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Type 1 diabetes and type 2 diabetes: what do they have in common?

by L. Groop, Sweden

About 180 million people suffer from diabetes in the world and, of these, more than 95% are considered to have type 2 diabetes. It has been predicted that this number will double within the next 15 years,¹ primarily due to the epidemic increase in type 2 diabetes. There are large ethnic and geographic variations in the prevalence of the 2 forms of diabetes. In Scandinavia, where type 1 diabetes is common, type 2 diabetes is thought to account for about 85% of all cases with diabetes. In

The distinction into 2 main forms of diabetes, type 1 or autoimmune diabetes and type 2 diabetes (with no signs of autoimmunity), may not be as simple as we hitherto have thought. The introduction of sensitive and reproducible assays to identify autoimmune markers for β -cell destruction like glutamic acid decarboxylase (GAD) antibodies has changed this picture. Latent autoimmune diabetes in adults (LADA) accounts for 5% to 10% of all cases with diabetes and is defined by the presence of GAD antibodies and onset after the age of 35 years. LADA is also called slowly progressing type 1 diabetes as the disease shows a steady progression (but slower than early-onset type 1 diabetes) toward insulin requirement. Unfortunately, no large treatment trials have been conducted to aid in the choice of treatment for LADA. A family history of type 1 diabetes can also influence the phenotype of type 2 diabetes even though the patients do not have autoimmune markers; they are younger at disease onset, have a lower body mass index and a more pronounced reduction in β -cell function and are less susceptible to develop cardiovascular complications. Conversely, a family history of type 2 diabetes in a patient with type 1 diabetes is often associated with a later onset, insulin resistance, and more macrovascular complications. It is obvious that these diabetic subgroups do not represent distinct entities but rather parts of a continuum where the proportion of the genetic influence from one or the other will differ. It should be an affordable challenge to provide a clearer picture of the gray area between type 1 and type 2 diabetes in the future.

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(see French abstract on page 337)

Keywords: type 1 diabetes; type 2 diabetes; family history; genotype; latent autoimmune diabetes in adults; maturity-onset diabetes of the young

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Asia, the figure is very different, only a few percent have type 1 diabetes while the majority have type 2 diabetes. The distinction into two forms of diabetes dates back 600 years BC when the Indian physicians Chakrata and Susruta recognized the 2 forms of the disease. In 1866, the British physician Harley reported “There are at least two distinct forms of diabetes requiring diametrically opposing forms of treatment.”² Almost at the same time, a French physician, Lancereaux, made the distinction between the fat and thin form of diabetes (*diabète gras* and *maigre*).³ In the mid 1930s, Falta and Boller divided patients into insulin-sensitive and insulin-resistant diabetes based upon their response to exogenous insulin.⁴ However, the paper by Himsworth (1936) seems to have ultimately introduced the 2 forms of diabetes: “In insulin-sensitive diabetics, the disease is due to deficiency of insulin, while in insulin-insensitive patients, diabetes results, not from the lack of insulin, but from an unknown factor that renders the body insensitive to insulin.”⁵ The terms type 1 and type 2 diabetes were introduced in 1940 and based upon anthropometric studies.⁶ With the introduction of, first, a bioassay and later the radioimmunoassay for insulin, it became clear that the degree of insulin deficiency distinguished the 2 forms.⁷ However, the distinction between type 1 and type 2 diabetes may not be as clear as hitherto thought and even after applying World Health Orga-

SELECTED ABBREVIATIONS AND ACRONYMS

AIDA	autoimmune diabetes in adults
GADA	glutamic acid decarboxylase antibody
ICA	islet cell antibody
IDDM	insulin-dependent diabetes mellitus
LADA	latent autoimmune diabetes in adults
MIN	mixed IDDM and NIDDM
MODY	maturity-onset diabetes of the young
NIDDM	non-insulin-dependent diabetes mellitus

nization (WHO) criteria for the 2 forms of diabetes, a relatively large proportion (up to 30%) of patients remain unclassified.⁸ This review will address this twilight zone between type 1 and type 2 diabetes but also address what the 2 forms have in common.

Type 1 diabetes

Type 1 diabetes indicates an autoimmune process of β -cell destruction that may ultimately lead to diabetes mellitus requiring insulin for survival or prevention of ketoacidosis, coma, or death.⁸ Genetic prediction determined by the human leukocyte antigen (HLA) locus together with immunological and environmental factors are key players in the pathogenesis of the disease. Autoimmune diabetes is further subdivided into a rapidly progressive form

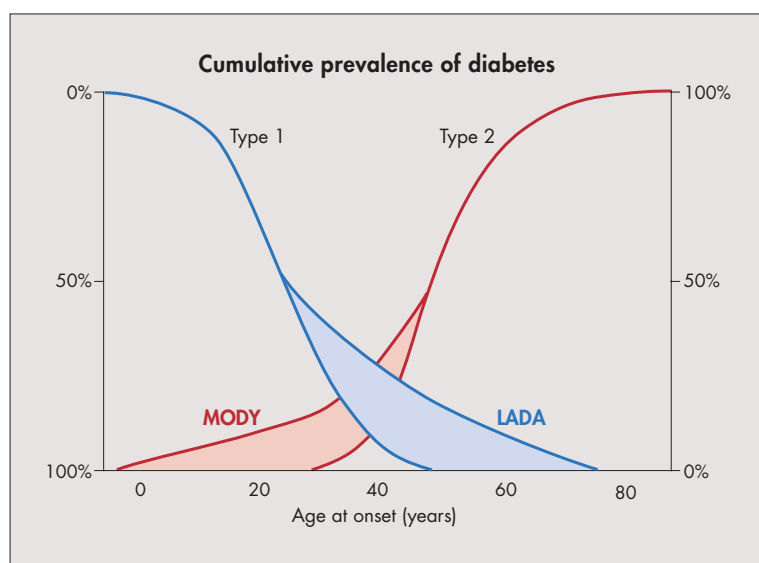


Figure 1. Type 2 diabetes and latent autoimmune diabetes in adults (LADA) increase after the age of 35 years whereas maturity-onset diabetes of the young (MODY) and classic type 1 diabetes peak before the age of 25 years.

