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PATHOGENESIS OF TYPE 1 DIABETES (D DABELEA, SECTION EDITOR)

# Is Autoimmunity or Insulin Resistance the Primary Driver of Type 1 Diabetes?

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**Abstract** Diabetes is usually classified as autoimmune or metabolic but, as difficulties have arisen with the taxonomy of diabetes, it may help to forego the conventional classification for a more inclusive model. Thus, all diabetes can be ascribed to beta cell insufficiency—hyperglycemia occurs only when the insulin supply fails to meet demand. Humans enter the world with a reserve of beta cells, which is eroded variably by apoptosis over the course of a lifetime. For most, the loss is slow and inconsequential but, for others fast enough to be critical within a lifetime. The challenge now is to define the factors that vary the tempo of beta cell loss, because tempo, not type, seems likely to determine whether diabetes occurs at all, in adulthood or in childhood. Insulin resistance is generally believed to underpin T2D, but has been a feature of insulin-dependent diabetes as well for nearly 80 years, though largely ignored until immunotherapy trials to test the autoimmunity hypothesis persistently failed to bring patient benefit. It seems possible that insulin resistance accelerates beta cell loss generally, its impact modulated by an immune response (autoimmunity) to the beta-cell stress whose intensity varies with immunogenotype. If so, the target for prevention of T1D might more logically lie with insulin sensitivity than with immunoregulation.

**Keywords** Insulin resistance · T1D · Accelerator hypothesis · Pathophysiology · Autoimmunity · Type 1 diabetes

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## Introduction

The categorization of diabetes into type 1 (T1D, autoimmune) and type 2 (T2D, metabolic) is a relatively recent construct. Insulin resistance is generally accepted to underpin the pathogenesis of T2D, and insulin resensitization can make an important contribution to its management. The rise in the incidence of T2D over recent years, and its ever earlier age at presentation tends to have dominated the field, yet T1D has behaved in an exactly parallel manner. The similarity of behavior, and the disappointing results of immunotherapy trials designed to test the autoimmune paradigm, have together raised questions as to whether autoimmunity drives T1D, or possibly insulin resistance.

## Background

Himsworth was the first to describe insulin resistance in diabetes nearly 80 years ago [1], but not, as is often thought, to distinguish adults from juveniles with the disease—insulin resistance was noted in both [2]. Others repeated Himsworth's observations using simple insulin-glucose tolerance tests [3–5], until a more sophisticated measure of insulin sensitivity, the glucose clamp, provided direct evidence that impaired insulin action is also '….a common feature of type 1 diabetes' [6]. Indeed, Elliott Joslin concluded that, while it was possible to separate patients according to insulin sensitivity, the overlap in their clinical phenotypes was so great as to make testing for it of little help [7]. Thus, insulin resistance was widely reported in juvenile diabetes form earliest times, but there seemed few implications and the unity of diabetes remained unchallenged.

## Observation vs Experiment

Diabetes remained a single disorder until the 1970s, when 3 observations made largely in children (lymphocytic insulitis [8], islet cell antibodies [9], and HLA genotype [10]) were interpreted by opinion leaders at the time to mean that childhood diabetes, unlike adult diabetes, was caused by dysregulation of the immune system (autoimmunity). A previously single disorder was now viewed as 2 categorically distinct entities of different etiology, and the autoimmune paradigm has become deeply rooted since. Importantly, however, the new classification into type 1 (autoimmune) and type 2 (metabolic) diabetes was based on observation, not on experiment. Some 20 human trials using immunotherapy to test the autoimmunity paradigm have since met with little success [11••], and none has translated into patient benefit. The relationship of insulin resistance to autoimmunity has only been raised in recent time because of mounting concern that the original interpretation may not have been correct [12]. Autoimmunity is clearly present in T1D, but its primacy in the sequence of events is being questioned. Rather than the driver of beta cell loss, 'autoimmunity' may be the response of a normal immune system to islets, which are stressed by the demands of insulin resistance [13].

