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Diabetes in other worlds: from Africa to India

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Abstract

We have a limited understanding of the etiology of the most common form of diabetes i.e., type 2 diabetes (T2D), and research into stratification is vital to improve clinical care. The global prevalence of diabetes continues to rise, with marked between-region differences in projected percentage increases. Because diabetes is such a heterogeneous disease, there is interest in whether different phenotypes are prevalent in certain geographic regions. There are at least three phenotypes for which the prevalence differs between regions: ketosis-prone diabetes (classified as a 'hybrid' form of diabetes), which is very prevalent in Africa; the rare fibrocalculous pancreatic diabetes mellitus, which is also called tropical diabetes due to being observed almost exclusively in tropical countries; and fulminant type 1 diabetes, which is prevalent in Japan, Korea, and China, and uncommon in Caucasians. Although defining between-country differences in T2D is challenging, there is evidence of different clinical profiles between Asian Indian patients and Caucasian patients. We have also found that migration from Africa to Europe may have some influence on the clinical features of T2D, although this needs further investigation. Different approaches to T2D stratification via data-driven cluster analysis are also being investigated, with the goal of predicting disease trajectory and thus optimizing clinical care.

Key words: classification, diabetes, geographic regions, phenotypes, prevalence

Introduction

In 2021, globally, an estimated 537 million adults were living with diabetes.[1] This number, which approximately corresponds to one in every ten adults, is predicted to rise to 643 million by 2030, and 784 million by 2045. The greatest increases in prevalence are expected to occur in Africa, including Western, Middle Eastern, and Northern Africa regions, and Southeast Asia. In Africa, the current prevalence of diabetes is low, at one in 22 adults; however, this region is expected to have the highest increase in prevalence.[1] By 2045, an estimated 55 million adults in Africa will have diabetes: an increase of 129% from 2021. This region also has the highest estimated proportion of undiagnosed diabetes at approximately 54%. In Southeast Asia, the prevalence in 2021 was double that in Africa, with one in 11 adults (~90 million) living with diabetes, and this number is expected to increase by 69% by 2045.[1] As with Africa, more than 50% of adults with diabetes are undiagnosed. The Middle Eastern and Northern Africa region had the highest prevalence of diabetes in 2021, at one in six adults, and has an expected increase of 86% by 2045.[1]

Diabetes is extremely heterogenic, and the inter-region variability in prevalence leads us to question whether different regions have different predominant disease phenotypes. This article provides a brief overview of diabetes classification, discusses region-specific phenotypes, and addresses some advances made in the stratification of type 2 diabetes (T2D).

Classification of diabetes

Because diabetes is extremely heterogeneous, accurate classification is vital for guiding clinical care.[2] For most forms of diabetes, our understanding of the etiology and pathogenesis is limited; therefore, regularly updating subtype classifications can help stimulate research to increase our knowledge, as well as provide a guide for studies of disease incidence and complications. The World Health Organization (WHO) updated their diabetes classification in 2019.[2] Their document recognizes that, while an ideal classification would assist with clinical care, etiopathology, and epidemiology, current knowledge and resources preclude meeting all three goals, and thus the focus of the 2019 classification is on clinical care.[2]

As we know, the two main types of diabetes are type 1 diabetes (T1D) and T2D, with the latter accounting for at least 90% of all diabetes.[2] There are also several specific types of diabetes and hyperglycemia first observed in pregnancy. Additionally, the 2019 classification included new types of diabetes, two 'hybrid forms' and 'unclassified diabetes.' The two hybrid forms are slowly evolving immune-mediated diabetes, previously known as latent autoimmune diabetes in adults (LADA), and ketosis-prone type 2 diabetes.[2] Our research group contributed classifying of this latter phenotype, as discussed in further detail below.

Within these classifications, we have some forms of diabetes for which the etiology is well defined: autoimmune T1D, with the presence of autoantibodies; certain types of monogenic diabetes, identified via genotyping; pancreatic diabetes, identified by abdominal imaging; and diabetes secondary to endocrine disorders. However, for the vast majority of patients with diabetes, the disease etiology is poorly defined, and we lack positive diagnostic markers. This group includes most patients with T2D, ketosis-prone diabetes, and non-identified monogenic diabetes. For these patients, stratification is needed in order to tailor treatment and improve their care; numerous researchers are working towards this goal.

