimed at the prevention of severe hypoglycaemia without compromising metabolic control. We evaluated mass-distribution of this material in a population-based study and we estimated costs and effects to see if such interventions have a potential to be cost-effective.

Our aim therefore was to investigate

- A method for prospective data registration (Paper I)
- Incidences of adverse events in children and adolescents with modern treatment (Paper II, III)
- The relation between severe hypoglycaemia and HbA1c level (Paper II, III)
- Seasonal variation in hypoglycaemia and HbA1c (Paper III, IV)
- Costs and other short-term effects from severe hypoglycaemia (Paper V)
- Preventive strategies based on patient information technologies (Paper VI)

Material and methods

Study base

The study base consisted of the approximately 130 patients yearly <19 years of age diagnosed with type 1 diabetes, belonging to the geographic population of Linköping University Hospital, Östergötland County, Sweden, from 1992 to 1999. We have followed them mainly using an open cohort design (mixed longitudinal study). As all patients in the catchment area were treated at the paediatric clinic, we were able to study an unselected geographic population. Their yearly clinical characteristics are given in table 3. There was a predominance of boys, a slight increase over years in prevalence of the disease, but only minor changes in average age, age at onset and duration of type 1 diabetes.

Table 3. Clinical characteristics of responding patients by year.

Year	n	Duration years (SD)	Age years (SD)	Onset age years (SD)	Insulin dose IU/kgx24h (SD)	Sex Boys/Girls
1992	102	4.9 (3.9)	13.1 (3.9)	8.3 (4.4)	0.93 (0.29)	65/37
1993	115	4.8 (4.0)	12.4 (4.2)	7.6 (4.1)	0.88 (0.32)	64/50
1994	126	4.8 (4.0)	12.7 (4.3)	7.9 (4.2)	0.88 (0.29)	74/52
1995	122	4.9 (3.7)	12.5 (4.4)	7.6 (4.0)	0.90 (0.27)	70/52
1996	129	4.8 (3.7)	12.4 (4.3)	7.6 (3.8)	0.93 (0.30)	74/55
1997	132	4.6 (3.8)	11.9 (4.3)	7.3 (3.9)	0.90 (0.31)	73/59
1998	130	4.3 (3.6)	11.8 (4.1)	7.5 (4.2)	0.93 (0.29)	74/56
1999	139	4.4 (3.7)	12.0 (4.1)	7.6 (4.2)	0.93 (0.28)	74/64

Treatment policy and glycaemic aim

Since the late 1970s the study clinic has aimed at the best metabolic control possible for the individual at all times (Ludvigsson 1976). Individually tailored multiple insulin therapy (87-96% on 4-7 doses daily) combined with active self-control, continuous problem-based education and psychosocial support have been

used from the very onset of the disease. Patients were seen by a multi-disciplinary diabetes team at visits scheduled quarterly.

As a result of this treatment policy, mean HbA1c levels improved significantly and long-term complications substantially decreased (Bojestig, Arnqvist et al. 1994), as aimed for in the declarations of St. Vincent and Kos (WHO and IDF 1990; Weber, Brink et al. 1995), and in the national guidelines (Berne and Agardh 1997).

A majority of patients had fast-acting mealtime insulin combined with evening intermediate-acting insulin. Many adolescents also had small doses of fast-acting insulin before afternoon and evening snacks. On some occasions mixtures were used as a complement during daytime hours that were difficult to cover with fast-acting insulin. The patients were educated to use different insulin regimens for different days of the week that were related to changes in patterns of meals and physical activity. The treatment policy is described more in detail in paper III.

In 1995, five patients (4%) were using pumps and 14 adolescents (14%) started to use a direct-acting insulin analogue. These subgroups increased gradually to 12 patients (9%) using pumps and 40 patients (29%) using direct-acting insulin to some extent in 1999. Except for this, the treatment policy remained stable during the study period.

The glycaemic aim for the study patients was an individual HbA1c level as close to normal as possible and preferably less than 7% (HPLC method, ref. 3.6-5.4%). A general target level for blood glucose comprised values before meals within the range of 4-7 mmol/L and values after meals within the range of 4-10 mmol/L (ISPAD, IDF et al. 1995).

Registration of data

Data regarding treatment variables such as insulin doses and outcomes like HbA1c and acute complications were collected by prospective questionnaire registration at each clinical visit, scheduled quarterly. Yearly individual mean values of HbA1c and other variables were calculated. Contents of the questionnaire used are listed in paper I, table 2. The evaluation of this method in long-term clinical practice was new.

Events of severe hypoglycaemia were registered as self-reported by patients and by separate questions divided into *"Number of events of severe hypoglycaemia without unconsciousness but needing the assistance of another person since the last visit" (NU)*, and *"Number of events of severe hypoglycaemia with unconsciousness since last visit" (U)*. No further criteria were used to define severe hypoglycaemia.

The yearly response rate was calculated as number of questionnaires returned out of all those expected in percent, and as number of patients returning at least one questionnaire out of all patients in percent.

Incidences of adverse events were calculated after correction at the population level for percentage of missing questionnaires. Incidences of severe hypoglycaemia were compared before and after significant decreases in HbA1c, and before and after intervention with self-study material.

Associations between yearly numbers of events of severe hypoglycaemia and HbA1c level, insulin dose, proportion of short-acting insulin out of the total daily dose, age at diabetes onset, duration of diabetes, age, sex, weight-to-height ratio, and history of previous severe hypoglycaemia were investigated. Seasonal variations of HbA1c, insulin dose and severe hypoglycaemia were studied from monthly data. As these samples were not standardised in time, HbA1c and insulin dose were analysed by calculating individual seasonal mean values.

In 1998, a postal questionnaire containing Visual Analogue Scales and open questions was used to investigate patients' attitudes to the prospective questionnaire method (McCormack, Horne et al. 1988).

Also in 1998, detailed data regarding unplanned short-term effects and costs due to severe hypoglycaemia were obtained by means of a separate questionnaire.

Validation of registration method

Out of 40 events of severe hypoglycaemia with unconsciousness noted in *case records* during 1994-1995, 36 (90%) had been prospectively registered. Out of severe hypoglycaemic events reported in *the separate questionnaire study* in paper V (appendix 2), 93% had been reported in the prospective registration. Out

of 35 patients in 1997 who prospectively reported severe hypoglycaemia, 32 (91%) reported this again retrospectively in an independent *postal questionnaire* in early 1998.

