**Brittle Diabetes Foundation Inc.**

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 Professional Practice Committee (PPC)

 Title:

The Case for the Reclassification of

Brittle Type 1 Diabetes (BT1D) as a Rare Disease

and as a Separate and Distinct form of Type 1.

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**The Case for the Reclassification of Brittle Type 1 Diabetes as a Rare Disease and as a Separate and Distinct Form of Type 1.**

**INTRODUCTION**

 The Brittle Diabetes Foundation (BDF), being the only organization recognized by the NIH as supporting the rare disease, Brittle Type 1 Diabetes (BT1D), respectfully requests the American Diabetes Association’s (ADA) Professional Practice Committee (PPC) reclassify “Brittle Diabetes” as a rare disease not only in its own right but as a separate and distinct form of Type 1 Diabetes (T1D).

 BDF believes the ADA’s position should be in concert with that of the National Institutes of Health (NIH) who on July 3, 2013 recognized BT1D as a rare disease separate and distinct from T1D. The NIH’s conclusion followed their five month review of the relevant medical literature after BDF’s formal request that they research and pursue this matter. Discussions with JDRF’s executive staff following the NIH’s new position resulted in their having found no inconsistencies with this new classification after a thorough review of both the NIH (<https://rarediseases.info.nih.gov/gard/11900/brittle-diabetes/resources/1>) and BDF ([www.bdtype1.com](http://www.bdtype1.com)) sites. An article attesting to this case is scheduled to be published on JDRF’s site before the close of the month.

 Since its inception in 2012, BDF has encountered many obstacles to accomplishing its goal of having BT1D recognized, classified and ultimately treated as a distinct condition outside of T1D, some preexisting and some placed in its path. In both our experiences and our research we have determined that there is a repetitive, if not superfluous nature inherent to the majority of opposing positions against our cause. That having been stated, BDF has summarized the majority of these opposing positions in the form of 10 essential questions. We endeavor to not only answer these questions but to ultimately break from their confines and classify Brittle Diabetes (BT1D) as a real entity, not a subset nor a myth.

1. **Why should the term brittle and/or brittleness be employed?**

 According to the Merck manual Brittle is a term that has no biological basis (1). Let us apply this mindset to other forms of diabetes.

 When the author of this reclassification proposal was growing up, the biological basis for the number 1 and number 2 was urination and defecation in that order. In 1995, the descriptive terms to distinguish between insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) gave way to a simplification of classification into Type 1 and Type 2 Diabetes. BDF researchers have been unable to find any biological significance for the numbers 1 and 2. This also holds true for Types 1.5 (LADA) and Type 3.

 Some authors have suggested that a person with brittle diabetes reacts negatively to slight “breaks” in their routine accounting for the use of the term brittle.(2)

 Brittle Diabetes, labile diabetes, uncontrolled, poorly controlled and unstable diabetes are common phrases used to describe this condition within the literature. (3,4,5,6)

 But, do they really convey the same message? If the clinical scientific researcher is seeking those with a brittle condition, he or she does so because brittle is perceived to be the severest form of T1D. If, as the literature implies, Brittleness is the severest form, then what are the quantitative values or cut points that distinguishes stable from those considered unstable and/or brittle?

 It simplifies matters, at least for the layman, if the PPC, and medical profession it supports, could focus on the use of one term or quantify the use of each of two terms, unstable vs brittle with the understanding that the term “brittle” has been employed for the last 85 years and deserves recognition by the ADA as the severest form of type 1 diabetes.

 There are those who suggest that brittle is an antiquated or old fashioned term and like the ADA, believe the term “should not be employed”. Let’s examine this more closely.

 The term Brittle Diabetes was introduced by Woodyatt in 1934 (7) but more importantly it remains in common use today. The Worldcast.org site and that of the University of Florida (UFL) Smathers Library, the academic home of ADA’s President Desmond Schatz M.D., lists 1,173 scientific papers, books and articles employing the term Brittle Diabetes in their title and/or within the body of their text. Of that 672 are peer reviewed with UFL maintaining 485 on file. Included in this list are 139 references cited in the last five years alone.

