

## Classification of type 1 diabetes (T1DM)

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### Abstract

Type 1 diabetes (T1DM) has emerged as a common and heterogeneous condition across the globe. Improved understanding of the pathophysiology and clinical features of T1DM has led to in-depth study of the condition. This review describes the classification of T1DM, as proposed by leading international bodies. It explains the importance of such a taxonomy, and proposes a novel, comprehensive clinic-etiologic rubric to classify T1DM. Such a classification based on etiological and clinical features, rather than complex investigations, should further enhance academics, clinical science, and research in T1DM.

**Keywords:** Acute T1DM, American Diabetes Association (ADA), fulminant T1DM, International Society for Paediatric and Adolescent Diabetes (ISPAD), LADA, Japan Diabetes Society (JDS), T1DM, slowly progressive T1DM.

### Introduction

T1DM is thought to be a homogenous clinical condition. For the practicing clinician, however, T1DM represents a wide spectrum of morbidity. This adds to the already confusing artificial construct dividing diabetes into two types: T1DM and type 2 diabetes. Yet more uncertainty arises with the use of the term 'type 1.5 diabetes' to describe both late onset diabetes of adults (LADA) and Flatbush diabetes.<sup>1-3</sup> This article reviews and compares the classification of T1DM as proposed by the American Diabetes Association (ADA), International Society for Paediatric and Adolescent Diabetes (ISPAD), and Japan Diabetes Society (JDS).

### American Diabetes Association

#### Definition

The ADA (American Diabetes Association) classifies diabetes into four types, including type 1, type 2, gestational, and specific types. It defines T1DM as being "due to beta-cell destruction, usually leading to absolute insulin deficiency". ADA qualifies its classification by

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stating that diabetes is a heterogeneous disease, with variable clinical presentation and progression. T1DM may present with classic osmotic symptoms, in diabetic ketoacidosis, or with atypical complaints. Age and obesity are not a criterion for the differential diagnosis of type 1 and type 2 diabetes now.<sup>4</sup>

### Etiology

T1DM was earlier known as 'insulin — dependent diabetes or 'juvenile-onset diabetes'. It is caused by cellular auto immunity, leading to destruction of beta cells. To 'define' autoimmune diabetes, an autoimmune marker, i.e., antibody has to be demonstrated. Some patients, usually of African or Asian descent, have no evidence of  $\beta$ -cell autoimmunity, but still have absolute insulinopenia and are at risk of ketoacidosis. This form of diabetes is known as idiopathic T1DM. While autoimmune T1DM has associations with both predisposing and protective HLA-DR/DQ alleles, no such linkage is reported for idiopathic T1DM.

### Presentation

ADA clearly describes the variable natural history of T1DM. It can occur in an acute setting, with rapid  $\beta$  cell destruction (usually in paediatric age group); in a sub acute manner ("modest fasting hyperglycaemia that can rapidly change to severe hyperglycaemia and/ or ketoacidosis with infection or other stress"); or in a slow manner. The latter presentation is seen in adults who "retain sufficient  $\beta$ -cell function to prevent ketoacidosis for many years", but finally become insulinopenic.

### Differential Diagnosis

T1DM is different from monogenic diabetes mellitus, which is a relatively rare form of dysglycaemia. Monogenic diabetes may present as neonatal diabetes (onset within six months of life) or MODY (maturity-onset diabetes of the young) (onset before age 25 years). A high index of clinical suspicion should be maintained for MODY in patients with features that are not typical of either type 1 or type 2 diabetes, who have a strong family history of diabetes, mild fasting hyperglycaemia, and negative diabetes-associated auto antibodies.

As MODY is a secretory defect, a case may be made for including it as a subtype of T1DM. The list of T1DM

phenotypes may then read as: autoimmune, genetic and idiopathic. However it is difficult to support this viewpoint, as the clinical presentation of MODY is totally different from that of T1DM.

### **International Society for Paediatric and Adolescent Diabetes (ISPAD)**

ISPAD follows the ADA classification of T1DM, and mentions two types: autoimmune and idiopathic. ISPAD highlights the heterogeneous etiology and clinical presentation of childhood diabetes. It mentions the need to exercise caution in diagnosis if 'stress hyperglycaemia' is detected, and notes the possibility of overweight in T1DM and ketoacidosis at time of diagnosis of type 2 diabetes.<sup>5</sup>

While differentiating between type 1 and type 2 diabetes, ISPAD states that the clinical presentation of the former is "most often acute, rapid", and that of the latter, "variable, from slow, mild (often insidious) to severe". ISPAD lists atypical forms of diabetes that have been reported from Africa and South Asia, including ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibrocalculous pancreatic disease.

Such a statement does not cover the existence of latent autoimmune diabetes of adults (LADA), also known as type 1.5 diabetes. LADA is an autoimmune form of diabetes that presents insidiously in adults. Though it may often be misdiagnosed, it is actually a form of T1DM.

