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HETEROGENEITY IN DIABETES AND BETA CELLS

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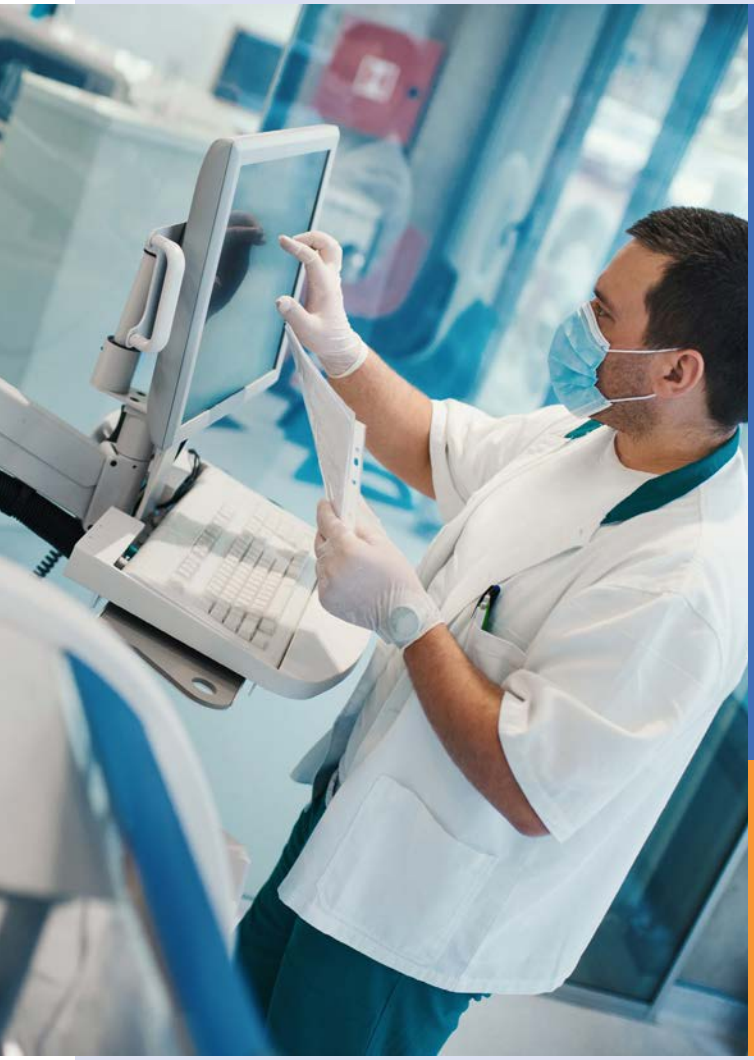

Patients at the heart of diabetes: going beyond subtype hallmarks

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Abstract

Although diabetes subtyping provides a good starting point for treatment selection, the field of diabetes is more complicated than historically thought, and incorrect subtyping can lead to inappropriate treatment decisions. This report uses published studies and case studies from our clinic to highlight the complexity of diabetes heterogeneity. Case studies include a patient diagnosed in the 1980s who, our current knowledge shows, was unnecessarily treated with insulin for 24 years. More recent case studies are examples of patients who have ketoacidosis and/or islet autoantibodies, both hallmarks of type 1 diabetes (T1D), but do not have T1D and do not require insulin treatment. We recently published an unusual case of a patient with autoantibody positive diabetes and pancreatic insulitis who had part of her pancreas removed, along with a tumor. This patient maintained significant insulin secretion for 8 years after surgery, possibly due to the protective nature of the invasive T cells. Studies have also shown that patients with T1D may have transient insulin resistance, while those with type 2 diabetes (T2D) can have reversible insulin secretory defects. Observations from our clinic reveal significant minorities of patients with T1D and T2D who do not meet the traditional definitions of these subtypes. It is thus important that individual patient diagnoses and treatment are regularly reviewed.

