Limitations of the so-called “intensified” insulin therapy in type 1 diabetes mellitus

S Jacqueminet, N Massebœuf, M Rolland, A Grimaldi, C Sachon

Summary

Intensive insulin treatment is defined by basal-prandial insulin therapy which tries to reproduce physiological insulin secretion. This requires 3 to 5 injections and self-monitoring of blood glucose 4 to 5 times a day. Patients who accept their disease and the demanding treatment regimen most often achieve HbA1c < 7.5%. Severe complications of diabetes can be avoided without increasing the risk of severe hypoglycemia. However, 50% of type 1 diabetic patients do not reach this objective. The reasons are: the disease itself, the diabetic patient, or the physician. Brittle diabetes with severe, repeated episodes of hypoglycemia and inversely persistent postprandial hyperglycemia prevents patients from reaching the ideal glycemic target. More often, the main obstacle is related to psychological problems: difficulties in self-regulation, denial of the disease, or phobia of hypoglycemia with avoidance behavior. Frequently, young women present eating disorders which can explain the poor diabetes control. The physician himself may be implicated in these poor glyemic results by not prescribing the right tools to obtain optimal glyemic control (staying with just two daily injections with premixed insulin) or by assigning glyemic targets inaccessible for the patient, or when an empathic relationship cannot be established between the patient and the physician. Patient empowerment is the key to the success of functional insulin treatment.

Key words: Brittle diabetes · Loss of control · Denial of the disease · Depression · Hypoglycemia · Eating disorders · Functional insulin therapy.

Résumé

Les limites de l’insulinothérapie dite « intensive » au cours du diabète de type 1


Mots-clés : Diabète instable · Locus de contrôle · Refus de la maladie · Dépression · Hypoglycémie · Troubles du comportement alimentaire · Insulinothérapie fonctionnelle.
Before examining the question of so-called “intensified” insulin therapy and its limitations, we must first establish a satisfactory definition and set out criteria of therapeutic success. In our opinion, intensive insulin therapy for type 1 diabetes mellitus can be defined as a “functional” basal-prandial therapeutic regimen based on three principles [1]:

1° evaluation of basal insulin requirement during a carbohydrate fast;
2° adapting doses of short-acting insulin analog injected before meals to the carbohydrate (and fat) content of the meal, the blood glucose level immediately before the meal, and the level of physical activity planned during the hours following the meal;
3° self-monitoring of blood glucose at bedtime, and if possible in mid afternoon, with, if needed, an adjustment by injection of supplementary short-acting insulin.

When can this therapeutic scheme be considered successful? The therapeutic goal cannot be a normal HbA1c level (the intention of the DCCT Research Group) [2]. In light of the DCCT results and the course of the HbA1c levels observed after the trial [3], it would be more reasonable to consider the treatment scheme successful if the patient has a HbA1c level below 7.5% and is free of repeated episodes of severe hypoglycemia.

Having defined the therapeutic goal and the means for reaching that goal, it can be estimated that intensive insulin therapy is unsuccessful in about 50% of patients for three reasons related to:

1° the disease and the insufficient therapeutic “tools”;
2° the diabetic patient;
3° the attending physician.

Limitations related to the disease and insufficient therapeutic “tools”

Three factors can be identified:

Glycemic instability

The characteristic feature of the 24h-glycemic profile in insulin-deficient patients treated with replacement insulin therapy is not simply a high mean blood glucose level but also glycemic instability, with levels fluctuating from day to day and during a given day [4]. This instability is inevitable because of the lack of reserve insulin secretion. Its intensity varies from one patient to another, but the therapeutic objective is the same for all patients: limit glycemic variability by controlling controllable factors, i.e. by improving assessment of carbohydrate intake, by measuring capillary blood glucose, and by using an appropriate injection technique and site of injection (avoid lipodystrophy, maintain the needle in the subcutaneous position for at least 10 seconds...).