Thirty-two voluntary patients participated in *logbook examination*. They had a slightly lower mean HbA1c than other patients (6.5% vs. 6.8%, p=0.017) but age, sex and diabetes duration did not differ. Correlations between logbook and questionnaire data were <3 mmol/L r=0.98 (p<0.001) and >10 mmol/L r=0.98 (p<0.001), respectively, for blood glucose tests, and r=1.00 (p<0.001) for insulin dose.

Glycosylated haemoglobin

Glycosylated haemoglobin HbA1c, reflecting average blood glucose levels during the preceding 2-3 months, was determined at every visit (Mortensen, Volund et al. 1984).

Some knowledge about minor changes in the HbA1c methods during the study is needed for interpreting the results (fig. 7).

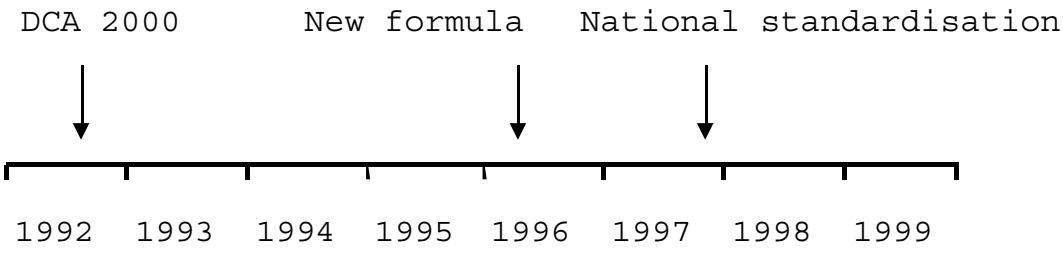


Fig. 7. Time points for modifications of HbA1c methods. See text for details.

The main HbA1c method used in the studies was the Diagnostic Chemistry Analyzer 2000 (DCA 2000) (Guerci, Durain et al. 1997). It was used as the routine clinical method starting in August 1992 and was recalibrated to the new national Mono-S standard starting on 11 December 1997 (Arnqvist, Wallensteen et al. 1997). The DCA 2000 values before 12 March 1996 were adjusted to give values corresponding to the high-performance liquid chromatography (HPLC)

method used by the hospital. Thirty-two parallel samples had resulted in the correlation DCA 2000 = 1.18 x HPLC (r=0.98; P<0.0001) (Ludvigsson 1994).
From 12 March 1996 until 10 December 1997 the DCA 2000 values were adjusted by subtracting 1.0 instead of dividing by 1.18. This resulted in a method more similar to the Steno method used in the DCCT, with a slight increase in the mean and a slightly wider interval.
The HPLC normal range was initially 3.2-6.0%, determined from a normal material of 85 healthy blood donors. From 20 September 1994 the HPLC normal range was narrowed to 3.6-5.4%, determined from a normal material of 100 healthy blood donors, which is consistent with other materials from other laboratories using this method.
Finally, the recalibration to Mono-S standard resulted in on average 0.5% lower values from 11 December 1997. The Mono-S reference range was 3.7-5.0 (Diabetolognytt 1997).
The DCA 2000 method was continuously controlled from January 1998 and onwards with the Swedish EQUALIS reference method (External Quality Assurance In Laboratory medicine In Sweden). This reference was determined from samples on different levels in the specific diabetic interval, as a mean from HPLC method analyses in five high quality laboratories in Sweden. There, the coefficient of variation (CV) in control samples sent from 127 Swedish DCA 2000 instruments every second week was generally 3-4%, and did not extend 5% (L Larsson, personal message, 1999). The DCA 2000 method thus was acceptable for clinical use, although a CV <3% would have been desirable (Arnqvist, Wallensteen et al. 1997).

HbA1c comparisons

There has been no international standardisation of HbA1c methods. However, in the early 1990s the HbA1c values (HPLC) in our hospital were found to be comparable to the Steno method used in the DCCT after adding approximately 1% (Kullberg, Bergstrom et al. 1996).

After the national standardisation in 1997, comparison with the DCCT is possible after the addition of on average 1.15% (Arnqvist, Wallensteen et al. 1997).

Quality of Life

A widely used, validated and inexpensive instrument for global quality of life measurements in different diagnosis groups, the EuroQol-5D (EuroQuolGroup 1994), was used in a postal survey in 1998 of patients with a duration of diabetes > 1 year. The adolescent or for younger children the parent most responsible for the treatment responded. With five separate questions, the EuroQol-5D monitors five parameters that assess quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is ranked at three levels: no limitation, some limitation, and severe limitation. By combining different levels from each dimension, the EuroQol-5D defines a total of 243 possible health states. Scores can be compared before-after within groups, in between groups and to the general population, but there is little data from children and adolescents.

Prevention

Up-dated and detailed self-study brochures regarding diabetes self-care and prevention of severe hypoglycemia were mailed to every patient in the study base both in early 1997 and in 1999. Two video programs (17 minutes + 18 minutes), the contents of which were related to that of the brochures, were mailed later in 1999 to patients with a duration of diabetes >6 months. The videos consisted of clips from focused interviews regarding treatment and hypoglycaemia with three patients aged 9-14 years and their parents, sequences from their daily lives, and brief comments from a diabetologist.

The informative material was developed in interaction with patients and parents and responded to specific questions raised by them. There was a basic optimistic attitude of support toward increasing one's skills in self-care. To avoid imposing guilt feelings, a team psychologist checked the language and content. Individual follow-up was given continuously as needed at regular visits after the interventions.

This new patient information material was developed in a multi-professional network of advisors, as recommended for development of such materials (Entwistle, Watt et al. 1998; Coulter, Entwistle et al. 1999). Contents were based on best evidence from the literature (Barton 2000), international guidelines (ISPAD, IDF et al. 1995) and 20 years of clinical experience in intensive treatment in this diabetes team.

In 1998 and 2000, postal questionnaires containing Visual Analogue Scales and open questions were used to investigate patients' attitudes to the intervention with self-study material (McCormack, Horne et al. 1988).

Statistics

For the statistical analysis, StatView software versions from 4.02 to 5.0.1 (Abacus Concepts Inc. and SAS Institute Inc., USA) were used. A probability level of <5% was considered to be statistically significant.

Student's t-test was used to compare large samples of population mean HbA1c values, while median values, the non-parametric Mann-Whitney U-test and Spearman's rank correlation were used when the material was smaller or did not have a normal distribution. The Chi-square was calculated for categories with different HbA1c intervals. Fisher's exact test was used for comparison of incidences in percentage of patients. Correlations with Fisher's r to z test and multiple regression analysis were analysed. Factorial ANOVA with season as the factor for single HbA1c values, and one-way ANOVA repeated measurements for seasonal mean values of HbA1c and insulin dose were used.