The wealth of experimental data cited in support of the autoimmunity hypothesis for T1D is largely drawn from prevention studies in animal models. Such studies are frequently successful, but animals are not human, and biomedical research is often confronted with hypotheses that worked in animals, but not in humans. In the case of T1D, the models are not just animals, but animals abnormal to the point where they fail to develop diabetes unless their environment is rigidly controlled. The models most used in T1D research, the NOD mouse and Biobreeding rat, are inbred for immunogenetic deficiencies that are not part of the human disease, but essential to the model [14]. Such models show that the immune system *can* destroy the beta cells of inbred rodents, but say little about the mechanisms responsible for T1D in outbred humans. The extensive and often elegant evidence from animals has nevertheless served to sustain the momentum of immunotherapy in human trials, and a clinical classification for which there is little human evidence.

## The Curse of Classification

Categorization has a prominent place in clinical medicine, because it enables doctors – and increasingly nurse specialists – to treat according to protocol. T1D is treated with insulin because it is classified as 'insulin-dependent' and type 2 with diet and/or hypoglycemic agents because it is 'insulin-independent'. But classification can also obfuscate. As Edwin Gale points out, '…classification may come to embody outworn concepts that prevent us from seeking or applying new information we need…. Does it act as a stimulus for thought, or a substitute for it?'[12]. One difficulty with classification is the way it systematically ignores findings that don't fit – 'orphan' observations. The classification of diabetes into type 1 and type 2 has run into difficulties in recent times [15], yet remains intact because evidence that doesn't fit is often ignored. Thus, islet-related autoantibodies, which have for decades been the exclusive hallmark of T1D, are regularly reported in patients whose phenotype is type 2 [16, 17]. The categorization of T1D as childhood or juvenile is patently suspect, when more than half of new cases present in adulthood [18], toddlers who go on to develop T1D are heavier than their peers [19], not lighter as the diabetes tradition would have it, ….and insulin resistance, long since the basis for T2D, was noted decades ago to be a 'common feature' of T1D [6]. The classification of T1D as an autoimmune disorder of childhood, and type 2 as a metabolic disorder of later life has become deeply rooted in the teaching of diabetes, its literature, its clinical practice, and even its research funding. Doubts nevertheless linger, doubts that relate primarily to the relationship between insulin resistance and autoimmunity.

## Doubts

Concerns over the duality of diabetes first emerged through epidemiology, though few noted their significance at the time. Yemenite immigrants to Israel in the 1950s suffered very little diabetes but, after 25 years in a land of plenty, experienced a 40-fold increase in its prevalence. Intriguingly, it wasn't just T2D – the proportion of insulin dependency among people with newly diagnosed T1D was similar to that among Israelis of European origin [20]. The observation is fundamentally important, because it suggests a common driver for both major forms of diabetes. Again, it is seldom remarked upon, but clearly documented, that wherever in the world there has been a rise in T2D, there has been a corresponding increase in T1D [21], and many studies report how the frequency of T1D among the relatives of those with T2D is many times greater than that in the general population [22, 23].

The possibility that autoimmunity might be a physiological response to beta cell stress, rather than its pathological cause, was addressed some 25 years ago [24], in the wake of Pierre Grabar's seminal papers on the immune system's primordial role as housekeeper, clearing up the detritus of apoptotic (and, where needed, necrotic) cell death [25]. Being shape-specific and clonal, the immune system was ideally adapted to expand and contract in response to specific housekeeping need. What to others before him had been a canon of absolute tolerance to self antigens, was to Grabar the absence of a technology sufficiently sensitive at the time to detect a natural process

of waste removal – until it was intense, when it was given the label 'autoimmunity' in order to comply with the tolerance paradigm [26]. Grabar's great contribution was to breach the doctrine of self-tolerance that had previously obliged autoimmunity to be viewed as pathology. His concept of autoimmunity as a physiological, if vigorous, 'housekeeping' reaction to stressed and rapidly apoptosing cells in people with particularly reactive immune response genes, points to its place in diabetes as effect rather than cause. Autoimmunity is nevertheless inflammatory, and may be expected to further accelerate apoptotic death of the beta cell.