that is commonly observed in children below the age of 15 years (but may also occur in adults) and into a slowly progressive form that is also referred to as latent autoimmune diabetes in adults (LADA) and defined as glutamic acid decarboxylase antibody (GADA)-positive diabetes with onset after the age of 35 years (Figure 1).⁹ A small proportion of patients with type 1 diabetes do not show signs of autoimmunity and have been called idiopathic.⁸ Nevertheless, it can be assumed that this form is heterogeneous and encompasses monogenic forms of diabetes like maturity-onset diabetes in the young (MODY) and even forms of neonatal diabetes. Patients with type 1 diabetes are at particular risk of developing microvascular complications.

Type 2 diabetes

Type 2 diabetes encompasses the group of diabetic patients previously called non-insulin-dependent diabetes mellitus (NIDDM). People with type 2 diabetes are usually obese and show both impaired insulin secretion and action. At least initially, these patients do not need insulin to survive and the disease often remains undiagnosed for many years. Type 2 diabetic patients are at increased risk of developing both micro- and macrovascular complica-

tions. Abdominal obesity is considered to play a crucial role in the pathogenesis of the disease, together with deposition of fat in organs where it normally does not belong, like skeletal muscle, liver, and islets leading to peripheral and hepatic insulin resistance and impaired β -cell function. There are, however, most likely several forms of type 2 diabetes, in which the contribution of impaired insulin secretion and action may differ.

The story of LADA

Autoimmunity in the form of circulating antibodies against islet structures (islet cell antibodies [ICA]) was recognized as a key player in type 1 diabetes as far back as the early 1970s. A few years later, the first reports of ICA in patients with apparent type 2 diabetes were published.^{10,11} In these first reports, there was a clear association with other endocrinopathies,¹⁰ but also with failure of treatment with oral antidiabetic drugs.¹¹

My own interest in the topic came through a 79-year old patient who participated in studies on the heterogeneity of type 2 diabetes in the 1980s.¹² She was treated with a sulfonylurea for 1 year, after which the disease rapidly deteriorated and she required insulin therapy. The serum sample taken at diagnosis turned out to be strongly positive for ICA. In our first description of ICA-positive patients with onset after the age of 35 years, we used the term latent type 1 diabetes and could show that there was a clear deterioration of β -cell function over time.¹³ This was more pronounced in patients who also had type 1-related HLA DR3 and/or DR4.¹⁴ In a metabolic characterization of these patients in 1988, we introduced the term autoimmune-diabetes in adults (AIDA).¹⁵ The name LADA was first introduced in 1991 when Ian Mackay suggested that we combine the terms latent and autoimmune diabetes in adults.⁹ In the WHO classification from 1999, LADA was named slowly progressing type 1 diabetes.⁸

◆ Definition and prevalence of LADA

The prevalence of LADA has differed between different studies and populations but also depending upon which definition has been used. In the following, we use the initial definition, ie, age at onset over 35 years and GADA positivity.⁹ With the increasing use of insulin in type 2 diabetes, it is no longer meaningful to include the criterion of no insulin therapy during the first year. We have defined GADA positivity as 5 RU (relative units), which corresponds to mean \pm 3SD of 296 healthy Finnish controls.¹⁶

Among 1122 type 2 diabetic patients from the Botnia study, the prevalence was 9.3%.¹⁶ The Botnia study includes mostly known type 2 diabetic patients from primary care centers. Similar prevalence rates have been reported in hospital-based Caucasian patient samples.¹⁷⁻¹⁹ The prevalence is also dependent upon age at onset; in the United Kingdom Prospective Diabetes Study (UKPDS), it was 34% for those aged 25 to 34 years at diagnosis and 7% for those aged 55 to 65 years at diagnosis.¹⁷ However, in population-based studies, the prevalence is clearly lower.^{20,21} In 4134 drug-naïve type 2 diabetic

patients from the A Diabetes Outcome Progression Trial (ADOPT), the prevalence was similar in North America (4.7%) and in Europe (3.7%).²² There might be a north-south gradient with a lower prevalence in southern than northern Europe.²⁰ In Asia and the Pacific, LADA is less frequent.^{23,24} Nevertheless, high prevalence rates have been reported from China.²⁵ In a large Japanese hospital-based study of 4980 diabetic patients with age at onset >20 years, GADA positivity was found in 3.8%.²⁶ Taken together, the prevalence of LADA varies from 3% to 10% to 15% based upon definition, ascertainment criteria, and ethnicity. More importantly, it is as common or even more common in many regions of the world than classic type 1 diabetes. *Figure 2* shows the spectrum of diabetes in Scandinavia.