Ethical considerations

The studies were approved by the regional Ethics Committee for Human Research at the Faculty of Health Sciences, Linköping, Sweden.

Results

Response rate (Paper I)

The yearly response rates for the prospective patient questionnaire increased over the years to 100% of patients and 96-98% of all expected questionnaires, as shown in fig. 8.

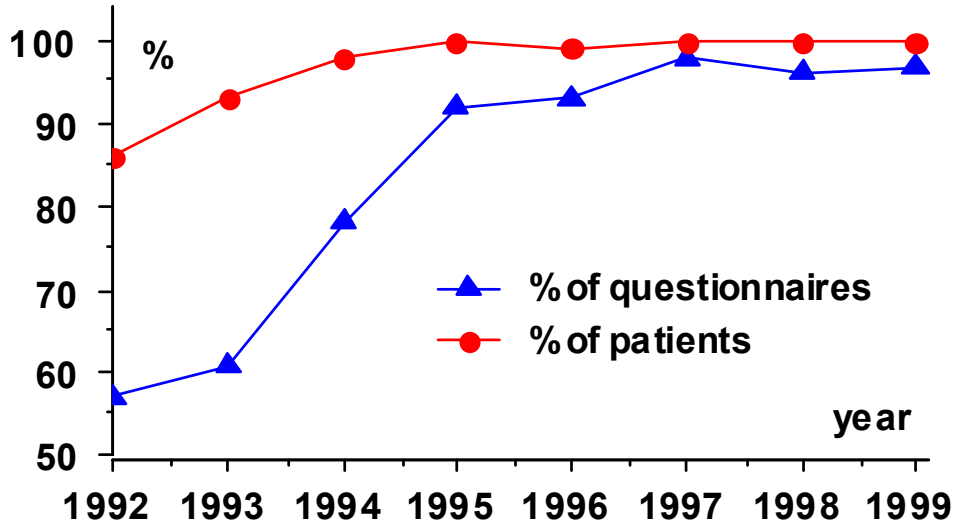


Fig. 8. Increasing yearly response rate for patient questionnaire, percentages of responding patients and of returned questionnaires.

Incidences of severe hypoglycaemia (Paper II-III, VI)

On average 40% of all patients reported severe hypoglycaemia yearly, 7-16% of whom reported yearly that they had events of hypoglycaemia with unconsciousness. During 1992-1999, 0.14-0.22 events of severe hypoglycaemia with unconsciousness per patient year were prospectively registered (table 4).

Factors related to severe hypoglycaemia (Paper II)

The NU events were weakly correlated to lower age ($r=0.12$; $p=0.027$) and to a lower proportion of short-acting insulin out of the total daily insulin dose ($r=0.12$; $p=0.028$), but they were not significantly correlated to the yearly mean HbA1c or any other factor.

Table 4. Yearly mean HbA1c and incidence of severe hypoglycemia with unconsciousness (U) and without unconsciousness (NU) given as total number of events per patient year, and as percentage of patients yearly reporting one or more events during the year. Intervention with self-study material in early 1997.

Year	n	HbA1c % Mean (SD)	U/pat	with U %	NU/pat	with NU %
1992	102	8.1 (1.6)	0.15	10	1.0	27
1993	115	7.7 (1.5)	0.19	13	1.0	38
1994	126	6.9 (1.3)	0.17	16	1.3	34
1995	122	7.1 (1.1)	0.17	12	1.3	34
1996	129	7.3 (1.2)*	0.22	12	1.5	37
1997	132	7.0 (1.1)	0.15	10	1.8	36
1998	130	6.4 (1.1)**	0.14	7	1.7	35
1999	139	6.6 (1.1)	0.16	10	1.6	37

Yearly mean HbA1c decrease significant from 1992 to 1994 ($p<0.0001$), 1993 to 1994 ($p<0.0001$), 1996 to 1997 ($p=0.042$) and from 1996 to 1998 ($p=0.006$) after correction for recalibration in 1997. Severe hypoglycaemia decrease n.s. (small numbers of events).
HbA1c values in this table not adjusted for (see Material and methods):
*From 12 March 1996 yearly mean increased by 0.2% as the DCA 2000 values were adjusted to the HPLC method by subtracting 1.0 instead of dividing by 1.18 as was done earlier.
**From 11 Dec 1997 the yearly mean decreased by 0.5%, to an average of 1.15% below the DCCT, due to recalibration of the DCA 2000 method to the national standard.

The U events were weakly correlated to lower age at onset ($r=0.13$; $p=0.016$) and simultaneously to longer duration ($r=0.15$; $p=0.0075$), but were not significantly correlated to the yearly mean HbA1c or any other factor. For all the severe hypoglycaemic events (U+NU), a weak correlation was found to lower proportion of short-acting insulin ($r=0.11$; $p=0.047$), but there was no significant correlation to the yearly mean HbA1c or any other factor.
In multiple regression analysis, (U+NU) was related to lower HbA1c ($p=0.0060$), higher insulin dose in IU/kg x 24hrs ($p=0.019$), and lower proportion of short-acting insulin out of the total daily insulin dose ($p=0.024$).

None of the factors was significant for U alone in multiple regression analysis, but NU showed a relation to lower HbA1c (p=0.014), higher insulin dose in IU/kg x 24hrs (p=0.0038), shorter duration (p=0.010) and lower age at onset (p=0.035).

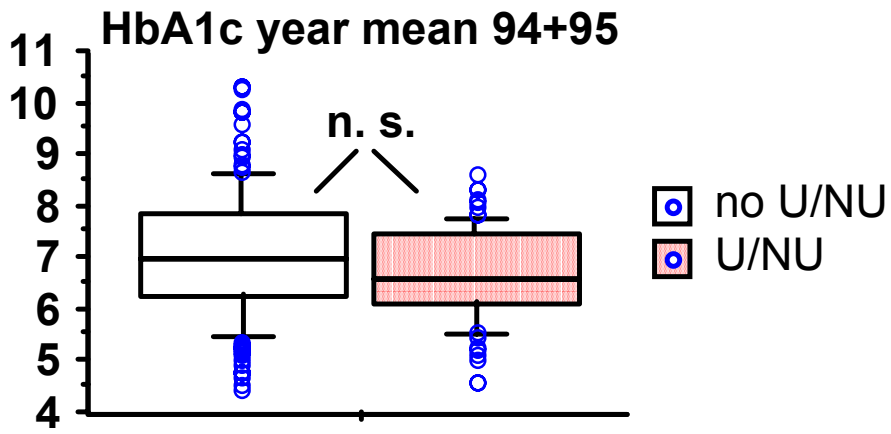
The square root of (U+NU) was calculated to reduce the statistical variance of (U+NU), as the yearly numbers of NU varied from 0 to 15. It was related to lower HbA1c (p<0.0001), higher insulin dose in IU/kg x 24hrs (p=0.0060) and lower age at onset (p=0.040) in multiple regression analysis.

