The many faces of diabetes: a disease with increasing heterogeneity

Tiinamaija Tuomi, Nicola Santoro, Sonia Caprio, Mengyin Cai, Jianping Weng, Leif Groop

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Department of Medicine, Helsinki University Hospital, Helsinki, Finland (T Tuomi MD); **Folkhälsan Research Center, Helsinki, Finland** (T Tuomi); **Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki, Finland** (T Tuomi); **Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA** (N Santoro MD, Prof S Caprio MD); **Department of Endocrinology, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China** (M Cai MD, Prof J Weng MD); **Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, Malmö, Sweden** (Prof L Groop MD); **and Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland** (Prof L Groop)

Correspondence to: Prof L Groop, Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, Malmö, Sweden **leif.groop@med.lu.se**

Diabetes is a much more heterogeneous disease than the present subdivision into types 1 and 2 assumes; type 1 and type 2 diabetes probably represent extremes on a range of diabetic disorders. Both type 1 and type 2 diabetes seem to result from a collision between genes and environment. Although genetic predisposition establishes susceptibility, rapid changes in the environment (ie, lifestyle factors) are the most probable explanation for the increase in incidence of both forms of diabetes. Many patients have genetic predispositions to both forms of diabetes, resulting in hybrid forms of diabetes (eg, latent autoimmune diabetes in adults). Obesity is a strong modifier of diabetes risk, and can account for not only a large proportion of the epidemic of type 2 diabetes in Asia but also the ever-increasing number of adolescents with type 2 diabetes. With improved characterisation of patients with diabetes, the range of diabetic subgroups will become even more diverse in the future.

Introduction

Diabetes is a disorder of chronic hyperglycaemia, and has traditionally been subdivided into type 1 diabetes (with autoimmune destruction of insulin-secreting β cells) and type 2 diabetes (with insulin resistance and features of metabolic syndrome). However, this subdivision is a gross oversimplification, and poorly describes the true range of diabetes. The notion of diabetes has widened in the past few decades with the realisation that several different overlapping mechanisms can lead to diabetes, and that these mechanisms and manifestations of the disease can be modified by genetic and environmental factors. Diabetes can result from destruction of pancreatic β cells as a result of autoimmune attack (advanced type 1 diabetes), resulting in total insulin deficiency (table 1). Less severe insulin deficiency occurs in patients with pancreatitis. The genetic characterisation of monogenic forms of diabetes (maturity-onset diabetes in the young [MODY]) implies the existence of another type of insulin deficiency, characterised by defective control of insulin secretion; β cells survive and produce insulin, but they respond poorly to increases in plasma concentrations of glucose.[6] Mechanisms of defective control also operate in neonatal diabetes and mitochondrial diabetes. Although patients with type 2 diabetes often secrete large amounts of insulin, insulin sensitivity and secretion are imbalanced, and the increased concentration of insulin is not sufficient to meet the increased demands imposed by obesity and insulin resistance.[7] Thereby, defective pancreatic β cells account for most, if not all, forms of diabetes.

In addition to these well established notions, many patients present with overlapping features. Indeed, if the processes leading to type 1 diabetes, type 2 diabetes, and MODY are thought to be separate, a proportion of the population might have features of two or more diabetes types. In this Review, we discuss some of the key factors contributing to this heterogeneity, including distorted age at onset for both type 1 and type 2 diabetes, different susceptibilities to obesity in different ethnic groups, and the role of genetic factors. We discuss changing notions rather than provide a complete overview of all diabetic subgroups. Although we discuss young-onset and adult-onset diabetes separately, they share similar aetiopathogenetic processes leading to diabetes. The group with highest heterogeneity and risk of misclassification is young adults (20–40 years of age), who are at the intersection of these two age groups.

Search strategy and selection criteria

For the section about type 2 diabetes in youth we searched PubMed with the terms "obesity", "type 2 diabetes", "children and adolescents", "youth", "puberty", "hepatic steatosis", "visceral fat", "fat partitioning", "IMCL", and "genes", and selected publications that we judged to be original and relevant to the topic. Only English-language articles were assessed. For the section about latent autoimmune diabetes in adults (LADA), we searched PubMed and the Cochrane Library with the terms "LADA" and "GAD antibodies" in combination with "type 2 diabetes", and selected publications with at least 100 patients with LADA or smaller studies with prospective follow-up data. Data for genetic variants reported in at least two separate studies were included. For the section about diabetes in Asia, we searched PubMed with the terms "China", "Middle East", "type 1 diabetes", "type 2 diabetes", "obesity", "prevalence", "incidence", "children", "adolescents", "body mass index", and "visceral fat", and selected articles that we judged to be relevant to the topic. We also searched the reference lists of articles identified by this search strategy and selected those that we judged relevant. Review articles are cited to provide more detail and references than this Review could accommodate.

