A COMMENTARY ON CLASSIFICATION OF DIABETES: LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA) OR INTERMEDIARY DIABETES MELLITUS (IDM)?

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Abstract

Diabetes Mellitus is a huge syndrome which can be detected from the first day of life until the last year of life of a centenarian. In the current classification of diabetes among the so-called “idiopathic phenotypes”, apart Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D) has been included provisionally term “Latent Autoimmune Diabetes in Adults” (LADA). This has unclear characterization regarding the age at onset, the presence of anti- β -cell antibodies and the level of insulin secretory function, in conformity with C-peptide levels. According to several recent publications, there are no specific biochemical or genetic markers for Latent Autoimmune Diabetes in Adults (LADA), but only a gradual transition from T1D to T2D. In addition, the word “latent” in the construction of “LADA” term is inaccurate because in this phenotype nothing is latent: both the autoimmunity and diabetes are present and are even parts of the diagnosis. So that, the best term should be what in reality this sub-phenotype is: an Intermediary Diabetes Mellitus (IDM). Some recent genetic data strongly support this designation.

Key words: Classification of diabetes, LADA, IDM, primary insulin dependence, secondary insulin dependence.

Diabetes mellitus is a huge and heterogeneous syndrome whose official classification began in 1965 with some minor rectifications in the four versions that followed. During past decades the discovery of various biochemical and immune markers (HbA1c, anti- β -cell antibodies, C-Peptide and others) has incited the use of multidimensional cluster analysis method (1) in order to identify sub-groups of diabetic patients. For instance, recently Ahlqvist *et al.* (2) using six clinical and biochemical variables obtained five “novel sub-groups adult-onset diabetes”. Such subdivision cannot be “a novel classification” of diabetes but only a subdivision of the classical diabetes phenotypes.

We remember that the roots of the first classification of diabetes syndrome was made by

Etienne Lancereaux, who in 1877(3), 1883 (4), and 1888 (5) made the first distinction between “slim” diabetes (called also “pancreatic” diabetes) and “fat” diabetes (or “constitutional” diabetes). By doing so, Lancereaux raised the stature of clinicians to the rank of experimental “scientist”, able to remain as a “landmark” in the history of diabetes. The following text from 1883 (4) is illustrative of this achievement. *“In summary, diabetes, as it is known today, is not a single disease, but a collection of different pathological entities. Among these, one is characterized by its sudden onset, strong clinical manifestations, rapid evolution and, above all, by weight loss and the accompanying pancreatic lesions: we call this type slim diabetes or pancreatic diabetes. Beside this type of diabetes, there is another characteristic form. It is much more frequent than the former one, it is generally inherited, it starts with persistent overweight and it is usually not accompanied by pancreatic lesions. Its symptoms are far less obvious than those of slim diabetes; its evolution is slow and duration is uncertain. ..We call this form fat diabetes or constitutional diabetes”.*

Today, no matter how hard we try to divide our entire “collection” of diabetic patients into one of the two major phenotypes of diabetes, known as type 1 (T1D) and type 2 diabetes (T2D) a third important category remains. This comprises about 15-30% of all diabetic patients depending on the ethnic population (6-9). It initially seems to be T2D responding to oral treatment, but after a shorter or longer period of time, these will be switched as a necessity to insulin treatment. It has been discovered that at least one anti- β -cell antibody can be found in the majority of these patients (10).

The first identification of this phenotype has been made in 1976 by Irvine *et al.* (11), who found in the serum of a non-diabetic subject who later became diabetic, the presence of pancreatic islet cell antibody. This could really be considered an “asymptomatic or latent diabetes” (11). Ten years later in 1986, Groop

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et al. (12), found islet cell antibodies in 14% of 154 diabetic patients aged between 35 and 75 years, initially treated by oral agents for at least one year, but which then rapidly progressed to metabolic decompensation needing insulin treatment. In fact, Leif Groop is the father of the so-called “Latent Autoimmune Diabetes in Adult” (LADA), being associated in many papers devoted to this new phenotype (13-18). Such patients have been identified over time by many researchers, using for their designation a large number of terms, such as: “Type 1 1/2 diabetes” (19), “Lady-like” (20), “Autoimmune diabetes not requiring insulin in adults” (21), “Type I diabetes masquerading as type II diabetes” (22), “Adult onset autoimmune diabetes” (23), “Type 2 diabetes with GAD antibodies” (24), “NIR” (Non Insulin Requiring), IRC (Insulin Requiring for Control), IRS (Insulin Requiring for Survival) “NIRAD” (Non Insulin Requiring Autoimmune Diabetes) (25, 26).