Finally, in multiple regression analyses the square root of NU was related to a lower HbA1c level (p=0.0003), a higher insulin dose in IU/kg x 24hrs (p=0.0024) and a lower proportion of short-acting insulin (p=0.031).

HbA1c and severe hypoglycaemia (Paper II, III)

The individual yearly mean HbA1c values of the patients who had had, and of those who had not had, severe hypoglycaemia with or without unconsciousness (U/NU) during 1994-1995 are shown in fig. 9. With a larger number of person years in 1992-1994, slightly lower HbA1c values had been shown in those with severe hypoglycaemia (p=0.047).

Fig. 9. Distributions of yearly mean HbA1c values in patients who had had and patients who



had not had severe hypoglycaemia with or without unconsciousness (U/NU). Shows overlap, no significant difference and no safe zone for clinical use. n=139, 248 patient-years. Percentile box plot with 50% of values inside box; rings represent the 10% outliers at each end.

Also in paper II, the relative risk for events of (U+NU) when the HbA1c yearly means were < 7.0% and ≥ 7.0%, respectively, was 1.24, and for NU alone the same relative risk was 1.29.

The number of U/NU episodes in 1995 was correlated to the number of U/NU episodes in 1994 ($r=0.38$; $p<0.0001$), but there was no correlation to the yearly mean HbA1c for U, NU or U/NU.

There were no significant differences in the incidences of U, NU or U/NU (% of patients) when patients with yearly mean HbA1c levels = 7.0% (n=129) were compared with patients with yearly mean HbA1c levels >7.0% (n=115), or when yearly mean HbA1c levels <6.5 (n=79), 6.5-7.3 (n=82) and >7.3 (n=83) were compared.

Seasonal variation (Papers III, IV)

An increase in U during the spring season was seen in 1994-1995 (fig. 10).

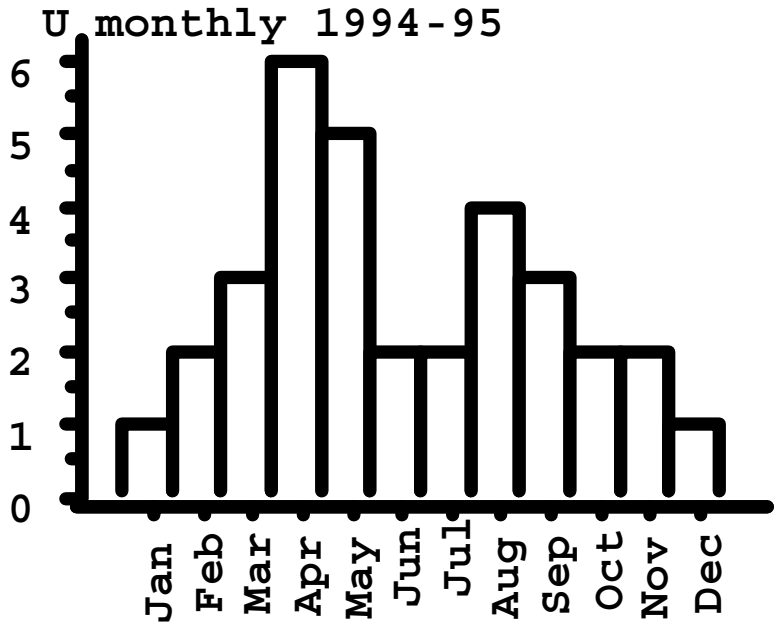


Fig. 10. Monthly distribution of severe hypoglycaemia with unconsciousness (U) showing seasonal peak in April-May.

Lower HbA1c values were seen in the spring and summer, but they were higher again in the autumn and winter periods of 1995-1996 (p=0.023) (fig. 11). Patients reporting severe hypoglycaemia more often had a seasonal variation in HbA1c as compared to patients without severe hypoglycaemia (p=0.019).

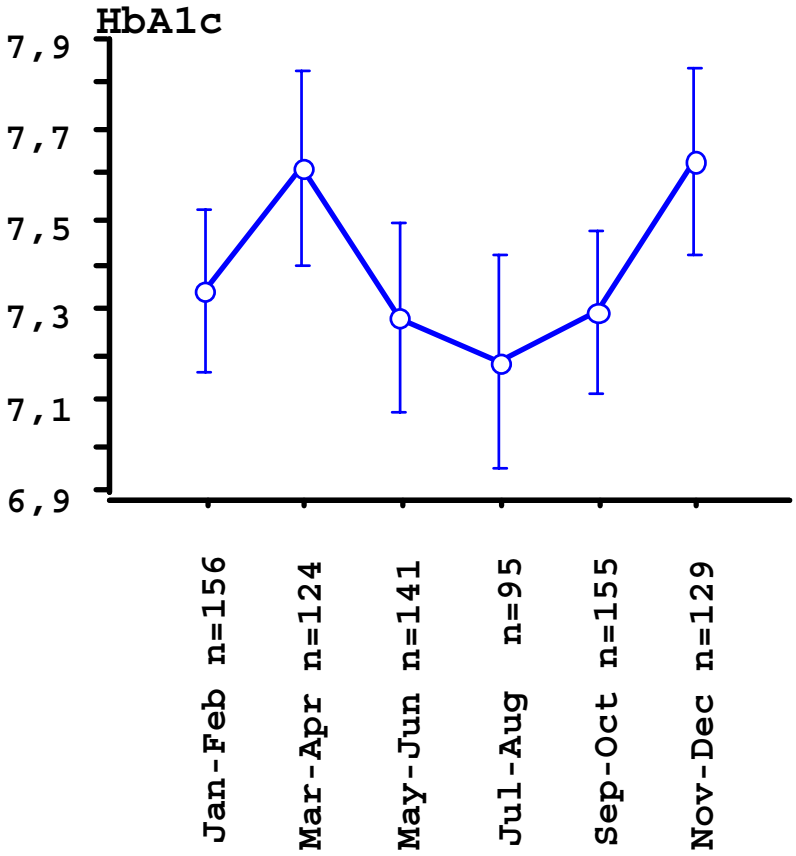


Fig. 11. Seasonal variation of all single HbA1c levels during 1995-1996. Shows seasonal variation with falling values in spring and summer.