One of the most important errors observed with suspensions of crystallized insulin, defective dissociation due to insufficient shaking of the bottle or vial, is avoided with long-acting insulin analog solutions. Predictability would also be better with detemir insulin due to its slow absorption after subcutaneous injection, permitted by the acylation of the insulin molecule with a long-chain fatty acid, allowing for the reversible binding of insulin detemir to albumin. In any event, among patients with unstable diabetes, there is a small group of patients, probably not more than 3 to 4% of diabetics, whose glycemic instability leads to repeated hypoglycemic coma [5]. These patients no longer perceive the warning signs of hypoglycemia and have a defective hormonal feed-back system. Many are hypersensitive to insulin with total daily doses of insulin ≤ 0.35 U/kg. One unit of short-acting insulin analog is sufficient to lower their blood glucose by 0.80 to 1 g/l. Inversely, the duration of action of low doses of slow-acting insulins is often too short, leading to glycemic excursions with blood glucose levels up to 3 g/l or higher. These patients can benefit from insulin pumps and pediatric pens with 0.5 U graduations. The basal insulin needs of these patients must be evaluated during a 24-hour glucose fasting test conducted in a hospital setting with capillary blood glucose monitoring every hour or half-hour (one of our patients greatly benefited from a diminution of the basal dose from 0.32 U/kg to 0.18 U/kg after two fasting glucose tests, e.g. one hypoglycemic coma per 3 months instead of 3 per week before the dose reduction). Obviously, the glycemic goal for this kind of patient should be higher: HbA1c, less than 8.0 or 8.5% could be considered as a therapeutic success.

Too short-acting basal insulin

For a few patients, an effective basal insulin is very difficult to obtain. For about 15% of patients undergoing a carbohydrate fasting test, insulin glargine does not cover 24 hours. If the basal insulin is too short-acting, a carbohydrate fast inevitably leads to glycemic excursions. Exceptionally, insulin glargine injected at a low dose can have an effective duration of action of less than 12 hours, with as a consequence, a morning hyperglycemia on the following day, as was frequently observed with NPH insulin. The only way to avoid end of night/early morning hyperglycemia is to use a subcutaneous insulin pump with a modulated basal output.

Postprandial insulin resistance

Practical experience with functional insulin therapy has demonstrated that postprandial hyperglycemia is not the consequence of the meal’s carbohydrate content alone, but is also related to its fat content. In practice, the impact of fat intake on postprandial glycemia varies greatly between individuals. Both the patient’s degree of insulin resistance and fasting triglyceride level have an effect. In certain type 1 diabetic patients, a high-fat meal can provoke postprandial hyperlipidemia leading to insulin resistance, and subsequently postprandial hyperglycemia lasting for several hours. Orlistat may be useful here [6] (in two of our patients on functional insulin therapy, this fat-intake-induced postprandial hyper-
glycemia was successfully controlled with orlistat). Experience with functional insulin therapy should include an individual evaluation of the quantitative and qualitative effects of diet content.

**Patient-related limitations of insulin therapy**

It is important to recognize, and if possible to treat five factors [7-10]:

**Insufficient self-regulation or poor locus of external control**

Patients undertaking functional insulin therapy must be sufficiently motivated to accept the burden of daily treatment. They must:

1°) be convinced of the risk of serious secondary consequences of chronic hyperglycemia;

2°) be persuaded that the risk is not only general but also personal, implying the ability for a personal projection into the future;

3°) believe the treatment is effective, which implies having confidence in the proposed therapy and the prescribing physician;

4°) accept their disease and the demands of daily treatment.

Problem solving, rational thinking, decision making, and self-confidence are personal qualities of great importance for successful functional insulin therapy. Taking pleasure in achieving good results is "a plus"! Patients who are at ease with decision making, who take action readily, and who enjoy learning, measuring, evaluating, and controlling, have the qualities required for successful functional insulin therapy. Inversely, functional insulin therapy will probably not be beneficial for patients who believe their health is basically a matter of fate, or who would rather apply rules dictated by a medical authority rather than thinking out a problem to find the right solution. At best, they will have great difficulty in achieving a successful treatment. This observation has led to the development of teaching tools adapted to each individual patient's personal cognitive style. Evaluating carbohydrate intake is particularly difficult since there are no calibrated instruments easily usable in an everyday setting. A kitchen scale can be helpful to get started. Despite these problems, many patients are very willing to adapt their insulin doses to their food, even though they don't want to or can't make all the calculations. These patients have to learn how to evaluate visually the quantity of food in their plate and then deduce the corresponding dose of short-acting insulin. The first step for patients who believe they are eating a fixed amount of carbohydrates at each meal consists in helping them become aware of the variability of their carbohydrate intake and the poor adaptation of their fixed dose of insulin. Several (at the very least two) teaching modalities must be proposed:

- functional insulin therapy with calorie counting,
- and functional insulin therapy without calorie counting.