Diabetes with onset in childhood or adolescence

Emergence of type 2 diabetes in pubertal and post-pubertal adolescents

Until three decades ago, all diabetic children and adolescents were assumed to have type 1 diabetes. In 1990–99, the age-adjusted incidence of type 1 diabetes per 100 000 children younger than 15 years per year in 114 populations varied from 0·51 in China to 40·9 in Finland;[8,9] the incidence has rapidly risen, particularly in white populations. Type 1 diabetes remains the most common form of diabetes in children.[10] However, the accelerating yearly increase in new cases of type 1 diabetes seems already to have levelled off in high-risk

countries (eg, Finland and Sweden).[11,12] At the same time, the unabated increase in childhood obesity has resulted in the emergence of type 2 diabetes as a new type of paediatric diabetes.[13,14]

Type 2 diabetes occurs after 10 years of age, usually after the onset of puberty, with an estimated incidence of 7·0–49·4 per 100 000 person-years in children aged 10–19 years in the USA.[10] In the USA in 2010, about 20 000 people younger than 20 years had type 2 diabetes; this number could increase to about 84 000 by 2050.[14] Findings from the SEARCH for Diabetes in Youth study[10] showed that the prevalence of type 2 diabetes had increased by 21% in American youths from 2001 to 2009, whereas type 1 diabetes increased by 23%. Thereby, 0·26% of people younger than 20 years have diabetes in the USA, and most have type 2 diabetes.[15]

The prevalence of type 2 diabetes is even higher in Asia. Findings from the China Health and Nutrition Survey[16] in 1989–2011 showed that Chinese teenagers had a rate of diabetes several times larger than that of their counterparts in the USA, with 1·9% having manifest diabetes and 14·9% having prediabetes at age 7–18 years. As in the USA, Chinese children who develop type 2 diabetes are typically overweight or obese. Overall, the prevalence of overweight and obesity increased from 1·7% in 1982, to 5·3% in 2002, in Chinese children aged 7–12 years.[17]

The link between obesity and type 2 diabetes: accumulation of ectopic fat

Obesity-related accumulation of ectopic fat in key insulin-sensitive organs (eg, skeletal muscle and the liver) causes changes to the insulin-signalling pathway.[18] These changes cause increased insulin resistance, characterised by defects in the non-oxidative pathway of glucose metabolism, high intramyocellular lipid content, and high fat content of the viscera and liver.[19–21] Fat accumulation in the liver is an important trigger of insulin resistance, and severe accumulation is associated with prediabetes in adolescents.[22] Importantly, in obese adolescents the negative effect of fatty liver on insulin sensitivity is independent of the degree of visceral fat and intramyocellular lipid content.[23] Findings from a longitudinal study[24] showed that baseline hepatic fat content correlated with 2 h glucose, insulin sensitivity, and insulin secretion at 2 year follow-up. These and other findings[25] suggest that accumulation of intrahepatic fat is more harmful than is accumulation of ectopic fat elsewhere in the body.[24] Although accumulation of hepatic fat is more pronounced in adolescence, it can start during the prepubertal period.[26] Furthermore, ectopic fat distribution also seems to impair insulin secretion. Alderete and colleagues[27] reported that accumulation of liver fat might affect β-cell compensation for insulin resistance. Taken together, these data strongly support the notion that distribution of ectopic fat is the actual link between obesity and type 2 diabetes.

	Insulin deficiency	Insulin resistance	Treatment of insulin deficiency
Destruction of β cells[1]			
Autoimmunity, type 1 diabetes	+ to +++	+/–	Insulin
LADA, autoimmunity?	+ to +++	+ to ++	OHA or insulin
Pancreatitis	+ to +++	+/–	OHA or insulin
Pancreatectomy	+++	+/–	Insulin
CEL-MODY[2]	++	+/–	Insulin
Defective response to glucose[1]			
Glucokinase-MODY	+	+/–	None (diet, rarely OHA)
HNF1α-MODY	++	+/–	OHA or meal-time insulin
HNF4α-MODY	++	+	OHA or meal-time insulin
Mitochondrial diabetes	+ to +++	+/–	OHA or insulin
Type 2 diabetes	+ to ++	++ to +++	OHA or insulin
Low β-cell mass from birth[1]			
HNF1β-MODY[3]	+ to ++	+/–	Insulin
PDX1-MODY—heterozygotes?	+	+/–	OHA
PDX1-MODY—homozygotes	+++	+/–	Insulin
Other MODY forms?	+++	+/–	Insulin
Defective processing of insulin			
WFS1-diabetes[4]	++	+/–	Insulin
Ketosis-prone diabetes[5]	+ to +++*	++ to +++	None, OHA, insulin

The grading of the severity of insulin deficiency or insulin resistance is our own interpretation. Severity of insulin deficiency: none or mild (+/–), mild (+), marked (++), severe (+++). LADA=latent autoimmune diabetes in adults. OHA=oral hypoglycaemic agents. CEL=carboxylesterlipase. MODY=maturity-onset diabetes in the young. HNF=hepatic nuclear factor. *At presentation or relapses.

Table 1: **A schematic presentation of the typical degree of insulin deficiency and insulin resistance in subgroups of diabetes**

Puberty and ethnic origin as major risk factors for type 2 diabetes in children

Type 2 diabetes usually manifests during midpuberty[10] together with a peak of transient insulin resistance,[28] probably because of increasing concentrations of growth hormone.[29] In healthy adolescents, transient insulin resistance is balanced by an increase in insulin secretion, but this increase is counterbalanced by the co-occurrence of obesity. Notably, β-cell failure in young people occurs faster than in adults; whereas in adults the transition towards type 2 diabetes takes about 10 years with roughly 7% yearly reductions in β-cell function,[30,31] in obese adolescents β cells deteriorate at a rate of roughly 15% per year,[32] with a mean transition time from prediabetes to overt diabetes of about 2·5 years.[33]

