Prevention of type 1 diabetes

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Introduction/background: Type 1 diabetes is a chronic autoimmune condition characterized by destruction of insulin-producing β cells within the pancreatic islets. It is associated with considerable morbidity and mortality. Incidence levels are rising worldwide.

Sources of data: Pubmed search (Nov 2010) using keywords: Type 1 diabetes, prevention, trials, immunotherapy.

Areas of agreement: The causes of disease are multifactorial with genetic and environmental factors playing a part. There is a long pre-clinical period before the onset of overt symptoms, which may be amenable to therapeutic intervention to prevent disease.

Areas of controversy: The exact nature of causative environmental factors is unknown and much debated. Immunotherapeutic intervention may therefore represent the best option for disease prevention.

Growing points: Enhancement of ‘regulatory’ immune mechanisms currently shows the most promise as an approach to disease prevention.

Areas timely for developing research: Clinical trials of early immunotherapeutic intervention may be the answer to disease prevention.

Keywords: clinical trials/immunotherapy/prevention/intervention/treatment/
Type 1 diabetes

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Introduction

Type 1 diabetes (T1DM) is a chronic autoimmune condition characterized by T cell-mediated selective destruction of insulin-producing pancreatic β cells within the islets of Langerhans. This results in inadequate insulin production, which ultimately leads to hyperglycaemia and the classic triad of symptoms seen at disease presentation—weight loss, polyuria and polydipsia. Left untreated, the condition is fatal.

T1DM affects up to 20 million people globally; incidence is increasing rapidly. In Europe the incidence of childhood T1DM has increased
by 4% per year since 1989, particularly in children under the age of five. Exogenous insulin has been the mainstay of treatment for T1DM since its discovery in 1921. While this enables most sufferers to lead a near normal daily life, it is not without shortcomings. In the short term, extreme highs and lows in blood sugars may precipitate diabetic ketoacidosis and hypoglycaemia. In the long term, the disease is associated with several chronic complications including retinopathy, nephropathy, neuropathy and vascular disease. Despite modern medical management, in the UK, T1DM is still associated with a mortality rate three to four times higher than that of the background population.

The development of interventions to prevent disease, and alternative treatments to insulin has so far proved an elusive goal. Cyclosporin trials in the 1980s reported temporary remission in newly diagnosed T1DM proving the principle that manipulation of the immune system can alter the course of the disease. Since then, knowledge of the pathophysiology and natural history of the disease has grown, but our ability to intervene effectively to delay or prevent the clinical onset of disease is unchanged. New strategies for intervention and disease prevention are required and the development of such interventions and treatments is an active area of research. This article reviews current progress in this field.

Pathophysiology, natural history and epidemiology of T1DM

T1DM is a complex illness, occurring as a result of multiple aetiopathological factors. It is important to understand the pathophysiology, natural history and epidemiology of T1DM when considering potential new interventions to prevent the development of clinical disease (Fig. 1).

Pathophysiology

Cellular immunity
T1DM is an organ-specific autoimmune disease in which self-reactive T lymphocytes, activated by autoantigen, destroy the insulin-producing β cells in the pancreatic islets. The primary autoantigen is unknown, though may be insulin itself. Over time, the immunoreactivity spreads and multiple islet antigens become recognized. Gradual destruction of β cells occurs, mediated by cellular immune responses from autoreactive CD8 and CD4 T cells and indicated histologically by inflammatory T cell infiltration of the islets. Whether β cell loss occurs as a progressive linear decline, or there are periods of variation in the rate
of progression due to waxing and waning of the inflammatory immune response remains a matter of debate.\(^7\)

In a normally functioning immune system, T cells with a high affinity for self-antigens are eliminated or their activity is controlled by a number of complementary mechanisms, resulting in immune tolerance.\(^9,10\) Autoreactive cells which have escaped these mechanisms are subject to regulation, preventing clinical disease in most individuals.\(^9\) It is thought that the loss of the immune system’s ability to recognize self-pancreatic tissue—a loss of ‘self-tolerance’—may in part be due to a failure of a specific subset of CD4 T cells known as ‘regulatory T cells (T\(_{\text{reg}}\))’.\(^9\) This subset of cells is a current focus of research to find new treatments for T1DM.

