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Autoimmune signatures for prediction and diagnosis of autoimmune diabetes in Kuwait

The incidence of autoimmune diabetes continues to surge despite several therapeutic advances and has long been noticed to be highly variable among countries. In 2017, the incidence rate varied by 803-fold, with 64.2/100,000 in Finland [1] and 0.08/100,000 in Papua New Guinea [2] (Fig. 1). As autoimmune diabetes may be predictable based on family history and the disease cannot go untreated, at least in familial cases [3].

Kuwaiti Autoimmune Diabetes Study (KADS) is the first familial cohort study of its type in the region.

The HLA accounts for 50% of the genetic susceptibility to autoimmune diabetes and is significantly associated with an increased risk of diabetes [3]. The impact of HLA haplotypes on the titer of anti-islet antibodies had been well-established [4]. The low incidence rate of autoimmune diabetes in Southeast Asia was significantly correlated with the low frequency of the DRB1*010;3-DQB1*020;1 and the DRB1*01:04-DQB1*03:02, which are the highly susceptible haplotypes reported in Caucasian populations [5]. On the other hand, the DRB1*04:05-DQB1*04:01 and the DRB1*09:01-DQB1*03:03 are the major susceptibility HLA haplotypes in Japanese and Korean populations [6]. In Africa, the DRB1*07:01-DQA1*03:01-DQB1*02:01 g haplotype increased the autoimmune diabetes risk [7].

Recently, different phases of autoimmune diabetes etiology have been endorsed internationally [4]. The pre-clinical, presymptomatic phase, was divided into two, normoglycemia and dysglycemia [4] (Table 1). The KADS's principal objective was to specify the later stages of autoimmune diabetes in a Kuwaiti population, where the disease is prevalent [8].

Islet cell antibodies (ICA) [9] is considered a composite of specific antiβ-cell antibodies, several of which have now been characterized at the molecular level [10] and include IAA, GADA, IA-2, and ZnT-8. Autoantibodies against GAD, IA- 2, IAA, and ZnT-8 are the most reliable biomarkers for autoimmune diabetes in both children and adults [10] and are currently the only biomarkers that can distinguish LADA from phenotypically type 2 diabetes [11].

The presence of two or more anti-islet autoantibodies indicates autoimmunity of pancreatic β-cells [12]. This phase is considered the initial preclinical signature of pancreatic β-cell autoimmunity, which precedes its destruction [12].

The appearance of anti-islet autoantibodies may not be the causes, but the consequences, of β-cell autoimmunity. The entire process of β-cell injury and autoimmunity is thought to transpire during the undiagnosed preclinical episode and upon initiation by triggering agents, which are not yet well-determined.

A systematic autoantibody screening using an inexpensive autoantibody assay for individuals with autoimmune diabetes and their first-degree relatives is the hallmark of KADS. Individuals with two or more autoantibodies can be enrolled in prevention and immunotherapy trials [13].

In short, diabetes is a multifactorial autoimmune disease caused by destruction of pancreatic islet β-cells. In our autoimmune diabetes population, characterization and identification of the HLA haplotype and pancreatic islet autoantibodies as the present biomarkers for β-cell destruction will enable us to develop a scientifically sound prediction algorithm. Screening of first-degree relatives of autoimmune diabetes patients can help predict the family members who are at risk of acquiring the disease and improve the management. There might be a therapeutic value in earlier interventions, when there are greater amounts of functioning β-cells to preserve, rather than at the clinical phase of diagnosis, when most β-cells have been destroyed or damaged.

Take home message

- The onset of autoimmune diabetes can be distinguished from other types of diabetes by measuring anti-islet autoantibodies ie IAA, IA2, GAD and ZnT8
- Production of autoantibodies is under influence of HLA risk values
- Understanding the disease sequela in a homogenous gene pool and highly consanguineous population of Kuwaitis could help solve the challenges and pathogenesis, as well as hasten the prevention, of autoimmune diabetes.