◆ *Is LADA a unique entity of diabetes?*

Do we really need a diabetic subgroup called LADA? Why not simply call it adult type 1 diabetes? I think the answer is yes, we do need one. The main argument is that before the era of antibody measurements, LADA was hidden within the group of type 2 diabetic patients, with whom LADA patients share many features. Although in our initial cohort, 76% of type 2 diabetic patients with relative insulin deficiency (glucagon-stimulated C-peptide <0.6 nmol/L) compared with only 12% of non-insulin-deficient patients had GAD antibodies, they rarely progress to absolute insulin deficiency and, if they do, they do it at a much slower rate than patients with early-onset type 1 diabetes. Similar figures were reported in another Finnish study in which 50% to 60% of GADA-positive patients but only 2% of GADA-negative patients required insulin therapy within 6 to 10 years.²⁷ Somewhat higher figures were seen in the UKPDS where 84% of GADA required insulin therapy within 6 years. However, the UKPDS included younger patients than the previous studies.

◆ *LADA versus type 2 diabetes*

There are clear differences between LADA and type 2 diabetes. LADA patients usually have a lower body mass index (BMI), and show less abdominal obesity and fewer features of the metabolic syndrome.¹⁶ Although they have a more severe reduction in β -cell function, they share insulin resistance with type 2 diabetes.²⁸ They are as prone to microvascular but less susceptible to macrovascular complications compared with patients with type 2 diabetes.²⁹ Hyperglycemia seems to be a stronger risk factor for macrovascular disease in LADA than in type 2 diabetes.

◆ *LADA versus type 1 diabetes*

LADA represents a continuum rather than a unique diabetic subgroup. High GADA titer and presence of antibodies against the tyrosine phosphatase-like protein IA-2 point to classic early-onset type 1 diabetes.³⁰ The presence of other autoantibodies directed against thyroid or adrenal tissue or gastric parietal cells suggests that the patient might have an autoimmune polyendocrine syndrome.³¹ It has also been suggested that epitope specificity of GADA differs between patients with early-onset type 1 di-

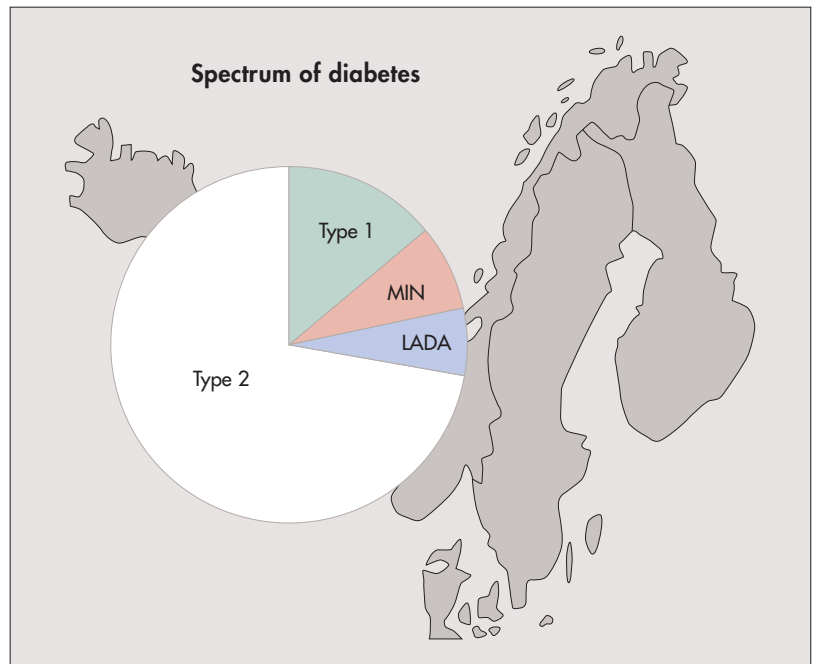


Figure 2. The spectrum of diabetic subgroups. In Scandinavia, latent autoimmune diabetes in adults (LADA) accounts for approximately 10% of all cases of diabetes; this means that almost 25% of all diabetic patients have an autoimmune origin. In addition to LADA, there is a clear genetic interaction between type 1 and type 2 diabetes which we have referred to as MIN (mixed insulin-dependent diabetes mellitus [IDDM] and non-insulin-dependent diabetes [NIDDM]).

abetes and LADA, ie, specificity is more narrow in type 1 diabetes whereas it is more widespread in LADA.³² The question is whether (i) there is something like rapidly progressing type 1 diabetes in adults and (ii) whether LADA differs from it. Few studies have tried to address this issue by analyzing the presence of high-risk (HLA DQB1*0201/0302, 0302/X etc) and protective (DQB1*0602) genotypes.^{16,33,34} We observed a lower frequency of type 1-associated HLA DQB1*0201/0302 in LADA than in type 1 diabetes but higher frequency of protective DQB1*0602 or 0603. However, there seems to be a decline in the heterozygous 0201/0302 with age, while DQB1*0302 persists conferring a similar risk of autoimmune diabetes throughout life.^{16,33} In contrast, no difference in HLA genotypes was observed between LADA patients and adult-onset type 1 diabetic patients (with insulin requirement from diagnosis) in a small study from Hungary.³⁴ In my view, the jury is still out on this issue, we would need much larger patient samples with truly adult-onset type 1 diabetes to be able to address this issue.