Sex and ethnic origin are additional risk factors. Whereas type 1 diabetes is prevalent in non-Hispanic white adolescents, type 2 diabetes is more frequent in adolescents from other ethnic groups. Similar to findings in adults, African-American, Hispanic, Asian-Pacific-Islander, and American-Indian adolescents have much higher incidence and prevalence of type 2 diabetes than do non-Hispanic white adolescents.[10] Within each ethnic group, girls have a higher risk than do boys (figure 1),[10] which can result from the fact that adolescent girls have a more severe degree of insulin resistance than do boys.[35] The ethnic difference is more complex. In the USA,

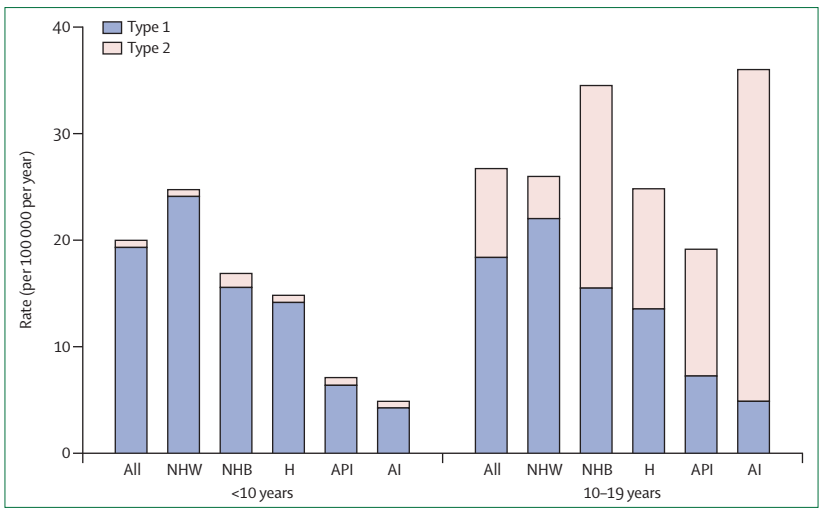

Figure 1: **The rate of new cases of type 1 and type 2 diabetes in US youths (<20 years) by ethnic origin, 2002–05**
NHW=non-Hispanic white. NHB=non-Hispanic black. H=Hispanic or Latino. API=Asian-Pacific-Islander. AI=American-Indian. Figure based on data from the US National Institute of Diabetes and Digestive and Kidney Diseases[34] and the SEARCH for Diabetes in Youth Study.[10]

African-American people have the highest rate of type 2 diabetes,[36–38] despite having higher insulin secretion (by comparison with insulin sensitivity) than do white people.[37,38] Very little is known about genetic variation associated with type 2 diabetes in adolescents. A variant of *TCF7L2*, which has the strongest association with type 2 diabetes in most populations, was more strongly associated with type 2 diabetes in African-American youths aged 10–22 years than in African-American adults (but not in non-Hispanic white youths), suggesting that the association with *TCF7L2* might have a more pronounced effect in patients with an earlier age at onset.[39,40] The co-occurrence of five common variants in or near genes modulating insulin secretion is associated with a higher risk of development of prediabetes and type 2 diabetes in youth.[41] This finding seems to support the theory that a stronger genetic load would lead to a lower age at onset of type 2 diabetes.

Difficulties with classification: type 1 diabetes, type 2 diabetes, or monogenic diabetes?

Although paediatric patients with type 2 diabetes are always obese and have features of metabolic syndrome, neither overweight nor metabolic syndrome protects from type 1 diabetes; in children and adolescents with newly diagnosed diabetes, differential diagnostics with testing for autoantibodies and alertness for development of ketoacidosis is therefore imperative. The diagnosis of type 1 diabetes is straightforward in normal weight, autoantibody-positive patients who present with ketoacidosis at 10 years or younger. Even older patients who are autoantibody-positive or ketotic usually have type 1 diabetes. However, similar to adult patients with ketosis-prone diabetes, ketoacidosis is detected in nearly 20% of young patients with clinical type 2 diabetes in the USA.[42] As type 2 diabetes becomes more common in young age groups, the discriminatory value of ketoacidosis will weaken, especially in children of African ethnic origin. Furthermore, a subgroup exists of patients with clinical type 2 diabetes and pancreatic autoantibodies. In Germany, 46 of 128 children and adolescents aged 1–19 years at diagnosis of type 2 diabetes (36%) had pancreatic autoantibodies. In a larger study from the USA, 118 of 1206 children aged 10–17 years at diagnosis of type 2 diabetes (9·8%) were antibody positive.[43,44] This subgroup has been called latent autoimmune diabetes in youth,[43] as an analogue to latent autoimmune diabetes in adults (LADA), but follow-up data are needed to establish whether these patients eventually develop insulin deficiency.

If the presence of antibodies and ketoacidosis do not always provide definitive criteria to separate type 1 from type 2 diabetes, ethnic origin might be even less useful. Type 1 diabetes is most prevalent in children of European decent. However, even ethnic differences can depend on environmental triggers. Somali children who had moved to Finland had as high an incidence of autoantibody-positive type 1 diabetes as did children of Finnish origin,[45] although the rate of type 1 diabetes is very low in Somalia.

