Chapter 4
Non-Genetic Factors in the Pathogenesis of Type 1 Diabetes

Serena Wai-Yan Chiu, R. David G. Leslie, and Huriya Beyan

Abstract Type 1 diabetes is an autoimmune disease characterised by immune-cell-mediated destruction of the pancreatic islet cells leading to insufficient insulin production and consequent clinical manifestations of hyperglycaemia. Many genetic variants have been identified through GWAS to detect common variants in alleles that are disease-associated; some of these variants are associated with protection from virus infection by interferon-releasing factors. Migration studies support a role for environmental factors causing a change in disease incidence. Extensive epidemiological, histological and immunological data have indicated a role for viruses in the pathogenesis of type 1 diabetes although it has proven difficult to find a causal relationship. Increasing wealth and industrialisation in developed countries may also contribute to the rising incidence of type 1 diabetes. Disproportionate maternal influences on risk of type 1 diabetes suggest that critical disease-inducing environmental events operate very early, even in utero. Early infant diet can affect the appearance of diabetes-associated autoantibodies. Disproportionate maternal influences on risk of type 1 diabetes suggest that critical disease-inducing events operate very early, even in utero. Identification of relevant disease-causing non-genetic effects, especially if they are environmental in origin, could point the way towards disease modulation or even prevention.

Non-Genetic Factors Involved in the Pathogenesis of Type 1 Diabetes

Type 1 diabetes is an autoimmune disease characterised by the immune-cell-mediated destruction of the pancreatic islet cells leading to insufficient insulin production and consequent clinical manifestations of hyperglycaemia. The aetiology of type 1 diabetes,

S. Wai-Yan Chiu • R.D.G. Leslie, M.B.B.S., M.R.C.S., M.D., F.R.C.P. (✉) • H. Beyan
Blizzard Institute, Queen Mary College, University of London, London, UK
e-mail: r.d.g.leslie@qmul.ac.uk

K.W. Taylor, H. Hyoty, A. Toniolo, A.J. Zuckerman (eds.), *Diabetes and Viruses*,
DOI 10.1007/978-1-4614-4051-2_4,

like other autoimmune diseases, can be thought of as a complex interaction between genes and the environment, although many contributing factors are yet to be elucidated. It is apparent that genes cannot be acting alone; however, it is still unclear how non-genetic events may lead to disease.

Evidence for Non-Genetic Effects

Many genetic variants have been identified through genome-wide association studies (GWAS) to detect common variants in alleles that are disease-associated. However, these variants seem to only have a small effect on disease risk, so only explain a small part of heritability, or familial clustering, which implies a role for non-genetic factors in disease development (Manolio et al. 2009). Certain human leukocyte antigen (HLA) alleles, particularly those located on the HLA class II region on chromosome 6, are known to be associated with type 1 diabetes susceptibility, e.g., HLA DRB1*03, *04; DQB1*0302 genotypes increase the risk of type 1 diabetes, while the HLA DQB1*0602 genotype confers a degree of protection (Atkinson and Eisenbarth 2001; Field 2002). However, less than 10% of people with the HLA susceptibility genes develop clinical diabetes, meaning that there must be other non-genetic factors crucial to the progression to type 1 diabetes (Knip et al. 2005). Gene associations point toward a gene–environment interaction and support a role for viruses. Associations between viral infections and type 1 diabetes, along with the discovery of a type 1 diabetes risk gene, IFIH1 (interferon induced with helicase C domain 1), have strengthened the view that viral infections may contribute to the pathogenesis of type 1 diabetes (Downes et al. 2010; Heinig et al. 2010; Todd 2010).

The incidence of autoimmune diseases has increased, particularly over the last three decades (Bach 2002). The evidence of non-genetic effect in type 1 diabetes comes from the study of populations, migrants and twins.

Populations

Population studies are of limited value in identifying the impact of non-genetic factors since it is difficult to segregate genetic from environmental influences. However, changes in disease incidence within a genetically stable population are important when disease incidence rises rapidly (Bach 2002). Such changes have been most striking in children diagnosed under 5 years of age, as in Switzerland where the incidence rose from 4.5/100,000 in 1965 to 10.5/100,000 in 2000 (Schoenle et al. 2001). In addition, a study in Sweden showed that the incidence of type 1 diabetes increased by almost double in the period from 1978 to 2000 but then remained stable from 2005 to 2007 (Berhan et al. 2011). These patterns of increasing incidence suggest that pathogenesis of type 1 diabetes may be non-genetically influenced.