◆ *A genetic interaction between type 1 and type 2 diabetes beyond LADA*

In Scandinavia, it is not uncommon for type 1 and type 2 diabetes to be seen in the same families. In the Botnia study, in 11% of 1000 families with type 2 diabetes, there was one family member with type 1 diabetes. A family history of type 1 diabetes had a clear influence on the phenotype of type 2 diabetes: they had earlier onset, lower BMI and C-peptide concentrations, and showed less hypertension and cardiovascular disease than patients with a family history of type 2 diabetes.³⁵ These patients also had less type 1-diabetes associated HLA DQB1 genotypes

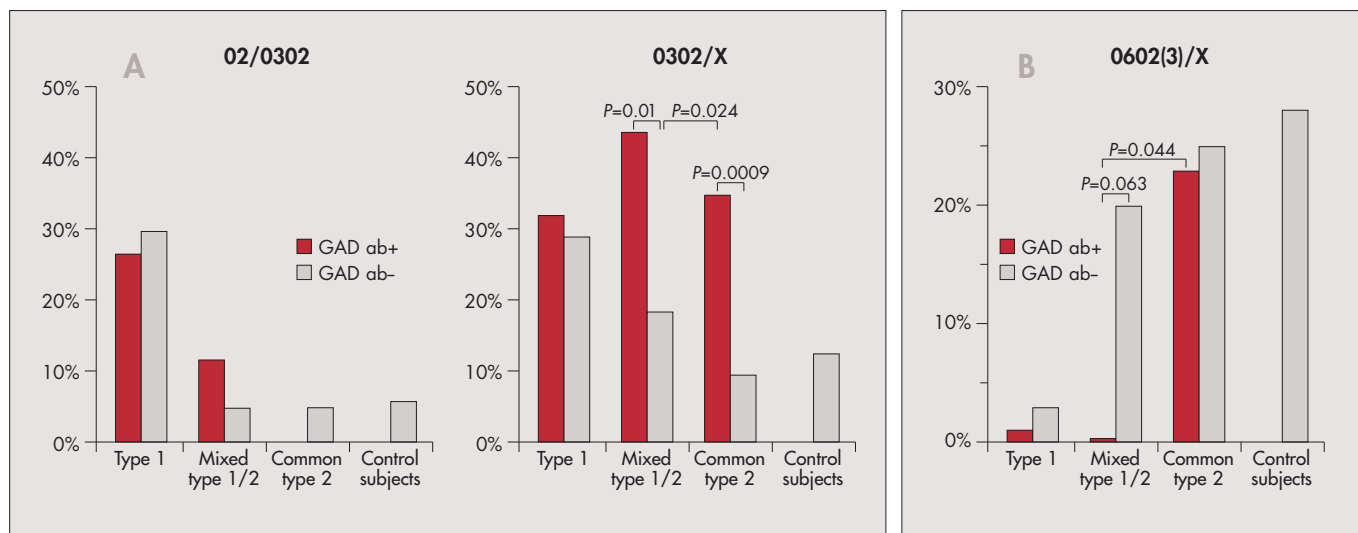


Figure 3 (A and B). Graphs showing the frequency (%) of type 1 diabetes-associated HLA DQB1 genotypes (0302/X, 02/0302/X, **Panel A**; and 0602(3)/X, **Panel B**) in adult-onset type 1 diabetic patients (n=126), type 2 diabetes from mixed type 1/2 families (n=93), or common type 2 families (n=195), and in nondiabetic control subjects (n=172). In Scandinavia, there are about 10% of patients with type 1 diabetes in families with type 2 diabetes. Type 2 diabetic patients from families show earlier onset, lower body mass index, and lower C-peptide concentrations than patients with common type 2 diabetes. They also share the presence of HLA DQB1*0302 genotypes with type 1 diabetes but have more of the protective genotypes, HLA DQB1*0602(0603)/X.

Abbreviations: ab, antibody; GAD, glutamic acid decarboxylase.

Modified from reference 36: Li H, Lindholm E, Almgren P, et al. Possible human leukocyte antigen-mediated genetic interaction between type 1 and type 2 diabetes. *J Clin Endocrinol Metab.* 2001;86:574-582. Copyright © 2001, The Endocrine Society.

(02/0302) than patients with early-onset type 1 diabetes, while there was no difference in the frequency of HLA DQB1*0302/X between the MIN patients (patients with mixed insulin-dependent [IDDM] and non-insulin-dependent diabetes mellitus [NIDDM]) and patients with type 1 diabetes. However, they clearly had more protective HLA DQB1*0602(3)/X than patients with type 1 diabetes (*Figure 3*).³⁶ This is in line with earlier reports showing less cardiovascular disease in type 2 diabetic patients with HLA-DR4 (corresponding to DQB1*0302)³⁷ and increased frequency of HLA-DR4 in long-term survivors of patients with type 2 diabetes.³⁸ We also studied in mixed families whether sharing the HLA haplotype with a type 1 diabetic family member would influence insulin secretion in patients with type 2 diabetes.³⁶ This was the case, with the insulin response to oral glucose being significantly reduced in type 2 patients sharing HLA high-risk haplotypes with a type 1 family member and this was seen regardless of the presence of autoantibodies. In contrast, in unrelated individuals, the same high-risk HLA genotypes did not influence insulin secretion. Similarly, in a study from the United Kingdom, it was suggested that type 2 diabetic parents and grandparents of patients with type 1 diabetes would in fact represent an auto-immune form of diabetes rather than type 2 diabetes.³⁹ Conversely, we observed that in patients with type 1 diabetes, a family history of type 2 diabetes was associated with later onset, higher BMI, and more microalbuminuria (H Li, unpublished observations). In other studies, a family history of type 2 diabetes has been associated with insulin resistance and a high frequency of cardiovascular disease in patients with type 1 diabetes.⁴⁰ Taken together, there is plenty of evidence suggesting a genetic interaction between type 1 and type 2 diabetes influencing the phenotype.