The clinical presentation of type 2 diabetes in children also hampers diagnosis of monogenic diabetes. The criteria used previously for monogenic diabetes (age at diagnosis <25 years, autosomal inheritance, and no insulin dependency) are met by most young people with type 2 diabetes. Thus the International Society for Pediatric and Adolescent Diabetes published clinical consensus practice guidelines to define features in children originally diagnosed with type 1 or type 2 diabetes that should raise a suspicion of monogenic diabetes.[46] For example, an atypical patient with type 1 diabetes, younger than 6 months at diagnosis, detectable C-peptide secretion after 3 years of disease duration, and no autoantibodies could have monogenic diabetes; an atypical patient with type 2 diabetes who is not obese and has no evidence of insulin resistance (no acanthosis nigricans, normal C peptide) could also have monogenic diabetes, particularly if they have an ethnic background associated with low prevalence of type 2 diabetes. The use of ethnic background, however, is controversial and can lead to underdiagnosis of MODY in patients of Asian or African origin.[47]

Diabetes with onset in adults

Classification of diabetes is mostly based on age at onset, together with the presence of either obesity and metabolic syndrome or insulin deficiency and autoantibodies; family history can assist with diagnosis. None of these criteria are clear cut. The cutoff for age at onset (35–40 years), traditionally used to distinguish between type 1 and type 2 diabetes, is of little clinical value nowadays. Classification can be particularly difficult in adults aged 20–50 years, during which not only type 1

and type 2 diabetes, but also MODY and secondary diabetes, often occur. Obesity and metabolic syndrome have generally been used as the basis for diagnosis of type 2 diabetes, but they are increasingly common both in the adult population worldwide and in people who develop type 1 diabetes. Thus rather than confirming type 2 diabetes, the diagnostic value of these criteria lies in their absence; patients who are not overweight and do not have features of metabolic syndrome do not have type 2 diabetes, and other types of diabetes should be considered. Moreover, patients with adult-onset type 1 diabetes often have residual β-cell function at diagnosis, making their clinical presentation similar to that for type 2 diabetes. However, many patients with type 2 diabetes can be undiagnosed for years until they present with severe hyperglycaemic symptoms, and can therefore need immediate initiation of insulin therapy to control hyperglycaemia. Additionally, a subgroup exists of patients who are diagnosed with type 2 diabetes and have pancreatic autoantibodies. These uncertainties in the diagnostic criteria of diabetes emphasise the need for an improved classification, and have led to the introduction of LADA as a diabetes classification. Whether LADA represents a clinical subtype on its own, or is merely a stage in the process leading to type 1 diabetes in adults, has provoked lively discussion.[48–52]

LADA

LADA is heterogeneous

Most patients with type 1 diabetes have pancreatic autoantibodies, which can react with non-specific cytoplasmic antigens in islet cells, glutamic acid

	Study design	Frequency of GAD antibody positivity	Duration of diabetes	Number of patients with LADA (year of study if more than one group)	Number of patients with type 2 diabetes (year of study if more than one group)	Selection criteria for LADA			Measurement of β-cell function	Measurement of insulin resistance or metabolic syndrome	Measurement of high *vs* low concentrations of GAD antibody	Other auto-antibodies
						Age at diagnosis (years)	Time free from insulin therapy (months)	Auto-antibodies				
UKPDS (UK)[56–58]	Prospective	13·2%	<1 year	526 (1997);[56] 378 (2006–07)[57,58]	4545 (1997);[56] 400 (2006–07)[57,58]	25–65	≥3	Islet-cell antibody, GAD antibody	Treatment with insulin, HOMA-β	HOMA-IR, BMI	Yes	IA-2 antibody
Botnia (Finland)[59–62]	Cross-sectional	9·3%	Any	104 (1999);[59] 217 (2000);[60] 294 (2010–13)[61,62]	1122 (1999);[59] 744 (2000);[60] 648 (2010–13)[61,62]	>35*	≥6–12	GAD antibody	C peptide, oral glucose-tolerance test, (intravenous glucose tolerance test[60])	HOMA-IR, BMI, waist circum-ference, blood pressure, lipids, (normoglycaemic hyper-insulinaemic clamp[60])	Yes	Islet-cell antibody, IA-2 antibody, ZnT8 antibody, thyroidal antibody
Castleden and colleagues (UK)[63]	Cross-sectional	7%	..	136	1923	>25	12	GAD antibody	Treatment with insulin	BMI	Yes	..
Fourlanos and colleagues (Australia)[64]	..	..	..	102	111	30–75	..	..	Treatment with insulin	BMI	..	..
ADOPT (USA, Canada, and Europe)[65]	Cross-sectional (drug inter-vention)	4·3%	<3 years†	174	3960	..	..	GAD antibody	Oral glucose-tolerance test	HOMA-IR, BMI, waist circum-ference, blood pressure, lipids‡	Yes	..
HUNT (Norway)[66,67]	Cross-sectional and prospective	10%	..	106–128	943–1134	≥20	12, or <12 if C-peptide concentration >150 pmol/L	GAD antibody	C peptide, treatment with insulin	BMI, waist circumference, blood pressure, lipids	Yes	IA-2 antibody, ZnT8 antibody
NIRAD (Italy)[68,69]	Cross-sectional and prospective	4·5%	6 months to 5 years	193 (2007);[68] 236 (2012)[69]	4057 (2007);[68] 450 (2012)[69]	..	..	GAD antibody, IA-2 antibody	Treatment with insulin	BMI, waist circumference, lipids	Yes	..