Key words: autoantibodies, diabetes, hallmarks, individualized treatment

Introduction

Globally, the age-standardized incidence of both type 1 diabetes (T1D) and type 2 diabetes (T2D) is increasing,[1,2] which highlights the importance of research into treatment optimization. Although classifying diabetes into subtypes can be a useful guide for treatment selection, it is equally important to individually assess treatment requirements for each patient. Choosing a medication based solely on a classification or the presence of certain hallmarks can lead to unnecessary or inappropriate treatment choices with possibly negative consequences. This report provides examples, from our clinic and published studies, of patients who may not meet the standard definitions of diabetes subtypes, and thus require a reassessment of treatment requirements.

Case study 1: diagnosis years prior to currently-available routine tests

This patient, who had family members with diabetes, was diagnosed with diabetes in the early 1980s, when aged in their late 40s. At diagnosis, body mass index (BMI) was normal, fasting blood glucose was 115 mg/dl and two-hour postprandial glucose was 260 mg/dl. The patient was initially treated with lifestyle intervention, followed by oral antidiabetic drugs (glibenclamide and metformin). After 9 years the patient's weight was stable, but hemoglobin A1c (HbA1c) had increased to 8.3%, so treatment with insulin Mix 30 (70% insulin aspart protamine and 30% insulin regular then aspart) and regular insulin injections was initiated. Subsequently, the patient's weight remained stable and HbA1c remained on target (<7%). Thirty-three years after diagnosis, the patient presented with severe hypoglycemia, having suffered a fall resulting in a fracture and hematoma. Testing showed no autoantibodies to glutamic acid decarboxylase (GAD), islet antigen 2 (IA2), or zinc-transporter 8 (ZnT8), which was unsurprising so many years after diagnosis. Based on a good response to a test meal (C-peptide increased from 0.56 to 1.37 nmol/l), prandial insulin treatment was discontinued, and repaglinide initiated; however, that was also discontinued because of hypoglycemia. One year later, their weight was stable and HbA_{1c} was 6.6% with glargine alone. Genetic testing for maturity-onset diabetes of the young (MODY) showed no mutations in the panel of 13 genes. Although our testing has brought us no closer to a diabetes subtype diagnosis, what it does illustrate is, if we had had the ability to run these tests upon initial diagnosis it may have been possible to avoid 24 years of unnecessary insulin treatment, as well as the accompanying severe consequence of hypoglycemia. Of course, in the early 1980s, autoantibody testing and insulin secretion assessment were not routine, and no MODY genes had been identified.

Does knowledge of autoantibody status change the game?

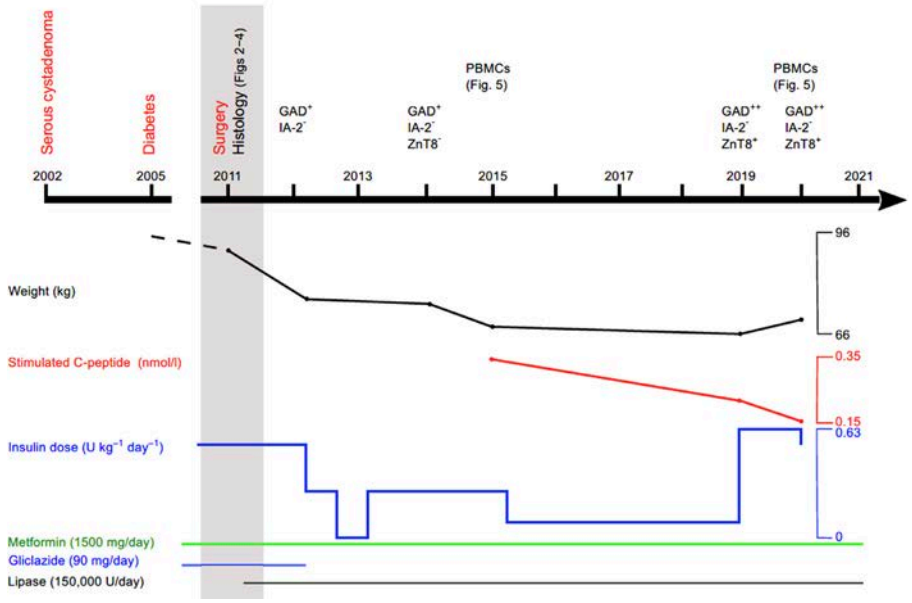
Insulin resistance is considered to be a hallmark of T2D, while the main etiology of T1D is thought to be islet autoimmunity,[3] with almost all T1D patients seropositive for at least one islet cell autoantibody. Thus, testing for autoantibodies has been used as a means to distinguish T1D from T2D.[4,5] However, the reality is not always this straightforward. As an example, my second case was diagnosed with diabetes at the age of about 50 years, presenting with a very high blood glucose level (>300 mg/dl), normal BMI, and a history of vitiligo, and was subsequently also diagnosed with Grave's disease. One parent and one adult sibling had T2D, and the patient's child was diagnosed with T1D and Grave's disease as a young adult. Testing 12 years after diagnosis showed significantly elevated levels of autoantibodies to GAD (37 U/l, upper limit of normal values: 1 U/l) as well as the presence of autoantibodies to IA2 and thyroid peroxidase (TPO), and a negative test for parietal cell antibodies (PCA). These results would suggest that the patient had T1D; however, at the same time point the patient also showed a very good response to a mixed meal test (MMT; C peptide increased from 0.46 to 2 nmol/l). And in fact, the patient has been successfully treated for many years with metformin. At the most recent follow-up, approximately 17 years after diagnosis, the patient was still receiving metformin and had an HbA_{1c} of 6.5%. Thus, although autoantibody status implied T1D, when combined with the other data it become unclear what type of diabetes the patient has.