Migrants

Migration studies also support a role for environmental factors causing a change in disease incidence (Serrano-Rios et al. 1999; Bach 2002). The incidence of type 1 diabetes in Asian children who migrated to Britain was much higher (11.7/100,000 per year in 1988–1990) than in their native Karachi (1/100,000 per year) (Bodansky et al. 1992; Staines et al. 1997). In a study of South Asian children in Leicestershire, UK, the incidence of type 1 diabetes was similar to those of white or other ethnic groups, and increased compared to the incidence in Asia (Raymond et al. 2001).

Twins

Monozygotic (MZ) twin studies are also of importance, as studying these genetically identical individuals will emphasise the effect of non-genetic events in influencing a phenotype, since any changes between MZ twins will be due to either environmental or stochastic events. Higher concordance rates for autoimmune diseases in identical MZ twins compared to non-identical dizygotic (DZ) twins is consistent with a genetic influence on these diseases (Hyttinen et al. 2003; Kyvik et al. 1995; Kumar et al. 1993). However, these studies generally involved small numbers, with limited follow-up and without biochemical tests. To partially resolve these problems, two clinic-based studies in the UK and the USA ascertained twins discordant for type 1 diabetes (Redondo et al. 2001). The combined analyses provided a powerful database to determine the proportion of MZ twins initially non-diabetic who subsequently developed diabetes, including the rate at which they did so and the factors that influenced this rate. The results indicate a high concordance rate in young age-at-onset diabetic twins; the rate falling substantially with age, implicating an increasing non-genetic effect with advancing age at diagnosis.

Pattern of Non-Genetic Effect

The temporal pattern of development of diabetes-associated autoantibodies such as those to glutamic acid decarboxylase (GADA), insulin (IAA), zinc transporter 8 (ZnT8A) and IA-2 (IA-2A) are indicative of a role for non-genetic factors in the development of type 1 diabetes (Ziegler and Nepom 2010). The appearance of these autoantibodies occurs in either neonatal life or later during puberty, with the characteristics of the antibodies differing at these distinct stages. In children who develop diabetes before 10 years of age, islet cell autoantibodies most commonly appear around 1–2 years of age, but are unlikely to develop in the first 6 months of life (Ziegler and Nepom 2010; Achenbach et al. 2005). At this stage, the type and affinity of these antibodies (IgG1 and high titre) are associated with particular HLA genotypes, and the first antibodies that do appear are often IAA, but quickly spread to include GADA, IA-2A and ZnT8A. In comparison, the later wave of autoimmunity

occurring during puberty is typically less strongly related to HLA genotype, generally involves IAA or GADA on their own and at lower titre, and autoimmunity does not spread to involve other antigens, i.e., only one autoantibody as a rule can be detected. The dissimilar characteristics of the two peaks point to non-genetic factors in the triggering of islet autoimmunity.

Spectrum of Autoimmune Diabetes

Type 1 diabetes has been seen broadly as a form of diabetes requiring insulin therapy. However, the severity of metabolic features, both before and at the time of diagnosis of type 1 diabetes, is wide-ranging. The diabetes disease process is increasingly seen as a spectrum, with childhood-onset insulin-dependent diabetes at one end, and adult-onset non-insulin requiring diabetes at the other. Although it has proven difficult to define forms of the disease, the presence of diabetes-associated autoantibodies does serve to exclude autoimmune diabetes patients from being designated under "type 2 diabetes". Autoantibodies are associated with both type 1 diabetes and latent autoimmune diabetes of adult-onset (LADA). The definition of LADA has been set by the Immunology of Diabetes Society and Action as: (1) age 30–70 years at diagnosis; (2) at least 6 months of non-insulin requiring diabetes, and (3) the presence of diabetes-associated autoantibodies (www.actionlada.org). LADA, taken as an entity, is clearly distinct from type 2 diabetes. That distinction is demographic (LADA patients tend to be younger and less obese), clinical (metabolic syndrome is less frequent), genetic (LADA is HLA-associated), immunological (LADA patients have autoantibodies and T-cell changes) and metabolic (insulin secretory capacity and insulin resistance are both lower in LADA patients). There are two schools of thought: one, which sees LADA as part of a spectrum extending across the clinical range of autoimmune diabetes, the second, which sees it as a distinct form of autoimmune diabetes. Evidence and opinion favour the former (Leslie 2010; Brooks-Worrell and Palmer 2011).