**Patient denial of the disease [11]**

Some patients who deny their disease for fear of losing their identity achieve very good glycemic control with intensive insulin therapy. For these patients, diabetes is a cross to bear. They rarely talk about their disease with family and friends and are often “clandestine” diabetics at work. When they achieve good glycemic control, it is at the cost of depressive psychic suffering which has a serious impact on their relational life. On the other hand, many patients avoid depression by simply denying their disease and the therapeutic constraints it implies. Such patients do not want to run the risk of hypoglycemia or self-monitoring and are satisfied with biphasic (pre-mixed) insulin injected morning and evening, which inevitably leads to under-insulization at meal time and over-insulization between meals. Theoretically, for these patients, the only way to control blood glucose is to fractionate food intake with three small meals and two or three snacks. But in the real life, and except for patients with prolonged asymptomatic hypoglycemia, particularly at night, optimal blood glucose control (HbA1c < 7.5%) is every exceptional with this type of scheme.

**Depression [12, 13]**

Depression is twice as frequent in diabetics as in non diabetics, even though insulin–dependent diabetics do not have a specific psychological profile. As in non-diabetics, depression is 1.5 to 2-fold more prevalent in women than men, and is observed more frequently in people living alone than in people integrated into a social network. It affects unoccupied persons (unemployed, retired) more than those who are occupationally active. Depression is also more frequent in patients with diabetic complications or co-morbid conditions than in patients free of complications. What is peculiar to diabetes is the potentially depressogenic effect of the demanding treatment scheme, the repeated never-ending daily injections, and especially the ups and downs of the results. This instability is related to the large number of uncontrollable factors: carbohydrate and fat intake, physical activity, stress, monitoring and injection errors, imprecision of capillary blood glucose measurements, and especially the variability of action of insulin injected subcutaneously. Even the most meticulous patient has unpredictable glucose levels, requiring a therapeutic correction in nearly half of the cases. The insulin dose to be injected must be calculated from the predicted needs and has to be adjusted as a function of the glycemic results observed over the preceding 3 to 7 days during the period of action of the injected insulin. In addition to this predictive insulin therapy, last minute corrections must be made because of variations in insulin resorption from one day to another and the consequent unpredictable fluctuations in blood glucose level. The diabetic patient must realize that the target level will only be achieved about half of the time, and only if the target is set wide enough (for example between 0.80 and 1.60 g/l). The fact that the patient, who
after all has a set of good but albeit mediocre tools, is in charge of his/her treatment, justifies, in our opinion the following measures:

1°) full reimbursement of anxiolytic and antidepressor treatments for type 1 diabetics;

2°) educating psychologists and psychiatrists treating diabetic patients with depression about the difficulties of treating diabetes.

**Phobia of hypoglycemia [14, 15]**

While fear of hypoglycemia is rather common among patients with insulin-dependent diabetes, phobia of hypoglycemia with avoidance behavior is exceptional, observed in about 5% of patients who deliberately sabotage the prescribed intensified insulin therapy to maintain a “safety margin”. Consequently, HbA1c level remains permanently above 8% in these patients.

There are many causes of this phobia, among others:
– fear of loosing self-control, particularly in public;
– fear of hypoglycemia at night in patients living alone;
– fear of somatopsychic consequences of hypoglycemia: severe migraine headache, acute attack of melancholia, panic attack with impression of imminent death.

Phobia of hypoglycemia is more common among patients who have an emotional state or even a personality trait of anxiety. This can be expressed by other phobias such as injection phobia leading to a tendency to skip injections or blood phobia which can explain less regular self-monitoring of blood glucose [16-18].

**Eating disorders [19-22]**

Eating disorders occur in a more general context of a “restrictive” syndrome. This new social disease affects more than half of the female population. Bulimia and anorexia nervosa do not appear to be more frequent in diabetic than non-diabetic patients, but the prognosis is less favorable. Generally, their “hidden” bulimia is not associated with voluntary vomiting and laxative abuse since the hyperglycemia leads to osmotic diuresis with massive glycosuria enabling weight control. HbA1c level is generally above 12%.

Minor eating disorders are more frequent in diabetic women, leading to deliberate under-insulinization to achieve weight control. In one survey [22], voluntary under-insulinization was observed in 30% of diabetic women aged 15 to 60 years who reduced their insulin doses or omitted an injection. Nearly 10% of women with insulin-dependent diabetes recognize that they use under-insulinization regularly to control their weight. Minor eating disorders can be transient and of good prognosis with cognitive-behavioral therapeutic education, paradoxically associating a ritualization of eating behavior with functional insulin therapy. These patients accept their insulin therapy better and achieve better glucose control if they are not obliged to eat three meals per day (or even snacks), as their insulin regimen is taking into account these patient’s dietary desires. The more serious eating disorders require both diabetology and psychological care based on cognitive-behavioral or analytical methods.