Ketosis-prone atypical diabetes

Patients with ketosis-prone diabetes present with two clinical abnormalities that distinguish them from those with T1D or T2D; ketosis, with or without acidosis, but with no T1D autoantibodies and typically with periods of remission, during which they do not require insulin.[2] This form of diabetes is very prevalent in Africa, where an estimated 15% of hospitalized patients with diabetes have ketosis-prone diabetes.[3] In our department (in France), this phenotype accounts for approximately 40% of patients from West Africa who are admitted with high blood glucose levels. Although these patients may relapse frequently, they can also have long periods of insulin-free remission, as observed in a 10-year study comparing the insulin secretion profiles of patients (all of sub-Saharan African origin) with T2D, T1D, and ketosis-prone diabetes.[4] In this study, 76% of patients with ketosis-prone diabetes were able to discontinue insulin treatment, and after an initial period of acute low insulin secretion, these patients showed improved insulin secretion lasting for several years, with levels similar to those observed in the patients with T2D.[2] Thus, in terms of clinical presentation, ketosis-prone diabetes is an intermediate phenotype that presents in a similar fashion to T1D at onset, but is more like T2D during follow-up.[5]

The sudden onset of ketosis-prone diabetes suggests that there may be precipitating factors in its development,[6]

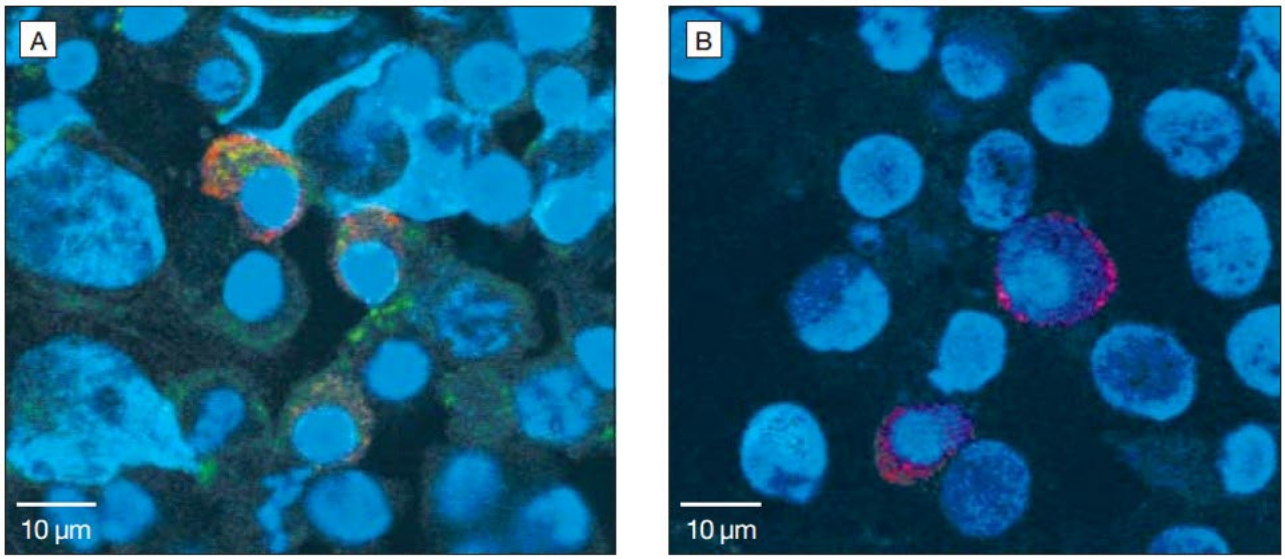
and researchers have investigated several possible etiologies. In 2005, a study from our group showed an association between ketosis-prone diabetes and a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme, although the prevalence of *G6PD* gene mutations was no higher in patients with ketosis-prone diabetes than in those with T2D or controls.[7] Several other genes have been investigated, including human leukocyte antigen (HLA) *DRB1* and *DQB1*,[8] but thus far, we have found no convincing genetic data to explain this phenotype.

A study of patients with diabetes hospitalized in Cameroon found that variations in admission rates were similar to variations in rainfall, with a (non-significant) increase in the incidence of diabetes during the rainy season.[9] One possible explanation for this is that infection may play an etiologic role, and as ketosis-prone diabetes is prevalent in patients of African descent, researchers have investigated common viruses in this population. In France, we found an association between human herpesvirus 8 (HHV8) infection and ketosis-prone diabetes in Black patients of African origin.[6] This association was based on three findings. Firstly, over 80% of patients with ketosis-prone diabetes were positive for HHV8 antibodies, compared with 15% of those with T2D and 40% of controls. Secondly, at disease onset, almost 50% of patients with ketosis-prone diabetes (vs. none of those with T2D) had circulating HHV8 DNA. Finally, *in vitro* experiments showed that HHV8 has the capacity to infect pancreatic β cells (**Figure 1**), suggesting a possible direct effect.[6] We have since shown that, during the acute (ketotic) phase of ketosis-prone diabetes, patients have increased levels of pro-inflammatory cytokines compared with patients with T2D.[5] Furthermore, we have found an association between HHV8-positive serology and low insulin secretion in sub-Saharan African patients with diabetes.[10] Further studies into inflammation and infection throughout the course of this phenotype are warranted.