Costs and intangibles (Paper V)

Twenty to 30% of hypoglycaemic events caused effects like needing assistance from people other than parents, school absence, parents' work absence, extra transports and/or phone calls (table 5). Hospital visits took place at 5% and hospitalisations at 3% of all events. Social activities for patients (families) were cancelled after 10% (5%) of events. Increased worry for parents was reported after 8% and poor sleep after 7% of events.

The average socio-economic burden for events of severe hypoglycaemia was estimated at EURO 17 400 yearly per 100 type 1 diabetes patients. Average cost was estimated at EURO 239 per event of severe hypoglycaemia with unconsciousness or EURO 478 yearly per patient with unconsciousness, and EURO 63 per event of severe hypoglycaemia without unconsciousness but needing assistance from another person or EURO 307 yearly per patient in this category. These figures are underestimations because costs for possible traffic accidents, disablement or premature deaths, and peoples' leisure time and other intangibles were not included.

Table 5. Self-reported medical and non-medical short-term effects at events of severe hypoglycaemia with unconsciousness (U) and all events of severe hypoglycaemia.

	Range (median)	U 16 events		All 111 events	
		Events	%	Events	%
Hospital visits	1 - 6 h (2 h)	3	19	6	5
Hospital admissions	0.5 - 5 d	1	6	3	3
Ambulance transports[a]	0 - 15 km	5	31	8	7
Blood glucose test at event[b]		12	75	86	77
Extra blood glucose tests after event	1 - 20 (3)	12	75	71	64
Assistance from other people	0.2 - 3 h (0.5 h)	3	19	33	30
Teacher absent from pupils				6	5
Patient absent from school	0.5 - 2 d (1 d)	9	56	26	23
Parent absent from work	0.5 - 5 d (1 d)	9	56	26	23
Extra phone calls	1 - 5 (3.5)	5	31	23	21
Extra private transports	0.5 - 70 km			23	21

[a] Four calls led to assistance but no transport.

[b] Nine values 2.5-2.9 mmol/l, 35 values 2.0-2.4 mmol/l, 35 values <2.0 or "Lo". 7 values higher (delayed test).

Quality of Life

The EuroQuol-5D was completed by 70/112 patients. The EuroQuol-5D score indicated lower quality of life for patients with U and/or NU severe hypoglycemia (n=35) compared to patients without severe hypoglycaemia (n=35) during 1997 (median 0.85 vs. median 1.0, p=0.0114).

Some "informative extremes" from responses to related open questions are shown in table 6.

Table 6. Examples of patients' and parents' comments to open questions.

Comment
❑ I felt bad in every way. I was ashamed, like I'd done something stupid, and I was nauseated and had a headache (18-year-old boy).
❑ Nauseated and scared it will happen again, and then I often eat more and take less insulin, and then my blood sugar is often high (17-year-old boy).
❑ Nervous, shaky, nauseated, a bit ashamed that I can't take care of myself and that I'm not normal (17-year-old boy).
❑ Nauseated and scared it will happen again, my arms and legs feel weak, I can't think clearly for 10 minutes, I feel tired, my hearing and sight are bad for a while (10-year-old girl).
❑ Fear, despair, powerlessness concerning the disease, which is always there, just waiting to take over (mother of 17-year-old boy).
❑ You're completely destroyed for a few days, and worried it will happen again. You become over-protective for several days. You try to think and plan so it won't happen again (mother of 10-year-old boy).
❑ Worried it will happen again, sleeping problems, it's terribly exhausting (panic!) to have to experience your child in that condition (mother of 9-year-old girl)
❑ Always worried as night approaches, often take an extra blood-sugar at night. Worried they don't watch her carefully enough at the day-care centre (father of 5-year-old girl).
❑ Very worried about leaving her with a baby-sitter. Relatives get scared and don't want to baby-sit. As a parent, you often feel very tired and sometimes you feel like giving up (father of 5-year-old girl).

Prevention of severe hypoglycaemia (Paper VI)

Patients' attitudes to the interventions with self-study brochures and videos were predominantly positive or highly positive, varying within wide ranges. Those with severe hypoglycaemia the preceding year indicated greater benefit from the hypoglycaemia brochure than other patients (p=0.039). The whole group of patients indicated greater benefit from the hypoglycaemia video than from the brochure (p=0.016). Eighty-six percent of responders stated that the video was valuable, and 51% indicated it was as beneficial as >66 mm (upper third of scale) on a visual analogue scale, "No benefit at all (0 mm) – Greatest possible benefit (100 mm)". After 6 months, the videos had been shown in the families up to 6 times, median 2 times (fig. 12). They had also been shown to others by 46% of families (fig. 13). Once produced, the material copy cost was only EURO 7 per patient.

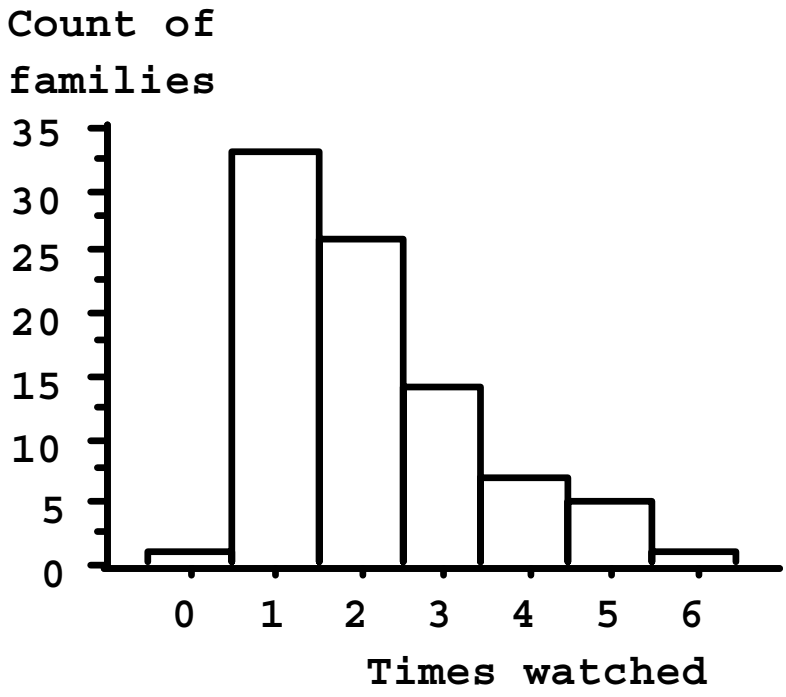


Fig. 12. Self-reported number of occasions that the videos had been watched within the families during a 6-month period. N=88.

