We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



3

Brittle Diabetes: A Contemporary Review of the Myth and Its Realization

Christina Voulgari and Nicholas Tentolouris
First Department of Propaedeutic Medicine,
Athens University Medical School,
Laiko General Hospital, Athens,
Greece

1. Introduction

Type 1 Diabetes is an intrinsically unstable condition. A small group of patients with Type 1 Diabetes (3‰), mainly young women, suffer chronically by poor metabolic control, characterized by a severe instability of glycemic values with frequent and unpredictable hypoglycemic and/or diabetic ketoacidosis episodes which cannot be attributed to patients or clinicians errors. The quality of life of these patients is dramatically compromised in particular because of the frequency of acute events, hospital recoveries and precocious appearance of chronic complications. This clinical condition has been defined as "brittle diabetes" (Tattersall, 1977).

A precise quantification of these patients is difficult because diagnostic criteria are still not well defined and it is often difficult to verify errors of patients in terms of inappropriate conduct with the pathology. Metabolic instability is manifested most obviously by chaotic glycemic profiles, which show greater and more unpredictable variation than in "stable" patients with diabetes. Patients with brittle diabetes cannot be controlled adequately, even by closely supervised, intensive insulin regimens, including continuous subcutaneous and/or intravenous insulin infusion (Bertuzzi et al., 2007). Their care is often very expensive of time and resources, and their lives are constantly at risk from metabolic catastrophe. Management of these patients can also be frustrating and demoralizing for all concerned, including the patient's family and associates and the diabetes care team.

This review will focus on a contemporary "painting" of brittle diabetes beginning with a few historical notes leading to its definition, ongoing researched pathophysiologic substrate, common and life-threatening clinical manifestations, diagnosis and treatment.

2. Brittle diabetes: Historical notes

In 1942 the Chicago physician Woodyatt suggested that "The history of diabetes has been marked by recurrence of certain ideas which decline and disappear; only to go through a similar cycle again in an altered form in the new generation" (Woodyatt, 1942). This is particularly true of the concept of brittle diabetes which Woodyatt himself introduced in the 1940s. Although, he never wrote a paper on the subject, contemporaries understood it to refer to excessive fluctuations of blood sugar which could not be otherwise explained; the

cardinal feature of brittle diabetes was unpredictability and unexpected hypoglycemic reactions. Also in the 1940s, practitioners of the newly formed psychosomatic movement took an interest in the effect of emotional factors on the course of diabetes and, in particular, patients who were "difficult" or "refractory". "Difficult" patients were marked by not following their doctor's instructions or having recurrent diabetic ketoacidosis.

By the 1950s the question was whether there were two distinct groups of patients; one whose lability could be cured by adjusting insulin, diet, and exercise, and another whose lability had an emotional origin. It remained a question whether in those patients in whom glycemic lability was attributed to an emotional cause, were in fact experiencing psychosocial problems as a consequence rather than a cause of the metabolic instability. Patients with factitious hypoglycemia, which remained undetected for weeks, suggested that neither close observation nor screening by a psychiatrist could rule out the factitious disease (Tattersall, 1997). Therefore in 1977 the definition of brittle diabetes was suggested by Tattersall for patients whose life was "constantly disrupted by episodes of hypo- or hyperglycemia, whatever their cause should be". This was widely accepted and there was a subtle shift towards regarding brittle diabetes as synonymous with recurrent ketoacidosis.

In the 1980s several groups investigated large series of such patients, using new methods to try to uncover a biochemical basis such as defective insulin absorption, accelerated degradation at insulin injection sites, and inappropriate secretion of various counterregulatory hormones (Schade et al., 1980; Fischer et al., 1980). Most of these patients were young overweight women and the eventual conclusion was that in most patients the instability was self-induced. In the 1980s recurrent, often warningless, hypoglycemia was recognized as a problem in its own right but in the current era it was reborn as also a problem of insulin pharmacokinetics, exact as Woodyatt originally conceived it.

3. Aetiology and pathophysiologic substrate: From the suspicion to ongoing research

Going back in literature, among the main causes of "brittleness" referenced are malabsorption, certain drugs (i.e. antipsychotics), defective insulin absorption or degradation, defect of hyperglycemic hormones especially glucocorticoid and glucagon, and above all delayed gastric emptying as a result of autonomic neuropathy (Vinik et al., 2003; Lehmann et al., 2003; Voulgari et al., 2010). Moreover, possible causes of hypoglycemic "brittleness" described are organic problems which comprise lost hypoglycemia warnings (Tattersall & Gill, 1991), such as alcohol abuse (Hepburn et al., 1990), renal failure, gastroparesis, hypopituitarism, and senile dementia (Potter et al., 1982).

Variable adherence to insulin treatment contributes to presentation of brittle type 1 diabetes in adolescents and young adults. The deterioration in glycemic control observed in patients aged 10-20 years is often associated with a significant reduction in the adherence index (the medically recommended insulin dose and cumulative volume of insulin prescriptions supplied for the calculation of the days of maximum possible insulin coverage per annum). The latter is inversely related to hospital admissions for diabetic ketoacidosis and all hospital admissions related to acute diabetes complications in young (<20 years) type 1 diabetes patients (Morris, 1990). Direct evidence of poor compliance with insulin therapy in young patients with type 1 diabetes and poor adherence to insulin treatment is a major factor that contributes to brittle diabetes with diabetic ketoacidosis in this age group.

Insulin requirements that apparently exceed 2.0 U/kg/day almost always indicate an underlying problem and frequently are suggestive of "brittleness". Causes of apparent or genuine insulin resistance in type 1 diabetes patients include: puberty (Amiel, 1996), overinsulinization (Rosenbloom & Giordano, 1977), the Mauriac Syndrome (Elder& Natarajan, 2010), chronic infections of the diabetic foot (Tentolouris et al., 1996; Tentolouris et al., 2010, Papanas & Maltezos, 2009), acromegaly (Elkeles et al., 1969), Cushing's Syndrome (Anagnostis et al., 2009), thyrotoxicosis (Jacobson et al., 1970) and phaeochromocytoma (Ishii et al., 2001). In few cases of recurrent diabetic ketoacidosis, there is some suggestion of a deliberate manipulation of diabetes control: patients with recurrent diabetic ketoacidosis are thought to be attention-seeking by omitting insulin due to marital problems and possible depression, and possibly personal gain from diabetic instability (Benbow et al., 2001); depression and manipulation are among the contributory factors to instability as well as chronic non-diabetic medical disease (Gill, 1992).

The aetiology of recurrent hypoglycemia includes impaired awareness of hypoglycemia, which can be associated with long-standing type 1 diabetes (Ryder et al., 1990), or induced by antecedent hypoglycemic episodes (Lager et al., 1986; Janssen et al., 2000), overinsulinization (Widom & Simonson, 1992), endocrinopathies (Hardy et al., 1994), and gastrointestinal diseases such as self-induced vomiting by patients with anorexia and/or bulimia (Lloyd et al., 1987; Stancin et al., 1989; Crow et al., 1999). Malabsorption, including celiac disease as it is analyzed later, which is associated with type 1 diabetes, can also cause decreased insulin requirements and unexpected and sometimes severe hypoglycemic episodes (Smith et al., 2000). Psychiatrically and psychological problems are more common than suspected. Psychosocial factors are very important and factitious "brittleness" may lead to a self-perpetuating condition. The factors reported are: as previously mentioned poor compliance (Pickup et al., 1983), family dysfunction (Diabetes Control and Complications Trial Research Group, 1993) and obsessional control of diabetes (Borch-Johnsen & Helweg-Larsen, 1993). Psychological problems (Tattersall & Gill, 1991), "life chaos" (Hepburn et al., 1990), factitious insulin overdose (Hepburn et al, 1990) and anorexia nervosa (Potter et al., 1982) also illustrate the aetiologic profile of hypoglycemic "brittleness". Suggested motives include escape from hostile situations to the security of hospital, attention seeking, and revenge on self or family and suicidal intent. Some patients induce hypoglycemia to"feel high" (Cassidy et al., 1999). Rarely cases of factitious overdose where insulin was given in excessive doses by a mother to her diabetic child (Munchausen's Disease by Proxy) are also referenced (Ludviksson et al., 1993; Gill & Lucas, 1999).

Acute psychological stress plays a role in the glycemic instability of some patients with brittle type 1 diabetes through an increased secretion of insulin-counteracting hormones. Psychological interviews showed that most patients with brittle diabetes perceive a link between life stress and their blood glucose control and they have much more difficulty in verbalizing their emotions (Dutour et al., 1996; Scantamburlo et al., 2001). Patients with brittle diabetes display distinct cardiovascular and neuroendocrine responses to psychological stress, as well as distinct psychological profiles (Jørgensen, 2007). Moreover, hormonal response to an acute psychological stress is more pronounced in brittle diabetes and might be one of its pathogenic factors (Dutour et al., 1996).

Psychosocial parameters interact with metabolic instability even in juvenile brittle type 1 diabetes. Feelings of dominance precede an increase of blood sugar variance, whereas depressive moods, anger and body symptoms are associated with metabolic instability

(Brosig et al., 2001). A family therapy session also results in an increase of the mean blood sugar variance. Multivariate time-series is a mean to demonstrate psychosomatic interrelations and may also contribute to an empirically rooted understanding of psychodynamic processes in psychosomatoses.

Schizophrenia, like other autoimmune disorders, is likely a heritable phenomenon, and a genetic liability in this disorder is hardly disputed. Research has indicated that physiologic connections between IFN-gamma and TNF-alpha are suggestive of a connection between the symptoms associated with schizophrenia and those of hypoglycemic events in type 1 diabetes patients (Kane et al., 2009). Autoimmune pathogeneses of schizophrenia have been hypothesized and the clinical delineation of a potentially corresponding subset of patients has been addressed in young female patients who carry the concomitant diagnoses of schizophrenia, brittle type 1 diabetes, and hypothyroidism. These patients when treated with corresponding antipsychotic medication on an acute basis, an apparent resolution of their brittle type 1 diabetes with the successful treatment of their psychotic disorder is observed (Balter et al., 2004; Ramaswamy et al., 2006). This well documented link between antipsychotic agents and changes in blood glucose may be of benefit in a subset of patients who suffer from both psychotic and diabetic disorders.

In autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, autoimmune destruction of the pancreatic beta-cells with development of brittle type 1 diabetes is possible, but rarer than in the other polyglandular autoimmune syndromes (Lankisch et al., 2009). The pathogenesis of this unique autoimmune disease is unknown (Vogel et al., 1992). However, cases of young female patients with the diagnosis of autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy have been presented and characterized by psychosomatic abnormal development, teeth alterations, post-puberal gonadal failure with dystrophic hypoplasia of external genitalia, previous vaginal candidiasis, and slowly developing juvenile brittle diabetes with an early onset and severe complications (Iannello et al., 1997). Such patients (and their female maternal relatives) need a long-term follow-up in order to evaluate the function of endocrine glands and to initiate early treatment for hormonal deficits, as well as to detect the non-endocrine components of disease.

Most patients with brittle diabetes are in the second or third decade of life and they are typically admitted with diabetic ketoacidosis rather than hypoglycemia or mixed patterns of instability. A "second peak" of prevalence at the age of 60-70 years has been recorded though much smaller than the main peak at 15-30 years (Gill et al., 1996). Causes for this "second round" of "brittleness" include medical disease (14%), hypoglycemic unawareness (6%), and memory or behavioral problems (8%).

