

# Clinical review

## Type 1 diabetes: recent developments

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Type 1 diabetes is one of the most common chronic childhood illnesses, affecting 18 to 20 per 100 000 children a year in the United Kingdom.<sup>1</sup> The American Diabetes Association committee recommends the term type 1A diabetes for immune mediated diabetes with its destruction of the islet  $\beta$  cells of the pancreas.<sup>2</sup> Non-immune mediated diabetes with severe insulin deficiency is termed type 1B. In this review, we will use the term type 1 diabetes to refer to immune mediated type 1A diabetes. At present, the development of type 1 diabetes is a life sentence to a difficult therapeutic regimen that is only partially effective in preventing acute and chronic complications. We will concentrate here on recent advances in our understanding of the epidemiology, pathogenesis, prediction, and prevention of type 1 diabetes and new treatments for the disease.

### Sources and selection criteria

This review is based on information obtained from a recent Medline search with type 1 diabetes, pathogenesis, prediction, prevention, and treatment as key words. We also consulted summaries of the literature on type 1 diabetes (available with teaching slides at [www.barbaradaviscenter.org](http://www.barbaradaviscenter.org)).

### Epidemiology

Although most attention has focused on the increase in type 2 diabetes, a parallel rise in type 1 diabetes has occurred (fig 1).<sup>1</sup> Type 1 diabetes has always been known as a disease of childhood, but more recent epidemiological studies have indicated that the incidence is comparable in adults.<sup>3</sup> The enormous international variation in incidence is now recognised. A child in Finland is almost 40 times more likely to develop type 1 diabetes than a child in Japan and almost 100 times more likely to get the disease than a child in the Zunyi region of China.<sup>1</sup> The EURODIAB collaborative study, a registry involving 44 countries in Europe, indicates an annual rate of increase in incidence of type 1 diabetes of 3-4%, with a larger increase in some central and eastern European countries.<sup>4</sup> The largest rate of increase is seen in children aged 0-4 years. Type 1 diabetes is associated with other autoimmune conditions; the most common association is with thyroid disease.<sup>5</sup> The Belgian Diabetes Registry indicated that the prevalence of thyroid peroxidase autoantibodies is 22% in patients with type 1 diabetes. Approximately 1 in 10 patients with type 1 diabetes express transglutaminase IgA autoantibodies, and more than half of these patients have coeliac disease

### Summary points

The incidence of type 1 diabetes is increasing rapidly worldwide, and it is also presenting at an earlier age

Genetically engineered human insulins have improved care of type 1 diabetes, and devices for continuous glucose monitoring may revolutionise care

An interplay between genetic susceptibility and environmental factors (triggering or suppressive) may account for the pathogenesis of type 1 diabetes

Many associations with various environmental triggers have been found in type 1 diabetes, but so far only congenital rubella syndrome has been conclusively associated with the disease

The expression of diabetes related autoantibodies in young children monitored from birth indicates that these markers are a major risk factor for the future development of type 1 diabetes

No treatment has been shown to safely prevent type 1 diabetes in humans, although islet transplantation and new immunosuppressive regimens show that the disease can be cured

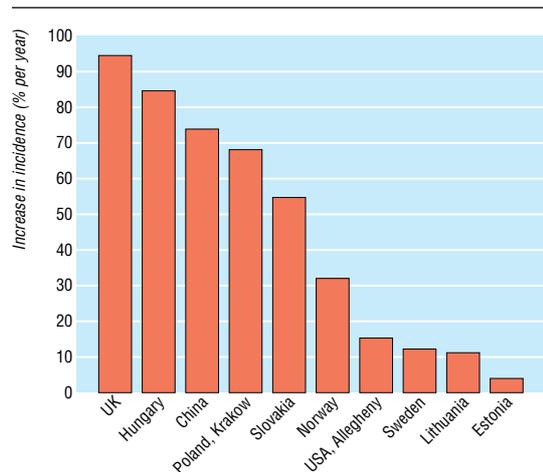
on intestinal biopsy. Approximately 1 in 50 people with type 1 diabetes have 21-hydroxylase autoantibodies, and approximately 25% of these patients progress to Addison's disease.