**Humoral immunity**

T1DM is characterized by the presence of circulating antibodies to auto-antigens. Antibodies develop sequentially,\(^11\) generally appearing in infancy, and can be present for many years before T1DM becomes clinically apparent.\(^12\) The role, if any, of these antibodies in the pathogenesis of the disease remains uncertain as they are not clearly involved in β islet cell destruction. They may however be clinically important in predicting individual risk of developing T1DM. The four established diabetes autoantibodies are antibodies to insulin (IAA), glutamic-acid decarboxylase 65 (GADA), tyrosine phosphatase islet antigen 2 (IA2A)
and islet cell antibodies (ICA). More than 95% of individuals with newly diagnosed T1DM have autoantibodies to at least one of these antigens. Combined measurement of IAA, GADA and IA2A can detect autoimmunity in up to 80% of those who are at risk of developing T1DM or have newly diagnosed disease, and additional testing for antibodies to the zinc transporter Slc30A8 (ZnT8), which has recently been identified as a further autoantigen increases the rate to around 98%.

Natural history

The onset of symptoms in T1DM is preceded by a long pre-clinical phase. Our current understanding of the natural history is that, in individuals with genetic susceptibility for disease development, as yet unidentified environmental exposures trigger the onset of β islet cell autoimmunity early in life. Sequential development of autoantibodies is gradually followed by changes in insulin secretion and ultimately glucose handling. Metabolic progression to T1DM is marked by a loss of the first phase insulin response to intravenous glucose. Oral glucose tolerance and stimulated C-peptide levels (C-peptide being a marker of endogenous insulin production) also decline over a period of at least 2 years before the classical symptoms of hyperglycaemia become apparent. During this period, the dynamics of C-peptide response to oral glucose tolerance testing alter before a decline in total C-peptide production is observed. C-peptide levels are initially reduced soon after oral glucose loading but enhanced towards the end of the test period. By the time of diagnosis, 80–95% of β cells have been destroyed. Once this point has been reached patients are dependent on daily exogenous insulin administration for life. In established diabetes, while there is often some evidence of residual β cell function by measurement of endogenous C-peptide, ~99% of cells have been destroyed.

Aetiology

T1DM occurs as the result of a combination of genetic susceptibility factors and environmental exposures triggering autoimmunity. While some genetic susceptibility factors are well established, the exact nature of causative environmental triggers continues to be debated.

Genetic associations

A total of 43 T1DM susceptibility loci have been identified to date. The human leucocyte antigen (HLA) region on chromosome 6P21, sometimes referred to as the IDDM1 locus, has consistently been
shown to be strongly associated with T1DM and is thought to account for 50% of genetic susceptibility associated with the condition. The strongest association is with the HLA class II region, where the haplotypes DRB1*0401-DQB1*0302 and DRB1*0302-DQB1*0201 confer the greatest susceptibility for disease.

Of the remaining susceptibility loci, the best validated associations are with the genes encoding for insulin (INS); the cytotoxic T lymphocyte-associated antigen-4 (CTLA4); the protein tyrosine phosphatase non-receptor-type 22 (PTPN22); the interleukin-2 receptor alpha chain (IL2RA), also known as CD25 and the interferon-induced helicase C domain-containing protein 1 (IFIH1). The underlying mechanism of each is postulated to be mediated by effects on the normal functioning of the immune system, playing a role in the pathogenesis, rather than the aetiology, of T1DM.

Environmental associations
T1DM has a monozygotic twin concordance rate of only 30–50%. The condition is being diagnosed at a younger age and overall incidence of T1DM is increasing even in those who would have previously been considered to be at low risk of developing the disease. These observations imply factors distinct from genetic susceptibility, must also be involved in the development of the disease and it is likely that these are environmental. Their exact nature is, however, the subject of much debate and conflicting evidence has often arisen from different epidemiological studies. Environmental factors most commonly proposed as potential causative agents, and currently under investigation in man, fall into two broad categories, infection and diet (Table 1).

Both specific childhood viral infections and a low overall infection load in childhood (the ‘hygiene hypothesis’) have been proposed as possible environmental determinants of T1DM. Viruses implicated include mumps, rubella, enteroviruses, cytomegalovirus, rotavirus and parvovirus. Direct β cell destruction, inflammation, molecular mimicry and transient lymphopenia have been suggested as immune-mediated mechanisms, but there is a lack of conclusive evidence that any of these infective agents is involved in causation of T1DM.