## An Alternative Paradigm

In most individuals, insulin resistance increases with aging [27], and demand for insulin accelerates the apoptosis of beta cells. As a result, the beta cell mass declines progressively over a lifetime but, for most, the loss is inconsequential because it is slow and the reserve substantial. The mechanisms have been recently reviewed [28]. Longer life expectancy will of itself mean a higher burden of diabetes as more people survive to breach the threshold, but only acceleration of the beta cell loss will shift its demography. Only tempo can explain how T2D, which a generation ago was confined to middle age and beyond, has now become the fastest growing chronic disorder of childhood and how T1D, for decades a disorder of adolescence, is now rising fastest in the under 5-year olds [29].

Insulin resistance, largely (but not exclusively) the result of excess weight gain, is generally believed to drive T2D. Upregulation, and the glucotoxicity and lipotoxicity that result from the metabolic disturbance associated with insulin resistance, are believed to stress the beta cell [30–32]. It has been known for 40 years that children who develop T1D—far from being undernourished and of low body mass—are heavier as toddlers than their peers who do not [19], and weight gain is a feature of childhood generally over recent time. The link between early weight gain and T1D resurfaced during the 1990s [33–35], and in 2001 the accelerator hypothesis proposed that insulin resistance, rather than autoimmunity, was the driver of T1D – *Type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different backgrounds*. The link to body weight is emphasized by a recent meta-analysis which found in all the studies it reviewed that people with T1D showed greater weight gain during the first year of life compared with controls [36•]. Crucially, the accelerator hypothesis does not dismiss autoimmunity. Rather, autoimmunity is deemed to be a response to beta cell stress, rather than its cause, and inflammatory in its own right. The hypothesis is conceptually simple, but potentially important if it resets the target for prevention of childhood diabetes from the immune system to insulin resistance.

Rising demand is the driver which stresses the beta cells, and the immune response is a secondary accelerator operating in those with particular HLA genotypes (eg, HLA DR3/DR4). The probability of developing diabetes reflects an infinitely variable interaction between level of demand and intensity of immune response (Fig. 1). Only a small change in demand may be needed to precipitate diabetes where the immune response to it is intense, while diabetes may never develop in the most insulin resistant individual whose immune response is weak.

Rather than categories diabetes into types 1 and 2 (or 1½, Double, LADA, or LADY), the accelerator hypothesis sees a continuous spectrum defining a single process, which progresses at different rates, from 'no' diabetes (most people) through 'slow' diabetes (adulthood) to 'fast' diabetes (childhood) (Fig. 2). Adult diabetes is not a type of diabetes, but diabetes in adulthood, just as childhood diabetes is not itself an entity, but diabetes in childhood. Time travels in 1 direction only so that, inevitably, those whose genotype encodes the most intense immune response present earliest in life. The variation in diabetes is one of tempo, not of type.

## Evidence

Evidence to justify reconsideration of the relationship between autoimmunity and insulin resistance has been detailed in a number of reviews [15, 37–40, 41•]. It moves from the indirect to the direct, but remains, for the moment, short of experimental. A hypothesis proposing that insulin resistance was the driver for T1D could not be sustained unless there was a rise in T1D which paralleled that of obesity, the single most important causal factor of insulin resistance. There are many such reports, though their importance lies not in arguing association, which is always vulnerable to ecological fallacy, but in their sine qua non. The hypothesis would sink without them.

An appropriate temporal association between weight gain and T1D is also a sine qua non. The weight gain must come first if it is to contend for the role of causation, and reference was made earlier to several reports that children who develop T1D are heaver (and taller) than their peers years in advance of clinical presentation.

Of greater importance, though still not proof of causality, is the inverse correlation between BMI and age at presentation in populations of children with T1D. Correlation is evidence of systematic association between variables within a population rather than merely parallel behavior between 2 groups. In this instance, the evidence is for acceleration of diabetes onset in heavier children.