In addition to the presence of autoantibodies, ketoacidosis has traditionally been considered a hallmark of T1D; however, it is now clear that it does not necessarily indicate T1D.[6] My third case study is an elderly patient, born in Africa, who was diagnosed approximately 10 years ago, after presenting with ketoacidosis. At diagnosis, BMI was at the lower limit of normal, GAD autoantibodies were strongly positive, and IA2 was negative. This suggested T1D, although the patient was elderly; a diagnosis of latent autoimmune diabetes in adults (LADA) was excluded because of the ketoacidosis at onset of diabetes. The patient was treated with a basal-bolus insulin scheme. In the 6 years following diagnosis, the patient was hospitalized 6 times for ketosis episodes. Six years after diagnosis,

the patient showed a good response to an MMT (C-peptide 0.1 to 0.5 nmol/l). At this time, the patient was weaned off basal-bolus insulin, and treatment with repaglinide was initiated, along with glargine to protect from ketoacidosis. At the most recent follow-up, the patient was responding well to treatment, with a normal blood glucose level. So, a patient can have ketoacidosis and islet autoantibodies, and yet not have T1D.

We recently published an interesting, and possibly rather unusual, case study of a female patient who had Hashimoto's thyroiditis and, in 2002 (aged 47 years), was diagnosed with a benign tumor of the pancreas (**Figure 1**).[7] Diabetes was diagnosed about 3 years later and was treated with metformin and gliclazide. In 2011, because the tumor size was increasing, a Whipple intervention was performed to remove the head of the pancreas. Prior to surgery, add-on insulin glargine was initiated, and after surgery she was treated with metformin, gliclazide, insulin glargine and pancreatic enzyme replacement therapy. What we found incredible was that, in spite of being positive for GAD autoantibodies before surgery, and having approximately one-third of her pancreas removed, she maintained significant insulin secretion for 8 years after surgery, as evidenced by well-controlled blood glucose levels with low-dose long-acting insulin. Approximately 8 years after surgery, the patient's insulin needs increased; at that time, she was also seropositive for a second autoantibody, ZnT8. Pancreatic samples, taken during surgery, showed evidence of β cell destruction (distorted α cell to β cell ratio), and insulitis; in addition to CD8+ and CD4+ T cells, the insulitis contained suppressive forkhead box protein 3 (FOXP3) positive T cells, which may explain the slow clinical progression. Thus, it appears that after initial destructive insulitis, the autoimmune process was spontaneously regulated, with the consequence of reduced β cell destruction, for several years.