Brittle diabetes in older (≥70 years) patients with a history of insulin therapy using mainly human recombinant insulin is reported and is attributed to a high titer of insulin antibodies and a higher level of insulin resistance (Park et al., 2008). Steroid pulse therapy reduces the possible effect of the insulin antibodies on insulin resistance and glycemic instability, successfully decreases their titer and binding capacity, increased glucose infusion rate and improved glycemic control with reduced blood glucose excursion (Matsuyoshi et al., 2006). Alteration in insulin pharmacokinetics induced by insulin antibodies seems to be a cause of brittle diabetes. Steroid treatment might be useful for the improvement of glycemic control in such patients.

Brittle diabetes in the elderly patients with diabetes is most frequent characterized by recurrent hypoglycemia (Benbow et al., 2001). In elderly patients with brittle diabetes,

contributing factors to instability are chronic, nondiabetic medical diseases. Unrecognized celiac disease is one such chronic disorder and recurrent hypoglycemia is ameliorated by adherence to a gluten-free diet, when coexisting colorectal disease has been ruled out by barium enema and colonoscopy. The fact that 19% of patients with adult celiac disease could be in the above 60 years of age group should alert us to the possibility of an association with brittle diabetes in older age as well (Mody et al., 2003). Furthermore, in the presence of otherwise unexplained brittle diabetes, the coexistence of iron-deficiency anemia should heighten suspicion, since this haematinic deficiency is the commonest extraintestinal manifestation of celiac disease with distinct episodes of microcytic and/or hypochromic anemia, responsive to iron supplements (Jolobe & Khin, 2002; Hershko & Skikne, 2009).

Brittle diabetes in the extremely elderly patients with diabetes (>80 years) is thought to be a depletion of endocrine insulin secretion due to marked beta-cell reduction and/or beta-cell exhaustion secondary to long term diabetes duration. It is usually characterized by frequent striking hypoglycemic episodes without clinical awareness. These patients often are presented with vascular dementia, visual disturbances, hearing difficulties and speech and motor disturbances. Daily detailed observation is required to care for such patients with brittle diabetes (Kawanishi & Miyashita 2003).

Sometimes, there is no obvious cause. Most patients with "idiopathic" brittle diabetes that oscillates between hypoglycemia and hyperglycemia have no obvious underlying cause, but many deliberately induce glycemic instability by interfering with their treatment. Nonetheless, organic causes of brittle diabetes are occasionally found and must always be sought, i.e. recurrent infections, especially if insulin dosage is not increased (Laffel et al., 2006; Voulgari & Tentolouris, 2010), endocrinopathies, i.e. hypoadrenalism (Gill & Williams, 2000), inappropriate treatment regimens or lifestyle, and pancreatic damage.

Diabetes after total pancreatectomy is commonly described as "brittle" with most series reporting outcomes after resection for pancreatitis alone (Jethwa et al, 2006). Brittle diabetes is also frequently developed in patients with chronic pancreatitis after partial pancreatectomy and its development is partially related to reduced pancreatic beta-cell area (Meier et al., 2009), as well as other clinical variables, i.e. pre-operative fasting glucose levels, HbA1c and body mass index (Schrader et al, 2010). This is further highlighted by the fact that different surgical procedures have an unequal impact on glucose control. Insulin secretion is diminished after pancreatic-head and pancreatic-tail resection, but post-challenge glucose concentrations can be ameliorated only after pancreatic-head resection (Menge et al., 2009).

Brittle diabetes in chronic pancreatitis due to the gradually loss of pancreatic parenchyma and the appearance of calcifications and of steatorrhea, is characterized by a high risk of hypoglycemia due to the decreasing output of insulin and glucagon. In most instances, measurement of fecal concentration of elastase may be sufficient to diagnose exocrine pancreatic insufficiency (Layer & Keller, 1999). Fecal fat analysis is useful to establish malabsorption and to monitor pancreatic enzyme replacement therapy (Dobrilla, 1989). Modern pancreatic preparations are also engineered and most patients reduce their steatorrhea, although in selected cases larger doses may be needed, depending on size of the meal and the severity of the disease. Efficacy of enzyme replacement therapy is influenced by the presence of diabetes and vise-versa (Hammer, 2010).

Acute tropical calculous pancreatitis was also reported as generative of brittle diabetes and oral pancreatic enzyme therapy was used for the glycemic control with favorable results regarding HbA1c, and fasting glucose levels (Mohan et al., 1998).

Recently, impaired metabolism of intestinally derived chylomicron remnants has been implicated in the development of atherosclerosis. A specific marker of chylomicron particle number (apoB48) has been associated with increased vascular disease such as obesity, metabolic syndrome, type 2 diabetes, and familial hypercholesterolemia (Otokozawa et al., 2009; Valdivielso et al, 2009). The role of these particles in the increased atherosclerotic risk associated with brittle type 1 diabetes is currently demonstrated. ApoB48 metabolism is shown to be altered in individuals with brittle diabetes even in the absence of classic dyslipidemia (Su et al., 2009). Disturbed plasma apoB48 remnants can potentially predict coronary artery disease in this population. Among the newest pathogenetic theories demonstrated is that plasma glucose levels in patients with brittle type 1 diabetes respond directly to the amount of transient electromagnetic fields ("dirty electricity") generated by everyday electronic equipment and wireless devices in their environment (Havas, 2008). In an electromagnetically clean environment, patients with type 1 diabetes require less insulin and have lower levels of plasma glucose (Li, 2005; Beale et al., 1997). Exposure to electromagnetic pollution in its various forms may explain the difficulty in glycemic control in patients with brittle diabetes who suffer from symptoms of electrical hypersensitivity (almost 35%). Reducing exposure to electromagnetic pollution by avoidance or with specially designed GS filters may enable some patients with diabetes to better regulate their blood sugar with less medication (National Toxicology Program, 2010). Figure 1 illustrates a summary of the cited causes of Brittle Diabetes.

4. Diagnosis and clinical manifestations

There are no universally agreed diagnostic criteria. Three forms of brittle diabetes have been described: recurrent diabetic ketoacidosis, predominant hypoglycemic forms and mixed instability (Figure 1). Previous studies have shown that over 90% of hospital admissions in patients with recurrent diabetic ketoacidosis or recurrent hypoglycemia are due to that particular type of glycemic instability (Gill, 1992). Hypoglycemic brittle diabetes makes up 17% of the total brittle spectrum, compared with 59% of ketoacidosis brittleness (Tattersall, 1991) and 24% (Gill, 1992) of mixed brittleness. Compared with patients with recurrent diabetic ketoacidosis, hypoglycemic brittle patients are significantly older; and are of approximately equal male: female ratio, compared with a female excess in recurrent diabetic ketoacidosis (Gill & Lucas, 1992). Also of interest is that patients with mixed brittleness are intermediate in both age and sex-ratio, between the groups with recurrent diabetic ketoacidosis and recurrent hypoglycemia. Idiopathic brittle diabetes is a label applied to those patients who remain poorly controlled despite modern intensified insulin regimens and have no obvious cause for their instability (Somogyi, 1959). Most display a pattern of general hyperglycemia with wide glycemic swings and recurrent episodes of ketoacidosis.

A scheme for investigating patients suspected for brittle diabetes is suggested in Figure 2. A thorough history and examination may elucidate drug-induced causes, infections or endocrine conditions (including puberty). Before moving on to more detailed investigations, the patients understanding of diabetes monitoring and treatment should be assessed. It should be reasonable to exclude chronic infections and specific endocrine diseases. If considered necessary insulin antibodies and insulin receptor antibodies should be measured. Should no cause for insulin resistance emerge, the possibility of factitious insulin



Fig. 1. Causes of Brittle Diabetes

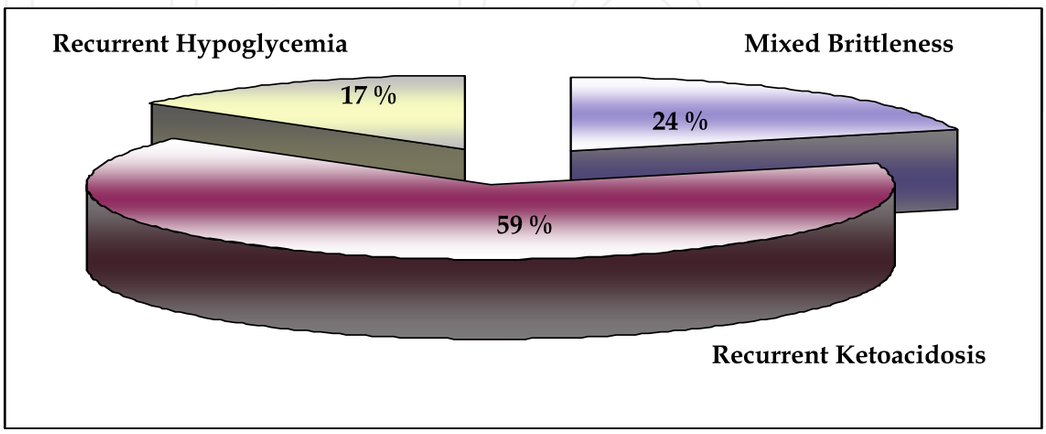


Fig. 2. The spectrum of Clinical Manifestations of Brittle Diabetes in Type 1 Diabetes Patients

resistance should be explored and an insulin challenge test should be performed (Serlin & Lash, 2009). Most patients who remain undiagnosed at this stage probably have factitious disease and may be skilled at manipulating their treatment, their families and physicians. Therefore, the test injections must be given by a member of the diabetes care team under conditions that guarantee the patients' cooperation. The need this must be explained to both patients and family. Hospital admission in such cases can provide formal psychological and psychiatric assessment of the patient and the family, without which investigation and management are incomplete.

It is essential to follow a logical protocol that initially excludes potentially remediable, organic causes. Cases remaining unexplained at the end of the process are most likely to be factitious in origin. Close observation during hospitalization is important: some brittle diabetes patients are skilled at stimulating hypoglycemia, possibly to gain attention or simply to obtain food that they desire (i.e. sweets) that are otherwise prohibited.

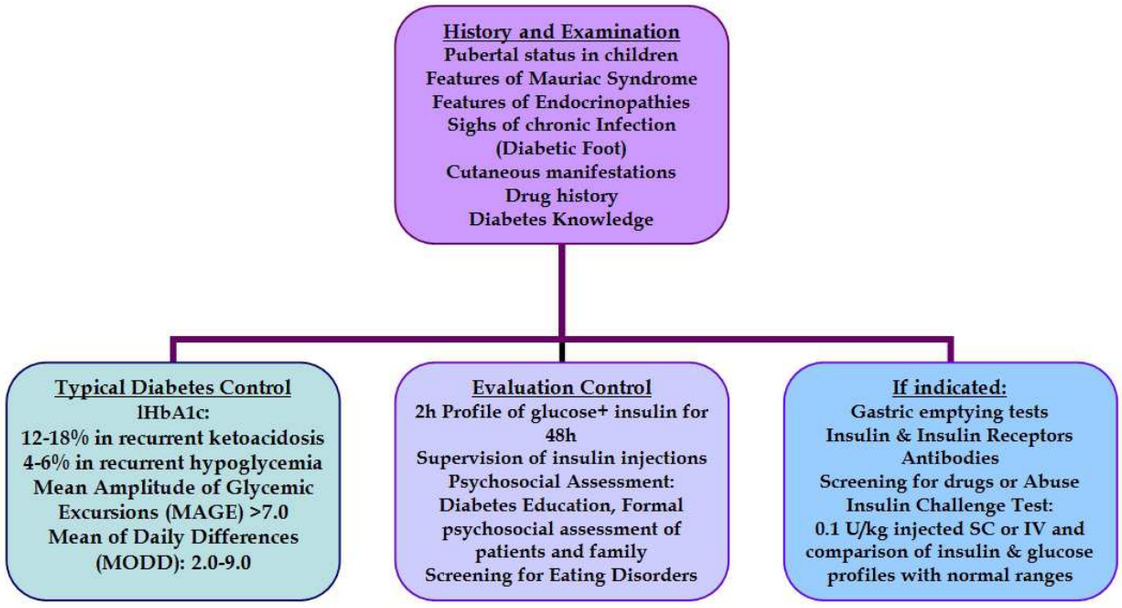


Fig. 3. Scheme for investigation of Brittle Diabetes

Among the life-threatening clinical manifestations, cases of spontaneous muscle infarction in young (mainly ≤30 years) women with a short duration (≤5 years) history of brittle type 1 diabetes that was not complicated by nephropathy, retinopathy or neuropathy have been described in the literature (Virally et al, 2007).