### **Japan Diabetes Society**

The wide clinical spectrum of T1DM, and other forms of diabetes, has spurred efforts to classify the syndrome. One such commendable effort has been made by the Japan Diabetes Society (JDS).<sup>6</sup> JDS classifies T1DM into three sub types: fulminant, acute, and slowly progressive. While the JDS has published diagnostic criteria for fulminant and acute T1DM, work on the criteria for slowly progressive T1DM is in progress.<sup>7,8</sup>

JDS classifies T1DM as fulminant, acute onset or slowly progressive T1DM based upon the clinical presentation and progression.<sup>9</sup> Acute onset T1DM includes a subset named as acute onset T1DM (autoimmune). Acute onset T1DM is diagnosed if diabetes ketosis or ketoacidosis occur at around <3 months after the onset of hyperglycaemic symptoms (thirst, polydipsia, polyuria, weight loss), and if there is a need for continuous insulin therapy after diabetes is diagnosed. Ketosis can be confirmed by either urine & / or serum estimation. The definition clarifies that ketosis may not occur if insulin therapy is instituted early, and that a honeymoon period may occur with regards to insulin requirement.

Patients with a positive anti-islet auto antibodies are classified as having a positive test result for anti-islet auto antibodies, at any time during the course of the disease. These include islet cell auto antibodies (ICA), glutamic acid decarboxylase auto antibodies (anti-GAD), insulinoma-associated antigen 2 auto antibodies (IA2A). Insulin auto antibodies can be used to diagnose autoimmune T1DM as well, but only if they are evaluated before or shortly after insulin therapy is initiated, as exogenous insulin administration can lead to antibody formation. Patients without verifiable anti-islet auto antibodies, but with documented insulin deficiency (fasting serum C peptide immunoreactivity < 0.6 mg/ml) are labeled as having acute T1DM mellitus (idiopathic).<sup>7</sup>

Fulminant T1DM is an independent subtype that has been demarcated as a separate entity by Japanese researchers. JDS has distinct criteria for the screening and diagnosis of fulminant T1DM. Screening criteria are ketosis/ ketoacidosis within 1 week after the onset of hyperglycaemic symptoms, and a plasma glucose >288 mg/dl at first visit. Three criteria have to be present for a confirmation of fulminant T1DM. There are occurrence of diabetic ketosis /ketoacidosis soon (~ 7 days) after the onset of hyperglycaemic symptoms; plasma glucose  $\geq$ 288 mg/dl and glycated haemoglobin level < 8.7% at first visit; and a low C peptide value. For the third criterion, urinary C-peptide excretion <10  $\mu$ g/day or fasting serum C-peptide <0.3 ng/ml or post meal or post intravenous glucagon serum C-peptide < 0.5ng/ml. The HbA1c may be higher in patients with previously diagnosed glucose intolerance. A high glycated albumin (GA) / HbA1c ratio indicating very recent deterioration in glucose control may be taken as a feature favouring fulminant T1DM.

Other findings of fulminant T1DM include undetectable antibodies, a short duration of disease, elevation of serum pancreatic enzymes (amylase, lipase, elastase-1) and history of flu like symptoms (fever, upper respiratory symptoms) or gastrointestinal symptoms (upper abdominal pain, nausea &/or vomiting) prior to onset of diabetes. Occurrence during pregnancy or in the immediate post- partum period, association with T2DM, and a link with HLA DRB1\*04:05-DQBI\*04:01 is reported as well.<sup>10</sup>

JDS has not published detailed criteria for diagnosis of slowly progressive T1DM, but this condition is similar to what is currently termed LADA.

### **Limitations of Current Classifications**

As it is, T1DM is a difficult condition to manage. This challenge is made tougher by lack of clarity regarding to classification. While a simple classification may have the

advantage of easy usage, it is unable to encompass the true diversity of the syndrome. As mentioned by JDS, this lacuna may lead to suboptimal decisions in therapy and research. On the other hand, creating new taxonomic structures and onomastic terms serves to make a muddled up picture even more confusing.

The currently accepted classification of T1DM (autoimmune and idiopathic) is based only upon etiology. Such taxonomy does not take clinical presentation (presence/absence of ketoacidosis), phenotype (obesity/overweight/ lean), or course of progression (rapid/slow) into account. This is a major limitation in current praxis, as it is these very factors which determine diagnostic and therapeutic decision-making, rather than the etiology.

It must be pointed out that the same argument does not apply to monogenic diabetes. While the definition of monogenic diabetes is based solely upon etiology, this term describes a group of well-demarcated, unifactorial conditions. This label prompts specific and focused screening, diagnosis and treatment, and helps differentiate patients from type 1 and type 2 diabetes.

What is needed, therefore, is a clinically oriented, clinically based rubric which helps the diabetes care professional recognize, diagnose and manage T1DM. This framework should be easy enough for generalists to appreciate, and comprehensive enough to include current (and future) knowledge of specialists. Such a rubric should be concordant to the 'definition' of T1DM, which recognizing the wide diversity that this label carries. This classification should facilitate respect for the tenets of 'good clinical sense' and quaternary prevention in diabetes as well.<sup>11,12</sup>

Any systematic framework should be broad and flexible enough to incorporate secular trends in T1DM. For example, the increasing prevalence of overweight/obesity, and gradual reduction in ketoacidosis at presentation should be reflected in the classification scheme of T1DM. This will help instill confidence in generalists when they encounter 'atypical' presentations in the clinic. Whatever scheme is followed should facilitate appropriate decision making. Using the words 'Ketosis-prone', for example, encourages insulin prescription. Conversely, the use of 'ketosis resistant' may prompt generalists to counsel against use of insulin. The choice of adjectives, e.g., fulminant, or slowly progressive, should be such that it does not place undue burden on students, who already grapple with a humungous medical dictionary.