### Genes

Alleles or genetic variants associated with type 1 diabetes provide either susceptibility to or protection from the disease. An interplay between genetic susceptibility and environmental factors is thought to provide the fundamental element for disease and provides potential targets for both prediction and prevention of disease.<sup>6</sup> The concordance for type 1 diabetes is



Additional references, two figures, and a table are on [bmj.com](http://bmj.com)



**Fig 1** Relative increase in incidence of type 1 diabetes in children aged less than 14 years. Modified from Onkamo et al<sup>1</sup> (Available in: Eisenbarth GS, ed. Type 1A diabetes: cellular, molecular and clinical immunology, teaching slides [www.barbaradaviscenter.org](http://www.barbaradaviscenter.org))

approximately 50% for monozygotic twins, and the risk to a first degree relative is approximately 5%.<sup>7</sup> The major genetic determinant of susceptibility to diabetes lies within the major histocompatibility complex (termed IDDM 1). More than 90% of patients who develop type 1 diabetes have either DR3, DQ2 or DR4, DQ8 haplotypes, whereas fewer than 40% of normal controls have these haplotypes.<sup>6</sup> DR3-DR4 heterozygosity is highest in children who develop diabetes before age 5 (50%) and lowest in adults presenting with type 1 diabetes (20-30%), compared with a US population prevalence of 2.4%. Only one non-HLA gene has been identified with certainty—IDDM 2 on chromosome 11p5.5—and this contributes about 10% of the familial aggregation of type 1 diabetes.<sup>8</sup> This locus is a polymorphic region that maps to a variable number of tandem nucleotide repeats (VNTR) 5' of the insulin gene. Studies in man indicate that different sizes of this VNTR 5' of the insulin gene are associated with risk for type 1 diabetes. The long form of the VNTR ( $\geq 100$  repeats, class III) is associated with protection from diabetes.<sup>9</sup> This influence of the insulin gene locus may relate to variation in expression of insulin within the thymus (greater thymic insulin message with protective VNTR). Table 1 shows a summary of the susceptibility loci for type 1 diabetes.

## Environment

Two major hypotheses exist that may account for the increase in incidence of type 1 diabetes. The first hypothesis is that an environmental agent such as a virus may account for this.<sup>10</sup> Seasonality, increasing incidence, and epidemics of type 1 diabetes, as well as many cross sectional and retrospective studies, suggest that certain viruses and some aspects of early childhood diet may influence risk of type 1 diabetes. Many associations with various environmental triggers have been found in type 1 diabetes, but so far only congenital rubella syndrome has been conclusively associated with the disease. Table 2 summarises the studies that have attempted to show an association with type 1 diabetes.

The DAISY (diabetes autoimmunity study in the young) study in Denver, Colorado, followed newborns from birth and to date has found no evidence that bovine milk ingestion, enteroviral infection, or vaccination contribute to risk of diabetes; nevertheless, reports about the first two environmental factors have been conflicting.<sup>11</sup> Recent reports (including from the DAISY study) that suggest that early ingestion of cereal or gluten increases risk of type 1 diabetes need to be confirmed (see fig A on [bmj.com](http://bmj.com)).<sup>12-13</sup> The reason why risk of islet autoimmunity is increased by exposure to cereal or gluten is not entirely clear and may result from a mechanism involving an aberrant immune response to cereal antigens in an immature gut immune system in susceptible individuals. Interestingly, several case reports exist of patients developing anti-islet autoantibodies and then type 1 diabetes (as well as other autoimmune endocrine disorders) after treatment with interferon alfa.<sup>14</sup> Compounds such as poly-IC (a viral RNA mimic) that induce  $\alpha$  interferon can generate insulinitis (selective  $\beta$  cell destruction) and diabetes in animal models, strengthening the link between induction of diabetes and  $\alpha$  interferon.<sup>15</sup>  $\alpha$  interferon has therefore been implicated as an important cytokine linking viruses and the initiation of type 1 diabetes, and neutralising this cytokine may potentially prevent the disease.<sup>14</sup>