◆ Treatment of LADA

What is the treatment of choice for patients with LADA? Unfortunately, there are few treatment studies to answer this question. A Japanese study compared the effect of insulin and sulfonylureas on progression to insulin dependency in 54 LADA patients.⁴¹ The C-peptide response to oral glucose decreased in the sulfonylurea-treated patients but was maintained unchanged in the insulin-treated patients. This was associated with a 30% progression toward insulin-dependency in the sulfonylurea group compared with 8.3% progression in the insulin-treated group. Given the small number of subjects included this difference was not significant; it became significant only in the individuals with high GADA titers. An attractive alternative is to prevent progression toward insulin dependency by vaccine-based therapy, eg, recombinant glutamic acid decarboxylase (GAD) vaccine. Such trials are ongoing in patients with LADA.⁴²

Do antibodies to CD38 detect a unique subgroup of diabetes?

Human CD38 (adenosine diphosphate [ADP] ribosyl cyclase/cyclic ADP-ribose hydrolase) is a transmembrane glycoprotein commonly used as a differentiation marker for hematopoietic cells. CD38 is also expressed in human islets.⁴³ It is a bifunctional enzyme that catalyzes both the conversion of oxidized nicotinamide adenine dinucleotide (NAD⁺) to cyclic ADP-ribose (cADPR) and the hydrolysis of cADPR back to ADP ribose. cADPR is thought to release Ca⁺⁺ from microsomes through interactions with the ryanodine receptor. Glucose increases the concentration of cADPR, which then stimulates insulin secretion. Glucose-stimulated insulin secre-

tion is enhanced in mice overexpressing CD38 and attenuated in CD38-knockout mice.^{44,45} Recently, autoantibodies to CD38 have been described in both type 1 and type 2 diabetic patients.⁴⁶⁻⁴⁸ Using Western blot, CD38 autoantibodies were detected in 19% of type 1 and 16% of type 2 diabetic patients in Italy.⁴⁵ In the Botnia study, the frequency of CD38 autoantibodies was 8.4% in type 2 diabetes but only 4% in type 1 diabetes.⁴⁷ The frequency was higher in GADA-positive than in GADA-negative patients (14% versus 6%). Functional studies have shown that anti-CD38 autoantibodies raise intracellular calcium and stimulate insulin release in human islets. In keeping with these findings, there was no reduction in insulin secretion in patients with anti-CD38 antibodies as seen in patients with GADA.^{45,46} In contrast, we could not confirm an early report of an interaction between a polymorphism in the *CD38* gene and CD38 autoantibodies.⁴⁸ The role of CD38 in insulin secretion is still debated, but the consistent finding of autoantibodies to this enzyme and cell marker point to new pathways involved in insulin secretion (see Figure 4).⁴⁹

Nonautoimmune ketosis-prone type 2 diabetes

During the past years, a new subgroup of diabetes has emerged, so-called nonautoimmune ketosis-prone type 2 diabetes. Patients are usually African Americans ("Flatbush diabetes")⁵⁰ or of sub-Saharan African origin.^{51,52} The disease manifests itself by ketoacidosis and insulin-dependence at the time of diagnosis followed by long remissions with no insulin requirement. In 76% of the patients, insulin therapy can be discontinued.⁵¹ There is a strong male preponderance and a strong family history of diabetes and the patients usually have a higher age and BMI than patients with type 1 diabetes. Autoimmune markers do not occur. They have less high-risk HLA genotypes than patients with classic type 1 diabetes. It was suggested that variants in a transcription factor, *Pax4*, could contribute to this form of diabetes.⁵³

Inflammation and cytokine-mediated β -cell damage

It has become apparent that autoimmunity is rarely sufficient to cause the β -cell destruction characteristic of type 1 diabetes. Instead a complex sequence of cytokine-mediated events is required to destroy the β cells.^{54,55} Apoptotic events have also been ascribed a role. Some of these events can be triggered by inflammation and may not be specific to type 1 diabetes. Although both impaired insulin secretion and action contribute to the development of type 2 diabetes, a progressive failure of the β cells seems to be responsible for the progressive nature of type 2 diabetes resulting in insulin requirements for metabolic control. Toxic effects of high concentrations of glucose and/or free fatty acids (glucotoxicity and lipotoxicity) have been suggested to promote these events. It is quite possible that similar mechanisms are operative in both type 1 and type 2 diabetes.

The twilight zone between type 1 and type 2 diabetes

There is no doubt that the simple subdivision into type 1 and type 2 diabetes or autoimmune and non-autoimmune diabetes is an oversimplification. Genetic predisposition to one form seems to increase susceptibility to the other and also the course of the disease.