(Continues on next page)

	Study design	Frequency of GAD antibody positivity	Duration of diabetes	Number of patients with LADA (year of study if more than one group)	Number of patients with type 2 diabetes (year of study if more than one group)	Selection criteria for LADA			Measurement of β-cell function	Measurement of insulin resistance or metabolic syndrome	Measurement of high *vs* low concentrations of GAD antibody	Other auto-antibodies
						Age at diagnosis (years)	Time free from insulin therapy (months)	Auto-antibodies				
(Continued from previous page)												
Sardinia (Italy)[70]	Cross-sectional	4·9%	<5 years	276	5292	..	..	GAD antibody	Treatment with insulin	BMI, waist circumference, blood pressure, lipids	Yes	IA-2 antibody, TPO antibody
Hungary[71]	Cross-sectional and meta-analysis	..	..	211	1297	>35	6	Islet-cell antibody, GAD antibody, IA-2 antibody, or insulin antibody	..	..	..	..
Action LADA (Europe)[72]	Cross-sectional	8·8%	<5 years	384	5558§	30–70	6	GAD antibody, IA-2 antibody, or ZnT8 antibody	Treatment with insulin	BMI, waist circumference, blood pressure, lipids	Yes	..
LADA China Study (China)[73]	Cross-sectional	5·9%	<1 year	287 (180 by genetic analysis)	4593 (174 by genetic analysis)	≥30	6	GAD antibody	..	..	Yes	..

GAD=glutamic acid decarboxylase. LADA=latent autoimmune diabetes in adults. HOMA-β=homoeostasis model assessment of β-cell function. HOMA-IR=homoeostasis model assessment of insulin resistance. BMI=body-mass index. IA-2=protein tyrosine phosphatase IA-2. ZnT8=zinc transporter 8. *No initial selection criteria for age but most patients were older than 35 years. †Untreated, fasting plasma glucose 7–10 mmol/L. ‡As defined by guidelines from the National Cholesterol Education Program Adult Treatment Panel. §114 patients had adult-onset type 1 diabetes, 24 had an intermediate phenotype (insulin started <6 months after diagnosis), and for 76 patients there was no information about time to insulin.

Table 2: **Pancreatic autoantibody positivity and clinical characteristics in adult participants diagnosed with type 2 diabetes**

decarboxylase (GAD), protein tyrosine phosphatase IA-2, insulin, or zinc transporter 8. However, these antibodies have been reported in a subgroup of patients clinically diagnosed with type 2 diabetes, a subgroup that had been given various names (eg, type 1½ diabetes, autoimmune diabetes in adults,[53,54] or slow-onset diabetes in adults) before LADA[55] was decided upon. LADA is a common form of diabetes, and its frequency in many regions of the world exceeds that of classic type 1 diabetes. No unified criteria exist for LADA, but three criteria have often been used: positivity for GAD antibody, older than 35 years at diagnosis, and no insulin therapy in the first 6–12 months after diagnosis, although all three criteria have specific drawbacks. However, autoantibody positivity is associated with a phenotype including younger age at onset, less secretion of insulin, faster progression to insulin dependency, and less evidence of metabolic syndrome than for antibody-negative patients. These features are also dependent on the strength of antibody reactivity.

The prevalence of antibodies to GAD differs between regions and ethnic groups in patients clinically diagnosed with non-insulin-dependent diabetes. Around 5–14% of patients in Europe, North America, and Asia have pancreatic autoantibodies (table 2). GAD antibody was reported in 8·8% of 6156 patients in the European multicentre Action LADA 7 study,[72] compared with 5·9% of 4786 participants in the nationwide LADA China study.[73] Antibody specificities for the other antibodies are reported in only 1–2% of patients.[72] Of all antibody-positive patients, 90% have GAD antibody and 18–24% have antibodies to protein tyrosine phosphatase IA-2 or zinc transporter 8.[72] The differences in prevalence estimates are mostly due to the varying sensitivity and specificity of assays used. By contrast with type 1 diabetes, in which circulating antibodies often disappear after diagnosis, the prevalence of GAD antibody in patients with type 2 diabetes is similar irrespective of duration of diabetes, which has been taken as evidence for persistence of antibodies. However, this view was challenged by the Norwegian HUNT Study,[67] in which 41% of patients with LADA seroconverted to antibody-negative status during a 10 year follow-up. Positivity for autoantibodies is also

age-dependent: 14–34% of patients diagnosed with type 2 diabetes at an age of 25–45 years had GAD antibody compared with 7–9% of patients diagnosed later.[56,59]

Clinical differences between LADA, type 1 diabetes, and type 2 diabetes in adults

Findings from several studies have shown that patients with LADA progress to insulin dependency more often than do antibody-negative patients. However, most studies were cross-sectional and included patients with long disease duration, and patients with LADA have substantial heterogeneity (partly related to variability in the strength of GAD-antibody reactivity). Positivity for GAD antibody has been consistently associated with reduced concentration of fasting C peptide and reduced insulin response during oral glucose-tolerance tests.[56,59,65,66,73] However, insulin secretion did not clearly differ between patients with newly diagnosed LADA and those with GAD-antibody-negative type 2 diabetes, whose transition from normal glucose tolerance to diabetes was followed up in the Botnia prospective study.[74,75] In the ADOPT study[65] of newly diagnosed (<3 years) untreated patients, the difference in insulin secretion disappeared after adjustment for insulin sensitivity. Infrequent use of sensitive tests to measure insulin secretion and glucose sensitivity can partly account for these findings, but insulin secretion between antibody-positive and antibody-negative patients clearly does not differ substantially in the early stages of diabetes. However, after several years, antibody-positive patients proceed to insulin treatment more often and have poorer C-peptide response to glucagon than do antibody-negative patients,[56,76] an effect which seems to be associated with GAD-antibody concentration.[66,68,72,73]