Spontaneous muscle infarction is a rare complication of diabetes, usually described in patients with multiple long-term diabetic complications (Woolley & Smith, 2006). Diabetic muscle infarction is more frequent in women (61.5%) and in type 1 diabetes (59%). The mean age of reported cases is 42.6 years, with a mean duration of diabetes of 14.3 years (Mathew et al., 2007). Multiple complications are usually present: 71% of patients have nephropathy (Madhan et al., 2000), 57% have retinopathy, and 54% suffer from autonomic neuropathy (Trujillo-Santos, 2003). Spontaneous diabetic muscle infarction is presented with necrosis of all muscle elements, with polymorphonuclear or mononuclear cellular infiltration and a varying but often limited degree of regeneration, depending on the age of the lesion. The presentation is usually acute, with pain and swelling localized to the thigh in

most instances. Systemic signs such as pyrexia are infrequent. Laboratory tests (such as white cell count and creatinine kinase) and plain radiographs are not helpful, although the erythrocyte sedimentation rate is often elevated. The diagnosis, in the appropriate setting, is strongly suggested by magnetic resonance imaging, which shows increased signal intensity and asymmetry of the muscle on T2-weighted scanning as well as fluid in the tissue planes. Management consists of resting the muscle, analgesics, and gradual mobilization. Recurrence is common and may be seen in more than 50% of the patients. Long-term prognosis is poor, with most patients dying from cardiovascular complications of diabetes within 5 years of diagnosis. Therefore, a high index of suspicion, when a poorly controlled patient with diabetes presents with non-traumatic limb pain is needed (Mathew et al., 2007).
All common causes of muscle infarction should be excluded, particularly microangiopathy and a hypercoagulable state. The differential diagnosis includes infection (pyomyositis, necrotic fasciitis), focal inflammatory myositis, vascular events, trauma, tumor and diabetic amyotrophy (Grigoriadis et al., 2000). When all of these are excluded, the possibility that the alternating states of transient acute hypoglycemia and hyperglycemia may be responsible for the myocardial infarction should be aroused and brought to the diagnostic table. "Brittleness" usually resumes after treatment with subcutaneous insulin infusion using a portable pump and no recurrence of muscle infarction is observed during the follow-up.
Although, integration of the patient's mental organization is an important part of all psychotherapeutic experiences and generally it is welcomed and thought well worth the effort needed to achieve it, however patients with brittle diabetes feel terrified by this process (Tallandini, 1999). They seem to think that integration involves a loss of the self: they feel it is dangerous and even resist it with psychotic-type defenses. For them, this reaction is always activated by separation, and it also appears prior to any developmental step they need to take- i.e. in recognizing self-boundaries, sexual identity, and facing the oedipal conflict. On all these occasions their reaction is to run away from treatment in a state of deep regression, feeling suicidal, and liable to seriously harm their self through the mistreatment of their diabetes (Hoffman, 2003).
Patients with long standing brittle diabetes with numerous episodes of diabetic ketoacidosis and frequent hypoglycemic episodes may present significant pathological changes in the gastric wall that affect all major components including muscle, neurons and interstitial cells of Cajal. Gastroparesis and severe malnutrition can occur in the presence of these changes, and may reflect vagal, central or hormonal influences (Pasricha et al., 2008). In juvenile brittle diabetes early diagnosed (in the first days of life) it is possible to develop severe secretory diarrhea. Extensive biochemical and serological investigation often fails to reveal the etiology of the diarrhea. Therapeutic trials with various agents (i.e. loperamide, cholestyramine, prednisone, indomethacin, and somatostatin analogue) often have no response. In some cases death from septicemia and malnutrition related to diarrhea and poor control of glycemia is reported before the completion of 1 year of age (Jonas et al., 1991; Roberts & Searle, 1995). Autopsy, may reveal absence of islets of Langerhans in the pancreas, and diffuse dysplastic changes in small and large intestinal mucosa. The entire alimentary tract may be lined by epithelia most typical of foregut mucosa: secretory-type glands, absent crypts of Lieberkuhn, and absent villi relating brittle type 1 diabetes with diffuse intestinal dysplasia independently or as part of a hyperimmunoglobulin syndrome (Peake et al., 1995).
Inhibition of the periodontal ligament cells which are the most important cells in the healing of wounds and the regeneration of periodontal tissues is the key explanation for the delayed

periodontal regeneration and healing in patients with brittle diabetes with recurrent diabetic ketoacidosis (Kim et al., 2006). This is relevant to the increased number of infections that compromise more distant structures (via direct spread and distant spread), i.e. intracranial, retropharyngeal and pulmonary pleural infections and the dissemination by bloodstream that can lead to primary rheumatic problems and secondary deposits on the valves of the heart, i.e. endocarditis (Jiménez et al., 2004; Lazow, 2005).
Pulmonary edema, cerebral edema and multiple infarctions of the brain and cervical spinal cord develop more frequent in brittle type 1 diabetes than in "stable" type 1 diabetes patients during diabetic ketoacidosis, despite appropriate treatment. This may result in spastic quadraparesis and permanent disability (Dixon et al., 2006).
Some of the cutaneous manifestations of brittle diabetes include necrobiosis lipoidica diabeticorum, diabetic dermopathy, scleredema adultorum and acanthosis nigricans (Jabbour, 2003).

5. Quality of life: Struggling towards its achievement

The disruption of life, which is fundamental to the definition of brittle diabetes, obviously dependents on the patient's usual lifestyle and on numerous independent factors, including the admission policy of the diabetes care team. Emergency admissions due to poor diabetic control are much more common and prolonged than in "stable" patients, and it is not unusual for patients with brittle diabetes to spend several months each year in hospital. Pragmatic definitions of lifestyle disruption and "brittleness" include frequency and duration of hospitalization, more frequent psychosocial disruptions, pregnancy complications (Kent et al., 1994; Gill et al., 1996) and higher risk of death due to diabetic ketoacidosis, hypoglycemia, and renal failure (Tattersall et al., 1991).
Epidemiological studies in patients with brittle diabetes have established higher prevalence rates of psychiatric disorders, in particular mood and anxiety disorders. However, the prevalence rate and symptom profile of depression was found to be homogeneous between psychiatric patients with or without diabetes (Eiber et al., 1997).
Health-related quality of life is among the benefits of islet transplantation, because of a significant improvement in the dimensions of satisfaction and impact of diabetes (Benhamou et al., 2009). Therefore, its assessment may help in the selection of candidates with brittle diabetes for islet transplantation.

6. Management strategies in brittle diabetes

6.1 Qualification of glycemic variability

Several measures have been developed to quantify metabolic instability in brittle diabetes, which include assessment of the Mean Amplitude of the largest Glycemic Excursions (MAGE), the Mean of Daily Differences (MODD), Lability Index (LI), Low Blood Glucose Index (LBGI), Clarke's score, Hyposcore, and continuous blood glucose monitoring (Vantyghem & Press, 2006).

6.2 Continuous glucose monitoring systems: Indications, advantages, and limitations

Accurate and reliable devices sensing glucose on a near-continuous basis may facilitate specific therapeutic adjustments that need to be made to avoid hypo- and hyperglycemic excursions, thereby improving metabolic control. Patients with brittle diabetes, who are

motivated to participate in their diabetes care and are technologically adept, may benefit from continuous glucose monitoring. Current continuous glucose monitoring systems indicate the glucose level, the direction and magnitude of change of glucose levels, and can be used to assess glycemic variability (De Block C et al., 2008). In addition, real-time continuous glucose monitoring sensors can serve as a tool to predict impending glucose excursions, thereby providing alarm signals of hypo- and hyperglycemic values warning the patient to take preventative actions (De Block C et al., 2008). Quality of life may also improve by using continuous glucose monitoring via reducing the fear of hypoglycemia (Weinzimer et al., 2004).

However, to successfully implement continuous glucose monitoring in daily practice, these devices must be accurate and reliable, and one must be aware of the limitations of current continuous glucose monitoring systems, that originate from physiological and technical aspects. Whether continuous glucose monitoring succeeds in ameliorating metabolic control and in reducing hypoglycemic episodes, as well as whether it improves quality of life in patients with brittle diabetes remains to be proven. Should this be the case, real-time continuous glucose monitoring may reduce chronic diabetic complications, and avoid hospitalizations, thereby reducing health care costs.

7. Treatment options

Therapy of brittle diabetes is based on education, glycemic control, intensive treatment and strict interaction between physicians and patients. Once psychogenic problems have been excluded, therapeutic strategies require firstly, the treatment of underlying organic causes of the "brittleness" whenever possible and secondly optimizing standard insulin therapy using analogues, multiple injections and consideration of continuous subcutaneous insulin infusion. However, patients with brittle diabetes characterized by recurrent diabetic ketoacidosis are often not improved by continuous subcutaneous insulin infusion, although there may be exceptions (Pickup & Keen, 2002). The introduction of insulin analogous, with either ultra-fast or ultra-slow action and the use of subcutaneous insulin pumps have significantly increased the possibility of treating most of these cases. However, there is a minority of patients resistant to therapy and alternative approaches are needed for these most severely affected patients. In similar cases, pancreas or islet transplantation represents an effective therapeutic option entailing good expected outcomes.

7.1 Lifestyle and education

Reduction of the rate of severe hypoglycemia has been noted with the Dose Adjustment for Normal Eating, a modern approach of advocating dietary freedom and appropriate flexibility of insulin doses, resulting in improved long-term metabolic control and better adherence to treatment goals (McIntyre, 2006).

The patient's ability to manage his or her own diabetes should be evaluated and reinforced if necessary, and guidelines drawn up with the patient's agreement for future treatment targets and follow-up. Any conclusions or diagnosis should be discussed in depth with the patient and family. Patients should be educated on self-management and insulin dose adjustments, since a main cause of brittle diabetes is failure of the patient to understand or manage his or her own diabetes (Rice, 2006). Effective education should provide knowledge within a context with which the patient can become familiar and should do justice to the unpredictability and complexity of actual life, as well as to the patient's own individuality

(Wroe, 2004). Efficacious education should transcend mechanical transmission of information to attain a deeper level of knowledge and inspire sustainable behavior changes and this is the only way to progress from incompliance to compliance and assimilation of fundamental principles, to active adherence, which is known to result in effective self-management (Lutfey et al., 1999). Thus, the patient is put in control to cope with the ever-changing situations of life (Papanas & Maltezos, 2008).

In recurrent hypoglycemia, all patients and their associates should be educated about the prevention and treatment of hypoglycemia (Dagogo-Jack, 2004). Moreover, appropriate information about hypoglycemia unawareness should take place upon diagnosis and regularly thereafter at follow-up consultations. Patients should be reminded to avoid usual behaviors that may contribute to hypoglycemia, such as taking excess insulin, delaying or missing meals, mistiming insulin/food intake around exercise, not monitoring before bed and appropriate increased food intake. Alcohol consumption can also lead to hypoglycemia and impair recovery from a hypoglycemic episode; the importance of not omitting food when drinking should be emphasized to patients. Additionally, patients should be advised to have a glucagon emergency kit on hand for severe hypoglycemic episodes (Aschner et al., 2010). Self monitoring of blood glucose can provide valuable information.