The hygiene hypothesis proposes the opposite scenario; that early childhood infections are required to facilitate the development of a mature immune system able to produce a wide repertoire of balanced immune responses, and that a reduced load of infection early in life increases the risk of future autoimmunity. This hypothesis is consistent with the concurrent falling rates of childhood infection and increasing incidence of T1DM.

When dietary factors are considered, evidence from epidemiological studies is again conflicting. For example, observational epidemiological
studies have reported early cow’s milk exposure to both associated with and independent of T1DM. Food exposures that have been reported to protect from future disease development include cod liver oil, breast milk, nicotinamide, zinc, and vitamins E and D, while those proposed as potentially causative include gluten, casein and cow’s milk protein. The observation that T1DM autoantibodies often arise early in infancy suggests that maternal diet during pregnancy, and gestational influences such as pre-eclampsia and maternal infections, may also play an important role in future disease development.

The retrospective nature of many epidemiological studies introduces a risk of bias that can make the findings hard to interpret. In the Environmental Determinants of Diabetes in the Young (TEDDY) prospective cohort study, 7000 children from the general population who are genetically at risk of developing T1DM are being followed from birth until 15 years of age to identify factors involved in the initiation of autoimmunity. In this study, very detailed monitoring of childhood exposures to possible causative agents, including dietary and infective agents is being related to the appearance of islet autoantibodies. Positive findings from this study may lead to future intervention trials to prevent T1DM-associated autoimmunity.

### Table 1. Environmental exposures proposed as potential causative factors in the development on T1DM.

<table>
<thead>
<tr>
<th>Pregnancy factors</th>
<th>Exposures in infancy</th>
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<tbody>
<tr>
<td>Exposure to rubella infection as a foetus</td>
<td>Infectious agents: enterovirus (especially Coxsackie B) and rotavirus</td>
</tr>
<tr>
<td>Exposure to enterovirus as a foetus</td>
<td>Improved hygiene (i.e. lack of exposure to infections)</td>
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<tr>
<td>ABO blood group incompatibility</td>
<td>Early gluten exposure</td>
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<tr>
<td>Hyperbilirubinaemia</td>
<td>Early cows’ milk protein exposure</td>
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<tr>
<td>Pre-eclampsia</td>
<td>Low levels of vitamin D, E and ascorbic acid</td>
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<tr>
<td>Maternal age</td>
<td>Low levels of omega-3-fatty acids</td>
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<tr>
<td>High birth weight for gestational age</td>
<td>Mycotoxins</td>
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<td>Maternal age</td>
<td>N-nitroso compounds</td>
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<tr>
<td>Maternal infections</td>
<td>Well water</td>
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Psychosocial factors

| Stress |

**How and when to intervene**

Residual β cell function after diagnosis of T1DM, as measured by preservation of C-peptide secretion or following islet cell transplantation, is associated with reduced risk of microvascular complications and fewer
episodes of severe hypoglycaemia, suggesting that some endogenous insulin secretion is better than none. On the basis of current understanding of the disease process, it is apparent that there are a number of time points at which intervention to prevent or delay progression towards T1DM could be possible. These are: before the development of islet cell autoimmunity; during islet cell autoimmune attack before the onset of clinically apparent disease; at diagnosis of T1DM and in established disease (Fig. 1).

Removing exposure to causative environmental factors early in life, before the initiation of islet autoimmunity, offers one possible approach to disease prevention. If this is to be a realistic option, a limited number of environmental determinants need to be identified for which the association with disease is proven beyond reasonable doubt. As T1DM is being diagnosed at a younger age, and it appears that islet autoimmunity can generally be detected in infancy, even in people who develop T1DM later in life, intervention would have to occur from around the time of birth and possibly prenatally. Once autoimmune attack on the islets has begun, modification of the environment is unlikely to halt the disease process.

