Management strategies for brittle diabetes

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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 brittleness include malabsorption, certain drugs (alcohol, antipsychotics), defective absorption or degradation, defect of hyperglycemic hormones especially glucocorticoid.

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

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 stability 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...
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 BRITTENESS**

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 hypoglycaemia 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 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. 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 life time 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 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>
<thead>
<tr>
<th>Table I</th>
<th>Main causes of brittleness.</th>
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<tbody>
<tr>
<td><strong>Psychosocial factors (74%)</strong></td>
<td><strong>Principales causes d’instabilité.</strong></td>
</tr>
</tbody>
</table>
| Malabsorption | • Coeliac disease  
• Fat malabsorption |
| Drugs | • Alcohol abuse  
• Antipsychotic drugs (Quetiapine) |
| Autonomic neuropathy | • Gastroparesis  
• Hypoglycemic unawareness |
| Subcutaneous causes | • Defective insulin absorption  
• Accelerated degradation  
• Insulin allergy |
| Defects of counter-regulatory hormones | • Adrenal insufficiency  
• Hypopituitarism  
• Glucagon deficiency (e.g. Post-pancreatectomy)  
• Abnormal GH regulation |
| Auto-antibodies | • Anti-insulin  
• Anti-insulin receptor |
Évaluation d’un diabète instable.

Table II
Assessment of brittle diabetes.

<table>
<thead>
<tr>
<th>Description</th>
<th>Formula</th>
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<tbody>
<tr>
<td>Mean and Standard deviation of blood glucose</td>
<td></td>
</tr>
<tr>
<td>MAGE: Mean Amplitude of the largest Glycemic Excursions*</td>
<td></td>
</tr>
<tr>
<td>Takes into account “intraday” reproducibility (stable diabetes: 20 to 60 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Mean Of Daily Difference (MODD): day to day reproducibility of blood glucose values</td>
<td></td>
</tr>
<tr>
<td>Mean variations in a normal subject 10 mg/dl, in stable diabetes 40 mg/dl, in labile diabetes 160 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Lability index *: based on the change in glucose levels over time.</td>
<td></td>
</tr>
<tr>
<td>Low Blood Glucose Index (LBGI)*: assessment of risk of hypoglycemia: a value &lt;2.5 corresponds to a low risk of hypo; &gt;5 to a high risk</td>
<td></td>
</tr>
<tr>
<td>Clarke’s score*: 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>
<td></td>
</tr>
<tr>
<td>HYPOSCORE*: takes into account the frequency and severity, but also the loss of symptoms of hypoglycemia. Normal subjects are at 0, stable diabetes around 200, labile diabetes with frequent severe hypoglycaemic reactions around 1000.</td>
<td></td>
</tr>
<tr>
<td>Data derived from continuous blood glucose monitoring systems* (CGMS*, Guardian RT*, Glucoday* etc)</td>
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</tr>
</tbody>
</table>

*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.

The lability index (LI) is an extension of this principle emphasizing the low values [23]. LBGI integrates the frequency and severity of hypoglycemia.

The Clarke score involves 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) [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 (eg, Medtronic’s Continuous Glucose Monitoring System (CGM*), 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 realise 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 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 glycaemic 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 hypoglycemia.

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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 steatorrhea 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 hypoglycemia 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
1 diabetes, offers a more physiological route for insulin administration and decreases the risk of severe hypoglycemia [3, 7, 19]. In these patients, another option, intraportal islet transplantation (IIT), is gaining acceptance as a biological alternative for IPII coupled with glucose sensing [21, 34]. The potential of each of these promising but not yet routinely available approaches, remains controversial. Nevertheless a recent communication suggests that metabolic results improve with both methods, but are significantly better at 3, 6 and 12 months with IIT than with IPII, at the expense of more frequent side effects [47].

IPII has been shown to be especially effective in patients suffering from defects of insulin absorption or degradation [33]. It requires surgical intra-abdominal implantation under general anaesthesia of a pump, and a brief hospital visit for the pump to be refilled once a month. The number of major side effects (i.e. requiring at least one night of hospitalization) observed with this strategy is similar to that associated with IIT. In France, there are EVADIAC guidelines for its use and it is reimbursed by social health insurance. It is hoped that it may be possible in the future to couple the pump to an implanted glucose sensor but this system remains experimental.

The advantages of IIT arise from the fact that the transplanted β-cells are able to sense ambient glucose levels and secrete appropriate amounts of insulin on a minute-to-minute basis. While the long term results are clearly not as good as for whole pancreas transplantation as far as insulin independence is concerned, it has been shown that diabetes is dramatically stabilised with near complete avoidance of hypoglycaemia even in patients in whom there is a continuing small insulin requirement [34, 35, 47]. Furthermore, patients who need to restart insulin have levels of HbA₁c, which are not significantly higher than patients who remain insulin independent [34]. In both cases, control is far better than can be achieved with conventional insulin administration and it remains to be seen whether the chronic complications of diabetes are stabilised or prevented to the same extent as with whole pancreas transplantation.

The present drawbacks are the need to transplant at least two islet preparations in most cases, the risk of haemorrhage from a transcutaneous portal vein puncture (which can be minimised with a surgical approach), the need for chronic immunosuppression and the possible risk of sensitisation, and above all the fact that cadaver donors provide enough islets for only a tiny percentage of diabetic patients. IIT may require several months off work and the professional consequences of this must be taken into account. Finally, IIT is expensive and to our knowledge, is currently only reimbursed in Canada, Belgium and Germany.

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 hypoglycaemic 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 III |
| Exclusion criteria for intraportal islet transplantation. |

**Tableau III**

Critères d’exclusion avant transplantation d’îlots intraportale.

- Diabetes duration <5 years or detectable C-peptide
- Age <18 or >65 years
- BMI >28 and/or insulin need >1.2 U/Kg/day
- Desire for pregnancy
- Addictions or psychiatric disorders
- Hepatic abnormalities
- Plasma creatinine (>1.5 mg/dl, >130 μmol/l)
- Albuminuria (>300 mg/day)

| Table IV |
| Categories of patients suitable for intraportal islet transplantation (IIT) or intraperitoneal insulin delivery (IPII) in brittle diabetes. |

**Tableau IV**

Propositions d’indications respectives de la transplantation insulaire et de la pompe implanteable.

<table>
<thead>
<tr>
<th>IIT</th>
<th>IPII</th>
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</thead>
<tbody>
<tr>
<td>Hypoglycaemic unawareness</td>
<td>Multiple hypoglycaemic episodes</td>
</tr>
<tr>
<td>Extreme lability (when not factitious)</td>
<td>Overweight/insulin resistance</td>
</tr>
<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