Although hypoglycemia avoidance restores awareness, it is difficult to be sustained. Hypoglycemia unawareness increases severe hypoglycemia risk. When adherence to treatment changes is compared by awareness status, reduced adherence to changes in insulin regimen in patients with hypoglycemia unawareness is compatible with habituation to hypoglycemic stress (Ly et al., 2009). Hypoglycemia unawareness in type 1 diabetes is largely secondary to recurrent therapeutic hypoglycemia, as assessed by neuroendocrine and symptom responses (Janssen et al., 2000) and cognitive function in patients with brittle type 1 diabetes and recurrent hypoglycemia (Bolli et al., 1998; Cryer et al., 2009). Reduced awareness of hypoglycemia in some patients with overzealous glycemic control may be partially restored by reducing insulin dosages and allowing mean blood glucose to rise (Fanelli et al., 1993). Respectively, after a short period (~2 weeks) of hypoglycemia prevention, the magnitude of symptom and neuroendocrine responses (with the exception of glucagon and norepinephrine) nearly normalizes, and cognitive function is deteriorated at the same glycemic threshold and to the same extent as in subjects without diabetes. At 3 months, the glycemic thresholds of symptom and neuroendocrine responses normalize, and some of the responses of glucagon are recovered (Fanelli et al., 1994). Hypoglycemia unawareness in type 1 diabetes is largely reversible and intensive insulin therapy together with a program of intensive education may substantially prevent hypoglycemia and at the same time maintain the glycemic targets of intensive insulin therapy in patients with brittle type 1 diabetes (Lager et al., 1986). Therapies aimed at reversing repetitive harmful behaviors may also be useful to restore hypoglycemia awareness, as well as protection from severe hypoglycemia.

7.2 Psychotherapy

Proven noncompliance to treatment requires careful handling. The "polarization" of brittle diabetic instability into hyperglycemic (recurrent diabetic ketoacidosis) or hypoglycemic behavior is well described, with relatively few displaying characteristics of "mixed brittleness" (Tattersall et al., 1991, Gill, 1992). Inpatient psychotherapy of patients with brittle diabetes and psychic reactions significantly stabilizes and improves blood glucose

after separation. Significant predictors for the average blood glucose are the therapist's vacation and the announcement of discharge from the hospital. A significant predictor for the daily blood glucose variation is mood (Milch et al., 2002). These results suggest the benefit of psychotherapy for young patients with brittle diabetes ((Mitchell et al., 2009).
Psychological therapy improves noncompliance as a primary cause of "brittleness" and in most cases patients are completed rehabilitated (Schade et al., 1985; Viner et al., 2003). However, in other groups the psychological management of "difficult" diabetes is less encouraging (Didjurgeit et al., 2002; Mitchell et al., 2009).

7.3 Alternative medicine

The Rauvolfia-Citrus tea is made by the boiling foliage of Rauvolfia vomitoria and the fruits of Citrus aurantium and is used to treat diabetes in Nigerian folk medicine. Chronic administration of the Rauvolfia-Citrus tea together with antidiabetic medication caused significant improvements in markers of glycemic control, such as blood glucose clearance, fasting and 2-h postprandial plasma glucose and HbA1c without adverse effects or hypoglycemia. Furthermore it ameliorated the fatty acid profile of skeletal muscle (Campbell-Tofte et al., 2010).
On healthy people vinegar delays gastric emptying and lowers postprandial blood glucose and insulin levels (Hlebowicz et al., 2008). The effect of 30 ml apple cider vinegar daily before breakfast on delayed gastric emptying rate on patients with brittle type 1 diabetes was assessed. Vinegar affected patients with diabetic gastroparesis by reducing the gastric emptying rate even further, with a concomitant disadvantage regarding to their glycemic control (Hlebowicz et al., 2007).

7.4 Insulin therapy

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 glycemic treatment goals. Severe complications of diabetes can be avoided without increasing the risk of severe hypoglycemia. However, patients with brittle diabetes do not reach this objective (Jacqueminet et al., 2005). Besides the usual reasons affecting all patients with type 1 diabetes, i.e. diabetes itself, the idiosyncrasy of the patient, or the physician, in Brittle Diabetes the main obstacle which prevents patients from reaching the ideal glycemic target is more often related to psychological problems: difficulties in self-regulation, denial of diabetes presence, or phobia of hypoglycemia with avoidance behavior. Frequently, young women present eating disorders which can explain the poor diabetes control. The physician may be implicated in these poor glycemic results by not prescribing the right tools to obtain optimal glycemic control (staying with just two daily injections with premixed insulin) or by assigning glycemic 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.
Cases of brittle type 1 diabetes in which recurrent hypoglycemia and peripheral edema were relieved after conversion from insulin lispro to insulin aspart have been reported (Tone et al., 2008) and stable glycemic control, as well as edema-free condition were maintained after conversion of insulin analogs. Several studies reported significantly fewer symptomatic

episodes of hypoglycemia with insulin aspart than with insulin lispro administrated by continuous subcutaneous insulin infusion in type 1 diabetes (Plank et al., 2002), which might be due to the differences in their pharmacokinetics and actions (O'Hare et al., 1983). On the other hand, plasma volume, intravascular albumin content and transcapillary escape rate of albumin change in response to hypoglycemia were also ameliorated by insulin conversion (Hilsted et al., 1991). Therefore, in cases of brittle type 1 diabetes, especially with peripheral edema, it may be worth using insulin analogs.

7.5 Insulin pump therapy

Though in use for more than 3 decades, insulin pumps are now being more commonly used because of their unique ability to continuously infuse insulin, closely mimicking that of physiological secretion from a normal pancreas. Unlike insulin shots with syringes, pump infusion sites need to be changed less frequently. Insulin pumps are reported to improve glycemic control, normalize blood glucose levels, reduce glycemic swings, and the dawn phenomenon. Fewer hypoglycemic episodes and a reduction in insulin dose per day are reported with insulin pump therapy as well as an improvement in sexual function, libido, and a significant relief of the intractable pain of peripheral neuropathy (Kesavadev et al., 2010). Quality of life is ameliorated by a reduction in the chronic fear of severe hypoglycemia, the more flexibility of lifestyle-no need to eat at fixed intervals, more freedom of lifestyle and easier participation in social and physical activity, and benefits for the patients' family (Cummins et al., 2010). The success of insulin pump therapy depends on selection of the right candidate, extensive education, motivation, and implementing the sophisticated programs with skill. Long-term follow-up of medical, psychological, and neurocognitive parameters in young patients with brittle diabetes have further summarized the same efficacy and safety of continuous subcutaneous insulin infusion in children ≤6 years of age (Eugster et al., 2006).

Insulin pump therapy can be initiated and used effectively in patients with brittle type 1 diabetes to improve metabolic control and quality of life. When diabetes and pump management are appropriately individualized, this kind of therapy can help patients with type 1 diabetes to achieve and to sustain metabolic control. Lifestyle flexibility, quality of life improvement, and independence can be maintained throughout young adulthood (Petrovski et al, 2007). Nocturnal glycemic control is improved with insulin pumps, and automatic basal rate changes help to minimize a pre-breakfast blood glucose increase (the "dawn phenomenon") often seen with injection therapy. Implantable pumps have advantages for patients who either weight more than 80kgs or have abnormalities of kidney or liver function or are highly sensitized. One study compared intraperitoneal insulin infusion through an implantable pump with intraportal islet transplantation (Vantyghem et al, 2009). Although the metabolic results (HbA1c, daily insulin need, glycemia) improved with both methods, they were significantly ameliorated with intraportal islet transplantation, though with more frequent side effects (hypoglycemia).

7.6 Islet transplantation

Islet cell transplantation is an attractive concept which holds great promise for the treatment of type 1 diabetes and for preventing brittle diabetes in patients undergoing pancreatic resection; given its potential high efficacy and that it is a relatively noninvasive procedure and a smart alternative to pancreas transplantation for restoring endogenous insulin

secretion, islet cell transplantation may effectively control blood glucose for brittle type 1 diabetes, resulting in a marked reduction in hypoglycemic episodes and improvements in glycemic control. In addition, approximately 70% of transplanted patients with type 1 diabetes have achieved insulin independence (Matsumoto et al, 2005).

Isolated islet transplantation, which restores glucose sensing, should be considered in cases of hypoglycemic unawareness and/or lability especially if the body mass index is <25kg/m^2, but with current immunosuppressive protocols patients must have normal renal function and preferably no plans for pregnancy (Matsumoto et al., 2007). The main limiting factor of beta-cell function replacement by transplantation is so far represented by the potentially severe side effects of the immunosuppressant therapy necessary to avoid graft rejection and recurrence of autoimmunity.

Advances in islet isolation methods and immunosuppressive regimens are leading to expanded clinical trials to develop islet transplantation as a therapeutic option for patients with type 1 diabetes (Sumino et al., 2003). However, the isolation process is still potentially harmful to the islets (Bottino et al., 2004) because it may expose them to damaging factors that induce a general proinflammatory state. Moreover, after transplantation, islets are subject to hypoxia and early nonspecific inflammatory events, mostly mediated by the recipient's immune cells that can compromise beta-cell viability and function. Locally secreted chemoattractants and proinflammatory molecules might recruit and activate immune cells to the transplant site, mediating irreparable damage to the islet graft. Islet survival in the early post transplantation period is influenced by inflammatory events in and around islets.

CD40, a member of tumor necrosis factor receptor family expressed mainly in nonhematopoietic cells, is generally associated with inflammation. CD40 contributes not only to physiological cell-mediated responses, but also to immune pathological conditions such as autoimmune and vascular diseases, leading to a chronic inflammatory state. It has been previously reported that the CD40 molecule is expressed also in human pancreatic beta-cells and that expression can be upregulated by incubation with a cocktail of proinflammatory cytokines (Klein et al., 2005). CD40 signals in beta-cells upregulate secretion of interleukin (IL)-6, IL-8, macrophage inflammatory protein (MIP)-1, and MIP-1β (Barbé-Tuana et al., 2006). These results in vitro indicate that the CD40 receptor expressed by beta-cells could be activated in vivo inducing proinflammatory responses contributing to early islet graft loss after transplantation. In this regard, the use of specific blockers immediately after the isolation process could improve islet viability and perhaps clinical success rates.

Reducing the islet proinflammatory state has been demonstrated to reduce the early post-transplant complications and perhaps improve islet engraftment (Bertuzzi et al., 2004). Moreover, increased percentage of insulin-independence at 1-year post-transplant and decreased percentage of cardiovascular events has been achieved with corticosteroids-sparing protocols in pancreas islet allotransplantation in patients with brittle diabetes. Lympho-depleting induction antibodies, such as rabbit anti-thymocyte globulin or alemtuzumab, calcineurin inhibitors and mycophenolate or sirolimus have been widely used in successful trials. However, since most of the studies were uncontrolled trials of low-risk patients and therefore the grade of evidence is limited, large-scale prospective studies with long-term follow up are necessary to assess risks and benefits of corticosteroids-sparing regimens in pancreas transplantation before recommending such strategies as standard practice.

