Type 1 diabetes in the tropics: the protective effects of environmental factors

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Introduction

Type 1 diabetes is caused by autoimmune destruction of the beta-cells in the pancreas, leading to a reduction in insulin secretion in response to glucose in the bloodstream and, as a result, inappropriately high levels of circulating glucose resulting in the classical triad of symptoms: polyuria (increased urination), polydipsia (increased thirst), and weight loss.[1] The disease typically presents in childhood/teenage years, with over 15 000 new cases diagnosed per year in the United States alone.[2] A great deal of research has been dedicated to the understanding of the pathophysiological processes underlying the autoimmune nature of cell destruction, but in spite of this the initiating factors remain unclear. It is thought that a genetic susceptibility may play a role, including human leukocyte antigen (HLA) genes, although it is observed that this cannot account for the vast majority of cases – only 10% of genetically susceptible individuals develop clinical disease and concordance in monozygotic twins is between 13 and 33%.[3,4] Therefore, environmental factors are thought to be vital in establishing pathogenicity. Several theories exist as to the cause of autoimmunity, including a viral trigger for the immune response, cross-reaction with ingested proteins (such as cow's milk) in infancy, and environmental toxins that specifically destroy beta-cells.[5]

Further support for a role for environmental factors in type 1 diabetes pathogenesis stems from the geographical incidence of the condition. There is marked variation in age-standardised incident rates for type 1 diabetes worldwide, with 0.1 per 100 000 males in China to 37 per 100 000 males in Finland.[6] Interestingly, this pattern seems to follow a latitudinal gradient where there is a relationship between incidence of disease and distance from the equator. In general, European countries show the highest rates, while countries in the tropics show lower rates.[7] In addition, it is noted that migratory populations, particularly those moving from an area of low incidence of type 1 diabetes to an area with a higher incidence, quickly converge and demonstrate a similar incidence to the indigenous population.[8]

There are relatively few epidemiological studies of

type 1 diabetes in Africa, but reports from Tanzania[9] and Sudan[10] show rates of 1.5 per 100 000 per year and 10.0 per 100,000 per year, respectively. Northern European rates are generally well in excess of 20.0 per 100 000 per year.

Differences between the indigenous populations within the same country may also be due to environmental factors. Thus, rural populations in Finland and Sweden demonstrate a higher incidence of disease.[11,12] The 'hygiene hypothesis' may be partially explanatory – a reduction in population density results in less contact with infectious agents, particularly in childhood, which provides insufficient stimulation for immune system development, thus leading to defects in autoimmunity.[8]

The aim of this paper is to review and discuss the relevant data related to the role of environmental factors associated with the development of type 1 diabetes. The incidence of disease in the tropics appears to be lower than in other parts of the world so I will focus on the role of tropic-specific environmental factors, including ultraviolet (UV) light exposure, infectious agents, and dietary factors.

The 'hygiene hypothesis'

The 'hygiene hypothesis' was originally developed in order to explain the incidence of allergic disease, stating that reduced exposure to infectious agents leads to an inexperienced immune system that is more likely to recognise harmless antigens as a threat and thereby produce an inappropriate response.[13] In conjunction with this it has been proposed that autoimmune disorders may be triggered in a similar fashion. In particular, research has focused on the role of early childhood infections and how these might modulate the immune system to provide 'protection' against inflammatory and autoimmune conditions, such as type 1 diabetes and rheumatoid arthritis. Parasitic infection by helminths has been one of the major agents considered in this respect, as they are most prevalent in the tropics (where type 1 diabetes is less common), and an inverse association between infection and type 1 diabetes can be demonstrated in certain populations.[14] Helminth infection is widespread worldwide (over 1.5 billion people infected) and has a low mortality; the co-existence of the parasite with the gut immune system suggests an effective immuno-modulatory mechanism that is both beneficial and harmful to the host.

Evidence from animal studies also supports a role

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for modulation of the immune system by parasites in protecting against type 1 diabetes. Non-obese diabetic (NOD) mice infected with *Schistosoma mansoni* are less likely to develop type 1 diabetes compared with their wild-type counterparts and further studies indicate that regulation of the T cell response and cytokine release may be provided by parasitic antigens.[15,16] The exact mechanisms of action for these processes are poorly understood outside of laboratory studies and a lack of human studies limits the conclusions that may be drawn.[17]

Interesting data are also emerging from animal studies, suggesting that viral agents may also be protective in type 1 diabetes. Filippi and colleagues demonstrate that in NOD mice infected with Coxsackie virus B3 the onset of diabetes is delayed or prevented as a result of immune system modulation and interference with diabetogenic T cell proliferation.[18] It is supposed that the immune response to viruses that acts to limit inflammation may interfere with the mechanisms that propagate inflammation in autoimmune disease. The therapeutic implications of such research include development of a vaccination against type 1 diabetes, although this remains purely theoretical at present.[19]