The second hypothesis, under the rubric of the "hygiene hypothesis," indicates that environmental factors can also inhibit the development of autoimmunity. As an oversimplification, our environment for young infants is far too clean, leading to a deficiency in immunoregulation such that "Th2" diseases (for example, asthma) and "Th1" diseases (for example type 1 diabetes) are increasing dramatically.<sup>16-17</sup>

## Pathogenesis

The hallmark of type 1 diabetes is the selective destruction of insulin-producing cells in the pancreas, or insulinitis. Studies measuring the expression of diabetes related autoantibodies in young children from birth suggest that the appearance of these markers is a major risk for the future development of type 1 diabetes.<sup>18</sup> However, the role of autoantibodies in the

**Table 1** Inherited susceptibility loci for type 1 diabetes with associated chromosome location and candidate genes or microsatellite markers

Locus	Chromosome	Candidate genes or microsatellites
IDDM 1	6p21	HLA-DQDR
IDDM 2	11p15	InsulinVNTR
IDDM 3	15q26	D15s107
IDDM 4	11q13	MDU1, ZFM1, RT6, FADD/MORT1, LRP5
IDDM 5	6q24-27	ESR, MnSOD
IDDM 6	18q12-q21	D18s487, D18s64, JK (Kidd locus)
IDDM 7	2q31	D2s152, IL-1, NEUROD, GALNT3
IDDM 8	6q25-27	D6s264, D6s446, D6s281
IDDM 9	3q21-25	D3s1303
IDDM 10	10p11-q11	D10s193, D10s208, D10s588
IDDM 11	14q24.3-q31	D14s67
IDDM 12	2q33	CTLA-4, CD28
IDDM 13	2q34	D2s137, D2s164, IGFBP2, IGFBP5
IDDM 14	?	NCBI # 3413
IDDM 15	6q21	D6s283, D6s434, D6s1580
IDDM 16	?	NCBI # 3415
IDDM 17	10q25	D10s1750-D10s1773

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**Table 2** Summary of studies investigating association of environmental factors in type 1 diabetes

Agent	Type of study	No of participants	Outcome
Enterovirus	Prospective <sup>w1</sup>	155	Associated with diabetes autoantibodies
	Case-control <sup>w2</sup>	260	In utero infection associated with type 1 diabetes
	Prospective <sup>w3</sup>	65	No association with type 1 diabetes
Mumps	Case-control <sup>w4</sup>	127	
Rubella	Retrospective <sup>w5</sup>	386	All these studies found associations with diabetes autoantibodies
Rotavirus	Case control <sup>w6</sup>	54	
Chickenpox	Prospective <sup>w7</sup>	n/a	
Cow's milk*	Prospective <sup>w8</sup>	725	Positive association with autoimmunity
	Cross sectional <sup>w9</sup>	253	Lack of association with autoimmunity
	Prospective <sup>w10</sup>	317	Lack of association with autoimmunity
Common childhood vaccinations	Case-control <sup>w11</sup>	3202	No association with autoimmunity
	Case-control <sup>w12</sup>	317	No association with autoimmunity
	Prospective <sup>w13</sup>	823	No association with autoimmunity
	Prospective <sup>w14</sup>	4400	Positive association with autoimmunity
Nitrates, nitrites, or nitrosamines	Prospective <sup>w15</sup>	867	Both these studies showed circumstantial evidence suggesting an association between type 1 diabetes and consumption of food and water containing nitrates
	Retrospective <sup>w16</sup>	1280	

\*The data on cow's milk are conflicting. The TRIGR study (Finland) is under way to determine if elimination of cow's milk from infants' diet can prevent type 1 diabetes.