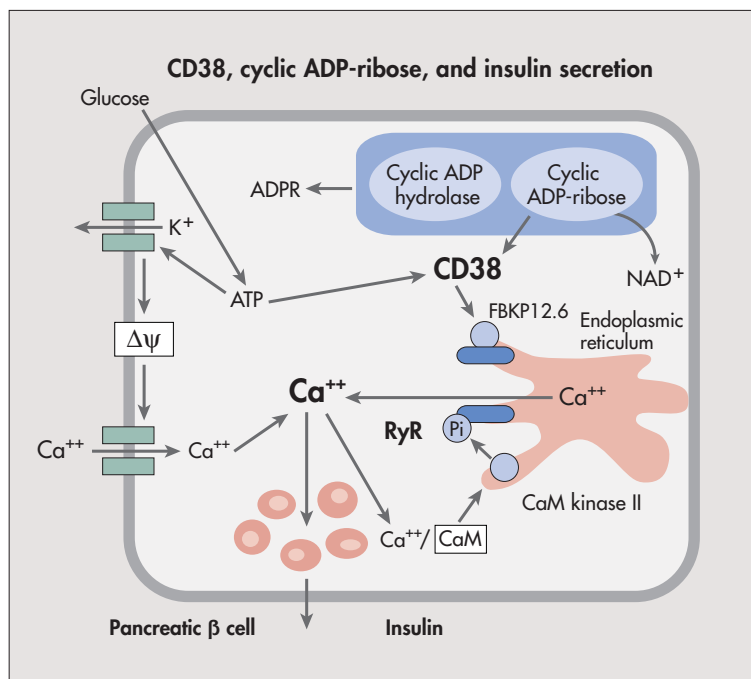


Figure 4. Antibodies to the transmembrane bifunctional enzyme CD38 (adenosine diphosphate [ADP]-ribosyl cyclase/cyclic ADP-ribose hydrolase) are observed in a proportion of patients with type 1 and type 2 diabetes. Functional studies have shown that anti-CD38 autoantibodies raise intracellular calcium and stimulate insulin release in human islets. The final role of these antibodies in the pathogenesis of diabetes is not known.

Abbreviation: ADPR, adenosine diphosphate ribose; ATP, adenosine triphosphate; CaM, calmodulin; NAD⁺, nicotinamide adenine dinucleotide, oxidized form; RyR, ryanodine receptor.

Modified from reference 49: Okamoto H, Takasawa S, Nata K. The CD38-cyclic ADP-ribose signalling system in insulin secretion: molecular basis and clinical implications. *Diabetologia*. 1997; 40:1485-1491. Copyright © 1997, Springer-Verlag.

Within this twilight zone, we find LADA but also type 2 diabetic patients with features of type 1 diabetes without apparent autoimmune markers (we called this form for simplicity MIN or mixed IDDM and NIDDM). Ketosis-prone type 2 diabetes without signs of autoimmunity clearly also falls into this gray area. At the moment, LADA can be best defined as GADA-positive diabetes with onset after the age of 35 years. There is, however, no clear distinction from rapidly progressing type 1 diabetes in adults. Ketoacidosis and an early insulin requirement would point to the latter. Much more research is required to understand this gray area. In the meantime, a careful family history of type 1 or type 2 diabetes (with information of age at onset and mode of therapy) as well as measurements of GADAs in all newly diagnosed adult patients will aid in the classification. A search for other autoimmune markers is worthwhile, as many of these patients also exhibit other endocrine disorders. Finally, we clearly need more therapeutic trials to define what is the treatment of choice in these individuals. □

