Management strategies for brittle diabetes

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Stratégie de prise en charge du diabète instable

M.-C. Vantyghem, M. Press


Le diabète de type 1 est une situation instable en elle-même. Cependant le terme de “brittle diabetes” est réservé aux cas dans lesquels l’instabilité devient une cause d’instabilité quelle qu’en soit la cause entraîne une désorganisation de la vie du patient avec hospitalisations récurrentes ou prolongées. Le diabète instable touche ainsi 3 000 patients diabétiques insulinodépendants, essentiellement des jeunes femmes. Son pronostic, médicole, s’associe à des scores de qualité de vie faibles, des complications macrovasculaires et périnatales plus fréquentes et une diminution de l’espérance de vie. Trois formes ont été décrites : la cétocéodose récurrente, les formes à prédominance hypoglycémique et les formes mixtes. Les principales causes d’instabilité correspondent aux malabsorptions, à la prise de certaines drogues (alcool, antipsychotiques), aux défauts d’absorption ou de dégradation de l’insuline, aux défauts de sécrétion des hormones de contre-régulation, notamment les glucocorticoïdes et le glucagon, et par dessus tout aux troubles de la vidange gastrique secondaires à une neuropathie autonome. Les facteurs psychosociaux sont très importants et l’instabilité factice peut entretenir une situation. L’évaluation d’un diabète instable requiert une appréciation de la variabilité des glycémies. Afin de quantifier cette instabilité, différents outils de mesure ont été développés, parmi lesquels l’amplitude moyenne des plus grandes excursions glycémiques (MAGE), la moyenne des différences quotidiennes (MODD), l’indice de labilité (LI), l’index d’hypoglycémies (LBGI), le score de Clarke, le score d’hypoglycémies (Hyposcore) et l’enregistrement continu des glycémies (MAPA). Lorsqu’un problème psychologique a été écarté, la stratégie thérapeutique requiert d’abord le traitement d’une cause organique sous-jacente, puis l’optimisation de l’insulinothérapie en utilisant les analogues, les injections multiples et éventuellement une insulinothérapie par voie sous-cutanée en pompe externe. Des approches alternatives peuvent être nécessaires chez les patients les plus instables. La transplantation d’îlots isolés, qui restaure une sensibilité au glucose, devrait être envisagée en cas d’hypoglycémies non ressenties et/ou d’instabilité sévère, tout spécialement si l’indice de masse corporelle est < 25, la fonction rénale normale et en l’absence de désir de grossesse chez les jeunes femmes. Les pompes implantables sont préférables chez les patients pesant plus de 80 kg, présentant des altérations hépatiques et rénales, ou hyperimmunisés.

Mots-clés : Diabète instable, transplantation d’îlots intraportale, pompe implantable.

Management strategies for brittle diabetes

Type 1 diabetes is an intrinsically unstable condition. However, the term “brittle diabetes” is reserved for those cases in which the instability, whatever its cause, results in disruption of life and often recurrent and/or prolonged hospitalization. It affects 3/1000 insulin-dependent diabetic patients, mainly young women. Its prognosis is poor with lower quality of life scores, more microvascular and pregnancy complications and shortened life expectancy. Three forms have been described: recurrent diabetic ketoacidosis, predominant hypoglycemic forms and mixed instability. Main causes of instability include malabsorption, certain drugs (alcohol, antipsychotics), defective insulin absorption or degradation, defect of hyperglycemic hormones especially glucocorticoid.

The definition of brittle diabetes has evolved with time. The term was introduced by Woodyatt in the 1930s to describe patients with excessive fluctuations of blood sugar which could not be explained by patient or physician errors, leading to the occurrence of unpredictable and unexpected hypoglycemic reactions [43]. Subsequently the psychosomatic movement took an interest in the effect of emotional factors on the course of diabetes and by the 1950s the question was whether there were two distinct groups of patients; one whose instability could be cured by adjusting insulin, diet, and exercise, and another whose liability had an emotional basis [43].