Figure 1: *Schematic timeline of the evolution of autoantibodies, clinical variables, treatments and related pancreas histopathology, and blood T cell analyses. The patient's clinical history before and after surgery (2011) is depicted. The time of sampling for pancreas tissue (2011) and PBMCs (2015, 2020) is indicated. Reprinted by permission from Springer Nature:* Diabetologia. *2021;64(12):2731-2740. Immunoregulated insulitis and slow-progressing type 1 diabetes after duodenopancreatectomy. Faucher P, Beuvon F, Fignani D, et al. © 2021.*



Can patients with T1D show insulin resistance?

Some years ago, we had the opportunity to look at nine patients at the very late preclinical stage of T1D, that is, they had autoantibodies, decreased insulin secretion, but still normal fasting blood glucose levels.[8] At this stage, when they were just on the border of developing clinical diabetes, we found that their insulin sensitivity was normal (as assessed by glucose clamp studies). These findings can be contrasted with those of an earlier study in 54 patients with recent onset T1D and 14 healthy controls.[9] Initial HbA_{1c} in the patients with T1D was 13%, and insulin sensitivity was substantially decreased. After insulin treatment for 1 week, blood glucose was normalized, and insulin sensitivity had increased. Insulin sensitivity was further increased at 2 weeks and 1 month after treatment, and during remission it was higher than in control individuals. What this shows is that just after strong metabolic derangements, patients with T1D can have at least transient insulin resistance.

Can patients with T2D have insulin secretory defects?

Insulin secretary defects are the hallmarks of T1D, but can they also be observed in T2D? Several years ago, a superb paper was published showing reversible insulin secretory defects in Chinese patients (N=382) with newly diagnosed T2D.[10] Baseline HbA_{1c} was approximately 10%. Patients were treated with either insulin (continuous subcutaneous insulin infusion [CSII] or multiple daily insulin injections [MDI]) or oral agents, and treatment was maintained for 2 weeks after the blood glucose target was reached. What was incredible is that intravenous glucose tolerance testing showed an absence of insulin response at baseline, while after just 2 weeks of normoglycemia the patients responded nicely to the glucose tolerance test. Therefore, based on their insulin secretion at baseline, many of these patients could have been considered to have autoantibody negative T1D, and thus treated with long-term insulin. However, after the initial transient treatment, many patients in the insulin groups were in glycemic remission at the 1-year follow up (51.1% in the CSII group, 44.9% with MDI, and 26.7% with oral treatment), meaning they did not meet diagnostic criteria for T1D.

Experience from our clinic

Although our observations are biased, because as a university hospital we receive more severe cases, and a disproportionate number of patients with T1D, they provide an interesting insight into diabetes subtyping. At our clinic, we have observed that a significant minority of patients with T1D have residual insulin secretion. We have also observed that small proportions of patients with T2D are C-peptide negative or autoantibody positive. I believe that patients belonging to these minorities should be reassessed; however, the manner of this assessment remains unclear.

Conclusion

Although diabetes subtyping provides a useful guide to treatment optimization, it is important that patients are not diagnosed and treated based solely on the presence of subtype hallmarks, as this may lead to a significant minority of patients being treated incorrectly. Among autoantibody-positive patients, most have T1D and will require insulin treatment; however, not all will progress to insulin dependency, some with a history of ketoacidosis may be weaned off insulin, some do not have insulitis, and some can transiently revert from destructive insulitis to protective insulitis. A small proportion of patients with T2D are also autoantibody positive. Furthermore, insulin resistance (a T2D hallmark) can be observed in T1D, transiently, while insulin secretory defects (hallmark of T1D) can be observed in patients with T2D, and can be reversible in both T2D and T1D. It is also possible to know the autoantibody status and C-peptide levels for a patient, but still not be able to provide a diagnosis of a diabetes subtype. It is therefore vital to regularly re-assess patient diagnoses and treatment, as the snapshot of data obtained at diagnosis may not provide us with a true picture of disease subtype and long-term treatment requirements.

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