actual pathogenesis of type 1 diabetes has not been established in humans. In fact, a recent case report showed the development of type 1 diabetes in a patient with X linked agammaglobulinaemia, suggesting that autoantibodies are not needed for either the initiation or the progression of type 1 diabetes.<sup>19</sup> In general, type 1 diabetes is considered primarily a T cell mediated disease, and extensive evidence exists in both man and mouse to support this. Examination of islet tissue obtained from pancreatic biopsy from patients with recent onset type 1 diabetes confirms insulinitis, with the presence of an infiltrate composed of CD4 and CD8 T lymphocytes, B lymphocytes, and macrophages, suggesting that these cells have a role in destruction of the  $\beta$  cells.<sup>20</sup> Early studies in mice showed that anti-CD3 treatment prevented diabetes, and a trial using humanised anti-CD3 antibody in patients with new onset type 1 diabetes is under way.<sup>21</sup> In figure 2 we describe a general model of  $\beta$  cell destruction leading to type 1 diabetes. The initial interaction of genes and environmental factors seem to trigger an immune mediated response, with the appearance of autoantibodies as the first sign of  $\beta$  cell destruction, followed eventually by the loss of the first phase insulin response. The progression to overt diabetes resulting in significant  $\beta$  cell destruction is triggered by the development of a more aggressive T cell phenotype and a change in the Th1 to Th2 balance towards a more proinflammatory milieu. The expression of FasLigand on cytotoxic T cells also marks the progression to overt diabetes. Examination of islets during insulinitis suggests that Fas mediated apoptosis occurs and therefore provides one possible mechanism of  $\beta$  cell destruction.<sup>22</sup>

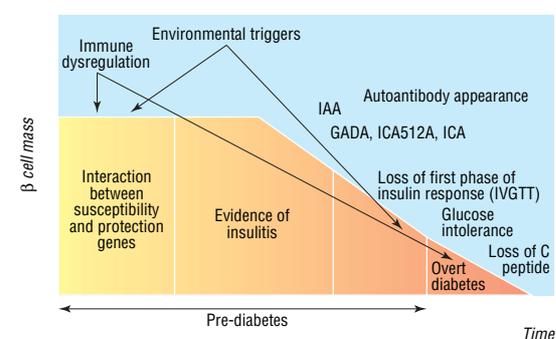
### Prediction

The long prodromal phase preceding the onset of type 1 diabetes suggests a potential to predict the disease and design trials for its prevention. The development of type 1 diabetes in relatives of patients with type 1 diabetes can now be predicted with reason-

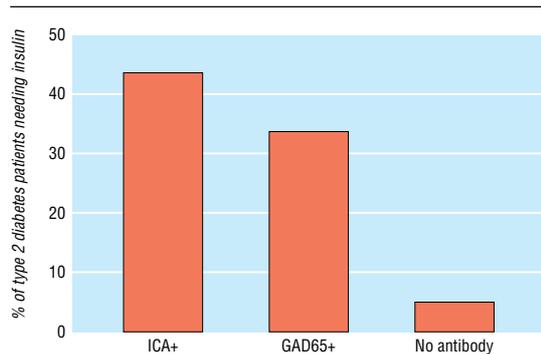
able accuracy by the detection of islet related autoantibodies (see table on [bmj.com](http://bmj.com)). Detection of two or more autoantibodies (GADA, IA-2, or insulin autoantibodies) in relatives of patients with type 1 diabetes has a positive predictive value exceeding 90% (see fig B on [bmj.com](http://bmj.com)).<sup>23</sup> Insulin autoantibodies are often the first autoantibody to develop, especially in younger children. Although most prediction studies using autoantibody markers have focused mainly on relatives of patients with type 1 diabetes, the presence of multiple diabetes related autoantibodies seems to be similarly predictive in the general population.<sup>24</sup> A study in Florida suggested that antibody positive people and their family members became anxious on learning their screening results; this subsided in most but not all people.<sup>25</sup> Although relatively good predictions of type 1 diabetes can be obtained by measuring autoantibodies, a successful method of prevention has not yet been discovered. Nevertheless, in the DAISY study high risk children with positive autoantibodies (without any interventions) seemed to have less severe diabetic ketoacidosis at onset of diabetes, better HbA<sub>1c</sub> at onset, and a lower rate of admission to hospital.<sup>26</sup> The use of autoantibody markers has been extended to define subsets of patients thought to have type 2 diabetes. Results from the United Kingdom prospective diabetes study (UKPDS) indicate that as many as 30% of younger "type 2" patients with diabetes may have an autoimmune process and that these patients usually progress to needing insulin within three years (fig 3).<sup>27</sup> This subgroup of patients has been termed latent autoimmune diabetes of adults.