Taxonomy should serve to unite, rather than divide. There

have been calls to consider all types of diabetes as part of a single continuum, marked by varying degrees of insulin deficiency and resistance. A classification of T1DM should be able to merge seamlessly into a larger scheme, using similar thought process and lexicon, to promote appropriate clinical action.

**Solution: Clinical Classification**

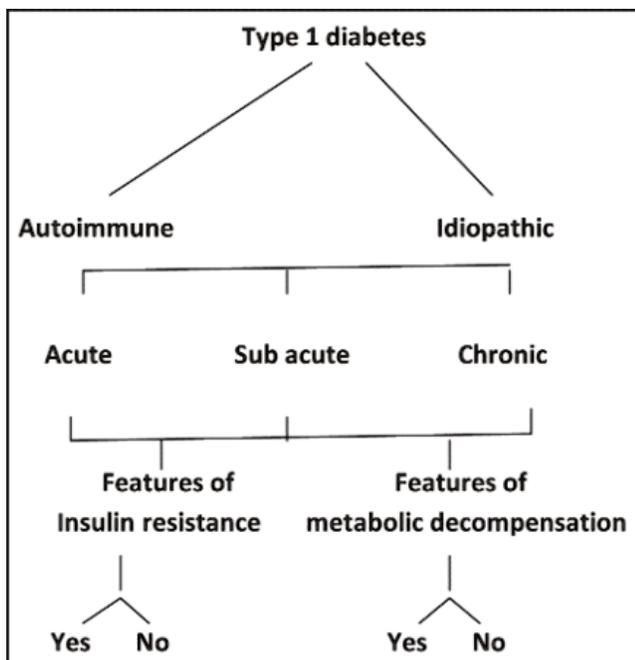
We propose a simple taxonomic structure for T1DM that will be of relevance to both clinicians and researchers (Figure). The proposed taxonomic structure is based upon three parameters: etiology (autoimmune vs idiopathic), method of onset (acute, sub acute, chronic), and clinical presentation (evidence of metabolic decompensation, insulin resistance). Thus, it is much more broad-based than existing standards of classification.

In this rubric, etiology retains primacy. Based upon etiopathogenesis and clinical presentation, this is syntactic with the basics of clinical medicine, and is understandable to generalists and physicians. The usage of the words 'acute', 'sub-acute', and 'chronic' is derived from standard medical texts. Therefore, this classification is student-friendly as well. The taxonomy also facilitates appropriate decision making, such as screening for associated autoimmune conditions and use of non-insulin therapeutic agents. The absence of metabolic decompensation, and/or presence of clinical features of insulin resistance, may prompt use of non-insulin drugs to control glycaemia, reduce insulin requirement, and modulate body weight.

In many resource-challenged parts of the world, however, it may not be possible to order or obtain reliable antibody values. Therefore, a glucophenotypic classification, or clinically-oriented taxonomy is required, as opposed to an investigation-based matrix. Table provides such a framework. In this, weightage is placed on mode of presentation, rather than on investigations. Thus, it highlights the importance of clinical medicine, without belittling the contribution of diagnostic tools. It encourages a holistic view of the person with T1DM, and promotes rational and personalized use of available

**Table:** Classification of type 1 diabetes.

<b>Etiology/Presentation</b>	<b>Autoimmune</b>	<b>Idiopathic</b>
Acute	With or without	With or without
Sub acute	· Metabolic decompensation (diabetic keto acidosis)	· Metabolic decompensation (diabetic keto acidosis)
Chronic	· Features of insulin resistance (e.g., overweight, acanthosis nigricans)	· Features of insulin resistance (e.g., overweight, acanthosis nigricans)



**Figure:** Classification of type 1 diabetes.

therapies. This helps strengthen and further the cause of diabetes care.

### Action Points

The aforementioned discussion creates food for thought, and raises important questions as well. From a macro-perspective, should T1DM be sub divided further? If yes, all relevant professions and specialties, across all nations, should create a harmonized classification of T1DM.

Such a classification will be useful only if it serves to enhance academic skills, clinical care, or research work. The rubric we have proposed needs to be tested in academic settings, to see if it improves students' understanding of T1DM. Long term will assess if various subtypes of T1DM have varying chances of remission, risk of co morbidities and vascular outcomes. Research must be done to evaluate the advantage and implication of labeling persons with T1DM as belonging

to a particular subset.

### Summary

Diabetes is a rapidly evolving syndrome, and so is the field of diabetology. To keep pace with this, we propose a glucophenotypic approach to T1DM classification, incorporating both clinical features and immune markers. While we understand that our suggestion will not be the final word in T1DM classification, it certainly contributes to enhanced understanding of the same.

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