 The Diabecon 2010 lecture series held in I*ndia* (the Diabetic Capital of the World)(8) featured a major discussion on Brittle Diabetes as being real and not a myth with recommended modes of diagnosis and the treatment of causes which accounted for the patient’s brittleness or glycemic variability.(9)

 Even today surgeons performing a pancreatectomy will remind their patients that a resulting complication will be “brittle diabetes”. (10,11,12,13) Physicians unable to stabilize their patient’s blood glucose in a hospital controlled environment will proceed to diagnose their patient as having brittle type 1 diabetes. Many current clinical trials include a request for patients diagnosed with Brittle Diabetes, as they are considered, for research purposes, to be the severest form of T1D.(14,15,16) Many of the newest technologies being advanced are to help cure “brittleness” - a rapid rise and fall in BG levels within a short period of time. The symptoms of brittleness, that triggers an individual’s survival skills, result in severe disruption of the daily life activities of those afflicted by this rare disease.(17,18)

 On line articles by practicing clinical physicians, David K. McCullock, M.D.,Thomas Higgins M.D., Ali Saima M.D., Jeff Unger, M.D., attests to current use practices by those presently working in the field. (3,19,20,21)

 As BDF will discuss in more detail, there is a body of patients for whom the medical rules or guidelines do not appear to apply. They (the patients) can do everything right and still remain “brittle”. (2,3,22,23)

 The ADA, by application, suggests that the use of the term unstable or uncontrolled type 1 diabetes is apparently preferred. (24,25) BDF’s concern, as noted in the following, is generated by our direct contact with those diagnosed with Brittle Diabetes. Many of them seek assistance when their physician, labels them as non compliant; has exhausted his or her knowledge of what to do next; or applies insulin mono-therapy as the only form of treatment. Many look for a referral to a physician or medical center with practical knowledge of their condition. It is BDF’s contention that the application of the terms “uncontrolled” or “unstable” within the context of Type 1 Diabetes is not enough to distinguish BT1D’s from the 1.5 million Type 1’s being seen by today’s clinical practitioners and their supportive health care team.

 Brittle patients have lost and continue to lose their identity within a medical practice that spends its limited patient time solely on disease management generally limited to insulin mono-therapy. This mode of treatment has repeatedly failed to provide this suffering minority with the much needed diagnostic acumen and treatment demanded by this separate and distinct form of Type 1 ie., Brittle Type 1 Diabetes (BT1D). “Brittle” and “brittleness” are terms that should be employed in the context of those diagnosed with severe glycemic variability, whatever the cause.

 As indicated by this terminology analysis, there appears to be, with good reason, very few listening to ADA’s recommendation of non-use.

1. **How do today’s medical experts define Brittle Diabetes?**

 The most common definition by experts in the field of diabetes care define Brittle Diabetes as a severe instability of blood glucose (BG) levels, whatever its cause, with frequent and unpredictable episodes of hypoglycemia and or hyperglycemic ketoacidosis (DKA) that disrupt quality of life.(2,3,21,26) These extremes in glycemic variability cannot be attributed to failure in management by either physician or patient and show greater and more unpredictable variation than in stable patients with T1D. (23) Those exhibiting this medical condition defy all attempts at orthodox glycemic control and have an absolute insulin dependency.(21,23) Thus they are virtually always symptomatic of type I diabetes (T1D).

 Should the PPC decide that BT1D be recognized as BDF hopes, we humbly request that the PPC consider including within the definition vernacular language alluding to or identifying the disabling nature or “disabling complication” of Brittleness. We make this request in part, due to the Social Security Administration having eliminated Diabetes as a disabling disease in 2011. It is the BDF’s position that a key defining feature of this disease is that it is “disruptive on a daily basis” preventing individuals from holding full time employment.

 The SSD having eliminated the classification of Diabetes as a “disabling disease” then instituted a complications only policy. They established a primary complication code for nephropathy, neuropathy, retinopathy, amputation, blindness and mental disorders resulting from diabetes and in particular T1D.

 However, brittleness has been overlooked by SSD despite the fact that a defining feature of this disease is that it is “disruptive on a daily basis”. This phrase is precisely the language used by the SSD itself to define a disease or condition worthy of the “disabling disease” connotation. This is imperative as those who suffer from BT1D find holding down full time employment nearly impossible, yet due to the SSD’s current position on Diabetes cannot apply for disability assistance.

 BT1D is a significant strain on financial and family resources as well as hospital and health care resources. Presently for a BT1D sufferer to have any chance of successfully petitioning for government assistance he or she literally needs to have one foot in the proverbial grave. Although harsh, the previous comment is based on the unavoidable fact, that only the complications referred to earlier, for which medical codes have been established, qualify the individual for government assistance.