### Prevention and new treatments

To date no treatment has been shown to prevent type 1 diabetes in humans. More than 100 different treatments prevent type 1 diabetes in the NOD mouse model, and this may indicate that disease prevention in this model is "too" easy.<sup>28</sup> Two major trials have been conducted to try to prevent type 1 diabetes. In the United States, the diabetes prevention trial (DPT-1) was started in 1994 with the aim of determining whether antigen based treatment with insulin (oral and parenteral insulin treatment in relatives at high and moderate risk) would prevent or delay diabetes. These treatments did not overall slow the progression to



**Fig 2** Model of pathogenesis and natural history of type 1 diabetes. Modified from Atkinson and Eisenbarth<sup>8</sup> (Available in: Eisenbarth GS, ed. Type 1A diabetes: cellular, molecular and clinical immunology, teaching slides [www.barbaradaviscenter.org](http://www.barbaradaviscenter.org))



**Fig 3** Latent autoimmune diabetes of adults in UK prospective diabetes study. Percentage of type 2 diabetes patients (25-34 years old) with ICA or GAD antibody needing insulin within six years of diagnosis. Adapted from Turner et al<sup>27</sup> (In: Eisenbarth GS, ed. Type 1A diabetes: cellular, molecular and clinical immunology, teaching slides [www.barbaradaviscenter.org](http://www.barbaradaviscenter.org))

diabetes. The European nicotinamide diabetes intervention trial (ENDIT) also found no difference in protection from diabetes when participants were assigned to either oral nicotinamide or placebo treatment (P Bingley, European Association of the Study of Diabetes, Budapest, September 2002). Many challenges remain in this field; in particular assays for pathogenic human T cells are not yet available. Such assays have the potential to provide surrogate markers to guide evaluation of immunotherapy; in the absence of such markers, the primary outcome of trials today is the preservation of insulin secretion (for example, measurement of C peptide secretion). TrialNet and the Immune Tolerance Network created by the US National Institutes of Health will be focusing not only on the prevention of diabetes but also on preventing further loss of islet  $\beta$  cells in patients with new onset type 1 diabetes.

Insulin remains the main treatment in type 1 diabetes. The diabetes control and complications trial (DCCT) showed the importance of strict metabolic control in delaying and preventing complications.<sup>29</sup> The risk of hypoglycaemia is still the major limiting factor in achieving euglycaemia with insulin treatment. The introduction of rapidly absorbed insulin analogues has reduced variability of insulin absorption and allows insulin administration in young children after meals.<sup>30</sup> Another recent introduction to the insulin market has been insulin glargine, which functions as a very long acting insulin (peakless basal insulin).<sup>31</sup> Combinations of engineered very long acting insulins and rapid acting insulins can provide control and convenience similar to that obtained with insulin pumps.

The use of metformin treatment alongside insulin has increased in patients with type 1 diabetes. Recent studies have suggested that metformin might benefit type 1 diabetes patients who are overweight, are receiving large doses of insulin, or have an  $HbA_{1c} > 8\%$ .<sup>32</sup> The coexistence of insulin resistance in patients with type 1 diabetes is a new area of interest. Islet transplantation with modified immunosuppressive regimens can cure type 1 diabetes. Islet transplantation is a consideration for the limited but important subset of patients with recurrent severe hypoglycaemic episodes not responsive to medical management.<sup>33</sup> Inability to control