Most patients with type 2 diabetes have features of metabolic syndrome—ie, obesity (particularly abdominal obesity), dyslipidaemia (high concentrations of triglycerides and low concentrations of HDL cholesterol), and hypertension—that are usually associated with insulin resistance and suggest an increased risk of cardiovascular disease.[77] Although patients with LADA have a better metabolic profile overall than do those with type 2 diabetes—with better insulin sensitivity (as assessed by the homoeostasis model assessment index), lower concentrations of serum triglyceride, higher concentrations of HDL cholesterol, lower body-mass index, smaller waist circumference, and slightly better blood pressure[56,59,61,65,66,68,70,72,73]—many still have features of the syndrome. Similar insulin sensitivities, as measured by normoglycaemic hyperinsulinaemic clamp, were reported between patients with LADA and those with type 2 diabetes, who were matched for age and body-mass index.[60] In the Finnish Botnia study, 83% of patients with type 2 diabetes and 33% of patients with LADA had features of metabolic syndrome (Tuomi T, unpublished). Whether the improved cardiovascular profile reported for LADA compared with type 2 diabetes translates to fewer cardiovascular events has not been studied in sufficiently large patient groups.

Studies comparing LADA with classic adult-onset type 1 diabetes in the same age ranges are scarce, with only 257 Finnish patients older than 35 years at diagnosis and 105 Norwegian patients older than 25 years at diagnosis.[61,67] Patients with LADA were older at diagnosis and had significantly more components of metabolic syndrome (higher body-mass index, concentrations of triglyceride, and blood pressure, and lower concentrations of HDL cholesterol) than did those with adult-onset type 1 diabetes.[61,67] However, this finding was mostly evident in patients with low or medium concentrations of GAD antibody.[61]

Genetic evidence for LADA as a hybrid form of diabetes

Both type 1 and type 2 diabetes are polygenic diseases; more than 60 susceptibility loci have been associated with type 1[78] or type 2 diabetes[79–82] in genome-wide association studies. LADA was previously thought to be a slowly progressing form of type 1 diabetes, which was supported by findings from early genetic studies suggesting that LADA shared *HLA-DQB1* risk genotypes with type 1 diabetes. The situation changed with the finding that a variant of *TCF7L2* was strongly associated with type 2 diabetes[83,84] but that its frequency was also increased in patients with LADA.[85]

Most genetic studies of LADA have focused on four genes associated with type 1 diabetes (*HLA-DQB1*, *INS*, *PTPN22*, and *CTLA4*) and four genes associated with type 2 diabetes (*FTO*, *PPARG*, *TCF7L2*, and *SLC30A8*). *HLA-DQB1* risk genotypes have been consistently positively associated, and protective genotypes have been negatively associated, with LADA.[57,59,61,68,85,86] The *HLA-DQB1* association is dependent on the strength of positivity for GAD antibody, because patients with LADA and high concentrations of GAD antibody had risk genotypes more often and protective genotypes less often than did those with low or no GAD antibody (figure 2).[59,61,85,86] Even patients with LADA and high concentrations of GAD antibody differed from those with adult-onset type 1 diabetes with respect to both protective and risk genotypes of *HLA-DQB1*.[61] Similarly, *PTPN22* has been associated with both LADA in general[61,85] and with high concentrations of GAD antibody,[61,89] although patients with high concentrations of GAD antibody still have a lower frequency of *PTPN22* risk genotypes than do patients with adult-onset type 1 diabetes.[61] The insulin gene locus is more controversial; a significant association between it and LADA was shown by findings from the UKPDS study[57] and a Swedish study,[85] but not in studies from Finland (the Botnia study[61]) or Norway (the HUNT study[86]). The studies differed in recruitment of patients, so inclusion of patients with adult-onset type 1 diabetes in the LADA groups of the UK and Swedish studies could account for this difference.

For the **Botnia study** see http://www.botnia-study.org

For the **ANDIS study** see http://snd.gu.se/en/catalogue/study/EXT0057

Findings from several studies have shown increased frequency of the type-2-diabetes-associated rs7903146 C→T allele of *TCF7L2* in patients with LADA,[71,85,87] but the HUNT study[86] did not replicate this finding. In a study in progress of all newly diagnosed patients with diabetes in southern Sweden (the ANDIS study) with more than 8000 patients, the rs7903146 C→T allele was strongly associated with LADA and type 2 diabetes, but not with type 1 diabetes (Groop L, unpublished). In common with type 2 diabetes, LADA is associated with increased frequencies of common variants of *SLC30A8*,[87] which encodes zinc transporter 8, and the obesity-associated variant of *FTO*.[86,87] Some evidence suggests that the association might be stronger in patients with LADA and lower concentrations of GAD antibody, who are phenotypically more similar to those with type 2 diabetes.

Taken together, genetics has provided clear support for the view that LADA is between adult-onset type 1 diabetes and GAD-antibody-negative type 2 diabetes, sharing genetic and clinical features with both forms, thereby justifying the term hybrid diabetes (figure 3).