1. **How many clinical forms of BT1D are there?**

The literature suggests that there are three clinical presentations of BT1D: predominantly recurrent hyperglycemia leading to DKA; predominantly, hypoglycemia leading to coma; and mixed instability ranging from hyperglycemic to hypoglycemic states.(3,17,18,23,26,35)

 Those with brittle diabetes report that glycemic variation occurs even under controlled conditions: the same insulin dose with the same type of insulin, with the same food being eaten at the same time of day. There is no predictive value associated with exercise, nutrition or treatment. This leads one to the primary feature of the disease that distinguishes it from stable or controllable T1D – viz., BT1D is unpredictable.

1. **Why is BT1D a rare disease distinct from stable T1D?**

 BT1D does meet the standard description or ADA guidelines established for a T1D diagnosis including auto-antibodies, c-peptide and HbA1c analysis.(24,25)

 However, the features that serve to distinguish BT1D from stable T!D include the following.

* People with Brittle Diabetes exhibit uncontrolled, unstable and unpredictable shifts in their glucose levels well beyond that exhibited by stable T1D patients. (23) The key feature is the unpredictable nature of the ailment along with the extreme glycemic variability exhibited.
* BT1D patients defy standard forms of treatment management which often tends to be limited to insulin mono-therapy.(21,23)
* Physicians have been trained to look for patterns in glycemic excursions based on exercise, diet, daily physical activity and nocturnal events. Unlike the stable TID – an endocrinologist who has worked with a true brittle individual will tell you that there is no blood glucose pattern to be discerned for the purpose of creating a basal/bolus insulin regimen.(2)

 Attempts at replicating BG levels by managing every aspect of a brittle patients existence fails miserably.

* There is no cure for T1D but “brittleness” does have a cure. By current definition, brittleness, which is disruptive in the life of a T1D patient, always has a secondary cause. (27,28) The medical literature is replete with articles that suggest that if a physician diagnoses and treats the cause, there is a 50% chance that the patient will return to a stable or controllable diabetes state.(28,29) BDF has reviewed 18 known secondary causes as described in the medical literature on its website and continues its search for additional metabolic causes.
* One way to distinguish a brittle patient is by

 the level of frustration exhibited by the healthcare team

 caring for said individual. The true BT1D, removed from

 those who are either non-compliant or factitious, defy

 standard modes of treatment. They require a physician

 willing to take the time and resources to play detective in

 a search for the cause of their brittleness.

 The ADA assumes that the mode of standard care includes

 a willingness and the ability to undertake this type of

 search. As Desmond Schatz M.D. will tell you that a BT1D

 patient needs to find a really good, if not great

 physician, to assist them.

 Unfortunately many physicians are mediocre, doing just

 enough to get by, and are generally unwilling to take the

 time to hunt or employ resources to deal with this minority

 group. That is why people with brittle diabetes have, of

 necessity, become their own best physician.

* The literature is replete with stories of stable T1D patients who carry on active life styles in sports, entertainment, the medical field, and all walks of life. The term stable or controllable suggests that physicians have been successful in establishing a treatment program that allows the patient to lead as near normal a life as possible.

 The estimated 4,500 true brittle individuals seek only to be stable. They do not seek a cure for T1D. They seek relief from their brittle condition whose symptoms and management serve to disrupt their daily life activities including the inability to hold a full time job. Recurrent trips to the ER and hospital stays are not uncommon.

 This disruptive nature of BT1D in a person’s daily life is

 a key feature that serves to distinguish it from those

 afflicted with stable T1D.

* The American Association of Clinical Chemistry (AACC) guidelines state “the glucose swings of someone who has ‘brittle’ diabetes will also not be reflected in the A1C.”(30)

Patients with similar HbA1c values can have markedly different glucose profiles with differences both in number and duration of glucose excursions. (31) The HbA1c test does not provide a measure of glycemic variability or hypoglycemia.

 As a result, if the physician follows ADA guidelines and finds A1C levels in the range as most of his stable patients, he is less inclined to search for the truth.

 What’s missing in this diagnostic process is the measurement of glycemic variability in which the standard deviation of those swinging from a BG level of 40 to 400mg/dl in ninety minutes on the part of a BT1D is greater than that of a stable T1D patient. The development of diagnostic tools to aid the clinical practitioner in distinguishing between stable and brittle is not fostered by physicians who hold that there is no difference in the treatment and/or management of Type 1 subjects. If, as ADA appears to suggest, all are perceived to be Type 1 with merely degrees of variation in glucose levels, then BTID patients simply get lost in the shuffle.