Enteroviruses

As an alternative to the protective effects of infection, it has also been postulated that viral infections can trigger autoimmune disease. Enteroviruses (EVs), in particular, are good candidates for such an effect: EV virus and proteins can be found in the pancreas of patients with type 1 diabetes; pancreatic islet cells strongly express EV receptors, EVs can infect and destroy pancreatic islet cells in vitro and seasonal infection with EVs matches that of type 1 diabetes peaks of occurrence.[20]

Geographical observations have noted that in regions of the world where type 1 diabetes incidence is highest, the rates of EV infection are low and vice versa.[21] However, the hygiene hypothesis can be modified in order to account for this apparent disparity. Parallels have been made between polio (caused by EV) and current more innocuous EV infections. As poliovirus infection rates decreased, the incidence of paralytic polio increased dramatically. This was due to the fact that children were older when they became infected with the polio virus, following the disappearance of maternal antibody protection. As such it is purported that increased sanitation in industrialised nations (non-tropics) leads to a reduction in maternal exposure to EV and a lack of antibody production, which is protective for the child. As a result, infection with EV is more damaging at a later age, leading to pancreatic islet cell destruction and development of type 1 diabetes. In essence, if EV infection is prevalent, younger children will have more robust immune responses against the viruses and would be less likely to develop virus-associated pancreatic destruction.[22] Therefore, geographical susceptibility to EV infection may be dependent upon industrialisation, sanitation,

and healthcare provision, which may be insufficient in tropical regions of the world.

Ultraviolet (UV) exposure

One of the most significant factors associated with geographical variation of autoimmune disease is the fluctuation in exposure to UV radiation. In tropical regions, UV exposure is more intense and more prolonged compared with non-tropical regions, therefore the potential for UV light as a protective factor against type 1 diabetes has been investigated. Hypotheses to this effect have implicated vitamin D and its metabolites in the pathogenesis as 80–95% of vitamin D is provided by exposure of skin to sunlight.[23] Epidemiological data support this finding, as the further one is from the equator the lower the UV exposure and the higher the risk of type 1 diabetes.[7] Further studies have looked at the role of vitamin D specifically in preventing type 1 diabetes, both in vivo and in vitro. Laboratory data indicate that the active metabolite of vitamin D, 25-hydroxyvitamin D, can modulate the immune response to foreign antigens and induce tolerance towards such antigens.

The protective potential of vitamin D has been explored in humans. Thus, over 10 000 children in Finland were followed from birth, with half receiving vitamin D supplementation (50 mcg/day) and the other half receiving no additional vitamin D. The risk of developing type 1 diabetes was lower in children receiving supplementation, indicating that the immune effects of the vitamin may have significant clinical implications.[24] Maternal vitamin D consumption during pregnancy has also been shown to influence the incidence of type 1 diabetes in infants, where vitamin D supplementation during pregnancy lowered the risk.[25] Furthermore, vitamin D taken during the third trimester specifically, resulted in a reduction in the appearance of islet cell auto-antibodies in their offspring, suggesting a reduced later risk of developing type 1 diabetes.[26]

In spite of these impressive results, there are several areas of contention remaining in this field. For instance, the epidemiological data are not necessarily perfect –changes in altitude affect UV radiation intensity and do not necessarily correlate with the incidence of type 1 diabetes. One reason for this may relate to the rural/urban distribution in the country and, specifically in relation to Scandinavian nations, the consumption of dietary sources of vitamin D.[27] For example, in Norway there is insufficient sunlight in the northern parts of the country to produce adequate vitamin D in winter, yet there are lower rates of type 1 diabetes in this area. It is thought that consumption of vitamin D-rich fatty fish compensates for UV-dependent vitamin D depletion in this case.[28]

Dietary factors

One of the major allergens in infants is cow's milk, which although having a chemical structure similar to human

milk, differs enough so that allergic responses may be mounted against the protein. Interestingly it has been found that the protein sequence difference between cow and human milk may also play a role in the development of type 1 diabetes. Studies have demonstrated that infants who are introduced to cow's milk at an earlier age exhibit a higher risk of developing beta-cell autoimmunity and later type 1 diabetes.[29,30] This is independent to a reduction in time of breast feeding. There is also much data which does not support such a link, although international variations in administration of cow's milk and hydrolysed formulae may be to blame for such discrepancies (as hydrolysed formulae are less immunogenic than cow's milk).[31] One interventional study has been conducted in order to establish the veracity of such an effect. In this pilot trial, 230 Finnish infants at high risk of diabetes were fed either hydrolysed or cow's milk formula and followed up for almost 5 years. Results suggested that signs of beta-cell autoimmunity had been reduced by 50–60% in those infants receiving hydrolysed formulae.[32] Thus it has been proposed that delaying infantile exposure to cow's milk proteins reduces the future risk of developing type 1 diabetes.