Environmental Factors

Numerous environmental factors have been implicated in the aetiology of autoimmune diseases: for example, temperate climate, increased hygiene and decreased rates of infection, vaccinations and antibiotics, and increasing wealth. In addition to these, some factors are specific to type 1 diabetes pathogenesis of type 1 diabetes, such as overcrowding in childhood, virus infections, early exposure to cows' milk, reduced rates or duration of breastfeeding, and vitamin D and nitrite consumption (Bach 2002; Leslie and Castelli 2004; Fava et al. 1994; Hyoty and Taylor 2002; Clements et al. 1995; Cooper et al. 2011). Environmental factors could act by either triggering an already established degree of autoimmunity, or causing the destructive inflammatory response, or both, which then sets off a chain of events culminating in clinical diabetes.

The Virus Hypothesis

Extensive epidemiological, histological and immunological data have indicated a role for viruses in the pathogenesis of type 1 diabetes although it has proven difficult to find a causal relationship (Hyoty and Taylor 2002). Details are provided elsewhere in this book. The current evidence, in our opinion, strongly supports a viral origin of the disease. Specifically, evidence for a genetic association with an anti-viral innate immune response network within macrophages provides persuasive evidence for a viral effect (Heinig et al. 2010). There is evidence that two viral factors operate to influence the rate of disease progression subjects with autoantibodies: firstly, a critical gene in this anti-viral network, the interferon helicase IFIH1, has such an effect, and secondly, enterovirus infections also appear to influence the rate of progression to type 1 diabetes (Winkler et al. 2011; Oikarinen et al. 2011).

The Accelerator Hypothesis

One theory explaining the growing incidence of diabetes is the accelerator hypothesis. This hypothesis proposes that type 1 and type 2 diabetes are part of a spectrum and are caused by the same disease process, only differing in the time taken to progress to onset of clinical symptoms; this discrepancy in time frame being determined by genetics (Wilkin 2009). It is suggested that patients with type 1 diabetes have a genotype that confers increased susceptibility to the environmental factors causing β-cell stress, therefore leading to an accelerated progression to clinical diabetes compared to type 2 diabetes. Insulin resistance, being related to weight gain, plays an increasingly important role as the prevalence of childhood obesity rises, which explains the rising incidence of not only type 2 diabetes, but type 1 diabetes as well. The up-regulation of the β-cells in response to insulin resistance can cause an extreme immune reaction leading to destruction of the islets, through β-cell apoptosis (Wilkin 2001). Since genetic background determines β-cell reserve and the response to an environmental insult, the interplay between genetic and environmental factors establishes the differences between type 1 and type 2 diabetes, in particular, the dissimilar timing of the onset of clinical diabetes.

The Overload Hypothesis

Increasing wealth and industrialisation in developed countries may also contribute to the increasing incidence of type 1 diabetes. The trend of rapid weight gain in infancy over the past few decades, for example as a result of better living standards, may add to this idea, as it has been shown to correspond to an increased risk of type 1 diabetes (Hypponen et al. 2000, 1999). Also, in areas of lower socioeconomic

conditions there is a decreased incidence of autoimmune diseases (Bach 2002). However, this may not be a reflection of differences in lifestyle as a result of wealth, but may be associated with the apparent reciprocal relationship seen between infection and autoimmunity, where factors such as crowded housing could increase the transmission of infections.

Improving lifestyles are mirrored in the pattern of increasing birth weights and accelerated childhood growth, both of which have implications for the development of type 1 diabetes. In support of the overload hypothesis, low compared to high birth weight by gestational age has been shown to correspond to a lower risk of type 1 diabetes (Patterson et al. 2001). Furthermore, studies have demonstrated that children who had increased linear growth, weight or BMI were more likely to progress to diabetes later in life (Hypponen et al. 2000, 1999; Blom et al. 1992; Johansson et al. 1994). Exposure to westernised heat-processed food could also affect the incidence of type 1 diabetes, and certainly there is a close relationship between T1D incidence and the gross national product of European countries (Patterson et al. 2001).

