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VIEWPOINT ARTICLE

Is it time to challenge the established theories surrounding type 1 diabetes?

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ABSTRACT

Type one diabetes (T1D) seems a well-defined disease, but its classification may be difficult. Evidence is weak that an autoimmune process with insulitis causes loss of the beta cells in all patients. Some scientists propose that it may be caused by a virus, increased hygiene or the early introduction of cow's milk or gluten, while views about the nerve supply, vascular function and the beta cells own role tend to be disregarded. Immune interventions have had limited success. There are differences, but also similarities, between T1D and type 2 diabetes (T2D).

Conclusion: Several views on T1D have become so widely accepted that they may actually hamper progress into the true cause of this disease. Research on T1D needs to be carried out with an open mind, and clinicians might be wise to recommend a lifestyle that aims to decrease both the risk of T1D and T2D.

INTRODUCTION

For a long time, diabetes was divided into insulin dependent and non-insulin dependent diabetes. With increasing knowledge, it was then a wise step to classify the main groups into Type 1 (T1D) and Type 2 diabetes (T2D). T1D was found to be characterised by lost residual function, showed signs of an autoimmune process and displayed an association to certain genes, particularly the human leucocyte antigen (HLA) locus. Meanwhile, T2D had different and weaker genetic associations and insulin secretion continued, but with a relative insulin deficiency, partly caused by increased insulin resistance. The T1D and T2D classifications led to enormous progress in the treatment of both forms of diabetes. Over time, however, these classifications may also have proved a disadvantage, with the picture becoming too black and white and hampering, or almost obstructing, new views.

We still do not know what causes T1D and we do not know why the insulin-producing beta cells stop producing insulin or how many of the beta cells lose their function or even die. In fact, we know very little about whether the beta cells themselves, or other pancreatic cells, are involved in the disease process. Despite this, there is still a common perception that we know how the disease develops as a result of an autoimmune process, and this has resulted in quite strong opinions on how to intervene and stop the process.

Thus, there are several views on T1D that are almost regarded as facts, even though our knowledge is still weak and fragmentary. This may explain why certain areas of research are less popular. These include studies on islet cell nerve supply and function, the local vascular supply, the interplay between different pancreatic, endocrine and exocrine cells and the role of the beta cells per se, for their own sensitivity to the autoimmune process, and beta cell death or dysfunction. However, we have to admit that there is little proof that autoimmunity alone causes beta cell death or dysfunction and that the effect of immune interventions is very limited.

POOR KNOWLEDGE ON THE DISEASE PROCESS IN HUMANS

Type 1 diabetes is regarded as the result of an autoimmune destruction of the pancreatic beta cells leading to lack of insulin. (1) In the 1950s, Le Compte described inflammation

in the pancreas, sometimes with insulitis, and this was confirmed many years later by Gepts (2). With the discovery of islet cell antibodies in 1974 (3) and HLA-connections (4) proof of the autoimmune concept seemed overwhelming. When Sutherland transplanted a pancreas from a healthy monozygotic twin to its diabetic twin, rapid cell-mediated destruction of the beta cells in the transplanted organ, with no sign of antibodies, became the final proof (5). However, Gepts found quite limited signs of insulitis. Later studies on pancreases from patients with T1D have shown that insulitis is quite rare. Needle biopsies of pancreases in a Japanese study only showed insulitis in some patients. Post-mortem examination of pancreases has confirmed that insulitis, even with a generous definition, is not seen in the majority of the islets in T1D patients (6).

Although several findings do not fit with the hypothesis that insulitis has destroyed most of the beta cells at diagnosis of T1D, the theory of insulitis remains strong. This has been strengthened by the picture found in experimental animal models, especially the non-obese diabetic (NOD) mouse. The NOD mouse was meant to be a useful model of autoimmune diabetes and it was. However, gradually, the NOD mouse seems to have received too much focus when findings in humans do not fit the patterns found in NOD mice; one can get the impression that this is explained as a methodological problem, rather than questioning the actual results. Research too often seems to be focused on efforts to confirm that the mechanisms found in NOD mice also exist in humans. Even though the NOD mice model is of great help when it comes to elucidating mechanisms and creating new ideas, we have to accept that the gap between autoimmune diabetes in mice and humans is huge. Clinical studies on human beings are necessary, even in children, as there is also a difference between T1D at different ages.

THE CAUSE OF TYPE 1 DIABETES IS UNKNOWN

Although the research community admits that the cause of T1D is unknown, there are several ideas that are regarded as more or less proven, while other mechanisms have been disregarded. In the 1920s, it was suggested that diabetes might be caused by infections, as some cases were diagnosed shortly after mumps pancreatitis. The virus hypothesis was revitalised at the end of the 1960s by Gamble and Taylor when they found indications that enterovirus, especially coxsackievirus, may play a role.

Ten years later, when Notkins and Yoon described isolating and transferring the coxsackievirus from a newly diagnosed diabetic child into an animal that developed diabetes (7), the concept was regarded as proven. But after decades of intensive research (8), and the most sophisticated modern methods, we have still not found a virus that can cause T1D in humans. There are studies, particularly from Finland, that suggest that the early introduction of cow's milk can cause T1D (9), while others have not been able to find such connections. The TRIGR (Trial to Reduce Insulin dependent diabetes in the Genetically at Risk) project will soon answer at least some questions. But it is unlikely that this project can more than give suggestions or indications in the special group of children involved in this trial: newborn babies with HLA-types associated with risk of T1D and with a first degree relative with T1D. The great majority of children who get diabetes do not have any first degree relative with T1D and may, in many aspects, differ from the TRIGR children.