REFERENCES

1. Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;404:782-787.
2. Harley G. Diabetes, Its Various Forms and Different Treatments. London, UK: Walton and Maberley; 1866.
3. Lancereux E. Le diabète maigre : ses symptômes, son évolution, son pronostic et son traitement. *Un Med Paris*. 1880;20:205-211.
4. Falta W, Boller R. Insularer und insulinresistenter diabetes. *Klin Wochenschr*. 1931;10:438-443.
5. Himsworth HP. Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types. *Lancet*. 1936;ii:127-130.
6. Draper G, Dupurtuis CW, Caughey JL. The differentiation by constitutional methods between pancreatic diabetes and of pituitary origin. *Trans Am Assoc Phys*. 1940;55:146-153.
7. Yalow RS, Berson SA. Plasma insulin concentrations in non-diabetic and early diabetic subjects. *Diabetes*. 1960;9:254-260.
8. Alberti KGMM, Zimmet PZ for the WHO Consultation Group. Definition, Diagnosis and classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Provisional Report of a WHO Consultation. *Diabet Med*. 1998;15:539-553.
9. Tuomi T, Groop L, Zimmet P, Rowley M, Mackay I. Antibodies to glutamic acid decarboxylase (GAD) reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes*. 1993;42:359-362.
10. Irvine WJ, McCallum CJ, Gray SR, et al. Pancreatic islet cell antibodies in diabetes mellitus correlated with the duration and the type of diabetes, coexistent autoimmune disease and HLA-type. *Diabetes*. 1977;26:138-147.
11. Irvine WJ, Sawers JSA, Feek CM, Prescott RJ, Duncan LPJ. The value of islet cell antibody in predicting secondary failure of oral hypoglycaemic agent therapy in diabetes mellitus. *J Clin Lab Immunol*. 1979;2:23-26.
12. Groop L. Heterogeneity of type 2 diabetes. A study of clinical, genetic, immunological and metabolic aspects [thesis]. Helsinki, Finland: University of Helsinki; 1982.
13. Groop L, Bottazzo GF, Doniach D. Islet cell antibodies identify latent type 1 diabetes in patients aged 35-75 years at diagnosis. *Diabetes*. 1986;35:237-241.
14. Groop L, Miettinen A, Groop P-H, Meri S, Koskimies S, Bottazzo GF. Organ-specific autoimmunity and HLA-DR antigens as markers for β -cell destruction in patients with type II diabetes. *Diabetes*. 1988;37:99-103.
15. Groop L, Eriksson J, Ekstrand A, Franssila-Kallunki A, Saloranta C, Miettinen A. Metabolic characteristics of autoimmune diabetes in adults. *Diabetologia*. 1991;34:46-51.
16. Tuomi T, Carlsson AL, Li H, et al. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes*. 1999;48:150-157.
17. Turner R, Stratton I, Horton V, et al, for the UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1997;350:1288-1293.
18. Gottsäter A, Landin-Olsson M, Lernmark Å, Fernlund P, Sundkvist G, Hagopian WA. Glutamate decarboxylase antibody predict rate of beta-cell decline in adult-onset diabetes. *Diabetes Res Clin Pract*. 1995;27:133-140.
19. DiMario U, Irvine WJ, Borsev DQ, Kyner JL, Weston J, Galfo C. Immune abnormalities in diabetic patients not requiring insulin at diagnosis. *Diabetologia*. 1983;25:392-395.
20. Bosi EP, Garancini NT, Poggiali F, Bonifacio E, Gallus G. Low prevalence of islet autoimmunity in adult diabetes and low predictive value of islet autoantibodies in the general adult population of northern Italy. *Diabetologia*. 1999;42:840-844.
21. Rolandsson O, Hägg E, Hampe C, et al. Glutamate decarboxylase (GAD 65) and tyrosine phosphatase-like protein (IA-2) autoantibodies index in a regional population is related to glucose intolerance and body mass index. *Diabetologia*. 1999;42:555-559.
22. Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed MI for the ADOPT Study Group. Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. *Diabetes*. 2004;53:3193-3200.
23. Medici F, Hawa MI, Giorgini A, et al. Antibodies to GAD65 and tyrosine phosphatase-like molecule IA-2 in Flippin type 1 diabetic patients. *Diabetes Care*. 1999;22:1458-1463.
24. Dowse GK, Zimmet PZ, Spark RA, Mavo B, Rowley MJ, Mackay IR. Lack of antibodies to glutamic acid decarboxylase in young adults of the high diabetes prevalence Wanigela people of Papua New Guinea. *Diabetes Res Clin Pract*. 1994;24:195-198.
25. Thai AC, Ng WY, Loke KY, Lee WR, Lui KF, Cheah JS. Anti-GAD antibodies in Chinese patients with youth and adult-onset IDDM and NIDDM. *Diabetologia*. 1997;40:1425-1430.
26. Takeda H, Kawasaki E, Shimizu I, et al. Clinical, autoimmune, and genetic characteristics of adult-onset diabetic patients with GAD autoantibodies in Japan (Ehime Study). *Diabetes Care*. 2002;25:995-1001.
27. Niskanen L, Tuomi T, Karjalainen J, Groop LC, Uusitupa M. GAD antibodies in NIDDM - Ten year follow-up from the diagnosis. *Diabetes Care*. 1995;18:1557-1565.
28. Carlsson AL, Sundkvist G, Groop L, Tuomi T. Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA). *J Clin Endocrinol Metab*. 2000;85:76-80.
29. Isomaa B, Almgren P, Henricsson M, et al. Chronic complications in patients with slowly progressing type 1 diabetes (LADA). *Diabetes Care*. 1999;22:1347-1353.
30. Seissler J, de Sonnaville J, Morgenthyaler N, et al. Immunological heterogeneity in Type 1 diabetes: presence of distinct autoantibody patterns in patients with acute onset and slowly progressing disease. *Diabetologia*. 1998;41:891-897.
31. Tuomi T, Perheentupa J. Type 1 Diabetes in Autoimmune Syndromes. In: Sperling MA, ed. *Contemporary Endocrinology: Type 1 Diabetes: Etiology and Treatment*. Totowa, NJ: Humana Press Inc; 2003:93-114.
32. Lernmark Å. Glutamic acid decarboxylase antibodies and diabetes complications. Assay reliability and validity. *Diabetes Care*. 1995;18:269-271.
33. Caillat-Zucman S, Garchon HJ, Timsit J, et al. Age-dependent HLA genetic heterogeneity of type 1 insulin dependent diabetes mellitus. *J Clin Invest*. 1992;90:2242-2250.
34. Hosszufalusi N, Vataj A, Rajczyk K, et al. Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. *Diabetes Care*. 2003;26:452-457.
35. Li H, Isomaa B, Almgren P, Taskinen M-R, Groop L, Tuomi T. Consequences of a family history of type 1 or type 2 diabetes on the phenotype of patients with type 2 diabetes. *Diabetes Care*. 2000;23:589-594.
36. Li H, Lindholm E, Almgren P, et al. Possible human leukocyte antigen-mediated genetic interaction between type 1 and type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:574-582.
37. Forsblom C, Sane T, Groop P-H, et al. Risk factors for mortality in Type II (non-insulin-dependent): evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia*. 1998;41:1253-1262.
38. Tuomilehto-Wolf E, Tuomilehto J, Hitman GA, et al. Genetic susceptibility to non-insulin dependent diabetes mellitus and glucose intolerance are ocated in the HLA region. *BMJ*. 1993;307:155-159.
39. Douek IF, Gillespie KM, Bingley PJ, Gale EA. Diabetes in the parents of children with type I diabetes. *Diabetologia*. 2002;45:495-501.
40. Fagerudd JA, Pettersson-Fernholm KJ, Gronhagen-Riska C, Groop PH. The impact of a family history of Type II (non-insulin-dependent) diabetes mellitus on the risk of diabetic nephropathy in patients with Type I (insulin-dependent) diabetes mellitus. *Diabetologia*. 1999;42:519-526.
41. Maruyama T, Shimada A, Kanatsuka A, et al. Multicenter prevention trial of slowly progressive type 1 diabetes with small dose of insulin (the Tokyo Study). Preliminary report. *Ann NY Acad Sci*. 2003;1005:362-369.
42. Agardh CD, Cilio CM, Lethagen ÅL, et al. Clinical evidence for the safety of GAD65 immunomodulation in adult-onset autoimmune diabetes. *J Diabetes Complications*. In press
43. Ikehata F, Satoh J, Nata K, et al. Autoantibodies against CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) that impair glucose-induced insulin secretion in noninsulin-dependent diabetes patients. *J Clin Invest*. 1998;102:395-401.
44. Kato I, Takasawa S, Akabane A, et al. Regulatory role of CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) in insulin secretion in pancreatic cells. Enhanced insulin secretion in CD-38 expressing transgenic mice. *J Biol Chem*. 1995;270:30045-30050.
45. Kato I, Yamamoto Y, Fujimura M, Noguchi N, Takasawa S, Okamoto H. CD38 disruption impairs glucose-induced increases in cyclic ADP-ribose [Ca²⁺] and insulin secretion. *J Biol Chem*. 1999;274:1869-1872.
46. Pupilli C, Giannini S, Marchetti P, et al. Autoantibodies to CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) in Caucasian patients with diabetes. Effects on insulin release from human islets. *Diabetes*. 1999;48:2309-2315.
47. Antonelli A, Baj G, Marchetti P, et al. Human anti-CD38 autoantibodies raise intracellular calcium and stimulate insulin release in human pancreatic islets. *Diabetes*. 2001;50:985-991.
48. Antonelli A, Tuomi T, Nannipieri M, et al. Autoimmunity to CD38 and GAD in type 1 and type 2 diabetes: CD38 and HLA genotypes and clinical phenotypes. *Diabetologia*. 2002;45:1298-1306.