It therefore seems that intervention which manipulates the underlying autoimmune process is more likely to succeed. Intervention could occur before the development of, or during, islet autoimmunity. The likely benefits of intervention at these time points would depend on the nature of the intervention and the degree to which the autoimmune process could be halted or reversed, but could result in prevention of disease. If an intervention were found which could ‘reset’ the immune system memory, treatment in newly diagnosed and established T1DM might be possible. At the time of diagnosis, 5–20% of β cells are still functioning and could therefore be preserved. Some β cells are present in up to 88% of individuals with established T1DM on post-mortem histological examination of the pancreas and there is currently considerable interest in the idea that these cells could regenerate, suggesting that intervention could be of potential benefit even in established disease.

**Intervention: risk versus benefit**

Insulin, while not a perfect treatment, is safe. The risks that clinicians and patients are willing to accept from any new treatment are likely to depend on the stage in the disease process at which that intervention is offered. This is particularly true for immune therapies, which can often be associated with adverse effects. An immune intervention may be considered acceptable to use to delay disease progression in a person...
with newly diagnosed diabetes but, even if known to prevent disease when administered early in the disease pathogenesis, may be considered to have a side effect profile that makes it unsafe to administer to a person who has a high genetic susceptibility for developing T1DM, but may never progress to clinical disease.

Before the onset of islet autoimmunity—i.e. before the appearance of autoantibodies—intervention, if very low risk, could be given at a population level. Alternatively, screening offered early in life could identify those who carry a high genetic susceptibility for future development of T1DM and intervention could then be offered to these individuals. The lifetime risk of developing T1DM is only 12% for an individual with the highest risk HLA type, 5% of these individuals will have T1DM by the age of 5 years. Therefore, even in individuals at highest genetic risk, any intervention would have to be safe and essentially free of side effects.

Once islet autoantibodies have been detected, individuals are at substantially greater risk of developing T1DM and some side effects of treatment may be acceptable. High throughput assays for islet autoantibodies are available and testing strategies have been developed so that screening children for islet autoantibodies will be feasible if an effective intervention becomes available. Persistent autoantibody positivity for multiple islet autoantigens, but not transient or single antibody positivity, is associated with very high risk of progression to diabetes. Antibody-positive individuals can be accurately stratified across the range 7–89% chance of developing T1DM within 5 years on the basis of number of antibodies present, antibody subclasses and titres, allowing interventions to be offered appropriately according to the likely balance of risk and benefit. The stage of multiple autoantibody positivity is clearly very closely related to development of diabetes but whether it represents an autoimmune process that is too advanced to be amenable to intervention to prevent clinical disease remains to be determined.

At diagnosis the risk–benefit ratio for intervention shifts considerably. An intervention may be considered clinically useful at this stage if it reduces micro- and macrovascular disease complications and results in some preservation of β islet cell function compared with insulin therapy alone, even at the expense of some adverse effects.

**Intervention studies in man**

Many clinical trials have been conducted with the aim of finding an intervention which will prevent or delay the onset of T1DM but, to date, no effective new treatments have emerged. Some recent studies,
mainly in the field of immune intervention, have however shown some early promise.

Intervention trials in humans have often been based on strategies, which have proved successful in preventing or delaying the development of diabetes in the non-obese diabetic (NOD) mouse model of T1DM. While over 230 effective therapeutic strategies have been identified in this model, only a few have proved to be of any clinical significance in man. Nevertheless, some important lessons can be learnt from these studies: prevention of diabetes in the NOD mouse is easy if intervention is undertaken early in life (in mice, at the age of 4–6 weeks) but difficult if it is applied later in the disease process; not all interventions are safe and dosing of the intervention is important. These findings suggest that intervention trials in humans should take place early in the disease process. However, safety of study subjects is of paramount importance in clinical trials and assessment of the risk–benefit ratio as discussed above often means that intervention studies, particularly if investigating an immunotherapy, are conducted much later in the immune process than may be optimal for achieving therapeutic benefit. This may result in negative trial outcomes even though an agent might be associated with clinically useful efficacy if given at an earlier stage in the disease process.