There are several other more or less popular theories related to factors such as gut flora (10), increased hygiene (11) and maturation of the immune system. Although these ideas are regarded as plausible and interesting, there are other possible explanations that are not as well accepted or rarely discussed. For example, the search for bacterial infections as a cause of T1D has just started. And there are suggestions that factors that are normally associated with the development of T2D may contribute to the development of T1D, such as rapid growth, being overweight and beta cell stress caused by numerous factors, such as low physical activity, trauma and psychological stress (12). These ideas are usually viewed with great scepticism, and sometimes researchers even suggest that considering these theories almost betray the 'truth' that T1D is a completely different disease to T2D. Although there are certainly big differences between typical cases of T1D and T2D, when it comes to factors such as residual insulin secretion, genetic associations, autoimmune phenomena and degree of insulin resistance, there is also evidence that suggests that T1D and T12 have a lot in common and that their classification may need to be re-evaluated. Furthermore, as hinted above, there are completely different mechanisms that might play a role in the development of T1D, such as factors related to the nervous system, connections between the brain and islets, vascular supply to the islets, interplay between the islet cells, the function of the exocrine pancreas, bacterial infections of the pancreas and the beta cells' own role in their tendency to die or at least lose their function (13).

TYPE 1 DIABETES MAY BE DIFFICULT TO DEFINE

With the exception of some rare groups, diabetes can be divided into T1D and T2D. T1D certainly differs from T2D, both phenotypically and genetically. Phenotypic T2D displays a relative lack of insulin, mainly because of increased demand. The classic sign of T1D is a pronounced lack of insulin, but it can still present with some residual, good insulin secretion although these levels are insufficient even for a thin, physically active person. Thus, even diabetic children may demonstrate a broad range of residual insulin secretion. In Sweden, which has a high incidence of classical T1D, many children with T1D have quite impressive residual insulin secretion, while in contrast, some children with T2D may actually have rather low C-peptide at diagnosis (14). There is certainly a gradual loss of C-peptide, but this is not as homogenous as we tend to believe. The decline of beta cell function is related to age at diagnosis, body mass index (BMI), season of diagnosis and ethnic origin (15). Another characteristic of T1D is

autoimmunity, manifested by signs such as auto-antibodies against the insulin-producing cells. However, not all children with T1D have auto-antibodies. The pattern of the cell-mediated immune response differs, and it has not been possible to agree upon certain criteria such as the deviation between Th1 and Th2 helper cells, the proportion of certain cytokines and chemokines, any specific proportion of T cells or regulatory cells or dysfunction of certain immune cells. Furthermore, patients with T2D also have signs of auto-immunity, both with auto-antibodies and with signs of cell-mediated immunity (16). Genetically, there seems to be a clear difference between T1D and T2D, with rather little overlapping in genetic associations. For example, the T2D genes do not increase the tendency of typical T2D characteristics such as autoimmunity (17). However, no specific gene is necessary for the diagnosis of either T1D or T2D, as all the genes are seen in patients with both types of diabetes as well as in non-diabetic individuals. Thus, although most patients who get T1D certainly have special so-called HLA risk genes, nowadays, some patients get T1D without having any HLA-type risk genes (18).

Many clinicians now subscribe to the established theory that T1D in children is characterised by severe insulin deficiency caused by an autoimmune process killing the beta cells. While this may be true in many cases of T1D, perhaps even in most cases, this does not always happen. This might provide one explanation for why immune interventions to preserve beta cell function have limited effect. Some years ago, the hope for successful immune interventions increased when phase II trials showed positive results (19–25), but unfortunately, these studies were followed by disappointing failures when it came to large phase III trials (26–29). There was substantial support for the theory that blocking the interleukin 1 cytokines that play a central role in the regulation of immune and inflammatory responses would be efficacious in T1D, but clinical studies failed (30). Problems with clinical trials may, to some extent, explain the difference in efficacy between the phase II and III trials. In large phase III trials, it is common to include many patients who may differ regarding form and severity of T1D, age, ethnicity, geography, BMI at diagnosis and clinical management, and all of these factors may influence the course of the disease process and decline of C-peptide. But as indicated above, a contributing explanation to lack of efficacy of immune interventions may also be that there are some T1D patients who do not have the type of autoimmune process that can be expected to respond to such interventions.

CONCLUSIONS

Knowledge about the aetiology and pathogenesis of T1D has increased, but at the same time, we have to admit that several basic questions remain unanswered. We do not know the cause of T1D, and we do not even know if an autoimmune process with insulitis is the sole cause, or a contributory factor, to beta cell death or dysfunction in some but not all patients. T1D is not completely homogeneous. The disease may be caused by different factors worldwide, depending on where people live, and it is important that we do not focus on finding one cause for all cases. We also need to be open minded about the pathogenetic mechanisms and look for other mechanisms, rather than just focusing on the autoimmune system. These include factors related to the beta cells' own role, their nerve supply, vascular supply, islet cell interplay, relationship to the exocrine pancreas and bacterial infections. And we also need to recognise that although T1D and T2D differ in many ways, these two entities also have a lot in common and there may be some overlap when it comes to both causal factors and pathogenetic mechanisms. While we wait for better solutions, it seems reasonable to try to prevent the increasing incidence of T1D by using similar approaches to tackling T2D, such as lifestyle changes, in addition to the approaches tried so far.

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