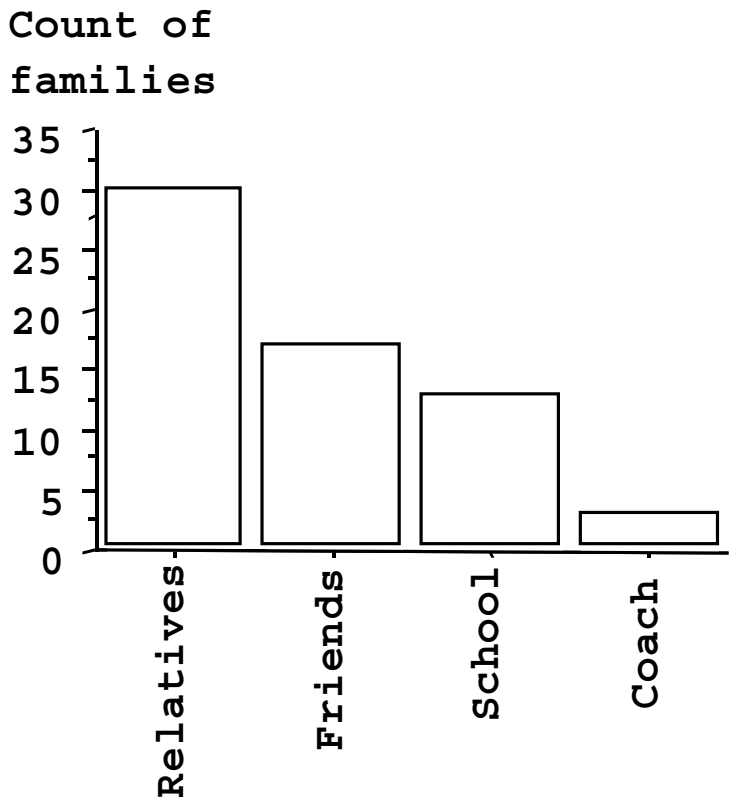


Fig. 13. Self-reported number of occasions that the videos had been shown to others during a 6-month period. N=88.

After the intervention, the average yearly incidence of severe hypoglycaemia with unconsciousness decreased from 13% of patients in 1994-1996 to 9% in 1997-1999 (table 4), and the increase in severe hypoglycaemia in the spring season was likewise reduced. The percentage of patients reporting severe hypoglycaemia without unconsciousness was unchanged, while there was a tendency to report higher numbers of events without unconsciousness. The population yearly mean HbA1c decreased as well from 1996 to 1997 ($p=0.042$) and to 1998 ($p=0.006$), (after correction for recalibration of the method on 11 December 1997).

Discussion

The use of an open cohort model enhances clinical follow-up through yearly before-after comparisons on a population level. Such a model also limits bias from dropouts and clustering, as the population is renewed continuously. Trends and changes over time in the clinical characteristics and/or treatment policy may affect the outcome and need to be controlled for. Even if open cohort data cannot reach the full hierarchic evidence quality of a randomised-controlled trial, long-term observational studies in particular may have a strong complementary value as they represent wider populations in the real world (Barton 2000).

Validity of the material

The study population was a complete geographic population consisting of all ages under 19 years, with all kinds of social backgrounds. This is in contrast to the often cited DCCT, where only selected, highly motivated patients from 13 years of age were included, and also in contrast to most other recent and earlier studies of childhood diabetes treatment and outcomes (DCCT 1993; Mortensen, Robertson et al. 1998).

The unselected large geographic population and the high response rate in the prospective data registration are two major strengths. A third strength is the long study period, preceded by extensive experience with a consistent intensive treatment policy on the part of our diabetes team. The minor changes at the end of the study period towards gradually increased use of direct-acting insulin treatment and also an increase in pump treatment did not alter the results or conclusions in paper VI.

Selection and drop-out effects

In paper II, the response rate in 1992-1993 was found to be poor, and the incomplete data might represent a selection. With continued data registration and analysis, however, the major conclusions could be confirmed in paper III.

A few drop-outs with respect to hypoglycaemia registration may have occurred in exceptional cases such as if a patient was not seen in the clinic for a longer period

due, for example, to temporary study abroad or when a clinical visit was delayed for some other reason. From 1995 and onward, the risk of losing patients who were less compliant to treatment was eliminated, as all patients reported data at least on some occasions. Therefore the selection and drop-out effects in the longitudinal studies were marginal.

Validity of the methods

Some earlier authors registered severe hypoglycaemia only when a blood-glucose level below a certain point was determined, when a Glucagon injection or glucose treatment was given orally or by infusion, and/or when there was a documented response to such treatment (Egger, Davey Smith et al. 1997). However, this excludes the proportion of events where patients rely merely on their recognition of patterns of symptoms (Pramming, Thorsteinsson et al. 1991). Even in our study, with patients trained in active self-control, 23% of 111 reported severe hypoglycaemia events had not been accompanied by a blood-glucose estimation (table 5). Blood glucose level criteria may also exclude clinically significant events with biochemically milder hypoglycaemia. We therefore have used a wider, more conservative definition which, if anything, might lead to an over-reporting of events.

Moreover, we used prospective registration with a patient questionnaire continually integrated in the treatment program (paper I). The hypoglycaemia questions were embedded in a context of relevant but more neutral questions. The questionnaire was part of a long-term close collaboration between our diabetes team and the patients and their families. This treatment policy included a strong emphasis on psychosocial support from the very onset of the disease. A large number of years were studied, showing data oscillating around a mean with rather high stability over the years since 1994. We believe this is the most reliable method for studying severe hypoglycaemia. Test-retests suggested >90% reliability (paper I).

However, the intervention in early 1997 may have caused increased interest, thereby resulting in higher relative reporting rates. The changes in reported rates

from 1997 (table 4) might represent a combination of such a higher reporting rate, at least for NU events, and a true decrease at least in U events after the intervention, but these effects are difficult to interpret.

HbA1c methods

Although our laboratory is of high quality, no laboratory can do better than the methods used. Even with a coefficient of variation (CV) of 3%, the confidence interval for a mean HbA1c on the 8% level is 7.5-8.5%, and with a CV of 5% it is as high as 7.2-8.8 (Diabetolognytt 1997). The Mono-S standardisation in Sweden starting in late 1997 aims at a CV < 3% (Arnqvist, Wallensteen et al. 1997), but this goal has been difficult to reach with respect to rapid HbA1c methods that are useful in outpatient practice. The many different glycosylated haemoglobin methods and their lack of standardisation have made comparisons between earlier studies even more difficult.