#### Additional educational resources

Diabetes UK ([www.diabetes.org.uk](http://www.diabetes.org.uk))—provides useful links for both patients and healthcare professionals in the United Kingdom

Barbara Davis Center for Childhood Diabetes ([www.uchsc.edu/misc/diabetes/books.html](http://www.uchsc.edu/misc/diabetes/books.html))—provides an online teaching guide for healthcare professionals and guidance on type 1 diabetes for patients and their families

American Diabetes Association ([www.diabetes.org](http://www.diabetes.org))—provides useful links for both patients and healthcare professionals in the United States

Immunology of Diabetes Society ([www.idsoc.org](http://www.idsoc.org))—provides an update on current immune intervention trials, links to the Immune Tolerance Network, and current updates on autoantibody assay technology

autoimmunity and alloimmunity and a lack of donor organs limit the application of islet transplantation.

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## Evidence based case report

# Perimacular retinal folds from childhood head trauma

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Editorials by Geddes and Plunkett and Harding et al

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A previously healthy 14 month old child was transferred to our medical centre with a severe head injury. The father had collected the boy and his 3 year old brother from their mother at his workplace car park and taken them home while their mother went to work. The children had been watching television while the father prepared dinner. After hearing something fall, the father found the boy on the floor with the television covering the right side of the head and anterior chest. A homemade television stand was partially across the child's lower legs. His older brother stated, "television fell." As soon as the father removed the television, he noticed the child's head beginning to swell. A neighbour drove them to the local hospital. According to the father and the neighbour, the child never stopped breathing and no resuscitative efforts were attempted.

Cranial computed tomography showed extensive head injuries. He had soft tissue swelling of the scalp, diffuse cerebral oedema with a subdural haematoma overlying the frontal convexities and layering along the falx cerebri, a left sided skull fracture adjacent to a widely diastatic coronal suture, cerebral contusions beneath the fracture, and a rightward midline shift measuring 8 mm. The paediatric ophthalmologist described bilateral dot and blot intraretinal haemorrhages, preretinal haemorrhages, and perimacular retinal folds (fig 1).

The child's condition deteriorated, and he died 18 hours after the incident. Child Protective Services removed the 3 year old sibling from the home because the retinal haemorrhages and retinal folds were considered diagnostic of abusive head trauma from shaking. This action was taken despite the father's repeated detailed, consistent account provided to emergency staff, the paediatric child abuse specialist, paediatric intensive care doctors, and law enforcement authorities.

## Postmortem evidence

A forensic autopsy showed no direct trauma to the orbits or eyes. There were prominent bilateral scalp contusions with soft tissue and intramuscular haemorrhage, symmetrical parietal skull fractures with coronal sutural diastasis, and a lacerated dura mater with extrusion of brain and blood. In addition to bilateral subdural and subarachnoid haemorrhages, a thin epidural haematoma partially covered the frontoparietal, calvarial lamina interna. The brain showed bilateral cortical contusions, severe cerebral oedema, and diffuse anoxic-ischemic injury. Postmortem ocular examination showed haemorrhages of the optic nerve sheaths with subdural haemorrhage greater than subarachnoid haemorrhage. Both eyes had extensive retinal haemorrhages with perimacular retinal folds (fig 2). Retinoschisis and peripapillary intrascleral haemorrhages were evident, and the retinal haemorrhages extended from the posterior pole to the ora serrata affecting the preretinal, intraretinal, and subretinal layers.

When investigators went to the house to recover the television before the family returned home, it was still on the carpeted floor. The 480 mm screen television with built in videocassette recorder weighed 19.5 kg. The homemade television stand measured 762 mm (height)×635 mm (width)×508 mm (depth) and had a bottom drawer that held videotapes. A greasy smudged area on the glass of the television corresponded with the impact site on the child's head.

A re-enactment in which a 11.4 kg weight (similar to the child's weight at autopsy of 11.8 kg) was placed on the partially opened drawer caused the television and



Details of the included studies are on [bmj.com](http://bmj.com)