Since the advent of self-glucose monitoring and continuous subcutaneous glucose sensing it has become apparent that Type 1 diabetes is intrinsically an unstable condition. However, the term “brittle diabetes” should be reserved for those patients whose instability is unpredictable and of sufficient severity as to lead to significant disruption of their lives, often with recurrent and/or prolonged hospitalization [43]. Fortunately, such patients are rare and account for only ~0.3% of insulin dependent patients. Although it may become more stable with time, it is associated with lower quality of life scores and more microvascular and pregnancy complications (46 vs 7% in stable diabetes). Furthermore, its prognosis is poor with a higher risk of death (19% at 10 years) related to...
and glucagon, and above all delayed gastric emptying as a result of autonomic neuropathy. Psychosocial factors are very important and factitious brittleness may lead to a self-perpetuating condition. The assessment of brittle diabetes requires quantification of the variability of blood glucose levels. To quantify instability, measures which have been developed, include Mean Amplitude of the largest Glycemic Excursions (MAGE), Mean Of Daily Differences (MODD), Lability Index (LI), Low Blood Glucose Index (LBGI), Clarke’s score, Hyposcore, and continuous blood glucose monitoring. Once psychogenic problems have been excluded, therapeutic strategies require firstly, the treatment of underlying organic causes of the brittleness whenever possible and secondly optimising standard insulin therapy using analogues, multiple injections and consideration of Continuous Subcutaneous Insulin Infusion. Alternative approaches may still be needed for the most severely affected patients. Isolated islet transplantation (IIT), which restores glucose sensing, should be considered in cases of hypoglycaemic unawareness and/or lability especially if the body mass index is <25, but with current immunosuppressive protocols patients must have normal renal function and preferably no plans for pregnancy. Implantable pumps have advantages for patients who either weigh more than 80kgs or have abnormalities of kidney or liver function or are highly sensitised.

**Key words:** Brittle diabetes, intraportal islet transplantation, implantable insulin pump.

**EPISTEMOLOGY**

Brittle diabetes is a small but significant problem, affecting 1/1000 diabetic patients and about 3/1000 insulin-dependent diabetes. It mainly affects young people (mean age 26±15 years) with a second frequency peak around 60-70 years. Two thirds of affected patients are female with a shorter duration of diabetes than stable controls (13±9 vs. 19±11 years) associated with higher HbA1c levels and greater insulin requirements [12, 13].

Three forms of labile diabetes have been described. The most common form is recurrent diabetic ketoacidosis, defined as at least three episodes per 2 years and accounting for 59% of labile forms. This form, which is more common in younger patients, is recognised as often reflecting simple non-compliance with insulin injections [12]. Predominant hypoglycaemic forms (defined as at least 3 severe episodes per year) account for 17% and mixed instability for 24%. These two last forms are more common in older age groups [11-13].

**MAIN CAUSES OF BRITTLENESSE**

The main causes of brittleness are listed in table I and include malabsorption [26], certain drugs (alcohol, but also antipsychotics) [2, 22], rare cases of defective insulin absorption or degradation [41], deficiencies of counter-regulatory hormones especially glucocorticoids [16] and glucagon, and above all autonomic neuropathy with delayed gastric emptying and hypoglycaemic unawareness [49]. Hypoglycaemic unawareness may be caused by recurrent hypoglycaemia and may thus also be self-perpetuating. Autonomic neuropathy is common in patients with hypoglycaemic unawareness. This may be because sympathetic neuropathy results in poor hypoglycaemic warning symptoms or it may be because such patients tend to run their diabetes high to avoid hypos and hence develop complications, which include neuropathy and gastroparesis.

The influence of anti-insulin auto-antibodies and the existence of a syndrome of subcutaneous insulin degradation is more hypothetical and patients with very large apparent insulin requirements and “impossible” diabetes often turn out on investigation to have a factitious basis for their problem.
The role of psychosocial factors has been emphasized by numerous studies [9, 12, 13, 43] and some have reported the need for psychological intervention in as many as 74% of cases. It can sometimes be exceptionally difficult to prove a factitious aetiology even when there are obvious psychiatric disturbances, however. In some cases, young women present with eating disorders, which can explain poor diabetes control [37]. Lability could reflect a depressive disorder. Type 1 diabetes is a chronic disease, which is always difficult to live with. The current prevalence rate of depression in diabetes is 11% and the lifetime prevalence 25% [9]. Difficulties in self-regulation, denial of the disease and phobia of hypoglycaemia with avoidance behaviour probably contribute to some cases of labile diabetes [18]. Finally, a high level of sensitivity to stress has been reported in patients with brittle type 1 diabetes [8].