The DCA 2000 method has proven to be a high quality method in a number of studies (Guerci, Durain et al. 1997), as well as in the hands of our laboratory. Further, temperature stability has been found to be satisfactory with regard to seasonal variation of indoor temperature in our hospital (Wikblad, Smide et al. 1998).

It would have been easier if the HbA1c methods and re-calculations had been entirely unchanged during the whole study period. However, we have described things as they were. The national standardisation in 1997 improved the situation (Arnqvist, Wallensteen et al. 1997).

In 1998, a minor drifting of higher values towards lower values was detected by EQUALIS and by the manufacturer in the USA. The method was thereafter corrected and users were informed by the manufacturer. This illustrates the importance of external quality control systems.

Statistical methods

We have calculated yearly mean values for measured data like age, HbA1c and insulin dose, and used these as approximations of the variables in our analyses. Different lengths of observation periods can be chosen, or sampling standardised

to fixed measurement points in time. We found yearly mean data most plausible with regard to the clinical situation with on average quarterly visits but some occasional irregularities, and also with regard to seasonal variation in biological systems.

As visits were sometimes closer when HbA1c levels were higher, mean values for those patients may tend to overestimate high values. One way to deal with this problem in serial measurements could be the use of area under the curve (Matthews, Altman et al. 1990). This should be considered for future studies.

In some figures the same patients are represented two or three times over a study period of two or three years in order to increase sample size. With this method the variation may hypothetically be underestimated. But the growth and development of children and adolescents, with treatment continuously adjusted accordingly, represents a multifactorial, complex and dynamic biological as well as behavioural situation. Data from one year rarely are identical to data from the previous year for a particular patient.

Finally, the comparison of yearly mean HbA1c values between patients with and without severe hypoglycaemia showed a slight difference in paper II, in contrast to no significant difference in paper III. This discrepancy was attributed to the smaller sample size with lower statistical power in paper III.

Observer bias

The observer bias issue is at risk of being overlooked in clinical research. As medical professionals, we need to be aware of how we affect the patient with our attitudes and the architecture of our information systems (Fahlén, Fahlén et al. 1997). We believe this question needs to be addressed in particular when issues such as patient satisfaction or complication rates are reported.

In our long-term registration method, observer bias was minimised by written and continuous registration and the correction method for missing data. In the evaluations of our registration method and our interventions, questionnaires were sent from an independent department at the University with clear statements

indicating that no individual patient's data would be recognisable to the diabetes team (paper I, VI).

When for the sake of simplicity we use the term "our" with respect to the clinic, diabetes team, treatment or patients, this refers only to the data. Physicians other than the author treated the study patients. They were therefore independent of the author.

Data registration (Paper I)

To evaluate the results of severe hypoglycaemia prevention strategies, and for continuous long-term follow up and health economic evaluation of treatment results in general, reliable primary data are necessary. Such data on benefits, complications, costs and social effects of medical treatments are often lacking (Banta and Luce 1993; Drummond, O´Brien et al. 1997). The high response rate achieved over the years for this prospective patient questionnaire in a complete geographic population of children and adolescents with a chronic disease is remarkable. This example also opens the way for local continuous assessment of treatment from different perspectives in other age groups and in other disease diagnosis groups.

Treatment policy and safety level (Paper II-III)

There is a need for comparable data on safety levels with regard to adverse events with different modern treatment policies for type 1 diabetes in children and adolescents. Treatment policies other than in the present study have also shown improved metabolic control (DCCT 1994; Dorchy, Roggemans et al. 1996), but comparable population studies are lacking. With our methods we have at least documented levels of severe hypoglycaemia and diabetic ketoacidosis that are not higher than an average of findings from previous studies, most of which had more unsatisfactory metabolic control (Soltesz 1993). Individually tailored multiple insulin therapy, continuous active self-control, psychosocial support and active problem-based education were fundamental elements of the treatment (Ludvigsson 1991). The combination of these elements and the continuity of this

practice from the very onset of the disease are probably of great importance regarding the outcome.

HbA1c and severe hypoglycaemia (Paper II-III)

Tightening metabolic control to near normal may increase the risk for severe hypoglycaemia (fig. 1) (DCCT 1991; Egger, Davey Smith et al. 1997). On the other hand, we have described a treatment policy that seems both to decrease the risk and improve metabolic control. As in our study, intensified education including detailed skills in the prevention of severe hypoglycaemia will probably reduce severe hypoglycaemia without compromising metabolic control (Bott, Bott et al. 1997; Fritsche, Stumvoll et al. 1998; Schiel, Ulbrich et al. 1998; Bolli 1999; Cox, Gonder-Frederick et al. 1999) (paper VI).

Other related factors (Paper II-III)

As was found in the DCCT, previous severe hypoglycaemia is a relatively strong predictor for future severe hypoglycaemia (DCCT 1991). It may be suggested that this is due to a combination of psychosocial, educational as well as genetic factors, as recent preliminary data indicate also a genotype more at risk for severe hypoglycaemia (Bjorgaas, Stene et al. 1994; Schiel, Ulbrich et al. 1998; Pedersen-Bjergaard, Larsen et al. 2000).

Also consistent with the DCCT, HbA1c level and insulin dose had some impact in our multivariate models (DCCT 1991). The association with a lower proportion of short-acting insulin may represent a higher risk for iatrogenic severe hypoglycaemia if less physiological insulin regimens are used (Cryer, Fisher et al. 1994). The association with lower age and lower age at onset may be an effect of a higher reporting rate for NU by parents of pre-school children, as they may have to assist the child at every event of hypoglycaemia. The various other weak findings in single correlations and multiple regression analysis merely illustrate the multi-factorial aetiology of severe hypoglycaemia.

There was a lack of psychobehavioural and socio-economic variables in our analysis. It has been reported by some that children whose parents were divorced

or single experienced more severe hypoglycaemia than other children (Bjorgaas, Stene et al. 1994).

Seasonal variation (Paper III-IV)

The seasonal variations in HbA1c and severe hypoglycaemia are consistent with findings from earlier studies (Ferrie, Sharpe et al. 1987; Daneman, Frank et al. 1989; Asplund 1997). The variations are probably related to changes in activity, meal patterns and counter-regulatory responses following climatological variations (Ferrie, Sharpe et al. 1987; MacDonald, Liston et al. 1987). It would therefore seem that the degree of self-control and adjustment of treatment, especially in the spring and early summer, may also need to be improved in intensively treated children and adolescents. A similar effort to improve self-control and adjust the treatment may be recommended for the period of change after the summer holidays. This should be included in education on prevention of severe hypoglycaemia.