It is often reported that islets from more than one donor are required to achieved insulin independence, even when an acceptable islet mass was transplanted in the first infusion. The success of recent clinical trials for allogeneic islet transplantation as well as the increasing centers that perform auto-transplantation is showing that the beta-cell replacement therapy for the treatment of patients with diabetes or total pancreatectomy has been firmly established. It needs only to be improved and made more widely available to the millions of desperate patients with brittle diabetes who search for alternatives to a life of insulin injections, hypoglycemia and the risks of end-organ damage. Important issues to be addressed before this treatment is widely applicable, including difficulty in maintaining insulin independence, low islet isolation success rate, multiple donor requirements, and side effects associated with the use of immunosuppressants. Steady progress has been achieved in recent years in different areas in the pancreatic islet transplantation process including islet cell processing, preservation, and immune therapies that justify optimism.

Combined islet and donor CD34+ hematopoietic stem cell infusion using an 'Edmonton-like' immunosuppression (daclizumab, sirolimus, tacrolimus), with a single dose of anti-TNF alpha antibody (Infliximab) adds to the induction without ablative conditioning, and may lead to stable chimerism and graft tolerance in patients with Brittle Type 1 Diabetes receiving a single-donor allogeneic islet transplant (Mineo et al, 2008). A prospective phase 1/2 trial investigated the safety and reproducibility of allogeneic islet transplantation and tested a strategy to achieve insulin-independence with lower islet mass in C-peptide negative Brittle Type 1 Diabetes patients with hypoglycemic unawareness. All patients received an equal mean total number of islets. Both the Edmonton immunosuppression regimen (daclizumab, sirolimus, tacrolimus) and the University of Illinois protocol (etanercept, exenatide and the Edmonton regimen) induced insulin-independence. However, combined treatment of etanercept and exenatide improved islet graft function and facilitates achievement of insulin-independence with fewer islets (Gangemi et al, 2008).

Optimal primary graft function has been associated with prolonged graft survival and better metabolic control (HbA1c, mean glucose, glucose variability assessed with continuous glucose monitoring system, and glucose tolerance defined by an oral glucose tolerance test) after islet transplantation (Vantyghem et al., 2009). This result was not significantly influenced by HLA mismatches or by preexisting islet autoantibodies. A pancreas transplant alone in a nonuremic patient with Brittle Diabetes is a rare procedure because the tradeoff for insulin independence is lifelong immunosuppression. However, a technically successful pancreas transplant alone is currently the only treatment option that allows nonuremic patients with Brittle Diabetes to become insulin-independent in the long term. Risk factors for subsequent kidney failure (13% at 5 years posttransplant) are serum creatinine levels >1.5 mg/dL at the time of the pancreas transplant and recipient age<30 years (Gruessner et al., 2008).

Donor shortage is another dilemma. To address the issue of donor shortage, living donor islet transplantation and bioartificial islet transplantation using pig islets are being evaluated. Bioartificial islet transplantation could be the ultimate solution of the donor shortage. Currently, overcoming immunological hurdles, establishing reliable islet isolation methods, and controlling porcine endogenous retrovirus are the primary obstacles to the implementation of this treatment. If bioartificial islet transplant becomes a clinical reality, it may even be applicable in the treatment of select patients with Type 2 diabetes. Beta-Cell regeneration from naïve pancreas and beta-cell generation from embryonic stem cells or induced pluripotent stem cells are poised as the next-generation treatments for Type 1 diabetes (Matsumoto, 2010).

Preemptive simultaneous kidney-pancreas transplantation in patients with Type 1 Brittle Diabetes, severe diabetic autonomic neuropathy and nephrotic syndrome due to diabetic nephropathy, with near-normal exhibited function of the native kidneys leads to rapid and nearly complete diminution of proteinuria although the residual function of the patient's native kidneys was reduced from 60% at about 40% at 3 months after transplantation and slightly lower at 12 months after simultaneous kidney-pancreas transplantation (Sedlak et al, 2007). Besides kidney microcirculation, islet transplantation alone has also a beneficial effect on the retinal microcirculation, since recently an early, significant increase of arterial and venous retinal blood flow velocities was found 1-year after islet transplantation (Venturini et al., 2006).

However, whether islet transplantation should be aimed at restoring insulin independence or providing adequate metabolic control and restoration of diabetic microvascular complications is still debated (Badet et al., 2007). Updated summary of results from Edmonton procedure and experience with combined results from different institutions reported to the Collaborative Islet Transplant Registry have largely substantiated the reproducibility of the Edmonton procedure (Ryan et al., 2001). Complete insulin-independence is achieved in the majority of patients 1-year after transplant (more then 55%) but this state is not sustained permanently. Although only a minority (10%) of patients remained insulin-free after 5 years, more then 80% of them had still detectable levels of C-peptide and substantially improved glycemic control without episodes of hypoglycemia. Even though currently, the islet graft is still not a remedy for every patient with Brittle Diabetes, islet transplantation has already obtained "nonresearch" status and is close to having a biological license status approved by the FDA in the United States that would further stimulate progress in the field (Witkowski et al., 2006; Alejandro et al., 2008).

8. Conclusions

There are many complexities involved in treating patients with brittle diabetes and helping them to achieve and maintain their euglycemia. Therefore, adopting a team approach that involves a broad range of disciplines is essential. Depending on circumstances and available resources, the multidisciplinary team should include the patient, diabetes specialist, primary care physician, nurse, dietitian, podiatrist and psychologist/psychiatrist, as well as family and friends. All members of the team should work together to ensure continuity of care. Communication and coordination within the team are also imperative to ensure that all members share and are working towards the same treatment targets and recommendations.

9. References

Alejandro, R, Barton, FB, Hering, BJ, Wease, S; Collaborative Islet Transplant Registry Investigators. (2008). Update from the Collaborative Islet Transplant Registry. *Transplantation*, Vol.86, No.12, (December 2008); 1783-1788.

Amiel, SA. (1996). Studies in hypoglycaemia in children with insulin-dependent diabetes mellitus. *Hormone research*, Vol.45, No.6, pp.285-290

Anagnostis, P, Athyros, VG, Tziomalos, K, Karagiannis, A, Mikhailidis, DP. (2009). Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. *The Journal of clinical endocrinology and metabolism*, Vol.94, No.8, (August 2009), pp.2692-2701

Aschner, P, Horton, E, Leiter, LA, Munro, N, Skyler, JS; Global Partnership for Effective Diabetes Management. (2010). Practical steps to improving the management of type 1 diabetes: recommendations from the Global Partnership for Effective Diabetes Management. *International journal of clinical practice*, Vol.64, No.3, (February 2010), pp.305-315

Badet, L, Benhamou, PY, Wojtusciszyn, A, Baertschiger, R, Milliat-Guittard, L, Kessler, L, Penfornis, A, Thivolet, C, Renard, E, Bosco, D, Morel, P, Morelon, E, Bayle, F, Colin, C, Berney, T; GRAGIL Group. (2007). Expectations and strategies regarding islet transplantation: metabolic data from the GRAGIL 2 trial. *Transplantation*, Vol.84, No.1, July 2007, pp.89-96

Balter, J, Mofsen, R, Pinninti, N. (2004). Quetiapine in the successful treatment of psychosis and comorbid brittle diabetes mellitus: a case report. *International journal of psychiatry in medicine*, Vol.34,No.3, pp.259-266

Barbé-Tuana, FM, Klein, D, Ichii, H, Berman, DM, Coffey, L, Kenyon, NS, Ricordi, C, Pastori, RL. (2006). CD40-CD40 ligand interaction activates proinflammatory pathways in pancreatic islets. *Diabetes,* Vol.55, No.9, (September 2006), pp.2437-2445

Beale, IL, Pearce, NE, Conroy, DM, Henning, MA, Murrell, KA. (1997). Psychological effects of chronic exposure to 50 Hz magnetic fields in humans living near extra-high-voltage transmission lines. *Bioelectromagnetics*, Vol.18, No.8, (December 1997), pp.584-594

Benhamou, PY, Milliat-Guittard, L, Wojtusciszyn, A, Kessler, L, Toso, C, Baertschiger, R, Debaty, I, Badet, L, Penfornis, A, Thivolet, C, Renard, E, Bayle, F, Morel, P, Morelon, E, Colin, C, Berney, T; GRAGIL group. (2009). Quality of life after islet transplantation: data from the GRAGIL 1 and 2 trials. *Diabetic Medicine*, Vol.26, No.6, (June 2009), pp.617-621

Benbow, SJ, Walsh, A, Gill, GV. (2001). Brittle diabetes in the elderly. *Journal of the Royal Society of Medicine,* Vol.94, No.11, (November 2001), pp.578-580

Bertuzzi, F, Verzaro, R, Provenzano, V, Ricordi, C. (2007). Brittle type 1 diabetes mellitus. *Current medicinal chemistry*, Vol.14, No. 16, pp.1739-1744, ISSN: 0929-8673

Bertuzzi, F, Marzorati, S, Maffi, P, Piemonti, L, Melzi, R, de Taddeo, F, Valtolina, V, D'Angelo, A, di Carlo, V, Bonifacio, E, Secchi, A. (2004). Tissue factor and CCL2/monocyte chemoattractant protein-1 released by human islets affect islet engraftment in type 1 diabetic recipients. *The Journal of clinical endocrinology and metabolism*, Vol.89, No. 11, (November 2004), pp.5724-5728

Bolli, GB. (1998). Counterregulatory mechanisms to insulin-induced hypoglycemia in humans: relevance to the problem of intensive treatment of IDDM. *Journal of pediatric endocrinology & metabolism*, Vol.11, Suppl.1, (March 1998), pp.103-115

Bottino, R, Balamurugan, AN, Tse, H, Thirunavukkarasu, C, Ge, X, Profozich, J, Milton, M, Ziegenfuss, A, Trucco, M, Piganelli, JD. (2004). Response of human islets to isolation stress and the effect of antioxidant treatment. *Diabetes*, Vol.53, No.10, (October 2004), pp.2559-2568

Borch-Johnsen, K, Helweg-Larsen, K. Sudden death and human insulin: is there a link? (1993). *Diabetic medicine,* Vol.10, pp. 255-259

Brosig B, Leweke F, Milch W, Eckhard M, Reimer C. (2001). Psychosocial predictors of metabolic instability in brittle diabetes--a multivariate time series analysis.

Psychotherapie, Psychosomatik,medizinische Psychologie, Vol.51, No.6, (June 2001), pp.232-238

Campbell-Tofte, JI, Mølgaard, P, Josefsen, K, Abdallah, Z, Hansen, SH, Cornett, C, Mu, H, Richter, EA, Petersen, W, Nørregaard, JC, Winther, K. (2010). Randomized and double-blinded pilot clinical study of the safety and anti-diabetic efficacy of the Rauvolfia-Citrus tea, as used in Nigerian Traditional Medicine. *Journal of ethnopharmacology*, October 2010

Cassidy, EM, O'Halloran, DJ, Barry, S. (1999). Insulin as a substance of misuse in a patient with insulin dependent diabetes mellitus. *BMJ*, Vol.319, No.7222, November 1999, pp1417-1418

Crow, SJ, Keel, PK, Kendall, D. (1998). Eating disorders and insulin-dependent diabetes mellitus. *Psychosomatics*, Vol.39, No.3, (May-June 1998), pp.233-243

Cryer, PE. (2008). The barrier of hypoglycemia in diabetes. *Diabetes*, Vol.57, No.12, (December 2008), pp.3169-3176

Cummins, E, Royle, P, Snaith, A, Greene, A, Robertson, L, McIntyre, L, Waugh, N. (2010). Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health technology assessment (Winchester, England)*, Vol.14, No.11, (February 2010), pp. iii-iv, xi-xvi, 1-181

Dagogo-Jack, S. (2004). Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. *Treatments in endocrinology*, Vol.3, No.2, pp.91-103

De Block, C, Vertommen, J, Manuel-y-Keenoy, B, Van Gaal, L. (2008). Minimally-invasive and non-invasive continuous glucose monitoring systems: indications, advantages, limitations and clinical aspects. *Current Diabetes Reviews,* Vol.4, No.3, (August 2008), pp.159-168

De Block, C, Manuel-y-Keenoy, B, Van Gaal, L. (2008) A review of current evidence with continuous glucose monitoring in patients with diabetes. *Journal of diabetes science and technology*. Vol.2, No.4, (July 2008), pp.718-727

Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England journal of medicine,* Vol 329, pp.977-986

Didjurgeit, U, Kruse, J, Schmitz, N, Stückenschneider, P, Sawicki, PT. (2002). A time-limited, problem - orientated psychotherapeutic intervention in Type 1 diabetic patients with complications: a randomized controlled trial. *Diabetic Medicine*, Vol.19, No.10, (October 2002), pp.814-821

Dixon, AN, Jude EB, Banerjee, AK, Bain, SC. (2006). Simultaneous pulmonary and cerebral oedema, and multiple CNS infarctions as complications of diabetic ketoacidosis: a case report. *Diabetic medicine* 2006, Vol.23, No.5, (May 2006), pp.571-573

Dobrilla, G. (1989). Management of chronic pancreatitis. Focus on enzyme replacement therapy. *International journal of pancreatology*, Vol.5, Supp.l, pp.17-29

Dutour, A, Boiteau, V, Dadoun, F, Feissel, A, Atlan, C, Oliver, C. (1996). Hormonal response to stress in brittle diabetes. *Psychoneuroendocrinology*, Vol. 21, No.6, (August 1996), pp.525-543

Eiber, R, Berlin, I, Grimaldi, A, Bisserbe, JC. (1997). Insulin-dependent diabetes and psychiatric pathology:general clinical and epidemiologic review. *Encéphale,* Vol.23, No.5, (September–October 1997), pp.351-357.