 There are presently five expert physicians in the diabetes field who are touting the value of a new diagnostic tool called GlycoMark (32) which is not mentioned in ADA’s 2016 guidelines. A major distinguishing characteristic between a stable T1D and BT1D individual is the degree of glycemic variability manifested by them. HbA1c is an average which fails, according to the AACC, to register glycemic excursions which are more prevalent in BT1D patients. The GlycoMark fills this gap providing additional information, in the short term, by reflecting on the degree of glycemic variation. This is accomplished by measuring daily peak glucose levels.

 In the case of one BTID, her HA1c declined, which would suggest progress. But, when her GlycoMark was run it declined significantly reflecting major post prandial glycemic excursions which were confirmed by CGM readings. Intuitively, one cannot control average glucose levels unless one first reduces glucose variability.(33)

1. **How many people are affected by BT1D?**

 Based on CDC statistics, Type 1 impacts approx. 1.5 million USA residents. Based on the literature, Brittle Diabetes impacts an estimated 3/1000 type 1’s or 4,500 people making it an extremely rare disease.(18,23,26,34)

1. **What are the known causes of brittleness?**

 BDF lists 17 organic causes of brittleness which have been culled from the medical literature, many of which are treatable. They include: Gastroparesis, Celiac Disease, Absorption Disorders/Malabsorption Syndromes, Vitamin D Deficiency, Hypothyroidism, Addisons Disease, Cushing’s Disease, Chronic Pancreatitis, Polyendocrine Syndrome, Cystic Fibrosis, Pheochromocytoma, Chronic Cryptic Infection, Lipodystrophy, Hemochromatosis, Scleroderma, Systemic Insulin Resistance, and Anti-Insulin Antibodies.

 ADA guidelines addresses physiological causes such as thyroid and adrenal issues along with celiac disease as a cause of diabetes making the assumption that physicians will automatically go down a checklist of metabolic causes without any formal guidance.

 It is heart wrenching to read in an e-mail from a BT1D that it took 31 years before he was diagnosed by his new endocrinologist with celiac disease and, after one month on a gluten free diet, is now a stable T1D. Or, to read letters from those who wonder why existing guidelines don’t extend beyond insulin mono-therapy.

 We tend to assume, that professionals follow guidelines in journals. Unfortunately, journal articles often go unread. Thus the need to improve information flow from the PPC into the hands of the practicing clinician. In this day and age of internet healthcare software platforms, it is surprising that ADA or the PPC has not created a vehicle for the direct distribution of data driven research findings or proposed guidelines, onto the desk of every endocrinologist and diabetologist, via the internet.

 As for psychological causes, BDF’s findings are disturbing. In the past, primarily 1960 through the mid 90’s, Brittle Diabetes was being dismissed by mainstream clinicians as being a psychosocial disease. With depression being one of the main causes of brittleness.

 However, there was a great deal of poor science applied in many of these studies. A departure from the scientific method would be a kind assessment. Over the past 25 years, studies have shown that there is bi-directionality to cause and effect and, for the most part, individuals employing insulin are more likely to become depressed as a function of being a T1D or BT1D. I would refer the PPC to the discussion on Depression on BDF’s website dealing with the psychosocial issues listed as the 18th known cause for brittleness.

1. **How does treatment differ between stable T1D and BT1D?**

 The statement often confronted when dealing with BT1D is that, with more careful and diligent monitoring and patient compliance with exercise, nutrition and insulin regimens, the condition will stabilize or even correct itself with time.(34)

 Most, if not all, BT1D patients are diagnosed as brittle within hospital settings following emergency room admissions for DKA or hypoglycemia. This occurs when, after several days of diligent and careful monitoring 24/7, the physician realizes that he or she is unable to stabilize or control their patient’s BG levels. Possibly, out of shear frustration, or because of familiarity with the subject, they deem the patient to be afflicted with “brittle” type 1 diabetes.

 If under controlled environmental conditions 24/7,

 physician’s cannot normalize or stabilize blood glucose

 levels, how can the patient be expected to do so when his or

 her next visit is three months away. A brittle diabetic

 recognizes that they must become their own best physician

 because there is a limit as to what their endocrinologist or

 primary care physician can do in a twenty to thirty

 minute office visit.