There are 2 contributions to the probability of developing a multifactorial disease such as T1D – environmental risk and genetic susceptibility to it. The 2 relate inversely to each other

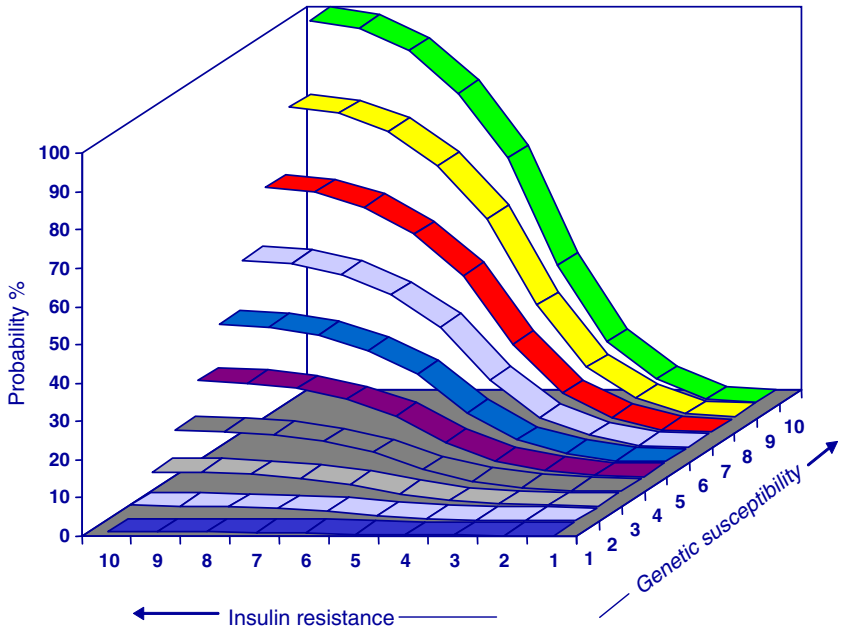


**Fig. 1** The probability of developing diabetes – an infinitely variable interaction between insulin demand and immunogenetic response (autoimmunity). (With permission from: Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: the accelerator hypothesis. Pediatric Diabetes. 2012;13:334–9.) [41•]

so that if the risk rises, the proportion of probability attributable to susceptibility must fall. There is good epidemiological evidence that the genetic contribution to the probability of T1D has fallen over recent years [42, 43], implying that the 3-fold rise since the 1980s is related to environmental change. Such evidence does not indicate what environmental change, and has to be interpreted sparingly on that account.

There are several reports, spanning decades, of insulin resistance among patients with insulin-dependence and, more recently, among patients with pre-T1D. Where insulin resistance was once an irrelevance to the pathophysiology of diabetes, it became for a time part of its duality. Increasing difficulties with matching the modern phenotype of diabetes with the criteria for its classification, and the disappointing results of immunotherapy prevention trials have led to some re-thinking and a reconsideration of the relationship between insulin resistance and autoimmunity.

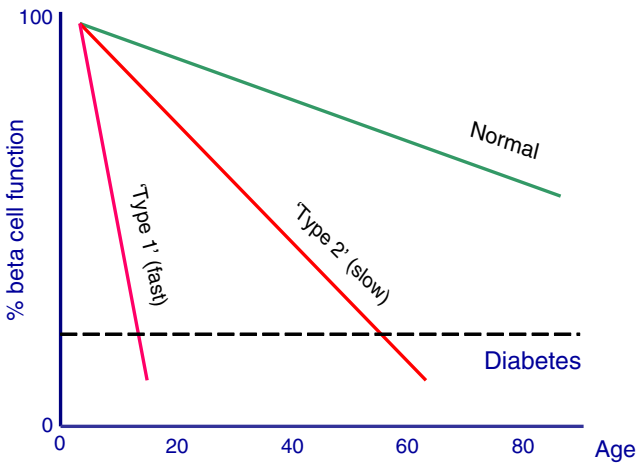


**Fig. 2** The concept of tempo in diabetes. (With permission from: Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: the accelerator hypothesis. Pediatric Diabetes. 2012;13:334–9.) [41•]

## Refutation

Paradigm change is challenging, and careful consideration should be given to arguments that seek to refute it. One early concern from geneticists was the lack of overlap between loci associated with T1D and those associated with type 2. How could the two be one and the same disease if they do not share susceptibility genes? This is a particularly genocentric position to adopt because, apart from monogenic states, genes do not cause disease. In multifactorial disorders, genes merely modulate risk – in this case the rate of beta cell loss – and Fig. 1 is an attempt to schematize the relationship between risk (environment) and susceptibility (genes). Indeed, the accelerator hypothesis from its inception proposed that '…type 1 and T2D are the same disorder of insulin resistance set against *different* genetic backgrounds.' By implication, those who succumb to diabetes early in life will carry 'fast' genes and those later in life, 'slow' genes (Fig. 2).