Elder, CJ, Natarajan, A. (2010). Mauriac syndrome--a modern reality. *Journal of pediatric endocrinology & metabolism*, Vol.23, No.3, (March 2010), pp.311-313

Elkeles, RS, Wright, AD, Lowy, C, Fraser, TR. (1969). Serum-insulin in acromegaly. *Lancet*, Vol.2, No.7621, (September 1969), pp.615-618

Eugster, EA, Francis, G; Lawson-Wilkins Drug and Therapeutics Committee. (2006). Position statement: Continuous subcutaneous insulin infusion in very young children with type 1 diabetes. *Pediatrics*, Vol.118 (No.4), (October 2006), pp. e1244-1249

Fanelli, CG, Epifano, L, Rambotti, AM, Pampanelli, S, Di Vincenzo, A, Modarelli, F, Lepore, M, Annibale, B, Ciofetta, M, Bottini, P, et al. (1993). Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes*, Vol.42, No.11, (November 1993), pp..1683-1689

Fanelli, C, Pampanelli, S, Epifano, L, Rambotti, AM, Di Vincenzo, A, Modarelli, F, Ciofetta, M, Lepore, M, Annibale, B, Torlone, E, et al. (1994). Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. *Diabetologia*, Vol.37, No.12, (December 1994), pp.1265-1276

Fischer, U, Jutzi, E, Bombor, H, Freyse, EJ, Salzieder, E, Albrecht, G, Besch, W, Bruns, W. (1980). Assessment of an algorithm for the artificial B-cell using the normal insulin-glucose relationship in diabetic dogs and men. *Diabetologia*; Vol.18, No.2, pp.97-107

Gangemi, A, Salehi, P, Hatipoglu, B, Martellotto, J, Barbaro, B, Kuechle, JB, Qi, M, Wang, Y, Pallan, P, Owens, C, Bui, J, West, D, Kaplan, B, Benedetti, E, Oberholzer, J. (2008). Islet transplantation for brittle type 1 diabetes: the UIC protocol. *American journal of transplantation*, Vol. 8, No.6, (June 2008), pp. 1250-1261

Gill, GV. (1992). The spectrum of brittle diabetes. *Journal of the Royal Society of Medicine*, Vol.85, pp.259 -261

Gill, GV, Lucas, S, Kent, LA. (1996). Prevalence and characteristics of brittle diabetes in Britain. *QJM: monthly journal of the Association of Physicians*, Vol.89, No.11, (November 1996), pp.839-843

Gill, G & Lucas, S. (1999). Brittle diabetes characterized by recurrent hypoglycemia. *Diabetes & metabolism*, Vol.25, No.4, (September 1999), pp.308-311

Gill, GV, Williams, G. (2000). Brittle Addison's disease: a new variation on a familiar theme. *Postgraduate medical journal*, Vol.76, No.893, (March 2000), pp.166-167

Grigoriadis, E, Fam, AG, Starok, M, Ang, LC. (2000). Skeletal muscle infarction in diabetes mellitus. The *Journal of rheumatology*, Vol.27, No.4, (April 2000), pp.1063-1068

Gruessner, RW, Sutherland, DE, Kandaswamy, R, Gruessner, AC. (2008). Over 500 solitary pancreas transplants in nonuremic patients with brittle diabetes mellitus. *Transplantation*, Vol.15, No.85, (January 2008), pp.42-47

Hammer, HF. (2010). Pancreatic exocrine insufficiency: diagnostic evaluation and replacement therapy with pancreatic enzymes. *Digestive diseases (Basel, Switzerland)* , Vol.28, No.2, pp.339-343

Hardy, KJ, Burge, MR, Boyle, PJ, Scarpello, JH. (1994). A treatable cause of recurrent severe hypoglycemia. *Diabetes Care*, Vol.17, No.7, (July 1994), pp.722-724

Havas, M. (2008). Dirty electricity elevates blood sugar among electrically sensitive diabetics and may explain brittle diabetes. *Electromagnetic biology and medicine*, Vol.27, No.2, (June 2008), pp.135-146

Hedman, CA, Lindstrom, T, Arnqvist, HJ. (2001). Direct comparison of insulin lispro and aspart shows small differences in plasma insulin profiles after subcutaneous injection in type 1 diabetes. *Diabetes Care*, Vol.24, pp.1120-1121

Hepburn, DA, Patrick, AW, Eadington, DW, Ewing, DJ, Frier, BM. (1990). Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. *Diabetic medicine,* Vol. 7, pp.711-717

Hershko, C, Skikne, B. (2009). Pathogenesis and management of iron deficiency anemia: emerging role of celiac disease, helicobacter pylori, and autoimmune gastritis. *Seminars in hematology*, Vol.46, No.4, (October 2009), pp.339-350

Hilsted J, Frandsen H, Christensen NJ, Nielsen SL. (1991). Plasma volume changes during hypoglycaemia: the effect of autonomic blockade. *European Journal of Clinical Investigation,* Vol. 21, No.1, (February 1991), pp. 22–26

Hlebowicz, J, Darwiche, G, Björgell, O, Almér, LO. (2007). Effect of apple cider vinegar on delayed gastric emptying in patients with type 1 diabetes mellitus: a pilot study. BMC gastroenterology MC Gastroenteroy, Vol.20, No.7, (December 2007), p.46.

Hlebowicz J, Lindstedt S, Björgell O, Höglund P, Almér LO, Darwiche G. (2008). The botanical integrity of wheat products influences the gastric distention and satiety in healthy subjects. *Nutrition journal*, Vol.27, No.7, (April 2008), p.12

Hoffman, I. (2003). Identity maintenance in the affectively distant patient. *Journal of the American Psychoanalytic Association*. Spring, Vol.51, No.2, pp.491-515

Iannello, S, Campanile, E, Cipolli, D, Gallina, M, Merola, A, Puglisi, S, Tabita, V, Belfiore, F. (1997). A rare case of juvenile diabetes mellitus associated with APECED (autoimmune poly-endocrinopathy, candidiasis and ectodermal dystrophy) with strong X-linked familial inheritance. *Minerva endocrinologica,* Vol.22, No.2, (June 1997), pp.51-59

Ishii, C, lnoue, K, Negishi, K, Tane, N, Awata, T, Katayama, S. (2001). Diabetic ketoacidosis in a case of pheochromocytoma. *Diabetes research and clinical practice*, Vol.54, No.2, (November 2001), pp.137- 142

Jabbour, SA. (2003). Cutaneous manifestations of endocrine disorders: a guide for dermatologists. *American journal of clinical dermatology*, Vol.4, No.5, pp.315-331

Jacobson, R, Horenstein, M, Kassel, L. (1970). Hyperglycemia and hyperosmolarity in a brittle diabetic with thyrotoxicosis. *Diabetes, Vol. 19, No.1,* (January 1970), pp.70-71

Jacqueminet, S, Masseboeuf, N, Rolland, M, Grimaldi, A, Sachon, C. (2005). Limitations of the so-called "intensified" insulin therapy in type 1 diabetes mellitus. *Diabetes Metabolism*, Vol.31, No.4 (September 2005), pp.4S45-4S50

Janssen, MM, Snoek, FJ, Heine, RJ. (2000). Assessing impaired hypoglycemia awareness in type 1 diabetes: agreement of self- report but not of field study data with the autonomic symptom threshold during experimental hypoglycemia. *Diabetes Care*, April 2000, Vol.23, No.4, pp.529-532

Jethwa, P, Sodergren, M, Lala, A, Webber, J, Buckels, JA, Bramhall, SR, Mirza, DF. (2006). Diabetic control after total pancreatectomy. *Digestive and liver disease*, Vol.38, No.6, June 2006, pp.415-419

Jiménez, Y, Bagán, JV, Murillo, J, Poveda, R. (2004). Odontogenic infections. Complications. Systemic manifestations. *Medicina oral, patología oral y cirugía bucal*, Vol.9, Suppl:143-7, pp.139-143

Jolobe, OM & Khin, N. (2002). Brittle diabetes in the elderly. *Journal of the Royal Society of Medicine*, Vol.95, No.1, January 2002, p.58

Jonas MM, Bell MD, Eidson MS, Koutouby R, Hensley GT. (1991). Congenital diabetes mellitus and fatal secretory diarrhea in two infants *Journal of pediatric gastroenterology and nutrition*, Vol.13, No.4, (November 1991), pp.415-425

Jørgensen, HS. (2007). Studies on the neuroendocrine role of serotonin. *Danish medical bulletin*, Vol.54, No.4, (November 2007), pp.266-288

Kane, JM, Correll, CU, Goff, DC, Kirkpatrick, B, Marder, SR, Vester-Blokland, E, Sun, W, Carson, WH, Pikalov, A, Assunção-Talbott, S. (2009). A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. *The Journal of clinical psychiatry*, Vol.70, No.10, (October 2009), pp.1348-1357

Kawanishi, K & Miyashita, H. (2003). A case of brittle diabetes in a 94-year-old man with vascular dementia, visual disturbance and hearing difficulty. *Nippon Ronen Igakkai zasshi. Japanese journal of geriatrics*, Vol.40, No.2, (March 2003), pp.156-159

Kent, L, Gill, GV, Williams, G. (1994). Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis. *Lancet*, Vol.344, No. 8925, (September 1994), pp.778-781

Kesavadev, J, Das, AK, Unnikrishnan, R 1st, Joshi, SR, Ramachandran, A, Shamsudeen, J, Krishnan, G, Jothydev, S, Mohan, V. (2010). Use of insulin pumps in India: suggested guidelines based on experience and cultural differences. *Diabetes technology & therapeutics*, Vol. 12, No.10, (October 2010), pp.823-831

Kim, HS, Park, JW, Yeo, SI, Choi, BJ, Suh, JY. (2006). Effects of high glucose on cellular activity of periodontal ligament cells in vitro. *Diabetes research and clinical practice*, Vol.74, No.1, (October 2006), pp.41-47