Studies in man: environmental intervention

Epidemiological observations of possible causes of T1DM have driven the design of intervention studies in this field, with trials focusing on removing or modifying exposure to potential environmental antigenic triggers before islet autoimmunity develops. Although the aetiology of T1DM is believed to be multifactorial, most studies have aimed to modify only a single exposure, which perhaps explains why these trials have not yet been successful in altering the disease process. The largest dietary intervention study, the ongoing Trial to Reduce IDDM in the Genetically at Risk (TRIGR) is investigating the effect of excluding cow’s milk protein, a potential antigenic trigger, from the diet of genetically at risk infants until 6–8 months of age. The preliminary pilot study suggested there were fewer autoantibody-positive children at 10 years of age if hydrolyzed formula milk was substituted for standard formula preparations, but data on the primary outcome, development of diabetes by age 10, will not be available until 2017. The BABYDIET study is similarly investigating whether delaying infant exposure to dietary gluten can prevent the development of T1DM. As discussed, many other interventions at this stage prevent disease in animal models and some of these would be safe to test in man, but the
logistics of a large randomized controlled trial such as TRIGR demonstrate that this is a formidable task.

Vitamin D is known to have multiple effects on the immune system. It has been implicated in the promotion of T<sub>reg</sub> responses and limitation of pathogenic immune responses at a cellular level, exerting its effects in a non-antigen-specific manner. Vitamin D deficiency has been associated with development of T1DM in epidemiological studies. A Phase 1 study of daily vitamin D administration is currently recruiting genetically at-risk infants. A similar pilot study is looking at the omega 3 fatty acid docosahexanoeic acid, which is thought to have anti-inflammatory effects on the immune system.

**Studies in man: immune intervention**

Intervention trials have focused on modulation of the immune system, in particular T cell activity, by either antigen-specific or non-antigen-specific mechanisms.

The largest disease prevention trials have been conducted in antibody-positive individuals, prior to development of T1DM (Table 2). It has been proposed that exposure of the immune system to the insulin molecule may result in induction of regulatory immune responses through the generation of T<sub>reg</sub> responses and/or as a result of β cell rest. Insulin administration has been shown to prevent diabetes in the NOD mouse. Pilot studies in autoantibody-positive individuals at high risk of progression to T1DM were also promising but there was no convincing evidence that oral or parenteral insulin treatment could delay or prevent the clinical onset of T1DM when more fully tested in the Diabetes Prevention Trial—Type 1 (DPT-1). Post hoc analysis of the oral insulin arm of this trial did, however, show a significant treatment effect in the subgroup of participants with strongest evidence of autoimmunity to insulin. The trial is being repeated by the TrialNet group in a larger group of relatives with these characteristics. In the Diabetes Prediction and Prevention (DIPP) study of intranasal insulin administered to autoantibody-positive individuals again no evidence of delay or prevention of T1DM was seen. An alternative Phase 2 study of nasal insulin (INIT II) is ongoing. Oral insulin administration is also being tested in children who are genetically at risk but antibody negative in a dose finding and safety study, ‘pre-POINT’. The subsequent prevention trial should help answer some of the questions regarding the timing of an intervention in relation to its potential to modulate the autoimmune process. Nicotinamide treatment has also been proposed as a potential modulator of the pathogenic process, which results in T1DM but, as with many of the insulin trials, treatment did not
delay or prevent clinical onset of disease in a large randomized controlled trial of nicotinamide administration to autoantibody-positive individuals.\textsuperscript{44}

Other immune intervention trials have been carried out in people with newly diagnosed T1DM, usually because of concerns about potential side effects. Here, preservation of C-peptide is used as a proxy measure of β cell mass and therefore treatment efficacy. As tight glycaemic control can have beneficial effects in terms of preservation of β cell mass in the early stages of disease,\textsuperscript{45} the design of these studies must incorporate measures to ensure this is achieved in both treated and untreated subjects.

Humanized non-mitogenic CD3-specific monoclonal antibody is the therapy at the most advanced stage of development. CD3 is a cell surface marker found on all T cells. Anti-CD3 is therefore a non-antigen specific treatment, theoretically affecting the activity of all