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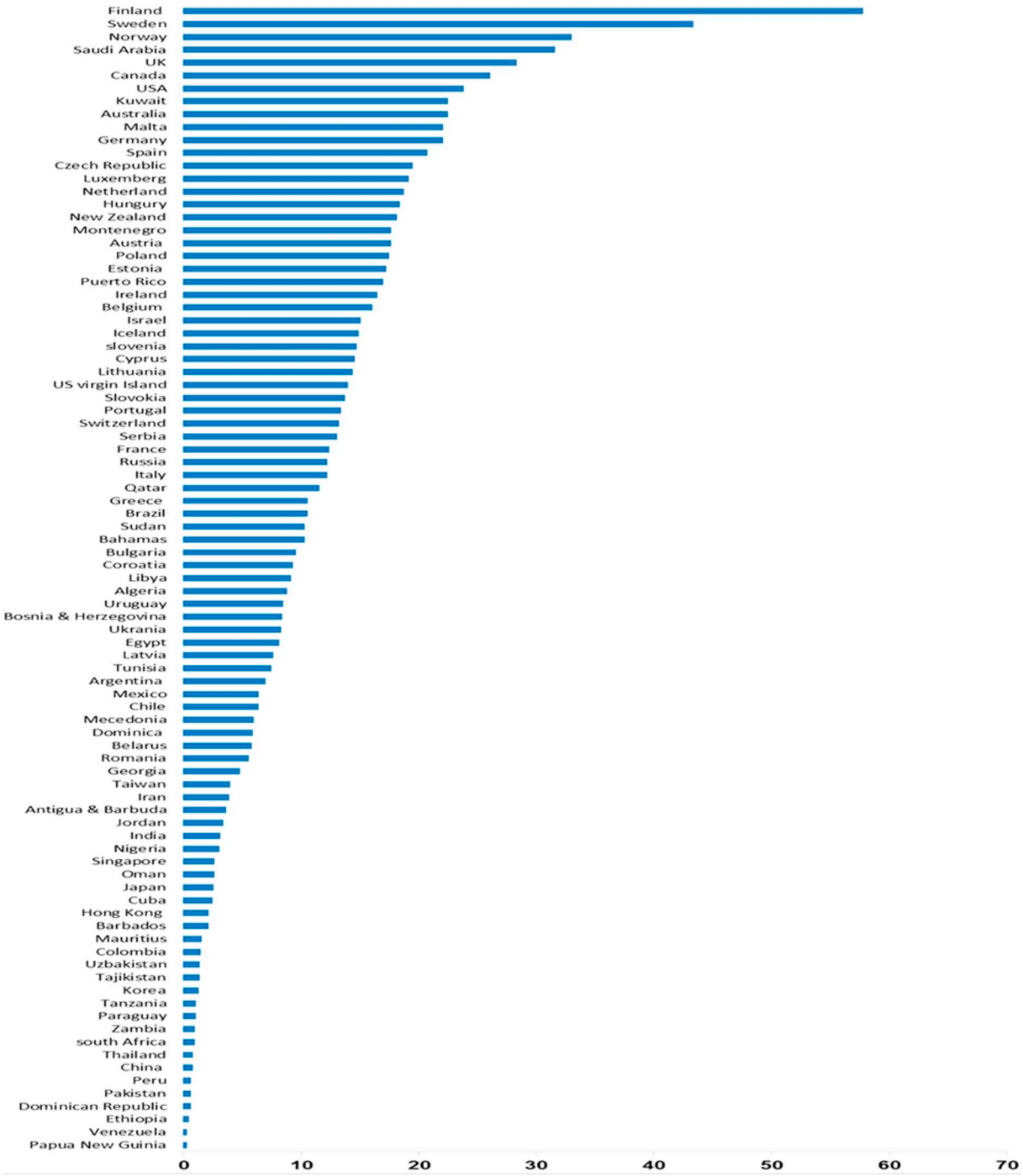

Fig. 1. Global distribution of countries according to the rate of autoimmune diabetes. The reported rates of incidence of autoimmune diabetes in different countries in 2017. The rate of incidence varied from 0.08/100,000 per year in Papua New Guinea and Venezuela to 64.2/100,000 per year in Finland with an approximately 800-fold gradient of among countries. The incidence varies within several other countries in different folds. For example, Sardinia in Italy is markedly greater than the incidence in Italy as a whole (51.0 vs 12.1 / 100,000 population). China is another country where there is such a variation by region (0.13–1.61/100,000). Kuwait and Saudi Arabia which are from high-income Arab countries are among the top ten countries with high incidence rates.

Table 1
Staging of pre-clinical phase of autoimmune diabetes.

Glycemia/Glucose intolerance	Phases	Presence of autoantibody	Diabetic symptoms	Endogenous insulin present
Normoglycemia	Presymptomatic	≥2	No	Yes
Dysglycemia	Presymptomatic	≥2	No	Yes
Dysglycemia	Symptomatic	≥2	Yes	No

The history of autoimmune diabetes is divided into three main divisions according to glucose intolerance. During pre-clinical phase, gray zone, majority of β-cell autoimmunity takes place under influence of complicated biochemical reactions. Anti-islet autoantibodies are consequence markers for any future intervention.

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