Klein, D, Barbé-Tuana, F, Pugliese, A, Ichii, H, Garza, D, Gonzalez, M, Molano, RD, Ricordi, C, Pastori, RL. (2005). A functional CD40 receptor is expressed in pancreatic beta cells. *Diabetologia*, Vol.48, No.2, (February 2005), pp.268-276

Laffel, LM, Wentzell, K, Loughlin, C, Tovar, A, Moltz, K, Brink, S. (2006). Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. *Diabetic medicine*, Vol.23, No.3, (March 2006), pp.278-284

Lager, I, Attvall, S, Blohmé, G, Smith, U. (1986). Altered recognition of hypoglycaemic symptoms in type I diabetes during intensified control with continuous subcutaneous insulin infusion. *Diabetic Medicine*, Vol. 3, No.4, (July-August 1986), pp.322-325

Lankisch, TO, Jaeckel, E, Strassburg, CP. (2009). The autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy or autoimmune polyglandular syndrome type 1. Seminars in liver disease, Vol.29, No.3, (August 2009), pp.307-314

Layer, P, Keller, J. (1999). Pancreatic enzymes: secretion and luminal nutrient digestion in health and disease. *Journal of clinical gastroenterology*, Vol.28, No.1, January 1999, pp.3-10

Lazow, SK. (2005). Orofacial infections in the 21st century. *The New York state dental journal*, Vol.71, No.6, (November 2005), pp.36-41

Lehmann, R, Honegger, RA, Feinle, C, Fried, M, Spinas, GA, Schwizer, W. (2003). Glucose control is not improved by accelerating gastric emptying in patients with type 1 diabetes mellitus and gastroparesis. A pilot study with cisapride as a model drug. *Experimental and clinical endocrinology & diabetes*, Vol.111, No.5, (August 2003), pp.255-261

Li, L, Dai, Y, Xia, R, Chen, S, Qiao, D. (2005). Pulsed electric field exposure of insulin induces anti - proliferative effects on human hepatocytes. *Bioelectromagnetics*, Vol.26, No.8, (December 2005), pp.639-647

Lloyd, GG, Steel, JM, Young, RJ. (1987). Eating disorders and psychiatric morbidity in patients with diabetes mellitus. *Psychotherapy and psychosomatics*, Vol.48, No.1-4, pp.189-195

Ludviksson, BR, Griffin, J, Graziano, FM. (1993). Munchausen's syndrome: the importance of a comprehensive medical history. Wisconsin medical journal, Vol.92, Bo.3, (March 1993), pp.128-129

Lutfey, KE, Wishner, WJ. (1999). Beyond "compliance" is "adherence". Improving the prospect of diabetes care. *Diabetes Care*, Vol.22, No.4, (April 1999), pp. 4635-4639

Ly, TT, Gallego, PH, Davis, EA, Jones, TW. (2009). Impaired awareness of hypoglycemia in a population-based sample of children and adolescents with type 1 diabetes. *Diabetes Care*, Vol.32, No.10, (October 2009), pp.1802-1806

Madhan, KK, Symmans, P, Te Strake, L, van Der Merwe, W. (2000). Diabetic muscle infarction in patients on dialysis. *American journal of kidney diseases*, Vol.35, No.6, (June 2000), pp.1212-1216

Mathew, A, Reddy, IS, Archibald, C. (2007). Diabetic muscle infarction. *Emergency medicine journal*, Vol.24, No.7, July 2007, pp.513-514

Matsumoto, S, Okitsu, T, Iwanaga, Y, Noguchi, H, Nagata, H, Yonekawa, Y, Yamada, Y, Nakai, Y, Ueda, M, Ishii, A, Yabunaka, E, Shapiro, JA, Tanaka, K (2005). Insulin independence of unstable diabetic patient after single living donor islet transplantation. *Transplantation proceedings*, Vol.37, No.8, (October 2005), pp.3427-3429

Matsumoto, S, Noguchi, H, Naziruddin, B, Onaca, N, Jackson, A, Nobuyo, H, Teru, O, Naoya, K, Klintmalm, G, Levy, M. (2007). Improvement of pancreatic islet cell isolation for transplantation. *Proceedings (Baylor University. Medical Center)*, Vol.20, No.4, (October 2007), pp.357-362

Matsumoto S. (2010). Islet cell transplantation for Type 1 diabetes. *Journal of diabetes*, Vol.2, No.1, (March 2010), pp.16-22

Matsuyoshi, A, Shimoda, S, Tsuruzoe, K, Taketa, K, Chirioka, T, Sakamoto, F, Sakakida, M, Miyamura, N, Araki, E. (2006). A case of slowly progressive type 1 diabetes with unstable glycemic control caused by unusual insulin antibody and successfully treated with steroid therapy. *Diabetes research and clinical practice* , Vol. 72, No.3, June 2006, pp.238-243

McIntyre, HD. (2006). DAFNE (Dose Adjustment for Normal Eating): structured education in insulin replacement therapy for type 1 diabetes. *The Medical journal of Australia*, Vol.184, No.7, (April 2006), pp.317-318

Meier, JJ, Menge, BA, Breuer, TG, Müller, CA, Tannapfel, A, Uhl, W, Schmidt, WE, Schrader, H. Functional assessment of pancreatic beta-cell area in humans. *Diabetes*, Vol.58, No.7, (July 2009), pp.1595-1603

Menge, BA, Schrader, H, Breuer, TG, Dabrowski, Y, Uhl, W, Schmidt, WE, Meier, JJ. (2009). Metabolic consequences of a 50% partial pancreatectomy in humans. *Diabetologia*, Vol. 52, No.2, February 2009, pp.306-317

Milch, W, Leweke, F, Brosig, B, Reimer, C. (2002). Separation during inpatient psychotherapy and its impact on the regulation of blood glucose in a patient with Brittle Diabetes. *Zeitschrift für Psychosomatische Medizin und Psychotherapie*, Vol.48, No.3, pp.286-298

Mineo, D, Sageshima, J, Burke, GW, Ricordi, C. (2009). Minimization and withdrawal of steroids in pancreas and islet transplantation. *Transplant international,* Vol.22, No.1, (January 2009), pp.20-37

Mineo, D, Ricordi, C, Xu, X, Pileggi A, Garcia-Morales, R, Khan, A, Baidal, DA, Han, D, Monroy, K, Miller, J, Pugliese, A, Froud, T, Inverardi, L, Kenyon, NS, Alejandro, R. (2008). Combined islet and hematopoietic stem cell allotransplantation: a clinical pilot trial to induce chimerism and graft tolerance. *American journal of transplantation*, Vol. 8, No.6, (June 2008), pp.1262-1274

Mitchell, SJ, Hilliard, ME, Mednick, L, Henderson, C, Cogen, FR, Streisand, R. (2009). Stress among fathers of young children with type 1 diabetes. *Families, systems & health* , Vol.27, No.4, (December 2009), pp.314-324

Mody, RJ, Brown, PI, Wechsler, DS. (2003). Refractory iron deficiency anemia as the primary clinical manifestation of celiac disease. *The American journal of pediatric hematology/oncology*, Vol.25, No. 2, (February 2003), pp.169-172

Mohan V, Poongothai S, Pitchumoni CS. (1998). Oral pancreatic enzyme therapy in the control of diabetes mellitus in tropical calculous pancreatitis. *International journal of pancreatology*, Vol.24, No.1, (August 1998), pp.19-22

Morris, AD, Boyle, DI, McMahon, AD, Greene, SA, MacDonald, TM, Newton, RW. (1997). Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. *Lancet,* Vol.350, No.9090, (November 1997), pp. 1505-1510

National Toxicology Program. (2010). Final Report on Carcinogens Background Document for Formaldehyde. *Report on carcinogens background document*, Vol.10, No.5981, (January 2010), p.i-512

Narendran, P, Creely, SJ, Syed, A, Tesfaye, S, Winer, J, Singh, BM. (2010). Aggressive and devastating neuropathy: the consequence of untreated slow-onset type 1 diabetes. *QJM*. July

O'Hare, JA, Ferriss, JB, Twomey, B, O'Sullivan, DJ. (1983). Poor metabolic control, hypertension and microangiopathy independently increase the transcapillary escape rate of albumin in diabetes, *Diabetologia*, Vol.25, No.3, (September 1983), pp. 260–263.

Otokozawa, S, Ai, M, Diffenderfer, MR, Asztalos, BF, Tanaka, A, Lamon-Fava, S, Schaefer, EJ. (2009). Fasting and postprandial apolipoprotein B-48 levels in healthy, obese, and hyperlipidemic subjects. *Metabolism*, Vol.58, No.11, (November 2009), pp. 1536-1542

Papanas, N, Maltezos, E. (2008). Education for dietary freedom in type 1 diabetes? Yes, it's possible. The *Diabetes educator*, Vol.34, No.1, (January-February 2008), pp.54-58

Papanas, N, Maltezos, E. (2009). The diabetic foot: a global threat and a huge challenge for Greece. *Hippokratia*, Vol.13, No.4, (October 2009), pp.199-204

Park, JY, Chong, AY, Cochran, EK, Kleiner, DE, Haller, MJ, Schatz, DA, Gorden, P. (2008). Type 1 diabetes associated with acquired generalized lipodystrophy and insulin resistance: the effect of long-term leptin therapy. *The Journal of clinical endocrinology and metabolism*, Vol.93, No.1, January 2008, pp. 26-31

Pasricha, PJ, Pehlivanov, ND, Gomez, G, Vittal, H, Lurken, MS, Farrugia, G. (2008). Changes in the gastric enteric nervous system and muscle: a case report on two patients with diabetic gastroparesis. *BMC gastroenterology*, Vol.30, No.8, (May 2008), p.21

Peake, JE, McCrossin, RB, Byrne, G, Shepherd, R. (1996). X-linked immune dysregulation, neonatal insulin dependent diabetes, and intractable diarrhoea. *Archives of disease in childhood. Fetal and neonatal edition*, Vol. 74, No.3, (May 1996), F195-199

Petrovski, G, Dimitrovski, C, Milenkovic, T. (2007) Insulin pump therapy with continuous glucose monitoring improves metabolic control in brittle type 1 diabetes. *Prilozi*, Vol.28, No.1, (July 2007), pp.129-135

Pickup, J, Williams, G, Johns, P, Keen, H. (1983). Clinical features of brittle diabetic patients unresponsive to optimised subcutaneous insulin therapy (continuous subcutaneous insulin infusion). *Diabetes Care,* 1983, Vol.6, pp. 279-284

Pickup, J, Keen, H. (2002). Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care*, Vol.25, No.3, pp.593-598

Plank, J, Wutte, A, Brunner, G, Siebenhofer, A, Semlitsch, B, Sommer, R, Hirschberger, S, Pieber, TR. (2002). A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care*, Vol.23, No.11, (November 2002), pp.2053-2057

Potter, J, Clarke, P, Gale, EAM, Dave, SH, Tattersall, RS. (1982). Insulin-induced hypoglycaemia in an accident and emergency department: the tip of an iceberg. *BMJ,* Vol. *285,* pp.1180-1182

Ramaswamy, K, Masand, PS, Nasrallah, HA. (2006). Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. *Annals of clinical psychiatry*, Vol. 18, No.3, (July-September 2006), pp.183-194

Rice DM. Diabetes education... lost in translation? (2006). *Diabetes Educator*, Vol. 32, No.6, (November-December 2006), pp.823-824

Roberts, J, Searle, J. (1995). Neonatal diabetes mellitus associated with severe diarrhea, hyperimmunoglobulin E syndrome, and absence of islets of Langerhans. *Pediatric pathology & laboratory medicine*, Vol.15, No.3, (May-June 1995), pp.477-483

Rosenbloom AL, Giordano BP. (1977). Chronic overtreatment with insulin in children and adolescents. , *American journal of diseases of children* (1960), Vol.131, No.8 (August 1977), pp.881-885

Ryan, EA, Lakey, JR, Rajotte, RV, Korbutt, GS, Kin, T, Imes, S, Rabinovitch, A, Elliott, JF, Bigam, D, Kneteman, NM, Warnock, GL, Larsen, I, Shapiro, AM. (2001). Clinical outcomes and insulin secretion after islet transplantation with the Edmonton protocol. *Diabetes*, Vol.50, No.4, (April 2001), pp.710-9.