49. Okamoto H, Takasawa S, Nata K. The CD38-cyclic ADP-ribose signalling system in insulin secretion: molecular basis and clinical implications. *Diabetologia*. 1997;40:1485-1491.
50. Banerji MA, Chaiken RI, Huey H, et al. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Flatbush diabetes. *Diabetes*. 1994;43:741-745.
51. Mauvais-Jarvis F, Sobngwi E, Porcher R, et al. Ketosis-prone type 2 diabetes in patients of Sub-Saharan African origin. Clinical pathophysiology and natural history of β -cell dysfunction and insulin resistance. *Diabetes*. 2004;53:645-653.
52. Maldonado M, Hampe C, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and β -cell functional classification, prospective analysis, and clinical outcomes. *J Clin Endocrinol Metab*. 2003;88:5090-5098.
53. Mauvais-Jarvis F, Smith SB, Le May C, et al. PAX4 gene variations predispose to ketosis-prone diabetes. *Hum Mol Genet*. 2004;13:3151-3159.
54. Kolb H, Mandrup-Poulsen T. An immune origin of type 2 diabetes? *Diabetologia*. 2005;
55. Mandrup-Poulsen T. Beta cell death and protection. *Ann NY Acad Sci*. 2003;1005:32-42.

DIABÈTES DE TYPE 1 ET DE TYPE 2 : QU'ONT-ILS EN COMMUN ?

*L*a distinction entre les deux formes principales de diabète, le diabète de type 1 ou diabète auto-immun et le diabète de type 2 (sans aucun signe d'auto-immunité) n'est pas aussi simple que nous l'avions cru jusqu'ici. L'introduction de dosages sensibles et reproductibles pour identifier les marqueurs auto-immuns de destruction des cellules β comme les anticorps de la décarboxylase de l'acide glutamique (GAD) ont changé le tableau. Le diabète latent auto-immun de l'adulte (DLAA) compte pour 5 % à 10 % de tous les cas de diabète et il est défini par la présence d'anticorps GAD et par une installation après l'âge de 35 ans. Le DLAA est aussi appelé le diabète de type 1 à progression lente car la maladie progresse régulièrement (mais plus doucement que le diabète de type 1 d'installation précoce) vers les besoins en insuline. Malheureusement, aucune grande étude n'a été conduite pour aider au choix du traitement pour le DLAA. Des antécédents de diabète de type 1 peuvent aussi influencer sur le phénotype du diabète de type 2 même si les patients n'ont pas de marqueurs auto-immuns ; ils sont plus jeunes à l'installation de la maladie, ont un indice de masse corporel plus bas, une réduction plus prononcée de la fonction des cellules β et sont moins enclins à développer des complications cardiovasculaires. À l'inverse, des antécédents de diabète de type 2 chez un patient ayant un diabète de type 1 sont souvent associés à une insulino-résistance d'installation tardive et à plus de complications macrovasculaires. Il est évident que ces sous-groupes de diabétiques ne représentent pas une entité distincte mais plutôt une partie du continuum dans lequel la proportion de l'influence génétique de l'un à l'autre différera. Le défi qui consiste à éclairer la nébuleuse entourant le diabète de type 1 et le diabète de type 2 deviendrait accessible.