**Limitations related to the diabetologist**

1. First of all, why French diabetologists took nearly twenty years to adopt functional insulin therapy developed around 1985 by several teams in Germany, particularly in Düsseldorf [23, 24], is an intriguing question. There are several reasons:

   1°) the aftermath of a conflict between adult and pediatric diabetologists: “free eating habits” was taboo for adult diabetologists and dietary balance a dogma applicable at each and every meal;

   2°) commonly overestimated long-acting insulin doses, leading to hypoglycemia late after meals and justifying the sacred snacks and prohibition of fasting;

   3°) the rule of adapting insulin doses as a function of the capillary glucose level observed the preceding days during the period of action of the injected insulin, which went hand in hand with considering use of last-minute modulation of the rapid-acting insulin dose as a deviant practice;

   4°) the widespread belief that glycemic control cannot be improved without increasing the risk of hypoglycemia, particularly those of severe hypoglycemia, a belief which was reinforced by erroneous interpretation of the DCCT data [25];

   5°) insufficient competence in practical dietetics and difficulty in accepting that the patient may be right and the physician wrong.

2. Keeping this in mind, the most common error of diabetologists is to believe that their personal relational and cognitive styles are universal and are necessarily shared by their patients, instead of trying to adapt to the individual relational and cognitive style of each patient [26]. Though there is probably some truth to the idea that diabetics will eventually find the diabetologist that fits their style, the argumentation is certainly not very satisfactory. Prolonged discordance can lead to long-standing poor glucose control for the patient. The goal of care is to help the patient integrate the healthcare projects into his/her own life projects, and also to adapt the therapeutic requirements to his/her personality and lifestyle. Diabetologists must realize that for some patients they must “waiver their duty of good-doing”, as proposed by Philippe Barrier [27]. At the same time, as emphasized by Gérard Reach [28], they must fully assume their power of “authority” explicitly delegated to them by other “weak-willed” patients. For all patients however, the mandatory ethics of benevolent goodwill must prevail. The diabetologist must at least ask with empathy, “What can I do to help you?”.

3. Unfortunately, the diabetologist can also aggravate the depressogenic nature of the treatment by placing the patient in a situation of failure, for example by assigning
unattainable goals (e.g. normal HbA1c [except during pregnancy], or glycemia 1 h 30 to 2 hr after meals < 1.40 g/l...) or not sufficiently encouraging self-management ("measure your blood sugar, fill in your diary carefully, and we’ll talk about it in three months at your next visit"). Self-empowerment is the number one remedy against anxiety and depression: every regular self-monitoring must be justified by an immediate action to be decided and taken by the patient. Inversely, total self-empowerment can aggravate the anxiety of a patient with an external locus of control, leading to absence of modulation of the insulin doses despite the physician’s orders.

4. Finally, there are four types of teaching tools more or less well adapted to self-education for adults [29]:
- the classical frontal or vertical teacher-pupil prescriber-executor method which introduces an adult-child relationship. Perhaps a satisfactory solution for certain physicians trained with this method or certain regressive patients.
- the behaviorist approach where the learning process involves setting limited goals reinforced by a system of rewards and punishments (the “Good Diabetic” prize!). A pitfall of therapeutic educational schemes lacking a pluridisciplinary safety buffer.
- the free system where each patient uses his/her personal resources to reach the goal of preserved health. The best diabetologist might very well be the diabetic, the “real” lay expert!
- a constructive self-learning method where the patient learns by trial and error to make the appropriate corrections and establish his/her own goals and treatment tools within the framework of an adult/adult partnership established with the different members of the healthcare team. This relationship is illustrated by the implementation of therapeutic behavioral contracts between the patient and the healthcare team.

In conclusion

Technical progress – slow-acting and fast-acting insulin analogs, nearly instantaneous self-monitoring of capillary blood glucose, fine needles, pens, insulin pumps – associated with better understanding of the physiology of insulin secretion, now enable a more functional approach to insulin therapy in an attempt to mimic physiological insulin secretion. Nevertheless, despite an optimized insulin therapy scheme, nearly 50% of patients do not reach the target of a HbA1c level below 7.5% without repeated episodes of severe hypoglycemia. There are diverse reasons for this failure, related to the disease itself (insulin hypersensitivity or insulin resistance), the patient (external control locus, denial of the disease, depression, phobic anxiety, eating disorders) and the diabetologist who develops counter-attitudes, or worse, becomes indifferent by self-preservation against the anxiety of failure.

References