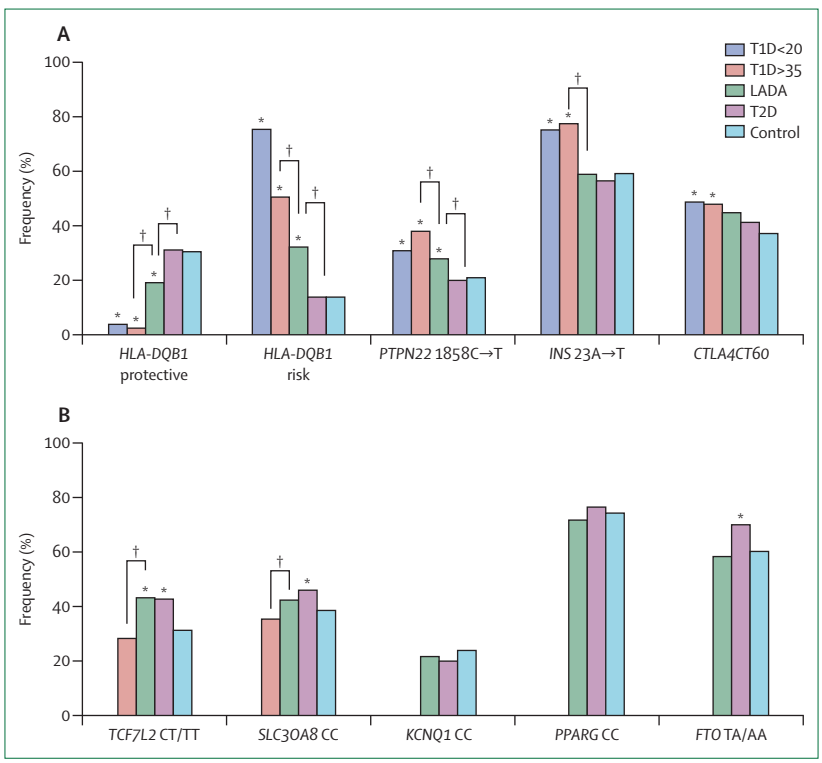

Figure 2: **Genotypes for type 1 and type 2 diabetes**
(A) Frequency of *HLA-DQB1* genotypes that protect from or confer risk for type 1 diabetes, and risk variants for type 1 diabetes in *PTPN22* (*PTPN22* 1858C→T, rs2476601), *INS* (*INS* 23A→T, rs689), and *CTLA4* (*CTLA4**CT60, rs3087243) in subgroups of diabetes. (B) Frequency of risk variants for type 2 diabetes in *TCF7L2* (rs7903146), *SLC30A8* (rs13266634), *KCNQ1* (rs2237895), *PPARG* (rs1801282), and *FTO* (rs9939609) in subgroups of diabetes. T1D<20=type 1 diabetes with onset before 20 years of age. T1D>35=type 1 diabetes with onset after 35 years of age. T2D=type 2 diabetes. LADA=latent autoimmune diabetes in adults. *Significant difference in genotype distribution compared with controls. †Significant differences in genotype distribution between patients with LADA, T1D>35, or T2D. Figure based on data from Andersen and colleagues,[61] Lundgren and colleagues,[87] and the Botnia study (Tuomi T, unpublished). Reproduced from Andersen[88] by permission of Mette K Andersen (Research Program for Diabetes and Obesity, Helsinki University, Helsinki, Finland).

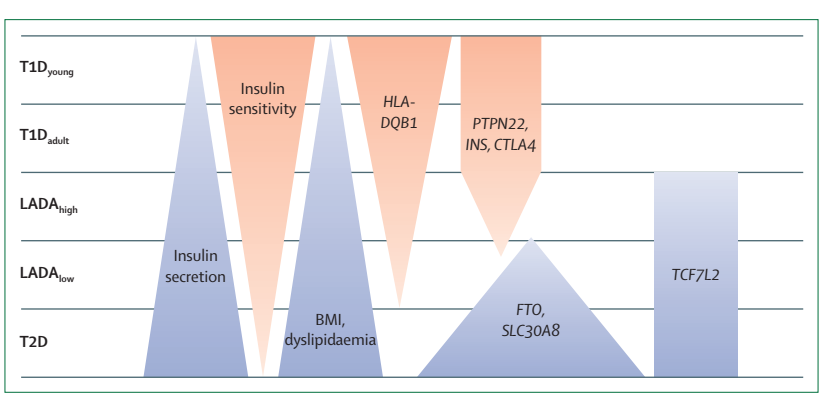

Figure 3: **A schematic view of factors affecting the phenotype of diabetic subgroups**
$T1D_{young}$=type 1 diabetes with onset before 20 years of age. $T1D_{adult}$= type 1 diabetes with onset after 35 years of age. T2D=GAD-antibody-negative type 2 diabetes. $LADA_{high}$=latent autoimmune diabetes in adults with high concentrations of GAD antibody. $LADA_{low}$= latent autoimmune diabetes in adults with low concentrations of GAD antibody. BMI=body-mass index. Adapted from Leslie and colleagues[90] by permission of John Wiley and Sons.