<table>
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<th>Table 2: Completed large immunological intervention trials conducted in antibody-positive individuals</th>
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<td><strong>Agent/intervention</strong></td>
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<tr>
<td>Insulin (oral administration), DPT-1\textsuperscript{40}</td>
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<td>Insulin (parenteral administration), DPT-1\textsuperscript{39}</td>
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<td>Insulin (nasal administration), DIPP study\textsuperscript{42}</td>
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<tr>
<td>Nicotinamide (oral administration) European Nicotinamide Diabetes Intervention Trial (ENDIT)\textsuperscript{44}</td>
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T cell subsets, not only those involved in the pathogenesis of T1DM. Anti-CD3 has multiple effects leading to immune tolerance and has been successfully used to preserve endogenous insulin secretion in patients with newly diagnosed T1DM in several trials. In humans, the effects of anti-CD3 administered at diagnosis of T1DM have not been permanent and in most individuals endogenous insulin production declines within 2 years after treatment. Side effects include fever, headache, arthralgia, rash and a transient reactivation of Epstein Barr virus. Phase 2 trials using various dosing regimens are ongoing and Phase 3 trials are underway. Other non-antigen specific agents tested include mycophenolate mofetil in combination with anti-IL2 (Daclizumab), anti-CD20 (Rituximab), CTLA4-Ig, IL2 in combination with sirolimus, anti-TNFα (etanercept) and anti-thymocyte globulin. The pilot study of etanercept showed favourable results in treated individuals in terms of C-peptide preservation 24 weeks after treatment. However, this study was small and larger trials would be required to confirm this result. The TrialNet Phase 2 trial of selective B lymphocyte depletion with anti-CD20 treatment in patients with newly diagnosed T1DM showed benefits in treated subjects, as measured by preservation of C-peptide secretion at 12 months after administration of treatment. The majority of subjects in the treatment arm experienced transient infusion reactions.

Antigen-specific immunotherapeutic agents offer the potential for focused intervention, obviating concerns regarding long-term immunosuppression and side effects of treatment but, apart from the insulin trials described above, this approach is in the early stages of development in human T1DM. A Phase 2 trial of GAD65-alum in newly diagnosed children did not achieve its primary endpoint of preservation of C-peptide levels in treated individuals after 15 months compared with controls. Some slowing of C-peptide decline over 30 months was however observed, though other metabolic parameters, such as glycaemic control, were unaffected. Treatment effect was greatest in children treated within 6 months of diagnosis. Further trials using GAD65 are underway to determine whether the benefits can be replicated. DiaPep277, a peptide derived from heat shock protein 60 (HSP60), which is expressed in the pancreatic islet, has also reached Phase 2 trials. This was associated with preservation of C-peptide at 12–18 months in adults but not in children. NBI-6024 (an altered peptide ligand of insulin) did not show any treatment benefit in Phase 2 trials. Antigen-specific therapies at earlier stages of development include proinsulin peptide and the insulin B chain.

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Studies in man: novel therapies

There is considerable interest in using stem cell therapy to treat T1DM. Laboratory protocols are currently being developed to produce viable insulin secreting cells, which are robustly responsive to glucose and are suitable for *in vivo* transplantation, from pluripotent progenitor cells. The therapeutic potential of two possible sources of naturally occurring stem cells, bone marrow and umbilical cord blood, are also under early investigation.

As well as mesenchymal stem cells, umbilical cord blood contains high numbers of T_{reg}. It has been proposed that treating children with newly diagnosed T1DM with autologous stored cord blood may induce immune tolerance and improve diabetes control, and that stem cells in cord blood may allow islet cell regeneration. A pilot study has started, although results 1 year after treatment do not suggest any preservation of β cell function. This is—and will remain—a very difficult field in which to conduct rigorous trials as only a small number of children with highly motivated parents have cord blood stored and randomization is difficult. Genetically modified dendritic cells (DC) can prevent diabetes in the NOD mouse by inducing immune regulation and Phase 1 trials of autologous transplantation of genetically modified DC have started in humans.

Conclusion

With increasing incidence and diagnosis occurring at an ever younger age, it is as important as ever to find new treatments to prevent or delay the progression of T1DM. Our understanding of the disease pathogenesis has increased considerably over recent years and has enabled new intervention trials to be designed. Immune intervention is probably the field most likely to result in new treatments for the disease. If this to become a reality, researchers and clinicians will need to reconsider their approach to treatment of T1DM; we will have to accept some risk of side effects associated with intervention therapies in the hope of long-term health benefit. For true success in preventing disease, interventions may have to be applied at earlier stages of the disease process than those targeted in the majority of current clinical trials. We will need to be cautious about ‘shelving’ therapies that yield negative trial results in the later stages of the disease, i.e. overt diabetes, without exploring their potential to prevent or delay islet autoimmunity or subclinical β cell destruction. A change in focus to concentrate on the early stages of disease may produce the T1DM treatments of the future.
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