The term “Latent Autoimmune Diabetes in Adults” (LADA) has been used by Leif Groop, Bottazzo and Doniath in 1986 (12) then, in 1993, by Tuomi from the Leif Groop team (27) and has been provisionally used in the last revision of the classification of diabetes mellitus (1999), despite the critical commentaries published in the meantime (28, 29). In 1994 Leslie and Pozzilli (22) had initiated a study group named “Action LADA” with the aim of better understanding the pathogenic significance of this “intermediary” category of patients interposed between type 1 and type 2 diabetes. Identification of this phenotype was based on the presence of islets cell antibodies (mainly GAD antibody) in diabetic patients with onset in adult age, which is not well defined, ranging between 20-74 years. A similar working group has been organized in China (8).

However, LADA term has a big problem, because nothing is latent in this phenotype: both the *autoimmunity* and *diabetes* are present, so not latent (30), therefore a neutral term (similar to T1D and T2D) is more appropriate. In our view, Intermediary Diabetes Mellitus (IDM) is a term that really reflects what this phenotype is. The only characteristic clinical features of IDM is the age of onset of this phenotype (higher than in T1D), a lower BMI (than in T2D), and an initial good response to oral drugs (like in T2D).

The distinction between these three phenotypes of diabetes: T1D, IDM and T2D, became obvious soon after a new WHO classification of diabetes was proposed in 1985. By an unfortunate decision, the two neutral terms for the major phenotypes of diabetes (T1D and T2D) were replaced by a name reflecting the therapeutic option: insulin treatment *vs.* oral treatment.

In this way, Type 1 Diabetes became IDDM (Insulin Dependent Diabetes Mellitus) while type 2, NIDDM (Non Insulin Dependent Diabetes Mellitus). Soon after this decision, practitioners were obliged to substitute, sometimes overnight, the diagnosis of type 2 diabetes with another one. Several *ad hoc* terms have been used, such as; Insulin treated type 2 diabetes; Type 2 diabetes necessitating insulin, or other descriptive formulations. Finally, we adopted the term Secondary insulin-dependent diabetes, considering Type 1 diabetes as being a Primary insulin-dependent diabetes (32-34).

In order to assess the significance of this new category of diabetic patients, we did a retrospective analysis of the last 5000 newly discovered diabetic patients registered over the last 10 years (31, 33). We looked at their initial treatment, and then at their treatment over the course of time. The primary insulin-dependent patients (T1D), constituted ~ 7.5%. However, each year around 1% of NIDDM patients became insulin-treated (“Secondary insulin-dependent diabetic patients”). These patients (recruited mainly from cases with onset between 20 and 40 years) surpassed in the following 10 years the number of T1D patients, accounting for 10%, that means ~ 17% (7.5 % + 10%) of all diabetic patients. Since, in the 8th decade of the 20th century, the determination of islet cell antibodies or of C-peptide was not routinely available, the only particularities of these patients were clinical, including age at onset (>20 years, but without a precise upper limit); a lower BMI at onset (< 30 Kg/m²), and the obvious need for insulin therapy, due to the decompensation of blood glucose regulation, sometimes associated with ketosis or ketoacidosis. Only later did we know that the majority of those patients are characterized by the presence of autoimmunity markers (as a rule GAD antibodies) and a decreasing plasma C-peptide level.

After the conception of the immunogenetic theory of Type 1 Diabetes in 1974 (34, 35) the first genetic analyses were carried out separately for Type 1 Diabetes (generally in patients with “juvenile” diabetes) and Type 2 Diabetes (35-38). Pettersen (39) later carried out separate genetic analyses of the HLA haplotypes in the so-called LADA phenotype. The main conclusions were very clear: the diabetogenic HLA haplotypes decreased slowly from “juvenile diabetes” to “intermediary diabetes mellitus” (IDM), to reach the level of non-diabetic controls, in Type 2 Diabetes cases. The HLA protective haplotypes were very low in the 0-20-year age group (T1D), progressively increasing in the 20-40-year age group to reach the levels of controls in T2D (Fig. 1).