The Hygiene Hypothesis

The hygiene hypothesis is linked with increasing socioeconomic standards, which, along with the introduction of antibiotics and vaccinations, may contribute to the decreasing rate of infections (Bach 2002). A reduced exposure to infections in childhood could lead to autoimmunity later in life, which could be explained by the relative inactivity of the immune system causing increased immune responsiveness. In support of this, a higher degree of social mixing in childhood, such as in daycares or in larger families, is associated with a decreased incidence of type 1 diabetes (Bach 2002).

Gut Immune System

The gut immune system, as a major T-cell organ, plays an important role in the regulation of immune responses and has the potential to be altered by non-genetic factors such as diet. It appears that some antigens, such as cows' milk protein, when introduced within a certain period of time during infancy, affect the development of autoimmune responses later in life. Autoimmunity, in this case, may be due to increased gut permeability in the first 2 months of life, which could lead to greater immune cell infiltration (Kuitunen et al. 1994). A study showed that NOD mice deficient in MyD88 were protected from diabetes development, as the absence of MyD88 caused gut overgrowth of a certain class of bacteria, which then prevented diabetes (Wen et al. 2008). MyD88-deficient mice raised in germ-free conditions lost that protection. The results of this study indicate that gut microbiota are a critical factor to diabetes prevention in these mice.

The Weaning Diet Hypothesis

Early infant diet has been shown to affect the appearance of diabetes-associated autoantibodies. For example, the early introduction of cows' milk protein into an infant's diet has been indicated in the development of autoimmunity in type 1 diabetes (Vaarala et al. 1995). Such early dietary introduction seems to evoke a stronger immune response than if the cows' milk was introduced later. It has been proposed that this overreaction may be due to the immaturity of the gut immune system causing overt immune responses to harmless antigens. A recent study demonstrated that infants weaned on hydrolysed formula compared to cows' milk were less likely to develop diabetes-associated autoantibodies, suggesting that there may be an antigen in cows' milk that is a triggering factor of type 1 diabetes (Knip et al. 2010).

Maternal-Related Events Influence Diabetes Risk

Disproportionate maternal influences on risk of type 1 diabetes suggest that critical disease-inducing environmental events operate very early, even in utero. Children of diabetic mothers are less likely to develop type 1 diabetes than children of diabetic fathers, and the risk in mothers is less than the expected risk based on their HLA make-up (Warram et al. 1984; Bleich et al. 1993). The mean risk of diabetes in offspring of diabetic mothers and fathers in one study was 1.3% and 6.1%, respectively. This low disease risk being confined to offspring of mothers who had become diabetic after the age of 8 years, perhaps due to reduced transmission of genetic susceptibility (Warram et al. 1984).

Epigenetics or Stochastic Events

Finally, epigenetic effects could be relevant to the development of type 1 diabetes. The term epigenetics refers to alterations in gene expression without modification of the DNA sequence. Epigenetic modifications, including DNA methylation and histone modifications, affect the phenotype without altering the genotype, and such changes may be markers for disease. Environmental stimuli or stochastic events may act to alter the epigenetic state of an individual, so may contribute to the non-genetic influence involved in the pathogenesis of type 1 diabetes, and may be the missing link between genes and the environment. Epigenetic modifications may act either at the level of DNA through the methylation of cytosine in CpG dinucleotides, through post-translational changes to histones such as methylation, acetylation or phosphorylation, or through microRNA activation (Litherland 2008; Miao et al. 2008; Rakyan et al. 2011).

Concluding Remarks

In summary, there is persuasive evidence that type 1 diabetes is due, in part, to non-genetic factors. Several factors have been implicated, but evidence is confined to the genetic association with anti-viral mechanisms, and the change in the production of autoantibodies following dietary modification (Heinig et al. 2010; Knip et al. 2010). The timing of environmental events is key, perhaps occurring in two distinct waves in childhood. The potent predictive power of type 1 diabetes-associated autoantibodies, if induced by non-genetic factors, suggests that relatively few events are required before the disease process is set on a path to clinical diabetes. Some of the conflicting evidence and hypotheses could be resolved by implicating at least two or more distinct non-genetic events operating in tandem.

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