Costs and other short-term effects (Paper V)

Our study of costs due to severe hypoglycaemia is novel. These costs consisted mainly of direct medical costs and indirect time costs. However, we were unable to estimate the total costs. The value of lost unpaid or non-labour activities is often undervalued or forgotten in cost analyses (Weinstein, Siegel et al. 1997). A number of intangibles, including consumption of people's leisure time, were omitted in our study due to lack of reliable data. Also, no severe accidents or deaths were registered during the cost study, but such costs may also need to be included (Sartor and Dahlquist 1995; Thordarson and Sovik 1995).

It is obvious that while severe hypoglycaemia may have a strong impact on daily life for some people, it may be less of a problem to others and on other occasions. The lower EuroQuol-5D scores among those with severe hypoglycaemia was attributed to differences in the parameters pain/discomfort, anxiety/depression and usual activities.

On average, severe hypoglycaemia causes the greatest magnitude of disturbance and fear regarding the short-and long-term complications of diabetes (Pramming, Thorsteinsson et al. 1991). Moreover, events of severe hypoglycaemia may have impact on subsequent insulin dosage, leading to worsened metabolic control even when previous metabolic control has been very unsatisfactory and even when a cause of the severe hypoglycaemia, independent of insulin dosage, has been identified (Tupola, Rajantie et al. 1998). These costs resulting from late complications remain unknown.

Prevention of severe hypoglycaemia (Paper VI)

The total impact of severe hypoglycaemia, including medical risks, socio-economic costs and quality of life aspects, motivates intensified prevention efforts on the population level (Cryer 1997). The multifactorial aetiology of severe hypoglycaemia offers several possibilities for systematic prevention. Except for more physiological insulin preparations and regimens, glucose sensors and alarms and other improved methods in the future, intensified education and training in the prevention of severe hypoglycaemia seems essential. Important practical information exists, based on best evidence and clinical experience, which patients may need easy access to, especially the large proportion of patients with recurrent severe hypoglycaemia (DCCT 1997; Cox, Gonder-Frederick et al. 1999). Much of this is part of general management and active self-control, and is covered in other educational methods (Bolli 1999).

We have presented this kind of information in a structured package clearly aimed at the prevention of severe hypoglycaemia, first in self-study brochures and later in mass-copied video programs for home use. It should be highlighted that this was only a complement to other education and support from the multi-disciplinary diabetes team. We found, however, that such self-study material is used and widely disseminated at a low cost. The material was appreciated more by the group with severe hypoglycaemia. In addition, it also seems to have contributed to a decrease in severe hypoglycaemia, but controlled studies are needed.

Summary and conclusions

- A very high response rate can be achieved over a period of years with a patient questionnaire method integrated in the treatment program, thereby providing data regarding current treatment and outcome in chronic disease. This finding may also have implications for use with other ages and other diagnosis groups (Paper I).
- There is a high incidence of severe hypoglycaemia even with the use of modern intensive treatment from the onset of type 1 diabetes. It is comparable to the average of incidences reported from earlier studies, most of which were conducted under less satisfactory metabolic control (Paper II).
- There is only a weak association between HbA1c and severe hypoglycaemia when using multiple insulin therapy with an individualised glycaemic target, combined with adequate self-control, active problem-based education and psychosocial support (Paper III).
- Seasonal trends in HbA1c and the risk for severe hypoglycaemia, which are related to climate and periods of changed behaviour, may have important implications for patient education and treatment as well as for the design of short-term studies of metabolic control (Paper III-IV).
- Severe hypoglycaemia results in significant disturbances and costs even with modern treatment. The impact varies greatly between episodes and between patients (Paper V).
- Mass-distribution of self-study material like videotapes and brochures that supports diabetes self-care, self-control and the prevention of severe hypoglycaemia may enhance dissemination of information at a low cost. This may also have implications for other topics in diabetes education, for other ages, and for other diagnosis groups (Paper VI).

Comments on further research

- Little is known about metabolic control after events of severe hypoglycaemia in young patients with intensive treatment.
- Little is known about fear of hypoglycaemia and self-esteem in young patients with intensive treatment, with or without a history of severe hypoglycaemia.
- Little is known about effects of severe hypoglycaemia on emotional status and relationships in young patients.
- Little is known about the prediction of severe hypoglycaemia in young patients by psychosocial variables.
- Little is known about the prediction of severe hypoglycaemia by genotype.
- Controlled studies on the effects of education and training in the prevention of severe hypoglycaemia in young patients are specifically needed.
- In safety evaluations of new insulin analogues and device technologies, data on adverse events may need to be stratified in the phase-specific age groups pre-school children, latency phase children and adolescents, and thereafter also to be broken down according to sex (Berg-Kelly and Kullander 1999).
- The costs for intensive treatment of type 1 diabetes in children and adolescents are unknown and need to be estimated using a bottom-up design based on reliable population data.
- The treatment costs for different treatment policies need to be modelled in relation to long-term socio-economic costs of type 1 diabetes, including possible prevention of complications by intensive treatment.

Clinical comments

- *24-h profiles.* Patient training in the evaluation of 24-h profiles and adjustment of treatment according to reproducible patterns may be suggested (Bolinder, Ungerstedt et al. 1993). The aim is also to prepare patients to make the best use of the forthcoming glucose-sensor technology that provides improved 24-h profiles.
- *Logbook.* Further efforts to improve traditional and electronic logbook systems and educate and motivate patients with respect to a more structured and systematic way of keeping a logbook regarding events of severe hypoglycaemia may be suggested. This may support the patient's growing self-knowledge and also enhance more systematic follow-up and research.
- *Structure of care.* Structured education on the prevention of severe hypoglycaemia, including checkpoints at certain times, may also be suggested after a longer duration (such as 8, 10, 12, 15 years) of type 1 diabetes, when the risk for unawareness of hypoglycaemia increases with longer duration (Pramming, Pedersen-Bjergaard et al. 2000).
- *Patient information.* There is great patient/consumer interest in high quality- and advanced information/education materials on different aspects of diabetes. It may be suggested that these should be developed very carefully in multidisciplinary collaboration among qualified individuals in the fields of medicine, psychology, pedagogy, and the media, and patients should also be included in the process (Entwistle, Watt et al. 1998; Coulter, Entwistle et al. 1999).

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