Figure 1. The contribution of diabetogenic and protective HLA haplotypes: continuous blue line - diabetogenic HLA; dashed red line - contribution of the protective HLA in various phenotypes of diabetes vs. control (Redrawn after Pettersen *et al.* (39).

Figure 2. Relationship between various genes associated with the three phenotypes of diabetes A-type 1 diabetes, B-type 2 diabetes and C-Intermediary Diabetes Mellitus (from 40).

Figure 3. The clear position of Intermediary Diabetes Mellitus (IDM) between type 1 diabetes and type 2 diabetes (from 40).

Recently, the group of Leif Groop and colleagues (17) published a careful study of the metabolite profile of LADA phenotype, aiming at potentially identifying a specific metabolite pattern in this important category of diabetic patients, that would represent a transition between type 1 diabetes (T1D) and type 2 diabetes (T2D). The authors concluded that they “could not find any unique metabolite profile distinguishing LADA from type 1 and type 2 diabetes” (17). According to their conclusion, the so-called LADA phenotype seems to be nothing more than “... an intermediate of type 1 and type 2 diabetes” (17), a sentence repeated several times in their paper.

That above-mentioned data confirm what we proposed in 2015 (40), i.e. that the more appropriate term for this phenotype is “Intermediary Diabetes Mellitus” (IDM). This proposal was based on the results of the analysis (using an original post-genomic method (40, 41) of the nucleotide sequences of promoters of genes reported to be associated either to T1D or T2D. The novelty of our method described in detail elsewhere (40, 41) was based on the generation of a visual pattern by plotting the (C+G)% content *versus* Kappa Index of Coincidence (KIC), a statistic cryptographic measure based on letter frequency distribution first described by Friedman (42). This method has been developed and successfully used for decoding the encoded messages running between the two army blocks during the First World War. In our medical application the letters are replaced by the nucleotides of the promoters DNA sequence, considered to contain complex encoded biological information. It is striking to see the degree of similarity between the graphic representation which clearly overlaps between T1D, LADA (IDM) and T2D presented in Figure 1 - resulting from the redrawing of data from the Swedish paper (39) and in Figures 2, 3 from our previous published data (40).

Due to availability to the GAD antibodies and C-peptide determination explain the high interest of the medical community on this topic. That explains the large number of papers published in the last 30 years. These reveal the high heterogeneity of the diabetic syndrome. In a relatively recent paper, David Leslie suggested that physicians must become “splitters”, subdividing diabetic patients into groups according to several key factors such as age, BMI, GAD or other anti β -cells antibodies, C-peptide or some HLA or non-HLA genetic markers (43-45). A such splitting has been published by Frohnert *et al.* (7) dividing the clinical type 1 diabetic patients (0-16 years old) in two parts: with onset < 8 years (early) and > 8 years

(late). Even in this “juvenile” diabetes the intensity of autoimmunity and evolution is significantly different between these subgroups, similar with the differences between type 1 diabetes and intermediary diabetes (or LADA). It is possible that subdividing each of the above mentioned subtypes (for instance diabetes with onset between 12-16 years old into 12-14 years old and 14-16 years old) to find some differences. Infinite subdivisions will not produce two patients with identical manifestations. The heterogeneity of diabetes has increased over the past 20 years due to the increase in the incidence of diabetes. This increase has been recorded in most of the countries and it is mainly attributed to the changing of the lifestyle and the environment (46, 47).

Recently it has been published by a large group of investigators (48) a genome-wide association study of latent autoimmune diabetes, which confirms our previous data (39) synthesized in Figs 2 and 3, showing better the clear position of the genes associated with the three phenotypes of diabetes: T1D, IDM and T2D.

In conclusion, we hope that, by combining the complementary data derived from different analytical approaches, the metabolic, immunologic and genetic one, there will be a strong argument to adopt the term Intermediary Diabetes Mellitus (IDM) in order to designate the large phenotype of diabetic patients (about 15-30% of all diabetics), which are really placed between T1D and T2D, based both on clinical characteristics (age, BMI, and response for a while to oral drugs), and our (39) and others’ (38, 46) genetic data.

Conflict of interest

The authors declare that they have no conflict of interest.

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