Another dietary factor that may be associated with type 1 diabetes is gluten: exposure to gluten prior to 4 months of age and following 7 months of age led to an increased risk of developing beta-cell autoimmunity, suggesting an appropriate window of exposure between 4 and 6 months.[33] Although there is no satisfactory theory to explain this finding, other data have shown that early exposure to cereal in infants leads to increased levels of autoimmunity.[34] The association between coeliac disease (which is characterised by an autoimmune response to gluten) and type 1 diabetes may lend further support to such a link, although the immunological mechanisms behind this association remain unclear.

Additional factors

Malnutrition-related diabetes (MRDM)
It has been noted that in Ethiopia the characteristics of type 1 diabetes contrasts markedly with that seen in the West: a predominance in males, older age of onset and predominance in impoverished parts of the country.[35] Childhood malnutrition was often associated with diagnosed cases of this type of diabetes in northern Ethiopia, and it has been suggested that this form of diabetes observed may be clinically and pathologically distinct from true type 1 disease. As such, several authors have called for the World Health Organization to recognise malnutrition-related diabetes mellitus (MRDM) independently, in order to differentiate the condition from type 1 diabetes. It is important to classify diabetes correctly in order to establish accurate epidemiological data, as this may demonstrate that the lower incidence of type 1 diabetes in the tropics is not necessarily clear cut.

Data collection
Further to the problems associated with diagnosing and classifying type 1 diabetes in developing nations, it must also be recognised that a paucity of data from these regions reflects poor healthcare infrastructures and a lack of screening and treatment programmes. Data from sub-Saharan parts of Africa indicate that type 1 diabetes is rare in this region, although it is a concern that rural patients may not recognise symptoms and have access to hospital treatment and that early mortality will skew data.[8] It is estimated that a child newly diagnosed with type 1 diabetes has a life expectancy of 1 year in sub-Saharan Africa, compared with over 50 years in industrialised nations.[36] Unfortunately, collection of good epidemiological data is likely to remain difficult, and interpretation of available geographical incidence data should be carried out with caution.

Discussion
In conclusion, the data presented in this paper suggest that a number of environmental factors contribute to the marked global variation in the incidence of type 1 diabetes. Evidence suggests that the incidence is lower in the tropics compared with further north or south of the equator.

Assuming that the observation that there is a direct relationship between incidence of type 1 diabetes and equatorial distance, a number of environmental factors appear to be protective against the development of an autoimmune pathological process. UV radiation results in increased levels of vitamin D, which is an important modulator of the immune system. Detailed studies have shown not only that lower levels of circulating vitamin D predispose to autoimmunity, but that vitamin D supplementation may also reduce the risk of developing type 1 diabetes. Further data are required to establish the clinical utility and cost-effectiveness of such interventions, including the demonstration of these positive effects over a longer period of time.

Other dietary considerations may also be important, with avoidance of cow's milk at an early age seemingly providing protection against autoimmunity. Again, it is unclear as to whether or not use of hydrolysed infant formulae instead of cow's milk for weaning will be of significant clinical benefit, as long-term prospective data of this type are lacking. However, the fact that cereal exposure at a young age may also provoke increased autoimmune activity reinforces the notion that antigen ingestion may affect immune system function.

The role for infectious agents in type 1 diabetes remains unclear, as there are variations on the hygiene hypothesis which suggest that certain infections may prove protective whereas others may be pathogenic. Certainly, evidence in animal models convincingly demonstrates an association between viral antigens and autoimmunity and human biopsies have shown viral particles in the pancreas of type 1 diabetes patients. However, there is a lack of data demonstrating a causal effect for viral infections. Furthermore, the intriguing prospect that parasitic infections may protect against type 1 diabetes

requires further study, so that molecular mechanisms may be elucidated for therapeutic purposes.

Future research needs to be conducted on a large scale, with the inclusion of both randomised and prospective studies in order to establish the link between environmental factors and type 1 diabetes pathogenesis. In particular, long-term follow-up of infants is required to assess the true benefits of interventional trials. In addition, consideration of the interaction of genetics with environmental factors is necessary to complete the picture, as it is likely that both mechanisms are involved in determining geographical variation of disease.

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