Fibrocalculous pancreatic diabetes mellitus

This diabetes phenotype is very rare, and is also called tropical diabetes because the majority of cases have been observed in tropical countries;[11] however, we have observed one case in our department in France. At presentation, patients are typically lean adolescents or young adults with high blood glucose levels and pancreatic calcification but no ketosis. They often have brittle diabetes, requiring multiple high-dose insulin injections.[12] In these patients, malabsorption responds well to pancreatic enzyme supplementation. The etiology of fibrocalculous pancreatic diabetes mellitus is unknown and probably multifactorial, with genetic, nutritional, and inflammatory factors proposed, as well as the possibility of dietary toxins from cassava.[11]

Figure 1: *Human pancreatic* β *cells cultured* in vitro *with and without human herpesvirus-8 (HHV-8) and co-stained with anti-insulin and anti-HHV8 protein antibodies. a) Two double-stained cells in green and red demonstrate HHV-8 infection in* β *cells. b) The control experiment without virus shows two red-stained* β *cells. Reproduced with permission from JAMA 2008. 299(23):2770-2776. Copyright © 2008 American Medical Association. All rights reserved.*



Fulminant type 1 diabetes

Fulminant T1D is prevalent in Japan, Korea, and China, but uncommon in Caucasian patients.[2,13] This phenotype of T1D is characterized by an extremely abrupt onset with ketoacidosis, a very short duration of hyperglycemic symptoms (<7 days), and close to normal (<8.5%) hemoglobin A1c (HbA1c) levels, despite marked hyperglycemia. At diagnosis, these patients also have very low C-peptide levels, and generally have undetectable islet-related autoantibodies, increased serum pancreatic enzyme levels, and infiltration of T cells and macrophages into islet cells. Although this disease is usually reported in Asian patients, a few cases of fulminant T1D have been observed in French Caucasians.[14] As an example, one of these patients was 18 years old, with normal weight and no personal or family history of diabetes or cardiovascular risk factors. She was admitted to an intensive care unit with severe ketoacidosis, accompanied by vomiting and confusion. Her blood glucose levels were very high (1200 mg/dL), but, remarkably, her HbA1c level was only 6.4%. She displayed brittle diabetes, and after 16 months of treatment, required a subcutaneous insulin pump.

Classification of type 2 diabetes

Differences between countries

As outlined above, there are at least three different forms of diabetes for which the prevalence differs markedly between regions or race. For the majority of patients with T2D, the etiology is poorly defined, and there is interest in investigating whether the clinical profile of T2D differs between countries. However, defining between-country differences is difficult as the T2D diagnosis is often made by default, due to the lack of any diagnostic biomarkers. Consequently, the prevalence of T2D is dependent on the availability in each country of diagnostic tests for markers, such as antibodies, genotypes, C-peptides, and fecal elastase, that define forms of diabetes other than T2D when positive.

Although distinguishing between-country differences in T2D is challenging, there are numerous data emerging from India showing that the clinical profile of T2D in Asian Indian people differs from that in Caucasian people.[15] Compared with Caucasians, Asian Indians have a younger age of onset, a lower body mass index (BMI; but higher levels of central obesity and insulin resistance), increased inflammatory markers (such as high-sensitivity C-reactive protein [hs-CRP]), early loss of β-cell function, and a higher risk of coronary artery disease. Of interest, in both T2D and non-diabetic people, blood insulin levels in Asian Indians are higher than in Caucasians.[16]

Our research group have also studied the influence of migration on T2D characteristics in patients of sub-Saharan African descent.[17] We compared three groups of patients with T2D; two groups were of African descent (one group were still living in Cameroon, and the other group had migrated to France as adults) and the third group were French Caucasians. We found that the mean age at diagnosis was younger for immigrants (43 years) than Caucasians (48 years), or Cameroon residents (52 years). While BMI was similar between the groups, median HbA1c levels were higher in Cameroon residents (9.9%) than in immigrants (8.6%) or Caucasians (8.1%). The rate of microvascular complications was also higher in people living in Cameroon, but the only difference that remained significant after adjustment for variables was the presence of nephropathy (74% of Cameroon residents vs. 32% of immigrants).[17] These results, however, may reflect improved diagnosis and care in France, compared with Cameroon, and large-scale studies are required to clarify this.

Cluster analysis

Data-driven cluster analysis, in which subtypes are determined using simple clinical parameters, is another approach to T2D stratification that has generated substantial interest.[18] Our laboratory is taking a different approach to data-driven cluster analysis based on circulating immune inflammatory cell phenotying. Our preliminary results of this approach are promising, and will be presented in the future. We think that these inflammatory profiles may be linked to clinical and metabolic factors, and phenotyping in this manner may help us predict different disease trajectories and, consequently, diabetes complications.

Conclusion

The prevalence of diabetes is expected to continue to rise, with the greatest increases predicted in Africa, including Western, Middle Eastern, and Northern Africa regions, and Southeast Asia. Diabetes is extremely heterogeneous, and for the majority of cases (including most of those with T2D), the etiology is poorly understood. Classification into subtypes is important for improving clinical care, driving further research into etiology, and guiding epidemiologic studies. There are at least three different forms of diabetes for which the prevalence differs markedly between geographic regions or race, and evidence is emerging for between-region differences in the clinical profile of T2D. Various approaches to T2D stratification via data-driven cluster analysis are also being investigated, with the goal of predicting disease trajectory and thus optimizing clinical care.

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