The important point to appreciate is that true brittleness cannot be caused simply by factors which cause, for example, insulin resistance or delayed gastric emptying, but only by intermittent insulin resistance or erratic and unpredictable gastric emptying. While brittle diabetes may be self-induced to start with [43], what starts as factitious may become self-perpetuating. In some cases this seems to be because of the development of abnormal growth hormone dynamics [29-31]. It is well recognised that growth hormone levels are elevated in poorly controlled diabetes [31] and fall towards normal as control is improved [29]. These elevated growth hormone levels are not innocent but actually serve to perpetuate the poor control [31]. Furthermore, in some patients with unstable diabetes, a rise in circulating insulin concentrations, even without any fall in blood glucose, can sensitize the pituitary to growth hormone releasing hormone and in some cases, is itself sufficient to raise growth hormone levels into the acromegalic range [30]. Teenagers, who naturally secrete large but variable amounts of growth hormone, especially at night, are probably more “brittle” for the same reason.

**ASSESSMENT**

The definition of brittle diabetes remains clinical and the first evaluation of brittleness includes the assessment of the number of hospital admissions for ketoacidosis or hypoglycaemia, and the number of severe hypoglycaemic episodes (i.e. those requiring third party assistance). Nevertheless, there are now different objective ways of quantifying brittleness (table II).

Measurements of mean blood glucose or HbA1c do not of course measure brittleness directly. They may however give clues to underlying problems. For example, even in the research setting of the DCCT, only 5% of the intensive control group reached a normal HbA1c. Faced with a patient whose HbA1c is near normal, one should wonder whether in fact the patient is hypoglycaemic more often than has been appreciated and has lost their warning symptoms. Conversely, many patients who have lost their warning symptoms deliberately allow their blood glucose to run high and have very high levels of HbA1c, thereby reducing their chances of losing consciousness without warning but at the same time exposing themselves to an increased risk of long term complications.

Direct measurements of brittleness are however available and these allow a comparison between patients for clinical research purposes. They require measurement of both variability and reproducibility of blood glucose levels during a given period [14, 38]. Since blood glucose levels are not necessarily normally distributed, a standard deviation is of limited use. However, a blood glucose range, or the number of values above or below a given threshold can be useful.

In 1965 Schlichtkrull devised the M-value in an attempt to introduce a standardised index of good control [36]. The M-value is a measure of how far a given glucose value de-
Table II
Assessment of brittle diabetes.

Évaluation d’un diabète instable.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mean and Standard deviation of blood glucose</td>
<td>Takes into account “intraday” reproducibility (stable diabetes: 20 to 60 mg/dl)</td>
</tr>
<tr>
<td>MAGE</td>
<td>Mean Amplitude of the largest Glycemic Excursions*. Takes into account “intraday” reproducibility (stable diabetes: 10 to 40 mg/dl)</td>
</tr>
<tr>
<td>Mean Of Daily Difference (MODD)</td>
<td>Day to day reproducibility of blood glucose values (Mean variations in a normal subject 10 mg/dl, in stable diabetes 40 mg/dl, in labile diabetes 160 mg/dl)</td>
</tr>
<tr>
<td>Lability index</td>
<td>Based on the change in glucose levels over time.</td>
</tr>
<tr>
<td>Low Blood Glucose Index (LBGI)*</td>
<td>Assessment of risk of hypoglycaemia; a value &lt;2.5 corresponds to a low risk of hypoglycaemia (and hence an increased risk of severe hypoglycaemic episodes).</td>
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<td>HYPOSCORE*</td>
<td>Takes into account the frequency and severity, but also the loss of symptoms of hypoglycaemia. Normal subjects are at 0, stable diabetes around 200, labile diabetes with frequent severe hypoglycaemic reactions around 1000.</td>
</tr>
<tr>
<td>Clarke’s score*</td>
<td>Eight questions answered by the patient who can score anywhere between 0 and 7. A score of ≥4 indicates reduced awareness of hypoglycaemia (and hence an increased risk of severe hypoglycaemic episodes).</td>
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<td>Data derived from continuous blood glucose monitoring systems*</td>
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*The NIH Clinical Islet Transplantation Trial Consortium has suggested that the indications for IIT should include either:
- Reduced hypoglycaemic awareness (Clarke score >4 and a HYPO score >90th percentile >1,047)
- Or marked glycaemic lability LI>90th percentile (≥433) despite optimal therapy
- Or a composite Clarke score >4 and HYPO score >75th percentile (≥329).