Two reports examined existing data sets opportunistically, concluding that the inverse relationship between BMI and age at presentation of T1D that defines acceleration was apparent only in children whose beta cell loss was already well advanced [44, 45]. However, in contrast to other studies, which incorporated whole clinic populations collected over decades, the 2 in question (SEARCH and ENDIT) analyzed children who had become diabetic during a brief window of time, and

for that reason may have selectively excluded children with less aggressive (slower) disease.

Another concern is why, if T1D and T2D are the same disorder, their insulin requirements are typically so different. An explanation might again be drawn from Fig. 1, and its representation of the infinitely variable interaction between beta cell load (insulin resistance) and immunogenetic response. Insulin requirement reflects not only beta cell reserve, but tissue sensitivity, and sensitivity clearly affects endogenous as much as administered insulin. Children with the highest susceptibility need only a small increase in beta cell load to mount the immune response that destroys their islets, and a correspondingly small dose of insulin in replacement. Lower susceptibility requires a higher load for diabetes to develop and, if load is now the major contributor to beta cell loss, the therapeutic dose required is likely to be higher. That said, it is a common experience to have required only small doses of insulin as a relatively slim child with 'fast' diabetes, but higher doses as a heavier adult. The same explanation might be directed toward another clinical difference that some believe distinguishes T1D from T2D—brittleness. Fluctuant control (variable blood sugar) should be differentiated from poor control (raised blood sugar). The latter is often associated with loss of tissue sensitivity, whereas brittleness, although multifactorial, generally needs tissue sensitivity. Children, who for the most part develop fast diabetes where the immune response is dominant, and adults with T1D who remain slim, tend to be more vulnerable to brittleness, whereas those whose diabetes develops slowly because insulin demand is dominant, tend not to be.

It is sometimes asked how T1D and T2D can be the same disorder, when autoimmune diabetes is associated with the autoimmune regulator gene (AIRE) [46], while type 2 is not. Mutations of AIRE, however, are implicated only in the rare polyglandular disorder of the autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, of which diabetes sometimes forms part [47]. Thus, dysregulation of the immune system by a single gene mutation *can* lead to autoimmunity as a primary cause of diabetes in man, as it can in the NOD mouse, but AIRE mutations are not found in nonsyndromic T1D [48] and do not seem relevant to the accelerator hypothesis.

## APT – Accelerator Prevention Trials

It is now a decade since the author and a number of international colleagues called for alternative approaches to that of immunotherapy in the prevention of T1D in children [49]. Attitudes towards the relationship of insulin resistance to autoimmunity have changed over this period, with a number of reports world-wide confirming the predictions of the accelerator hypothesis, and others providing direct evidence for insulin resistance in children at risk of T1D. The weight of circumstantial evidence for the accelerator concept, and the disappointing outcome of immunotherapy trials, have this year (2013) led an international funding agency to consider a multi-stage intervention trial to reduce beta cell load in children at risk of T1D. The outcome of stage 1, if funded, will be known in late 2015.

## Conclusions

Hyperinsulinemia resulting from insulin resistance appears to precede all forms of diabetes except for the single gene disorders of glucose sensing or insulin release. Nature's weight gain experiment of the past 40 years—almost certainly the largest 'clinical trial' of recorded time—has been associated with an exponential rise in insulin resistance, and in T1D as well as T2D [50]. Hypotheses need mechanisms to guide the interventions used to test them. The issues here are whether there is now sufficient evidence to justify an intervention study based on the accelerator principle and sufficient benefit to be expected from the outcome. The hypothesis that T1D and T2D are the same disorder has a mechanism to explain it, but so far only circumstantial evidence to support it. The perceived outcome—reclassification of diabetes as a single entity—might strengthen resolve to redirect resources toward the prediabetic state, where the opportunity for prevention surely lies. A single disorder, targeting a single issue (insulin resistance) for prevention, could have considerable impact on the burgeoning problem of childhood diabetes.