Forms of diabetes that are difficult to classify

Ketosis-prone diabetes in adults

Other hybrid forms of diabetes have features of both type 1 and type 2 diabetes without the autoimmune characteristics of LADA. A peculiar form of non-autoimmune ketosis-prone diabetes was described in African-American youths in the Flatbush suburb of Brooklyn, NY, USA.[91,92] This finding was followed by reports of similar forms of diabetes in patients of sub-Saharan-African descent.[5] Although these patients presented with ketosis and severe insulin deficiency, 76% later achieved remission from insulin dependency. However, ketotic relapses preceded by progressive hyperglycaemia were reported in 90% of patients within 10 years.[5] Obese males seem to be most susceptible to this form of diabetes, and insulin resistance together with β-cell dysfunction seems to trigger ketotic episodes. The search for genetic variants to account for this subtype of diabetes has not been very successful; Mauvais-Jarvis and colleagues[93] reported that a variant of *PAX4* might be associated with ketosis-prone type 2 diabetes, but this association has not been investigated in any further studies. A proposal to further subclassify patients with diabetic ketoacidosis into four categories on the basis of the presence of autoimmunity (A +/–) or preserved β-cell function (β +/–) has not been generally adopted.[94,95]

Mutations in *WFS1* cause not only Wolfram syndrome but also a disease similar to type 1 diabetes

Recessive mutations in *WFS1* cause Wolfram syndrome, also referred to as DIDMOAD syndrome, characterised by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.[96] More recently, autosomal dominant mutations in *WFS1* have been reported in patients presenting with only a type-1-diabetes-like disease, and the mutation was accompanied by impaired β-cell function and diabetes in a Finnish family.[4,97] The mutations in *WSF1* have been shown to alter endoplasmic reticulum stress.[4]

Changes in type 2 diabetes in Asia and China

The traditional form of type 2 diabetes is also changing in its presentation, particularly in Asia, where the population seems to be supersensitive to risk factors for type 2 diabetes. Of the Asian countries, China seems to be at highest risk, and its epidemic of type 2 diabetes will soon match that of the Middle East, which has the highest comparative prevalence of diabetes (11%) and health-care expenditures due to diabetes (2·3%).[98]

China has made astonishing advances in economic development during the past 30 years, but the prevalence of diabetes has risen much more sharply in China than in other countries: from 2·0% in 1995, to 5·5% in 2001, and 9·7% in 2009.[99–102] According to the latest nationwide survey of people aged 20 years or older in 2007–08, 92·4 million people have diabetes and 148·2 million have prediabetes.[102] Nutritional changes and increasingly sedentary lifestyles[103] are the main causes of the epidemic of diabetes in China.[16,104,105] The high prevalence in less urban areas and across all incomes suggests that the risk is pervasive across rural and urban China.[16] However, these risks are modifiable; findings from the Daiqing Impaired Glucose Tolerance and Diabetes Study[106] showed that lifestyle modification could result in statistically significant reductions in diabetes risk by 50%.

Chinese people seem to be susceptible to even slight increases in body-mass index. Although body-mass index is often more than 30 kg/m² at diagnosis of type 2 diabetes in Europe and the USA, the mean value at diagnosis in China was 25·9 kg/m².[102] Findings from the Nurses' Health Study[107] showed that for the same body-mass index, people of Asian ethnic origin had more than double the risk of developing type 2 diabetes than did white people. One explanation for this paradoxical finding could be that Asian people have more abdominal adipose tissue than do white people of the same body-mass index.[108,109] The International Diabetes Federation acknowledge this suggestion in their criteria for metabolic syndrome, in which the cutoff for waist circumference is lower for Asian people than for white people.[110] Because of the strong link between abdominal obesity, insulin resistance, and metabolic syndrome, insulin resistance could be the cause of the diabetes epidemic in Asia. However, diabetes does not develop without failing β cells. Findings from the Saku study[111] in Japan showed that, in 1550 participants with insulin secretion and action established at baseline, the odds ratio for development of diabetes per 10 000 person-years was 8·27 for those with isolated β-cell dysfunction at baseline, 4·90 for those with isolated insulin resistance at baseline, and 16·93 in those with both disorders at baseline. Notably, the population-attributable fraction of type-2-diabetes onset was highest (50·6%) for those with isolated β-cell dysfunction, and was only 14·2% for insulin resistance, emphasising the key role of β-cell dysfunction in the pathogenesis of type 2 diabetes in Asian populations. Because of the rapid progression from prediabetes to diabetes that occurs in Asian people, the Asian population is ideal for trials of interventions aimed at prevention of type 2 diabetes.

Conclusions

Diabetes is a much more heterogeneous disease than the present subdivision into type 1 and type 2 diabetes assumes. Both type 1 and type 2 diabetes seem to result from a collision between genes and environment. The rapid increase in incidence of both forms of diabetes suggests that many patients are genetically predisposed to both forms of diabetes. This epidemic also substantially affects and changes the age at onset of the disease. With the increasing possibilities to genetically and clinically or metabolically characterise patients with diabetes, we predict that the range of diabetic subgroups will be even more diverse in the future. We hope that delineation of these subgroups will assist in the development of individualised therapy.

Contributors

All authors contributed to the literature searches and writing of the Review. NS and SC wrote most of the section about diabetes with onset in childhood or adolescence, and JW and MC wrote the section about diabetes in Asia and China.

Conflicts of interest

JW has received funding from Novo Nordisk, Eli Lilly, Sanofi, Johnson & Johnson, Bayer, Medtronic, and Tonghua Dongbao Pharmaceutical Co for Guangdong T1D Translational Study. TT, NS, SC, MS, and LG declare that they have no conflicts of interest.

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