In each case the assessments should refer to a recent six month period.

Table II
Assessment of brittle diabetes.

Évaluation d’un diabète instable.

- Mean and Standard deviation of blood glucose
- MAGE: Mean Amplitude of the largest Glycemic Excursions*.
- Takes into account “intraday” reproducibility (stable diabetes: 20 to 60 mg/dl)
- Mean Of Daily Difference (MODD): day to day reproducibility of blood glucose values (Mean variations in a normal subject 10 mg/dl, in stable diabetes 40 mg/dl, in labile diabetes 160 mg/dl)
- Lability index*: based on the change in glucose levels over time.
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- Data derived from continuous blood glucose monitoring systems* (CGMS*, Guardian RT*, Glucoday* etc)

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In 1970 Service introduced the Mean Amplitude of the largest Glycemic Excursions (MAGE) [38], designed to count the swings in blood glucose, which exceeded 1 standard deviation of a 48 hour profile. By today’s standards, the index was based on glucose sampling which was rather infrequent. Furthermore, since excursions were only counted if they exceeded 1 standard deviation, subjects with large but consistent standard deviations would have low scores.

The Mean Of Daily Differences (MODD) measurement was introduced by George Molnar in 1972 [27]. He sampled blood glucose every 5 minutes for 48 hours and subtracted blood glucose values from the corresponding values obtained at the same time the following day. The MODD was then the mean of these 576 differences. Other authors subsequently simplified this to use fewer time points [24] or indeed just the fasting level [41].

The lability index (LI) is an extension of this principle [35]. It requires at least 4 finger-prick blood glucose measurements per day for at least 4 weeks. It is calculated as the sum of all the squared differences in consecutive glucose readings divided by the time interval between the readings. Most subjects have scores <300 mmol/12/h.wk⁻¹. The 75th percentile is 329 and the 90th is 433. Scores greater than this indicate severe glycemic lability.

Objective quantification of hypoglycaemic frequency and hypoglycaemic awareness is crucial in the assessment of the brittle patient.

The Low Blood Glucose Index (LBGI), which is an assessment of risk for severe hypoglycaemia, is a variability index emphasizing the low values [23]. LBGI integrates the frequency and severity of hypoglycaemia.

The Clarke score involves eight questions answered by the patient. Patients can score anywhere between 0 and 7. A score of ≥4 indicates reduced awareness of hypoglycaemia (and hence an increased risk of severe hypoglycaemic episodes) [4].

The HYPO score uses a scoring system, which is available at http://diabetes.diabetesjournals.org. It requires a patient to keep a record of hypoglycaemic episodes and a record of capillary blood glucose levels over a 4 week period, as well as a recall of all severe hypoglycaemic episodes in the preceding 12 months. Points are awarded for each documented episode of hypoglycaemia with extra points depending on the severity of the associated neuroglycopenic symptoms. Extra points are also given if outside assistance is required. No points are awarded if autonomic symptoms gave adequate warning of impending hypoglycaemia. A HYPO score of ≥1,047 (90th percentile) indicates that the patient has severe problems with hypoglycaemia [35].

Today, near-continuous measurements of tissue glucose levels (e.g., Medtronic’s Continuous Glucose Monitoring System (CGMS*) and Guardian RT* and Menarini’s Glucoday*) introduce further scope for the development of more accurate and sophisticated measures, obviate the practical problems associated with frequent blood sampling, and make it possible to look at what happens to patients during a normal day rather than in a hospital setting. It is very sobering to look at a 3 day tracing, even from a patient with relatively stable Type 1 diabetes, and see just how unstable the condition is!