### Compliance with Ethics Guidelines

**Conflict of Interest** Terence J. Wilkin is employed by the University of Exeter.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Himsworth HP. Diabetes mellitus: Its differentiation into insulin-sensitive and insulin-insensitive types. Lancet. 1936;I:127–30.
2. Himsworth HP, Kerr RB. Insulin sensitive and insulin-insensitive types of diabetes mellitus. Clin Sci. 1939;4:119–52.
3. Martin FIR, Stocks AE. Insulin sensitivity and 131l-insulin metabolism in juvenile-type diabetics. Aust Ann Med. 1967;76:289–96.

4. Ginsberg HN. Investigation of insulin sensitivity in treated subjects with ketosis prone diabetes mellitus. Diabetes. 1977;26:278–83.
5. Harano Y, Ohgaku S, Hidaka H, Haneda K, Kikkawa R, Shigeta Y, et al. Glucose, insulin and somatostatin infusion for the determination of insulin sensitivity. J Clin Endocrinol Metab. 1977;45:1124–7.
6. Defronzo RA, Bendler R, Simonson D. Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes. 1982;37:795–801.
7. Joslin EP, Root HF, White P, et al. The treatment of diabetes mellitus. London: Henry Kimpton; 1947. p. 144–6.
8. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes. 1965;14:619–33.
9. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet. 1974;2:1279–83.
10. Nerup J et al. HLA antigens and diabetes mellitus. Lancet. 1974; 2:864–6.
11. •• Bonifacio E. Immunotherapy in T1D: a shorter but more winding road? Diabetes. 2012;61:2214–5. *A balanced and compelling appraisal of the difficulties that have met immunotherapy trials in their attempts to prevent T1D.*
12. Gale EAM. Declassifying diabetes. Diabetologia. 2006;49:1989–95.
13. Wilkin TJ. The accelerator hypothesis: Weight gain as the missing link between Type I and Type II diabetes. Diabetologia. 2001;44: 914–22.
14. von Herrath M, Nepom GT. Animal models of human type 1 diabetes. Nat Immunol. 2009;10:129–32.
15. Wilkin TJ. Changing perspectives in diabetes: their impact on its classification. Diabetologia. 2007;50:1587–92.
16. Reinehr T, Schober E, Wiegand S, et al. Beta-cell autoantibodies in children with type 2 diabetes mellitus: Subgroup or misclassification? Arch Dis Child. 2006;91:473–7.
17. Tuomi T, Groop LC, Zimmet PZ, et al. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a noninsulin-dependent onset of disease. Diabetes. 1993;42: 359–62.
18. Molbak AG, Christau B, Marner B, et al. Incidence of insulin-dependent diabetes mellitus in age groups over 30 years in Denmark. Diabetic Med. 1994;11:650–5.
19. Baum JD, Ounsted M, Smith MA. Weight gain in infancy and subsequent development of diabetes mellitus in childhood. Lancet. 1975;2:866.
20. Keen H, Jarrett RJ. Environmental factors and genetic interactions. In: Creutzfeld W, Kobberling J, Neel JV, editors. The genetics of diabetes mellitus. Berlin: Springer-Verlag; 1976. p. 203–14.
21. Gale EAM. The rise of childhood type 1 diabetes in the 20th century. Diabetes. 2002;51:3353–61.
22. Gottlieb MS. Diabetes in offspring and siblings of juvenile- and maturity-onset-type diabetics. J Chronic Dis. 1980;33:331–9.
23. Dahlquist G et al. The Swedish childhood diabetes study: results from a 9 year case register and a 1 year case-referent study indicating that type 1 (insulin-dependent) diabetes mellitus is associated with both type 2 (noninsulin-dependent) diabetes mellitus and autoimmune disorders. Diabetologia. 1989;32:2–6.
24. Wilkin TJ. Autoimmunity: attack, or defence? Autoimmunity. 1989; 3:57–73.
25. Grabar P. Autoantibodies and the physiological role of immunoglobulins. Immunol Today. 1983;4:337–40.
26. Hypothesis GP. Auto-antibodies and immunological theories: an analytical review. Clin Immunol Immunopathol. 1975;4:453–66.
27. Basu R, Breda E, Oberg AL, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribu
28. Costes F, Langen R, Gurlo T, et al. β-cell failure in type 2 diabetes: A case of asking too much of too few? Diabetes. 2013;62:327–35.
29. Patterson CC, Dahlquist GG, Gyürüs E, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. Lancet. 2009;373:2027–33.
30. Maedler K et al. Glucose induces b-cell apoptosis via upregulation of the Fas receptor in human islets. Diabetes. 2001;50:1683–90.
31. Donath MY et al. Hyperglycaemia–induced β-cell apoptosis in pancreatic cells of Psammomys obesus during development of diabetes. Diabetes. 1999;48:738–44.
32. Robertson RP et al. Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. Diabetes. 2004;53 Suppl 1:S119–24.
33. Johansson C et al. A high weight gain in early life is associated with an increased risk of type 1(insulin-dependent) diabetes. Diabetologia. 1994;37:91–4.
34. Hypponen E et al. Infant feeding, early weight gain and risk of type 1 diabetes. Diabetes Care. 1999;22:1961–5.
35. Bruining GJ. Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. Netherlands Kolibrie study group of childhood diabetes. Lancet. 2000;356:655–6.
36. • Harder T et al. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: Systematic review and meta-analysis. Am J Epidemiol. 2009;169:1428–36. *The most comprehensive evidence available that children who develop T1D are heavier from early life than their peers who do not.*
37. Wilkin TJ. The great weight gain experiment, accelerators, and their implications for autoantibodies in diabetes. Arch Dis Child. 2006;91:456–8.
38. Wilkin TJ. The accelerator hypothesis. In: Bantle JP, Slama G, editors. Nutritional management of diabetes mellitus and dysmetabolic syndrome. Karger: Nestle International Workshops; 2006. p. 139–53.
39. Wilkin TJ. Diabetes: 1 and 2, or one and the same? Progress with the accelerator hypothesis. Pediatric Diabetes. 2008;9:23–32.
40. Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type 1 as well as type 2 diabetes. Int J Obesity. 2009;33(7):16–26.
41. • Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: the accelerator hypothesis. Pediatric Diabetes. 2012;13:334–9. *The most recent update of the accelerator hypothesis and the role of insulin resistance in T1D.*
42. Hermann R, Knip M, Veijola R. Temporal changes in the frequencies of HLA genotypes in patients with type I diabetes—indication of an increased environmental pressure? Diabetologia. 2003;46:420–5.
43. Gillespie KM, Bain SC, Barnett AH. The rising incidence of type 1 diabetes is associated with a reduced contribution from high-risk HLA haplotypes. Lancet. 2004;364:1699–700.
44. Dabelea D, D'Agostino Jr RB, Mayer-Davis EJ. SEARCH for Diabetes in Youth Study Group. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1 (autoimmune) diabetes. Diabetes Care. 2006;29:290–4.
45. Bingley PJ, Mahon JL, Gale EA. Insulin resistance and progression to type 1 diabetes in the European Nicotinamide Diabetes Intervention Trial (ENDIT). Diabetes Care. 2008;3:146–50.
46. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet. 1997; 17:399–403.
47. Meloni A, Willcox N, Meager A, et al. Autoimmune polyendocrine syndrome type 1: an extensive longitudinal study in Sardinian patients. J Clin Endocrinol Metab. 2012;97:1114–24.
48. Turunen JA, Wessman M, Forsblom C, et al. Association analysis of the AIRE and insulin genes in Finnish type 1 diabetic patients. Immunogenetics. 2006;58:331–8.
49. Wilkin TJ, Ludvigsson J, Greenbaum CJ, Palmer JP, Becker DJ, Bruining J. Future trials for the prevention of type 1 diabetes. Diabetes Care. 2004;27:996–7.
50. Wilkin TJ. The great weight gain experiment, accelerators and their implications for autoantibodies in diabetes. Arch Disease in Childhood. 2006;91:456–8.