 Treatment must extend well beyond simple management

 attempts of normalizing glucose levels with insulin and

 guidelines need to be established to assist the clinical

 physician. The clinician must begin a systematic series of

 diagnostic tests to eliminate as many of the known causes

 of brittleness as possible. Once this is done, a

 treatment program geared to eliminating the cause of the

 patient’s brittleness, with the intent of returning the

 patient to a more stable condition, can be initiated.

 Establishing CGM monitoring of a patient in

 conjunction with insulin pump therapy, and the establishment

 of a basil/bolus insulin regimen is, if available and

 affordable, a BDF recommendation for management of a BT1D

 individual.

 For the small group of patients who fail to respond to normal treatment modes, pancreas and islet cell transplantation should be considered, weighing immunosuppressive agents against the complications associated with BT1D.(3,36)

 If a patient shows signs of psychological impairment, a psychiatrist or psychologist should be included as part of the health care treatment team. Treatment for both psychological as well as physiological issues should occur simultaneously.

1. **What is the significance of physician frustration when**

 **dealing with a BT1D patient?**

 The fact that the diagnosis of Brittle Type 1 Diabetes is the immediate inclination of endocrinologists after being unable to stabilize and/or control their patients BG levels, speaks volumes.

1. It first suggests an awareness of the brittle condition which means the term’s usage reflects current not antiquated thinking.
2. It also reflects a historical shift in thinking about the disease diabetes from ‘How do we cure’? to ‘How do we manage’? Ever since insulin’s discovery the clinical practitioner has spent his time managing type 1 diabetes. And, when a physician is unsuccessful in that attempt he or she reflects frustration. It’s only recently that medicine is re-examining this approach and beginning to look beyond clinical management of the diabetes within the physician’s office setting.
3. The frustration also stems from a lack of knowledge about the disease process and, having exhausted that knowledge, the clinical practitioner finds he has no-where to turn for assistance.
4. When these points are coupled with limitations imposed on a physician’s time and resources, they add to the level of frustration exhibited by those members of the medical health team who truly care about the well being of those they tend.

1. **How can we assist the clinical physician in diagnosing and**

 **treating BT1D patients?**

 BDF proposes four ways to accomplish this task.

1. Increase the physician’s awareness of alternatives to non-compliance when a patient’s test results don’t conform to the expected T1D treatment program.
2. Provide the clinician with a tool- an APP – based on mathematical algorithms that have evolved over the last 30 years. Incorporate into the APP, patient data obtained from a CGM which would allow the physician to track disease progression and levels of BG severity. Apply glycemic and variability indices which would allow the physician to differentiate between a factitious patient and one who is truly Brittle.
3. Provide the physician with a place to go for expert input- a regional team of research experts, current in the field, who are willing to review a troubling case and make recommendations as to how he or she should proceed diagnostically and treat according to test results.
4. PPC should consider modifying existing healthcare software platforms, for the rapid distribution of both research findings and PPC guidelines. Though unwritten, most physicians engaged in T1D research, recognize, that there exists a five year gap in information flow between the basic researcher and the practicing clinician.
5. The PPC should encourage the development of a national center of excellence specific to BT1D where the clinical practitioner can refer his severest of BT1D patients.
6. **What is the impact of ADA’s decision on this matter on**

 **existing and future clinical trials?**

 If it is the position of ADA and/or the PPC that all patients meeting the diagnosis of type 1 diabetes differ only in degrees of glucose variability, making no distinction between stable and brittle forms, future clinical trials will continue mixing two different disease entities, thereby skewing trial results. On the other hand, separation of the two would result in brittle subjects being tested with an eye on how specifically BT1D differs from stable T1D individuals.

 Biomarker data specific to the difference between these two disease entities is presently lacking. Areas in need of differential exploration include, genetics, variation in number and types of auto-antibodies, HbA1c blood glucose levels, and glycemic variability predicated on standard deviations and rates and limits of glycemic excursions. This data may alter and or modify future trials or require a look back at former studies using meta data techniques separating out subjects classified as brittle in previous combined studies.

**Conclusion:**

 BDF believes that it has presented enough significant evidence to warrant serious consideration on the part of ADA’s Professional Practice Committee to reclassify Brittle Type 1 Diabetes as a rare disease in its own right and as a separate and distinct form of T1D.

 The NIH, JDRF and BDF recognize Brittle Diabetes as a rare disease and this fact alone should suggest to the PPC that, at least in future clinical trials, separating these two groups would be a prudent step toward collecting data on a condition for which little clinical diagnostic findings exist.

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