**THERAPEUTIC STRATEGIES**

One must first realize that Type 1 diabetes is intrinsically an unstable condition. The first priority with all patients is therefore to ensure that the patient has had sufficient education in the management of their diabetes, that they are making appropriate adjustments to their insulin...
doses to match their meals and activity level and so on. One also needs to be sure that the targets they are setting themselves are not unrealistic and, for example, that they are not inducing recurrent mild hypoglycaemia and hence counterregulation and instability, in the mistaken belief that they may lose their eyesight if they ever allow glucose levels to rise.

**Optimization of standard insulin therapy**

Thorough education of patients by a team including diabetologist, diabetes specialist nurse, dietician and, when necessary, psychologist may uncover unsuspected misunderstandings of diet or insulin dosage adjustment, or inappropriate expectations of control. An intensive course teaching the patient how to adjust insulin doses to match meals and to allow for exercise may help. Insulin regimens using multiple injections of insulin analogues, with intensive self-monitoring of blood glucose, and if necessary continuous subcutaneous insulin infusion (CSII) are often necessary [25, 28]. Such approaches avoid the brittleness resulting from the high inter-injection coefficients of variability observed with conventional intermediate acting insulins (59% with NPH, 46% with glargine and 27% with detemir). Glucose meter accuracy, attention to injection technique and needle length to exclude intramuscular injections and examination of injection sites to exclude lipohypertrophies and lipodystrophies must all be checked. Finally, an empathetic relationship and patient empowerment often prove to be key-factors to the success of diabetic imbalance. Nevertheless 50% of type 1 diabetic patients do not reach the objectives recommended by current guidelines [18]. In some of these patients, other therapeutic strategies can be offered after careful psychological evaluation but it is essential not to leave the patient feeling they are a failure. It may be that it is the target which is wrong.

**Treatment of organic causes of brittleness**

Referral to a specialist centre is mandatory for brittle patients. The first priority is to make every effort to identify an underlying organic cause and to treat it. In patients who are unusually insulin sensitive, coeliac disease and pancreatic or adrenal insufficiency must be considered (and orthostatic hypotension must not be assumed to be due to autonomic neuropathy). A negative test for antibodies to transglutaminase makes coeliac disease very unlikely, as does a normal short 1-24 corticotrophin (Synacthen*) test for adrenal insufficiency. Pancreatic failure is less easy to exclude and if there is a history consistent with steatorrhoea or malabsorption, a therapeutic trial of pancreatic enzyme supplements may be appropriate, though diarrhoea may be due to autonomic neuropathy and associated with gastroparesis. The latter, which is often intermittent, can be exceptionally difficult to manage. Giving ultrashort acting insulin after rather than before meals can sometimes be useful. Cisapride, sadly no longer available, often used to help but a therapeutic trial of alternatives such as domperidone or erythromycin (which in addition to its antibiotic properties is a motilin agonist and stimulates gastric emptying) is worthwhile. There are occasional reports of gastric pacemakers being beneficial and a feeding jejunostomy, pyloroplasty or gastrojejunostomy are also occasionally necessary but none of these is uniformly successful and they are best regarded as the last resort. Although disorders of insulin absorption or action have been described, they are clearly exceptionally rare and many such cases usually prove on thorough investigation to be factitious.

**Psychological causes of brittleness**

One should never underestimate the psychological effects of diabetes. As indicated above, many patients with diabetes have secondary psychological problems as a consequence of their chronic disease. Equally however, severely disturbed patients who also have Type 1 diabetes can cause appalling problems with their diabetic control. From straightforward induction of brittleness by deliberately taking large amounts of sugar intermittently or missing or taking extra insulin injections to more sophisticated approaches, there is scarcely a limit to the scope for factitious manipulation of their diabetic control and one must adopt an extremely suspicious attitude to such patients. It is essential to identify patients with factitious hypoglycemia to avoid treating them with sophisticated methods since their likely compliance is low. This is not to say, of course, that a psychological cause equates to a factitious cause of the brittleness. On the contrary, treating a patient’s depression and managing their anxiety and fear of hypoglycaemia may have a major impact on their control [32].

**Alternative therapeutic strategies**

Several studies, including the DCCT, have shown that CSII results in better glycaemic control than multiple injections, with an improvement of HbA1c of about 0.2 to 0.4% and, more importantly, a decrease in hypoglycaemia frequency [15, 17, 25, 28, 44, 50]. Moreover, the use of CSII with an insulin analogue gives better glycaemic results than with soluble (regular) insulin with a reduction in HbA1c of 0.26% [5]. Continuous intraperitoneal insulin delivery through an implantable pump (IPII), offered to patients with labile type
Whole pancreas transplantation provides a possible alternative (and has been shown to reverse diabetic nephropathy and retinopathy if done early enough in the disease [6, 10]). However, because it requires major surgery and is associated with a high incidence of post-operative complications and a small adverse effect on survival [48], it is usually reserved for patients requiring a simultaneous renal transplant in whom, despite the high morbidity associated with the pancreatic exocrine secretions, no such adverse effect on survival is seen.

In a given patient there may be a particular indication for one or the other approach but in general IPII and IIT are usually complementary. Thus, while IPII has been shown to reduce the frequency of severe hypoglycemic episodes [21], IIT may be particularly beneficial in patients with gastroparesis since the transplanted β-cells will only secrete insulin when the stomach empties and the blood glucose rises. Even more importantly, they “switch off” when glucose levels fall, thus obviating hypoglycaemia. In patients with high insulin requirements, concomitant morbidities, abnormal renal function or a desire for pregnancy, IIT is normally contraindicated. The respective indications for these two sophisticated treatment methods are summarised in tables III and IV [34, 46].

<table>
<thead>
<tr>
<th>Table III</th>
<th>Exclusion criteria for intraportal islet transplantation.</th>
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<tbody>
<tr>
<td><strong>Critères d’exclusion avant transplantation d’îlots intraportale.</strong></td>
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<tr>
<td>Diabetes duration &lt;5 years or detectable C-peptide</td>
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<tr>
<td>Age &lt;18 or &gt;65 years</td>
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<tr>
<td>BMI &gt;28 and/or insulin need &gt;1.2 UKg/day</td>
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<tr>
<td>Desire for pregnancy</td>
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<tr>
<td>Addictions or psychiatric disorders</td>
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<tr>
<td>Hepatic abnormalities</td>
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<tr>
<td>Plasma creatinine (&gt;1.5 mg/dl, &gt;130 μmol/l)</td>
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<td>Albuminuria (&gt;300 mg/day)</td>
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<thead>
<tr>
<th>Table IV</th>
<th>Categories of patients suitable for intraportal islet transplantation (IIT) or intraperitoneal insulin delivery (IPII) in brittle diabetes.</th>
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<tbody>
<tr>
<td><strong>Propositions d’indications respectives de la transplantation insulaire et de la pompe implantable.</strong></td>
<td></td>
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<tr>
<td>IIT</td>
<td>IPPI</td>
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</tr>
<tr>
<td>Hypoglycaemic unawareness</td>
<td>Multiple hypoglycaemic episodes</td>
</tr>
<tr>
<td>Extreme lability (when not factitious)</td>
<td>Overweight/insulin resistance</td>
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<tr>
<td>Gastroparesis</td>
<td>Abnormal renal or liver function</td>
</tr>
<tr>
<td>Failure of CSII</td>
<td>Sensitisation</td>
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</tbody>
</table>
CONCLUSION

In the management of the patient with brittle diabetes, it is mandatory to try to identify the underlying cause of the instability and to exclude psychological problems leading to factitious brittleness. Having done so, it is important to optimize standard insulin therapy using analogues, multiple injections and, if necessary, CSII. Alternative approaches may still be needed for the most unstable patients. IIT should be considered for hypoglycemic unawareness which does not reverse with avoidance of hypoglycaemia or for extreme lability, especially in patients whose body weight is below 80 kg and who have normal renal function. In countries where they are available, implantable intraperitoneal pumps have an important place in heavier, less insulin sensitive patients, in those with kidney or liver disease and in those who are sensitised. In the future, immunosuppressive strategies which are less toxic to islets and kidneys will make IIT more attractive in larger numbers of patients, particularly when alternative sources of β-cells on a large scale become available.

REFERENCES