Ryder, RE, Owens, DR, Hayes, TM, Ghatei, MA, Bloom, SR. (1990). Unawareness of hypoglycaemia and inadequate hypoglycaemic counterregulation: no causal relation with diabetic autonomic neuropathy. *BMJ*, Vol.301, No.6755, October 1990, pp.783-787

Sabek, OM, Hamilton, DJ, Gaber, AO. (2009). Prospects for future advancements in islet cell transplantation. *Minerva chirurgica*; Vol.64, No.1, (February 2009), pp.59-73

Scantamburlo, G, Ansseau, M, Legros, JJ. (2001). Role of the neurohypophysis in psychological stress. *Encéphale*, Vol.27, No.3, (May-June 2001), pp.245-259

Schade, DS, Eaton, RP, Spencer, W. (1980). Normalization of plasma insulin profiles in diabetic subjects with programmed insulin delivery. *Diabetes Care*, (January-February 1980), Vol.3, No.1, pp.9-14

Schade DS, Eaton RP, Drumm DA, Duckworth WC. (1985). A clinical algorithm to determine the etiology of brittle diabetes. *Diabetes Care*, Vol.8, No.1, (January-February 1985), pp.5-11

Schrader, H, Menge, BA, Zeidler, C, Ritter, PR, Tannapfel, A, Uhl, W, Schmidt, WE, Meier, JJ. (2010). Determinants of glucose control in patients with chronic pancreatitis. *Diabetologia*, Vol.53, No.6, (June 2010), pp.1062-1069

Serlin, DC, Lash, RW. (2009). Diagnosis and management of gestational diabetes mellitus. *American family physician*, Vol. 80, No.1, (July 2009), pp.57-62

Smith, CB, Choudhary, P, Pernet, A, Hopkins, D, Amiel, SA. (2009). Hypoglycemia unawareness is associated with reduced adherence to therapeutic decisions in patients with type 1 diabetes: evidence from a clinical audit. *Diabetes Care*, Vol.32, No.7, (July 2009), pp. 1196-1198

Smith, CM, Clarke, CF, Porteous, LE, Elsori, H, Cameron, DJ. (2000). Prevalence of coeliac disease and longitudinal follow-up of antigliadin antibody status in children and adolescents with type 1 diabetes mellitus. *Pediatric diabetes*, Vol.1, No.4, December 2000, pp.199-203

Somogyi, M. (1959). Exacerbation of diabetes by excess insulin action. *The American journal of medicine*, Vol.26, No.2, (February 1959), pp.169-191

Stancin, T, Link, DL, Reuter, JM. (1989). Binge eating and purging in young women with IDDM. *Diabetes Care*, Vol12, No.9, (October 1989), pp.601-603

Su, JW, Lambert, JE, Clandinin, MT, Proctor, SD. (2009). Impaired postprandial metabolism of apolipoprotein B48-containing remnant particles in normolipidemic subjects with brittle type 1 diabetes. *Diabetes Care*, Vol.32, No.2, (February 2009), pp.e21

Sumino, H, Ichikawa, S, Kumakura, H, Takayama, Y, Kurabayashi, M. (2003). Genetic influence of hormone-replacement therapy on venous thromboembolism. *Lancet*, Vol.362, No.9391, (October 2003), p.1242.

Tallandini, MA. (1999). The dread of integration. Integrative processes in a chronically ill borderline patient. *The Psychoanalytic study of the child*, Vol.54, pp.289-315

Tattersall, RB, Gill, GV. (1991). Unexplained deaths of Type 1 diabetic patients. *Diabetic medicine,* Vol.*8,* pp.49-58

Tattersall, RB, Gregory, R, Selby, C, Kerr, D, Heller, S. (1991) Course of brittle diabetes: 12 year follow up. *BMJ*; Vol.302, No. 6787, (May 1991), pp.1240-1243

Tattersall, RB. (1997). Brittle Diabetes. *Clinics in endocrinology and metabolism*, Vol.6, No.2, (July 1997), pp.403-419

Tattersall, RB. (1997). Brittle diabetes revisited: the Third Arnold Bloom Memorial Lecture. *Diabetic Medicine*, Vol.14, No.2, (February 1997), pp.99-110

Tentolouris, N, Jude, EB, Smirnof, I, Knowles, EA, Boulton, AJ. (1999) Methicillin-resistant Staphylococcus aureus: an increasing problem in a diabetic foot clinic. *Diabetic Medicine*, Vol.16, No.9, September 1999, pp.767-771

Tentolouris, N, Voulgari, C, Liatis, S, Kokkinos, A, Eleftheriadou, I, Makrilakis, K, Marinou, K, Katsilambros N. (2010). Moisture status of the skin of the feet assessed by the visual test neuropad correlates with foot ulceration in diabetes. *Diabetes Care*, Vol.33, No.5, May 2010, pp.1112-1114

Tone, A, Shikata, K, Nakagawa, K, Hashimoto, M, Makino, H. (2008). A case of hypoglycemic brittle diabetes with peripheral edema successfully managed by conversion from insulin lispro to insulin aspart. *Diabetes research and clinical practice,* Vol.81, No.3, (September 2008), e15-e16

Trujillo-Santos, AJ. (2003). Diabetic muscle infarction: an underdiagnosed complication of long-standing diabetes. *Diabetes Care*, Vol.26, No.1, (January 2003), pp.211-215

Vaisrub, S. (1980). Pump and brittle circumstance. *JAMA*, Vol.13, No.243 (22), (June 1980), pp.2331-2332

Valdivielso, P, Puerta, S, Rioja, J, Alonso, I, Ariza, MJ, Sánchez-Chaparro, MA, Palacios, R, González-Santos, P. (2010). Postprandial apolipoprotein B48 is associated with asymptomatic peripheral arterial disease: a study in patients with type 2 diabetes and controls. *Clinica chimica Acta*, Vol.411, No.5-6, (March 2010), pp.433-437

Vantyghem, MC, Press, M. (2006). Management strategies for brittle diabetes. *Annales d'endocrinologie (Paris)*. Vol.67, No.4, (September 2006), pp.287-296

Vantyghem, MC, Kerr-Conte, J, Arnalsteen, L, Sergent, G, Defrance, F, Gmyr, V, Declerck, N, Raverdy, V, Vandewalle, B, Pigny, P, Noel, C, Pattou, F. (2009). Primary graft function, metabolic control, and graft survival after islet transplantation. *Diabetes Care*, Vol.32, No.8, (August 2009), pp.1473-1478

Vantyghem, MC, Marcelli-Tourvieille, S, Fermon, C, Duhamel, A, Raverdy, V, Arnalsteen, L, Kerr-Conte, J, Noel, C, Fontaine, P, Pattou, F. (2009). Intraperitoneal insulin infusion versus islet transplantation: comparative study in patients with type 1 diabetes. *Transplantation*, Vol.87, No.1 (January 2009), pp.66-71.

Venturini, M, Fiorina, P, Maffi, P, Losio, C, Vergani, A, Secchi, A, Del Maschio, A. (2006). Early increase of retinal arterial and venous blood flow velocities at color Doppler imaging in brittle type 1 diabetes after islet transplant alone. *Transplantation*, Vol.81, No.9, (May 2006), pp.1274-1277.

Viner, RM, Christie, D, Taylor, V, Hey, S. (2003). Motivational/solution-focused intervention improves HbA1c in adolescents with Type 1 diabetes: a pilot study. *Diabetic Medicine*, Vol.20, No.9, (September 2003), pp.739-742

Vinik, AI, Maser, RE, Mitchell, BD, Freeman, R. (2003). Diabetic autonomic neuropathy. *Diabetes Care*. Vol. 26, No.5, (May 2003), pp.1553-1579

Virally, M, Laloi-Michelin, M, Médeau, V, Meas, T, Kévorkian, JP, Mouly, S, Guillausseau, PJ. (2007). Muscle infarction in a young woman with brittle type 1 diabetes. *Diabetes & Metabolism*, Vol.33, No.6, (December 2007), pp.466-468

Vogel, A, Strassburg, CP, Obermayer-Straub, P, Brabant, G, Manns, MP. (2002). The genetic background of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and its autoimmune disease components. *Journal of molecular medicine*, Vol.80, No.4, (April 2002), pp.201-211

Voulgari, C, Tentolouris, N. (2010). The performance of a glucose-ketone meter in the diagnosis of diabetic ketoacidosis in patients with type 2 diabetes in the emergency room. *Diabetes technology & therapeutics*, Vol.12, No.7, July 2010, pp.529-535

Voulgari, C, Psallas, M, Kokkinos, A, Argiana, V, Katsilambros, N, Tentolouris, N. (2010). The association between cardiac autonomic neuropathy with metabolic and other factors in subjects with type 1 and type 2 diabetes. *Journal of diabetes and its complications* (August 2010)

Weinzimer, SA, Tamborlane, WV, Chase, HP, Garg, SK. (2004). Continuous glucose monitoring in type 1 diabetes. *Current diabetes reports*, Vol.4, No.2, (April 2004), pp.95-100

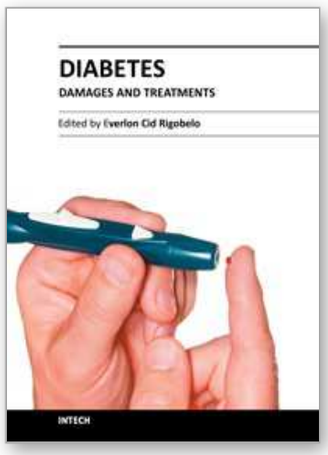
Widom B, Simonson DC. (1992). Intermittent hypoglycemia impairs glucose counterregulation. *Diabetes*, Vol.41, No.12, (December 1992), pp.1597-1602

Witkowski, P, Zakai, SB, Rana, A, Sledzinski, Z, Hardy, MA. (2006). Pancreatic islet transplantation, what has been achieved since Edmonton break-through. *Annals of transplantation,* Vol.11, No.2, pp.5-13, discussion 32-43

Woodyatt, RT (1942). The American Diabetes Association. *Science*, Vol.7, No.96 (2484), (August 1942), pp.138

Woolley, SL, Smith, DR. (2006). Acute compartment syndrome secondary to diabetic muscle infarction: case report and literature review. *European journal of emergency medicine*, Vol. 13, No.2, (April 2006), pp.113-116

Wroe, J. (2004). The second international DAWN summit: a call to action to improve psychosocial care for people with diabetes. *Practical Diabetes International*, Vol.21, pp.201 -208



Diabetes - Damages and Treatments

Edited by Prof. Everlon Rigobelo

ISBN 978-953-307-652-2
Hard cover, 348 pages
Publisher InTech
Published online 09, November, 2011
Published in print edition November, 2011

Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Christina Voulgari and Nicholas Tentolouris (2011). Brittle Diabetes: A Contemporary Review of the Myth and Its Realization, Diabetes - Damages and Treatments, Prof. Everlon Rigobelo (Ed.), ISBN: 978-953-307-652-2, InTech, Available from: http://www.intechopen.com/books/diabetes-damages-and-treatments/brittle-diabetes-a-contemporary-review-of-the-myth-and-its-realization

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen