A Global Perspective of Adult Autoimmune Diabetes

ABSTRACT

Latent autoimmune diabetes in adults (LADA) is characterized by initial insulin independence and the presence of pancreatic islet autoantibodies, which can lead to the frequent misdiagnosis of type 2 diabetes (T2D). The frequency of LADA cases among patients with apparent T2D can be as high as one in ten, and therefore it is potentially the most common form of autoimmune diabetes. That said, there is ongoing debate regarding the exact definition of LADA, so understanding its genetics basis when contrasted with the better characterized T1D and T2D is one potential strategy to gain insight to its etiology. However, the lack of routine autoantibody screening when diagnosing adult diabetes has hampered the ascertainment of patients for well-powered genetic studies of LADA, especially in populations that are more susceptible to the disease. This review highlights recent genetic and epidemiological studies of LADA, perhaps better described as adult-onset autoimmune diabetes, in populations of diverse ancestries, as well as the importance of autoantibody screening in facilitating future studies.

INTRODUCTION

Genetic studies of type 1 diabetes (T1D) and type 2 diabetes (T2D) have yielded dozens of loci associated with diabetes risk. However, the genetic etiology of Latent Autoimmune Diabetes in Adults (LADA) remains substantially less well characterized compared to the two classic forms of diabetes, thus highlighting a major undeveloped area in the field. Given our interest in the genetics of diabetes, we are motivated to understand where LADA sits with respect to T1D and T2D. We aim to address the apparent challenges of performing genetic studies for LADA and the discrepancy in prevalence rates reported across the globe, including the debate on LADA's clinical definition and phenotypic heterogeneity. Despite being defined as a slowly progressive form of T1D by the World Health Organization[1], LADA exhibits clinical features of both T1D and T2D, earning the nickname "type 1.5 diabetes". Additionally, existing genetic studies have portrayed LADA as a genetic intersection of the two diseases[2]. However, given that LADA is an adult-onset disease, with initial insulin independency, there is still a high misdiagnosis rate among those with T2D (5-10%). As a result, LADA is often overlooked in clinical practice without no clear diagnostic guidelines. In particular, the underuse of autoantibody screening has led to the underdiagnosis of LADA, hampering the ability to estimate accurate prevalence rates and to assess the genetic architecture of the disease. Strikingly, the prevalence estimates based on current reports for T1D, T2D, and LADA differ widely across populations, and this is influenced by genetic, environmental and socioeconomic differences and notably between clinic-based or population-based studies [3]. For instance, the prevailing view is that there is a higher misdiagnosis rate of LADA in populations of African ancestry compared to populations of European ancestry, but challenges exist related to sample size. In this review, we highlight the need for consistent and thorough, well-powered genetic studies in populations of diverse ethnicities to aid in the full characterization of the pathogenesis of autoimmune diabetes; however, these studies cannot be performed if autoantibody screening is not performed immediately after the diagnosis of diabetes.

Clinical implications of LADA

Patients diagnosed with LADA are typically defined by an adult age-at-onset accompanied by insulin independence for at least the first six months after diagnosis, plus the presence of circulating diabetes-associated pancreatic islet autoantibodies (autoimmunity)[1]. The definition

is widely considered inadequate as the need for insulin therapy is arbitrary and the six month cut-off, in some classifications, fails to capture patients from one month to six months post-diagnosis who have all the same clinical and immunological features of LADA[4]. The role of autoantibodies in the pathogenesis of LADA is unclear but given they are critical to the diagnosis of T1D, screening for diabetes-associated antibodies is crucial for diagnosis; patients should be monitored more closely for various reasons outlined below, but specifically if they require insulin therapy at an early stage[5]. Similar to T1D, insulin producing pancreatic β-cells in those with LADA tend to be compromised, presumably by the adverse immune response. Consequentially, the risk of progression to insulin therapy in those with LADA is higher and earlier than in those cases with T2D. If inadequately treated, ketoacidosis can result, representing a substantial complication given that it is the most common cause of death among pediatric diabetic cases [6]. While the destruction of β-cells leads to hyperglycemia in T1D, this complication is also common in T2D via a distinct pathogenesis, such that patients have inadequate insulin secretion due to pancreatic β-cell dysfunction or decreased β-cell mass leading to insulin insensitivity[7].

Thus, adult autoimmune diabetes and T2D are presumed to have two distinct mechanisms for disease progression, and therefore should be treated appropriately immediately following diagnosis. Indeed, studies have indicated that those with LADA should not be treated with sulfonylureas, which is a common treatment for T2D[8], as these drugs further exhaust β-cell reserves, though one caveat is that these studies have limited power [9-11]. Agents which augment the incretin pathway will be of limited value if the C-peptide levels (a proxy for insulin secretion) are very low[12]. The more rapid progression to insulin dependence when linked to the misdiagnosis of a LADA patient as a T2D case could be life threatening, and thus accurate diagnoses are imperative.

Several factors are important in making an accurate diagnosis. First, inadequate treatment is reflected in higher HbA1c levels, with nearly all studies to date finding that HbA1c levels are higher in LADA cases than in T2D cases in the same cohort[13, 14]. A recent study found that the rate of deterioration of HbA1c in LADA was double that of other patients with antibody-negative T2D[15]. Furthermore, individuals with LADA have higher HbA1c independent of insulin usage[16]. More intense follow-up is required owing to this more rapid decompensation in some cases. Second, co-morbidities are different, where there is a higher risk of metabolic

syndrome and cardiovascular disease among those with T2D, although large prospective studies are still ongoing on this context. Recent studies suggested macrovascular disease is as common in LADA as in T2D[17]. However, in LADA there is a higher risk of thyroid and parietal cell autoimmunity, leading to a need for either thyroid replacement or vitamin B12 supplementation[18]. Finally, LADA patients who are obese and scheduled for bariatric surgery should consider avoiding the operation as they are actually at risk of progression to insulin therapy independent of their insulin resistance status.

GENETIC COMPONENT OF ADULT AUTOIMMUNE DIABETES

Lack of awareness of LADA and relatively unclear diagnostic criteria has hindered progress in understanding the genetics of this common disease. However there have been many genetic studies regarding T1D and T2D, both of which have a clear heritable component[19, 20]. First-degree relatives of individuals with T2D are three times more likely to develop the disease than individuals without a family history[21, 22], while first-degree relatives of T1D cases are at approximately 15 times greater risk than the general population. T1D and T2D appear to be due to distinct biological mechanisms, as shown by the paucity of overlapping significant loci identified by genome-wide association studies (GWAS)[23-25]. However, some overlapping signals from the major histocompatibility complex (MHC) loci are beginning to emerge from the most recent GWAS of T2D[26, 27], potentially due to the presence of misdiagnosed individuals with autoimmune diabetes. The MHC accounts for approximately 50% of the genetic risk for T1D, yet there is no clear role of the MHC in T2D. This region harbors human leukocyte antigen (HLA) genes that are the strongest predictors of T1D risk[17] in particular, MHC class II *HLA* genes encode highly polymorphic antigen-presenting proteins (DR, DQ, and DP; **Figure 1**)[28, 29]. The MHC class I genes *HLA-A* and *HLA-B* have also been pinpointed through conditional analyses as increasing T1D risk[30]. However, a signal from the *HLA-B* locus has Another has emerged in a T2D GWAS meta-analysis in African Americans along with a signal from the *INS-IGF2* locus, which has been strongly implicated in LADA[31], further suggesting potential misclassification among those diagnosed with T2D.

Association of T1D and T2D signals in LADA

Multiple loci are robustly associated with T1D and T2D[26, 27, 32-34]. Established GWAS-implicated loci for these diseases have subsequently been investigated in multiple cohorts of European cases diagnosed with adult autoimmune diabetes[31, 35, 36]. In particular, candidate locus association analyses and the use of genetic risk scores suggest that LADA is genetically closer to T1D[35]. However, the genetic load of the strongest T1D risk loci in LADA, particularly *HLA*, *INS*, *PTPN22* and *SH2B3*, is less severe than in childhood-onset T1D, potentially accounting for the later disease age-at-onset of LADA. Several studies have shown that T2D genetic risk, particularly at the *TCF7L2* and *HNF1A* loci, is also associated with LADA. However, the role these T2D loci play in LADA has been inconsistent across the different cohorts studied, such as *TCF7L2* being associated in Swedish and Finnish cohorts but less so in a cohort of individuals from the United Kingdom and Germany[31, 35]. Still, there is an emerging picture for a role for the *TCF7L2* locus in the pathogenesis of autoimmune diabetes, where it has been implicated in T1D heterogeneity[37]. In particular, T1D carriers of the *TCF7L2* risk allele are associated with less severe immunological and metabolic phenotypes in an age–dependent effect (>12 years at diagnosis being the cut-off above which the association was noted)[38]. Therefore, it is unclear to what extent T2D loci contribute to the onset of LADA, but these recent studies suggest a T2D-like pathophysiological mechanism for a subset of affected individuals. A study of diabetes cases from Hungary[39] suggested that body mass index (BMI) influences the genetic effect on LADA risk, such that the lower the BMI, the higher the T2D genetic effect in LADA, as also predicted in a smaller American study[37]. Overall, much larger studies are warranted to detect potentially novel associations unique to LADA or genetic modifiers that delay the onset of autoimmune diabetes. However, it is evident that the HLA locus plays a strong role in LADA and is thus a key genomic region to search for unique features that can aid in disease classification.

TID susceptibility HLA haplotypes role in LADA

Specific HLA haplotypes, which are sets of alleles inherited together from a single parent, have been shown to be significantly associated with T1D. In particular, the haplotypes *HLA-DR3* and *HLA-DR4* play a consistent role across multiple ethnicities[40-45]. Moreover, there is a greater increase in risk for patients with DR3/DR4 heterozygosity than those with only the DR3

haplotype. *HLA-DR9* and *HLA-DR15* have also been observed as significantly associated with T1D world-wide[43, 46, 47]. In a major Chinese study, protective T1D haplotypes were enriched in LADA compared to T1D, while, conversely, susceptibility T1D haplotypes were diminished in LADA when compared to T1D[43]. Perhaps not surprisingly, another study in the same Chinese population comparing LADA and T2D found that these T1D susceptibility haplotypes had a significantly higher frequency in LADA cases (63.9%) than in either T2D cases (47.1%) or controls (43.2%); indeed, the converse was also observed for the frequency of protective haplotypes (LADA: 22.8%; T2D: 33.3%; controls: 32.7%)[48]. Taken together, these findings support the idea that the HLA region contributes to LADA, although attenuated when compared to childhood-onset T1D. In-depth comparative analyses of this HLA region have not been performed to date.

Population-specific susceptibility

Susceptibility at the HLA region also appears to present with population-specific signatures that should be carefully considered due to the extensive haplotypic diversity of this genomic region across ethnicities[43, 49-51]. For instance, there are two subtypes of the European T1D susceptibility haplotype DR3, namely *HLA-DRB1*0301* and *HLA-DRB1*0302*, which confer opposite effects in African Americans, where *HLA-DRB1*0301* is a strong risk haplotype and *HLA-DRB1*0302* is highly protective[46]. Populations of African ancestry have shorter stretches of linkage disequilibrium between markers than other ethnicities, given that this ethnicity is relatively ancient and thus enough time has elapsed to allow for more recombination events to occur; as a result, there is greater haplotypic diversity, which can also help narrow down the causal regions for a particular disease. Additional genetic studies of populations of African ancestry investigating the role of HLA and non-HLA alleles in both T1D and LADA are warranted to further understand the genetic etiology of autoimmune diabetes and would indeed have great utility in fine mapping these key regions in order to better understand how they operate in the pathogenesis of both of these related diseases. This is particularly important, given that populations of African ancestry have been disproportionately impacted by a rise in diabetes, most notably T2D, principally due to the upturn in obesity prevalence, economic development and urbanization.

GLOBAL PREVALENCE OF DIABETES

Diabetes is dramatically on the rise across the globe. Based on the studies available, the overall rate of diabetes is approaching epidemic levels, with a global prevalence projected to reach 10.4% by 2040, and with 5 million deaths as of 2015[52]. T2D is by far the most prevalent form of diabetes[1], accounting for approximately 90-95% of total diabetic cases world-wide, totaling approximately 400 million adults[52]. Additionally, an increased rate of obesity and rise in socioeconomic status has been shown to influence the rate of T2D[53]. In contrast, T1D makes up only a small percentage (4-10%) of the total burden of diabetes worldwide but has a stronger genetic etiology and has clear variation in prevalence around the world[54, 55]. In 2013, worldwide prevalence estimates indicated that there were almost 500,000 children under the age of 15 years old with T1D, with the largest populations being in Europe and North America[54, 56].

The recent increase in T1D prevalence in certain areas could be explained by an environmental effect, such as that proposed in the hygiene hypothesis[57], which posits that an environment with a high incidence of infectious diseases protects against allergic and autoimmune diseases. However, there is a paucity of well-powered studies which have systematically addressed the prevalence of T1D in the under-developed regions of the world. Despite the limited studies available, the epidemiological studies performed thus far have shown T1D to be widespread, with an overall increase in the number of new cases per year (incidence rate) especially in young children. However, trends reported on T1D are likely only available from countries with well-established public health and diabetes research programs. Therefore, there is a need for comparable research on T1D in developing countries. Additionally, many of the T1D studies reported represent the prevalence in children, even though approximately one out of four cases are diagnosed with T1D in adulthood[58]. For example, a recent study[59] demonstrated that T1D is almost as common in adulthood as in childhood using genetic risk scores (GRS) to genetically identify T1D cases in a cohort with adult-onset diabetes. The GRS in this particular study was based on data from a cohort of childhood-onset T1D, the majority of which were diagnosed under the age of 16 years. However, substantial evidence points towards age-dependent differences in the genetic risk to develop autoimmune diabetes. Specifically, the genetic risk to develop autoimmune diabetes declines with increasing age-at-diagnosis without a clear cut-off but in a graded fashion[60-62]. Additionally, LADA was not addressed in the recent

cohort study[59] yet a proportion of diabetes cases genetically defined as T1D using a childhood-onset T1D derived GRS did not need insulin at diagnosis. Those defined as T1D represented only 22% of the whole cohort on insulin treatment and only 66% of those developing ketoacidosis. Therefore, it currently remains unclear how to discriminate T1D and LADA. Consequently, the prevalence rates reported for these subtypes of diabetes should be carefully interpreted.

In contrast to T1D and T2D, there have been much fewer studies conducted on LADA, especially in ethnicities beyond European ancestral populations, with existing studies being somewhat underpowered. Additionally, the validity of autoantibody measurements and the application of diagnostic criteria may differ significantly across regions, and in turn is likely to influence prevalence estimates, leading to overly conservative reports and conclusions. Here, we report global trends in LADA and highlight how they compare to the two more classic forms of diabetes across populations of European, African, Asian and Middle Eastern ancestry.

Prevalence of diabetes subtypes in populations of European Ancestry

Approximately 5-12% of cases in European populations with apparent T2D are in fact misdiagnosed LADA cases[2, 4, 13, 63-70](**Table 1**). However, trends in LADA diagnosis across European populations have been shown to differ even between regions within a given country, especially between population-based and hospital clinic-based cohorts. For instance, there is a dramatically lower prevalence of LADA in a population-based study Northern Italy (0.19%) [70] when compared to a much larger study of subjects recruited throughout Italy from hospital clinics (6.6%)[71]. The reason for this discrepancy is likely due to the greater metabolic severity of LADA so hospital clinics are more likely to be enriched for these cases. Indeed, there is also regional variation reported across Spain, where the south of the country has a higher prevalence rate of LADA compared to the north (10.9-14.7% vs 5.6-7.2%, respectively)[72]. These discrepancies could be attributed in part to sample size; however, genetic and environmental factors could well be influencing LADA prevalence, an idea that is supported by the wide range in disease prevalence observed across the globe. An unexplored area is the proportion of cases with transient autoantibodies who therefore show as autoantibody negative but otherwise have most of the features of LADA. This possibility was highlighted in a recent large (n=14,775 cases) population-based study from Scandinavia of adult onset diabetes, in

which 6.4% had LADA but 17.5% had the same features including low C-peptide levels but were autoantibody negative[73].

The prevalence of T2D in Americans of European ancestry was 10.2% in one study in 2014[27]. Indeed, the United States had the third highest number of adults with diabetes worldwide as of 2011, after China and India (**Table 2**). Although approximately 60% of the total population in the USA are of European ancestry, this high prevalence rate could be influenced by admixture of genetic risk from other ethnicities or from specific environmental factors[74]. Additionally, the vast majority of adult-onset diabetes cases have T2D; therefore, these prevalence rates are driven by trends in T2D diagnoses. Thus, assuming 8% of T2D cases are LADA cases and 90% of diabetes cases are diagnosed with T2D, the prevalence of LADA in European populations is substantially higher than previously reported prevalence of T1D in the same ancestral group (~0.3%)[75-77]. T1D, however, is by far the most common type of diabetes in children and adolescents and is more frequent in populations of European ancestry[75].

Prevalence of diabetes subtypes in populations of African Ancestry

The estimated prevalence of diabetes in adults across Africa ranges widely, but is overall lower than in other parts of the world (**Table 2**)[52]. Despite the African region having the lowest world-standardized prevalence of diabetes in adults, this region is also expected to have the world's largest proportional increase of adults with diabetes (**Table 3**)[52, 78]. On average 3% of the adult population in Africa has diabetes. To put these numbers in context, in Africa approximately 90% of diabetes cases have T2D[79], with a high proportion of cases with undiagnosed diabetes, over two thirds of cases being unaware that they have the disease[80]. The majority of people in Africa with T2D live in cities, despite the population being predominantly rural, suggesting that environmental factors like urbanization play a major role in susceptibility. In fact, the reported prevalence of T2D can vary largely between rural and urban areas[44, 45, 81, 82].

There is also a lack of corresponding published studies on T1D in Africa, presumably leading to inaccurate incidence/prevalence estimates. Studies from Nigeria, Zambia, and Tanzania have principally driven the estimated incidence and prevalence rates. However, in 2010, approximately 35,700 individuals in Africa (excluding North Africa) were said to be diagnosed

with T1D[56]; reflecting a very low incidence rate of less than 1 per 100,000 individuals as reported in Tanzania and Ethiopia, though based on previously diagnosed cases and not on population screening[56]. Additionally, poor healthcare and high mortality rates leave many cases unaccounted for in such estimates[83].

It has been reported that 10-14% of West Africans with apparent T2D cases are misdiagnosed, higher than their European counterparts (8-10%)[84-87] (**Table 1**). However, there may be a lower LADA prevalence in East Africa, most obviously in Kenya (5.7%)[88]. However, these findings should be interpreted carefully given differences in study design, selection criteria and potential variation in access to healthcare. Additionally, current studies have been largely concentrated in West Africa, and therefore further studies expanding to regions throughout Africa are still required. Larger studies will undoubtedly lead to more accurate comparisons of LADA prevalence between populations of European and African ancestry.

Prevalence of diabetes subtypes in African-American populations

There remains very limited research on the prevalence of LADA in African Americans, as the relative scarcity of study sample collections continues to be a challenge. There is currently only one study of LADA in African Americans, where diabetes-associated autoantibodies were measured in 295 non-Hispanic black adults resulting in 4.7% of subjects being autoantibody positive[69]. This prevalence estimate was significantly different from the frequency of autoantibody positive nondiabetic controls (1.3%) and was significantly lower than the frequency of autoantibody positive non-Hispanic whites (8.6%) that were examined in the same study. In this particular analysis, there was a higher prevalence of autoantibody positive non-insulin requiring diabetics in non-Hispanic white adults than in non-Hispanic black adults **(Table 1)**.

With respect to T2D and the difference in incidence between those with European and African ancestry, racial admixture should also be taken into account when addressing prevalence estimates of diabetes in African Americans. One of the highest prevalence rates of T2D has been seen in African Americans (18.7%) compared to 10.2% observed in European Americans[89]. This African American prevalence estimate is likely due to socioeconomic and behavioral risk factors that have resulted in relatively unhealthy lifestyles and higher rates of obesity[90]. However, and in support of a genetic influence, African-European mixed-ancestry individuals have a higher risk of T2D compared to those of European ancestry alone[91]. Indeed, one

American study, which considered racial admixture, found a 30-40% increased risk of T2D for those in the highest versus lowest tertile of African ancestry [92]; thus, African Americans with a higher admixture of African ancestry are shown to be at a higher risk for T2D. Although T2D is more prevalent in African Americans than Africans[93], this increased prevalence has been observed in both African[44] and Asian migrants[94, 95], suggesting a strong impact of environmental factors also contributing to the progression of T2D.

Similarly to LADA, the T1D prevalence in African Americans has also been reported to be relatively less prevalent than in European Americans (approximately 1.62 per 1000 individuals as of 2009 versus 2.55 per 1000 individuals, respectively)[77]. Furthermore, one study observed a higher incidence of T1D among African American children living in Allegheny, Pennsylvania (11.8 per 100,000) than in Jefferson County, Alabama (4.4 per 100,000)[93], where the genetic admixture is 21.2% and 17.0%, respectively. These results likely reflect European Americans being at higher risk for childhood-onset T1D than African Americans. The trend in LADA diagnoses in racially admixed individuals remains unclear, and more studies with larger samples are needed to fully understand the epidemiology of LADA in African American populations.

Prevalence of LADA in Asian and Middle Eastern ancestry

Asian Ancestry

Despite the high prevalence of T2D in populations of Asian ancestry, LADA prevalence when compared to populations of European ancestry has been reported to be generally lower in China, Japan, Korea and India (2.5-9.2%) (**Table 1**)[48, 96-102]. In a study comparing a European ancestry cohort with three ethnic groups from Singapore (Indian, Malay and Chinese)[103], glutamic acid decarboxylase (GAD) autoantibodies were more frequent in the European cohort, while islet antigen 2 (IA-2) antibody positivity was higher in the Asian ethnic groups. Specifically, GAD autoantibody positivity was 13.9% in the white European cohort compared to 11.4% positivity in Indian, 6.0% in Malay and 5.8% in Chinese participants[103]. An even higher prevalence of LADA was observed in a small hospital-based study in Kerala, India[104] where 25% of 83 lean patients with apparent T2D were positive for GAD autoantibody(**Table 1**). However, studies based on hospital patients are more likely to show a

greater frequency of autoantibody positive patients given that they have a more severe disease, as noted above. Overall, countries across Asia have collectively reported a relatively lower prevalence of LADA compared to European and African ancestral groups.

Populations of Asian ancestry, however, have the highest frequency of overall diabetes compared to populations of European and African ancestries. India and China combined are projected to comprise more than 30% of all diabetes cases in the world. China has one of the highest prevalence of diabetes among East and South East Asian countries, where an estimated 109 million adults have diabetes (**Table 2**). Despite the high prevalence of T2D in populations of Asian ancestry, the T1D prevalence and incidence rates are reported to be relatively low[77, 105]. Indeed, China is considered to have the lowest recorded T1D incidence in childhood, while LADA is by far the most common form of autoimmune diabetes in this country. Collectively, however, both T1D and LADA have a lower prevalence in Asia, with T2D being by far the most prominent form of diabetes in this part of the world.

Middle East and North Africa

The prevalence of LADA in Middle Eastern countries has been reported to be up to 14% (**Table 1**)[14, 106]. In contrast, a large cross-sectional population-based study in the United Arab Emirates reported LADA and classic T1D in 2.6% and 0.2% respectively of 17,072 subjects with adult-onset diabetes (>30 years) [14]. Prevalence rates of adult-onset diabetes vary substantially across Africa and the Middle-East.

Saudi Arabia and Egypt have the highest prevalence rates of adult onset diabetes (20.2% and 15.6% respectively), while Afghanistan and Yemen have the lowest (6.3% and 6.1%, respectively). Overall, both the Middle East and North Africa experience a high prevalence of adult diabetes (9%)[52, 80]. According to the International Diabetes Federation, the total number of adults with diabetes in the Middle East is predicted to see the largest increase in the prevalence of diabetes over time[78]. A high T1D prevalence has now been reported in the Middle-East (**Table 2**); Saudi Arabia had a highest prevalence of children with T1D in 2013, accounting for approximately a quarter of the region's total classic T1D population[80], but the incidence rates in Kuwait have recently been reported to be amongst the highest in the world[107]. Given these strikingly high prevalence estimates in Middle Eastern countries for bothT1D and T2D, but also a potentially for LADA cases, this region would particularly benefit

from improvements in classification of diabetes subtypes. Additionally, more research on LADA in the Middle East is required.

In conclusion, the majority of autoimmune diabetes studies have, thus far, been in populations of European ancestry, with only limited research conducted in other ethnicities, which are almost invariably underpowered and scientifically limited. Childhood-onset T1D is known to be more prevalent in populations of European ancestry compared to populations of African ancestry, but strikingly the converse can be true for adult-onset autoimmune diabetes including LADA. Indeed, the prevalence of LADA varies across the Middle East and Asia. Unfortunately, populations most likely affected by this adult-onset form of autoimmune diabetes frequently have the least access to autoantibody screening, hampering efforts to distinguish LADA from T2D. Only with proper diagnoses and ascertainment of individuals afflicted with LADA from large populations of diverse ancestries can genetic studies be implemented.

IMPORTANCE OF AUTO-ANTIBODY SCREENING

Given the likely high, failure to identify LADA patients, even in Europe, more extensive autoantibody screening would be valuable. As noted earlier there are a number of clinical implications in making that distinction between LADA and T2D. Autoantibodies are biomarkers of autoimmunity with clinical value in the prediction and diagnosis of autoimmune diseases as well as disease management, e.g. tissue transglutaminase autoantibodies in coeliac disease[108]. In addition to GAD, three additional autoantibodies are highly predictive of adult-onset autoimmune diabetes, namely islet cell autoantibodies (ICA), IA-2 autoantibodies and insulin autoantibodies (IAA)[108]. In certain populations, notably the Chinese in whom the frequency of GAD and IA-2 autoantibody positivity is low, zinc transporter (ZnT8) autoantibodies serves as an additionally marker that has been shown to improve diagnostic sensitivity on the basis of GAD and IA-2 autoantibody positivity[109].

Notably, IA-2 autoantibodies against a specific epitope, is associated with increased BMI in patients with T2D[18] and patients positive for IA-2 autoantibodies to this epitope had a substantially slower progression to insulin requirement than patients who were only GAD

autoantibody positive. These observations have led to two hypothesized mechanisms by Buzzetti *et al.* for the onset of LADA, which proposes that diabetes can result from either chronic inflammatory responses in individuals with obesity or through classic T1D autoimmune response in leaner individuals [110]. However, an alternative explanation could be that autoantibodies are not necessarily pathogenic unless they recognize certain epitopes of an antigen. As with IA-2 autoantibodies, we have found that autoantibodies to the carboxyl-terminus of GAD are associated with a different clinical profile (younger and leaner with more multiple autoantibodies) and increase risk of progression to insulin therapy compared with autoantibodies to the amino-terminus of GAD alone (unpublished; in press)**.**

The heterogeneity of LADA is also evident not only in those cases in which autoantibodies are present but also in the varying levels of these autoantibodies. The distribution of GAD titers across LADA patients has been shown to be bimodal in some populations, resulting in two subgroups with distinct characteristics[48, 64, 65]. However, more detailed analyses of bimodality, specifically performed on untransformed assay signals, should be performed. Typically, those with high GAD titer are younger[68, 111] with lower BMI, lower prevalence of metabolic syndromes[63], higher levels of HbA_{1c}, lower C-peptide levels and a higher frequency of other diabetes-related autoantibodies (**Figure 1**)[48]. As a result, this particular subgroup resembles T1D more closely than individuals with lower GAD titer; alternatively, those with low GAD titer have metabolic presentation and loss of β-cell function that resemble a phenotype more closely aligned with T2D[112]. This observation resonates with patterns seen in a cohort of individuals recently diagnosed with childhood-onset T1D, where those who were positive for a single autoantibody (among those >12 years old) were associated with T2D-associated *TCF7L2* locus, and had higher C-peptide and lower glucose levels in an oral glucose tolerance test[38, 113].

The presence of a single autoantibody alone, however, cannot be relied on for a categorical diagnosis of adult-onset autoimmune diabetes given the potential for false positive and false negative assay results, as well as the variation in observations across racial/ethnic groups [114]. Notably in cross-sectional study[115] in Ethiopia measuring islet-cell associated antibodies in

T1D,T2D and non-diabetic controls, IA-2 autoantibodies were absent in all groups , suggesting that the clinical utility of IA-2 autoantibodies may be limited in some populations. Furthermore individuals with LADA in China, India and Sri Lanka also have lower average autoantibody titers, especially for GADA and IA-2 autoantibodies, than their European counterparts, making LADA much more challenging to diagnose in these populations[48, 116, 117]. Given that some autoantibodies are less prevalent in certain populations, it is crucial to measure more than one marker in these populations to capture the true frequency of autoimmune diabetes.

Despite a high frequency of misdiagnosed cases and the availability of clinical screening tools for identifying LADA risk[118], antibody screening is not commonly in practice and is usually limited to only those who are considered to be at very high risk (invariably, young adults who are lean with a high HbA1c [119, 120]. However, this approach will miss a substantial number of cases and the point has been made elsewhere that it is challenging to clinically identify adult-onset autoimmune diabetes, particularly LADA, because a proportion of them can be obese, with metabolic syndrome and mild metabolic dysfunction[4]. Current standards for high risk patients still dismiss true LADA cases as a consequence of stringent criteria, such as high BMI[63]. Thus, identifying at risk patients through routine autoantibody screening for adult onset autoimmune diabetes will substantially decrease the amount of misdiagnosed cases and ultimately reduce the substantial burden to health care costs. Development of oral therapy used to treat T1D, e.g. SGLT2 inhibitors (sotogliflozin)[121], and immune therapy to limit the immune effect would add weight to this argument.

CONCLUDING REMARKS

Despite the limited number of LADA studies in the ethnicities highlighted in this review, and the challenges in defining the trait, this disease appears to be more prevalent than T1D, particularly among populations of African ancestry. A proportion of T2D are misdiagnosed LADA cases irrespective of ancestry, and this misdiagnosis rate is perhaps highest in cases of West African ancestry. It is unclear whether diagnostic practices are significantly different across regions, impacting prevalence estimates; thus the differences between African and European ancestries will require larger studies to fully understand these differences and determine if differences are genetically or environmentally determined. Furthermore, the prevalence of

autoantibody positivity in diabetes cases with Asian ancestries is lower than in European populations with misdiagnosis likely due to relatively low levels of GAD autoantibodies. Screening programs designed for populations at risk should enable earlier intervention with improved metabolic outcome, appropriate therapy and improved identification of co-morbidities [8, 53].

Finally, genetic studies are particularly needed in African and Asian populations to identify ancestry-specific genetic susceptibility loci for autoimmune diabetes, most specifically LADA. Of the studies published, sample sizes have been relatively small and thus statistically underpowered to fully dissect the issues raised in this review. The polymorphic nature of the MHC region means that the frequency of susceptibility and protective alleles vary widely between and within ethnicities, further highlighting the need for population-specific studies. Future studies should focus on comparing genetic features among different subtypes across ethnic groups affected with diabetes in order to further improve prognosis, diagnosis and treatment of diabetes mellitus, and ultimately allowing us to move beyond depending solely on autoantibodies to make such diagnoses.

REFERENCES

1. Alberti, K.G. and P.Z. Zimmet, *Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation.* Diabet Med, 1998. **15**(7): p. 539-53.

2. Tuomi, T., et al., *Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies.* Diabetes, 1999. **48**(1): p. 150-7.

3. Basile, K.J., et al., *Overlap of genetic susceptibility to type 1 diabetes, type 2 diabetes, and latent autoimmune diabetes in adults.* Curr Diab Rep, 2014. **14**(11): p. 550.

4. Hawa, M.I., et al., *Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7.* Diabetes Care, 2013. **36**(4): p. 908-13.

5. Poudel, R.R., *Latent autoimmune diabetes of adults: From oral hypoglycemic agents to early insulin.* Indian J Endocrinol Metab, 2012. **16 Suppl 1**: p. S41-6.

6. Tasker, R.C. and C.L. Acerini, *Cerebral edema in children with diabetic ketoacidosis: vasogenic rather than cellular?* Pediatr Diabetes, 2014. **15**(4): p. 261-70.

7. National Center for Health Statistics (U.S.), *National Center for Health Statistics data presentation standards for proportions*. Vital and health statistics Series 2, Data evaluation and methods research. 2017, Hyattsville, Maryland: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. p.

8. Leslie, R.D., et al., *Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment.* Diabetologia, 2016. **59**(1): p. 13-20.

9. Kobayashi, T., et al., *Small doses of subcutaneous insulin as a strategy for preventing slowly progressive beta-cell failure in islet cell antibody-positive patients with clinical features of NIDDM.* Diabetes, 1996. **45**(5): p. 622-6.

10. Kobayashi, T., et al., *Insulin intervention to preserve beta cells in slowly progressive insulin-dependent (type 1) diabetes mellitus.* Ann N Y Acad Sci, 2002. **958**: p. 117-30.

11. Maruyama, T., et al., *Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus.* J Clin Endocrinol Metab, 2008. **93**(6): p. 2115-21.

12. Dennis, J.M., et al., *Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-Term Glycemic Response to DPP-4 Inhibitor Therapy.* Diabetes Care, 2018.

13. Zaharieva, E.T., et al., *Prevalence of Positive Diabetes-Associated Autoantibodies among Type 2 Diabetes and Related Metabolic and Inflammatory Differences in a Sample of the Bulgarian Population.* J Diabetes Res, 2017. **2017**: p. 9016148.

14. Maddaloni, E., et al., *Latent Autoimmune Diabetes in Adults in the United Arab Emirates: Clinical Features and Factors Related to Insulin-Requirement.* PLoS One, 2015. **10**(8): p. e0131837.

15. Donnelly, L.A., et al., *Rates of glycaemic deterioration in a real-world population with type 2 diabetes.* Diabetologia, 2018. **61**(3): p. 607-615.

16. Andersen, C.D., et al., *Worse glycaemic control in LADA patients than in those with type 2 diabetes, despite a longer time on insulin therapy.* Diabetologia, 2013. **56**(2): p. 252-8.

17. Hernandez, M., et al., *Preclinical carotid atherosclerosis in patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes and classical type 1 diabetes.* Cardiovasc Diabetol, 2017. **16**(1): p. 94.

18. Buzzetti, R., et al., *Tyrosine phosphatase-related islet antigen 2(256-760) autoantibodies, the only marker of islet autoimmunity that increases by increasing the degree of BMI in obese subjects with type 2 diabetes.* Diabetes Care, 2015. **38**(3): p. 513-20.

19. Metcalfe, K.A., et al., *Concordance for type 1 diabetes in identical twins is affected by insulin genotype.* Diabetes Care, 2001. **24**(5): p. 838-42.

20. Olmos, P., et al., *The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins.* Diabetologia, 1988. **31**(10): p. 747-50.

21. Florez, J.C., J. Hirschhorn, and D. Altshuler, *The inherited basis of diabetes mellitus: implications for the genetic analysis of complex traits.* Annu Rev Genomics Hum Genet, 2003. **4**: p. 257-91.

22. Poulsen, P., et al., *Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study.* Diabetologia, 1999. **42**(2): p. 139-45.

23. Qu, H.Q., et al., *Association analysis of type 2 diabetes Loci in type 1 diabetes.* Diabetes, 2008. **57**(7): p. 1983-6.

24. Schernthaner, G., et al., *Progress in the characterization of slowly progressive autoimmune diabetes in adult patients (LADA or type 1.5 diabetes).* Exp Clin Endocrinol Diabetes, 2001. **109 Suppl 2**: p. S94-108.

25. Hyttinen, V., et al., *Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study.* Diabetes, 2003. **52**(4): p. 1052-5.

26. Scott, R.A., et al., *An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans.* Diabetes, 2017.

27. Ng, M.C., et al., *Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes.* PLoS Genet, 2014. **10**(8): p. e1004517.

28. Bjorklund, G., et al., *Immune dysfunction and neuroinflammation in autism spectrum disorder.* Acta Neurobiol Exp (Wars), 2016. **76**(4): p. 257-268.

29. Undlien, D.E., B.A. Lie, and E. Thorsby, *HLA complex genes in type 1 diabetes and other autoimmune diseases. Which genes are involved?* Trends Genet, 2001. **17**(2): p. 93-100.

30. Nejentsev, S., et al., *Localization of type 1 diabetes susceptibility to the MHC class I genes HLA-B and HLA-A.* Nature, 2007. **450**(7171): p. 887-92.

31. Cervin, C., et al., *Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes.* Diabetes, 2008. **57**(5): p. 1433-7.

32. Wellcome Trust Case Control, C., *Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls.* Nature, 2007. **447**(7145): p. 661-78.

33. Bradfield, J.P., et al., *A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci.* PLoS Genet, 2011. **7**(9): p. e1002293.

34. Morris, A.P., et al., *Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes.* Nat Genet, 2012. **44**(9): p. 981-90.

35. Mishra, R., et al., *Relative contribution of type 1 and type 2 diabetes loci to the genetic etiology of adult-onset, non-insulin-requiring autoimmune diabetes.* BMC Med, 2017. **15**(1): p. 88.

36. Howson, J.M., et al., *Genetic analysis of adult-onset autoimmune diabetes.* Diabetes, 2011. **60**(10): p. 2645-53.

37. Redondo, M.J., et al., *Association of TCF7L2 variation with single islet autoantibody expression in children with type 1 diabetes.* BMJ Open Diabetes Res Care, 2014. **2**(1): p. e000008.

38. Redondo, M.J., et al., *TCF7L2 Genetic Variants Contribute to Phenotypic Heterogeneity of Type 1 Diabetes.* Diabetes Care, 2017.

39. Lukacs, K., et al., *The type 2 diabetes-associated variant in TCF7L2 is associated with latent autoimmune diabetes in adult Europeans and the gene effect is modified by obesity: a meta-analysis and an individual study.* Diabetologia, 2012. **55**(3): p. 689-93.

40. Desai, M., et al., *An association analysis of the HLA gene region in latent autoimmune diabetes in adults.* Diabetologia, 2007. **50**(1): p. 68-73.

41. Manan, H.H., *Genetic and diabetic auto-antibody markers in Saudi children with type 1 diabetes.* Human immunology. **71**(12): p. 1238-1242.

42. Rhee, B.D., et al., *HLA and insulin-dependent diabetes mellitus in Koreans.* The Korean journal of internal medicine, 1987. **2**(2): p. 135-140.

43. Luo, S., et al., *HLA genetic discrepancy between latent autoimmune diabetes in adults and type 1 diabetes: LADA China Study 6.* The Journal of Clinical Endocrinology & Metabolism, 2016: p. jc. 2015-3771.

44. Mbanya, J.C.N., et al., *Diabetes in sub-Saharan Africa.* The Lancet, 2010. **375**(9733): p. 2254-2266.

45. Motala, A.A., M.A.K. Omar, and F.J. Pirie, *Epidemiology of Type 1 and Type 2 Diabetes in Africa.* European Journal of Cardiovascular Risk, 2003. **10**(2): p. 77-83.

46. Howson, J.M.M.J., *HLA class II gene associations in African American type 1 diabetes reveal a protective HLA-DRB1*03 haplotype.* Diabetic medicine. **30**(6): p. 710-716.

47. Imagawa, A., et al., *Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus.* Diabetologia, 2005. **48**(2): p. 294-300.

48. Zhou, Z., et al., *Frequency, immunogenetics, and clinical characteristics of latent autoimmune diabetes in China (LADA China study): a nationwide, multicenter, clinic-based cross-sectional study.* Diabetes, 2013. **62**(2): p. 543-50.

49. Al-Jenaidi, F.A., et al., *Contribution of Selective HLA-DRB1/DQB1 Alleles and Haplotypes to the Genetic Susceptibility of Type 1 Diabetes among Lebanese and Bahraini Arabs.* The Journal of Clinical Endocrinology & Metabolism, 2005. **90**(9): p. 5104-5109.

50. Stayoussef, M., et al., *Influence of Common and Specific HLA-DRB1/DQB1 Haplotypes on Genetic Susceptibilities of Three Distinct Arab Populations to Type 1 Diabetes.* Clinical and Vaccine Immunology : CVI, 2009. **16**(1): p. 136-138.

51. Kelly, M.A., et al., *Genetic and immunological characteristics of Type I diabetes mellitus in an Indo-Aryan population.* Diabetologia, 2000. **43**(4): p. 450-6.

52. Ogurtsova, K., et al., *IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040.* Diabetes Res Clin Pract, 2017. **128**: p. 40-50.

53. Martinell, M., et al., *Education, immigration and income as risk factors for hemoglobin A1c >70 mmol/mol when diagnosed with type 2 diabetes or latent autoimmune diabetes in adult: a population-based cohort study.* BMJ Open Diabetes Res Care, 2017. **5**(1): p. e000346.

54. Maahs, D.M., et al., *Epidemiology of Type 1 Diabetes.* Endocrinology and Metabolism Clinics of North America, 2010. **39**(3): p. 481-497.

55. Prevention, C.f.D.C.a., *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. 2014, US Department of Health and Human Services: Atlanta, Georgia.

56. Soltesz, G., C. Patterson, and G. Dahlquist, *Diabetes in the young: a global perspective.* IDF Diabetes Atlas. Brussels: International Diabetes Federation, 2009.

57. Bach, J.F., *The effect of infections on susceptibility to autoimmune and allergic diseases.* N Engl J Med, 2002. **347**(12): p. 911-20.

58. Haller, M.J., M.A. Atkinson, and D. Schatz, *Type 1 diabetes mellitus: etiology, presentation, and management.* Pediatr Clin North Am, 2005. **52**(6): p. 1553-78.

59. Thomas, N.J., et al., *Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank.* Lancet Diabetes Endocrinol, 2017.

60. Steck, A.K., et al., *Can Non-HLA Single Nucleotide Polymorphisms Help Stratify Risk in TrialNet Relatives at Risk for Type 1 Diabetes?* J Clin Endocrinol Metab, 2017. **102**(8): p. 2873-2880.

61. Pugliese, A., et al., *HLA-DRB1*15:01-DQA1*01:02-DQB1*06:02 Haplotype Protects Autoantibody-Positive Relatives From Type 1 Diabetes Throughout the Stages of Disease Progression.* Diabetes, 2016. **65**(4): p. 1109-19.

62. Frohnert, B.I., et al., *Late-onset islet autoimmunity in childhood: the Diabetes Autoimmunity Study in the Young (DAISY).* Diabetologia, 2017. **60**(6): p. 998-1006.

63. Zinman, B., et al., *Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe.* Diabetes, 2004. **53**(12): p. 3193-200.

64. Buzzetti, R., et al., *High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes.* Diabetes Care, 2007. **30**(4): p. 932-8.

65. Maioli, M., et al., *Number of autoantibodies and HLA genotype, more than high titers of glutamic acid decarboxylase autoantibodies, predict insulin dependence in latent autoimmune diabetes of adults.* Eur J Endocrinol, 2010. **163**(4): p. 541-9.

66. Radtke, M.A., et al., *Heterogeneity of patients with latent autoimmune diabetes in adults: linkage to autoimmunity is apparent only in those with perceived need for insulin treatment: results from the Nord-Trondelag Health (HUNT) study.* Diabetes Care, 2009. **32**(2): p. 245-50.

67. Wod, M., et al., *Lower mortality and cardiovascular event rates in patients with latent autoimmune diabetes in adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes: A Cohort Study of 4,368 Patients.* Diabetes Res Clin Pract, 2018.

68. Turner, R., et al., *UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group.* Lancet, 1997. **350**(9087): p. 1288-93.

69. Barinas-Mitchell, E., et al., *Islet cell autoimmunity in a triethnic adult population of the Third National Health and Nutrition Examination Survey.* Diabetes, 2004. **53**(5): p. 1293-302.

70. Bosi, E.P., et al., *Low prevalence of islet autoimmunity in adult diabetes and low predictive value of islet autoantibodies in the general adult population of northern Italy.* Diabetologia, 1999. **42**(7): p. 840-4.

71. Genovese, S., et al., *Clinical phenotype and beta-cell autoimmunity in Italian patients with adult-onset diabetes.* Eur J Endocrinol, 2006. **154**(3): p. 441-7.

72. Soriguer-Escofet, F., et al., *Prevalence of latent autoimmune diabetes of adults (LADA) in Southern Spain.* Diabetes research and clinical practice, 2002. **56**(3): p. 213-220.

73. Ahlqvist, E., et al., *Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables.* Lancet Diabetes Endocrinol, 2018.

74. Whiting, D.R., et al., *IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030.* Diabetes research and clinical practice, 2011. **94**(3): p. 311-321.

75. Maahs, D.M., et al., *Epidemiology of type 1 diabetes.* Endocrinol Metab Clin North Am, 2010. **39**(3): p. 481-97.

76. Scott, R.S. and L.J. Brown, *Prevalence and incidence of insulin-treated diabetes mellitus in adults in Canterbury, New Zealand.* Diabet Med, 1991. **8**(5): p. 443-7.

77. Dabelea, D., et al., *PRevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009.* JAMA, 2014. **311**(17): p. 1778-1786.

78. Guariguata, L., et al., *Global estimates of diabetes prevalence for 2013 and projections for 2035.* Diabetes Research and Clinical Practice, 2014. **103**(2): p. 137-149.

79. Levitt, N.S., *Diabetes in Africa: epidemiology, management and healthcare challenges.* Heart, 2008. **94**(11): p. 1376-82.

80. Federation, I.D., *IDF Diabetes Atlas, 7th edn*. 2015.

81. Jackson, W.P., *Epidemiology of diabetes in South Africa.* Adv Metab Disord, 1978. **9**: p. 111-46.

82. Jackson, W.P., *Diabetes and related variables among the five main racial groups in South Africa: comparisons from population studies.* Postgrad Med J, 1972. **48**(561): p. 391-8.

83. Hall, V., et al., *Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review.* BMC Public Health, 2011. **11**: p. 564.

84. Adeleye, O.O.O.O., *Latent Autoimmune Diabetes Mellitus in Adults (LADA) and it's characteristics in a subset of Nigerians initially managed for type 2 diabetes.* International archives of medicine, 2012. **5**(1): p. 23.

85. Ipadeola, A.A., *Latent autoimmune diabetes amongst adults with type 2 diabetes in a Nigerian tertiary hospital.* Primary care diabetes, 2015. **9**(3): p. 231-236.

86. Agyei-Frempong, M.T.M., *The prevalence of autoimmune diabetes among diabetes mellitus patients in Kumasi, Ghana.* Pakistan journal of biological sciences, 2008. **11**(19): p. 2320.

87. Muazu, S.B., I. Okpe, and F. Anumah, *The prevalence and characteristics of latent autoimmune diabetes in adults subset among type two diabetes mellitus patients in Northern Nigeria.* Ann Afr Med, 2016. **15**(4): p. 163-170.

88. Otieno, C.F., et al., *Type 2 diabetes mellitus: clinical and aetiologic types, therapy and quality of glycaemic control of ambulatory patients.* East Afr Med J, 2008. **85**(1): p. 24-9.

89. Cooke, J.N., et al., *Genetic risk assessment of type 2 diabetes-associated polymorphisms in African Americans.* Diabetes Care, 2012. **35**(2): p. 287-92.

90. Cowie, C.C., et al., *Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002.* Diabetes Care, 2006. **29**(6): p. 1263-8.

91. Ng, M.Y., *Genetics of Type 2 Diabetes in African Americans.* Current Diabetes Reports, 2015. **15**(10): p. 1-8.

92. Cheng, C.-Y., et al., *African Ancestry and Its Correlation to Type 2 Diabetes in African Americans: A Genetic Admixture Analysis in Three U.S. Population Cohorts.* PLoS ONE, 2012. **7**(3): p. e32840.

93. Tull, E.S. and J.M. Roseman, *Diabetes in African Americans.* Diabetes in America, 1995. **2**.

94. Misra, R., *Immigrant Asian Indians in the US: A Population at Risk for Diabetes and Cardiovascular Disease.* Health Educator, 2009. **41**(1): p. 19-28.

95. Routley, V.M. and M. Australia, *The emerging epidemic of type 2 diabetes: an Asian Pacific perspective.* On The Risk, 2011. **27**(3): p. 72-76.

96. Xiang, Y., et al., *Latent autoimmune diabetes in adults in Asians: Similarities and differences between East and West (亚洲成人隐匿性自身免疫糖尿病的特点：东西方种族差异之比较).* Journal of Diabetes, 2013. **5**(2): p. 118-126.

97. Takeda, H., et al., *Clinical, autoimmune, and genetic characteristics of adult-onset diabetic patients with GAD autoantibodies in Japan (Ehime Study).* Diabetes Care, 2002. **25**(6): p. 995-1001.

98. Park, Y., et al., *LADA prevalence estimation and insulin dependency during follow-up.* Diabetes Metab Res Rev, 2011. **27**(8): p. 975-9.

99. Hwangbo, Y., et al., *Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic Acid decarboxylase antibody.* Diabetes Metab J, 2012. **36**(2): p. 136-43.

100. Qi, X., et al., *Prevalence and correlates of latent autoimmune diabetes in adults in Tianjin, China: a population-based cross-sectional study.* Diabetes Care, 2011. **34**(1): p. 66-70.

101. Brahmkshatriya, P.P., et al., *Characteristics and Prevalence of Latent Autoimmune Diabetes in Adults (LADA).* ISRN Pharmacol, 2012. **2012**: p. 580202.

102. Sachan, A., et al., *Low prevalence of latent autoimmune diabetes in adults in northern India.* Diabet Med, 2015. **32**(6): p. 810-3.

103. Ong, Y.H., et al., *Glutamic acid decarboxylase and islet antigen 2 antibody profiles in people with adult-onset diabetes mellitus: a comparison between mixed ethnic populations in Singapore and Germany.* Diabet Med, 2017. **34**(8): p. 1145-1153.

104. Unnikrishnan, A.G., S.K. Singh, and C.B. Sanjeevi, *Prevalence of GAD65 antibodies in lean subjects with type 2 diabetes.* Ann N Y Acad Sci, 2004. **1037**: p. 118-21.

105. Park, Y. and G.S. Eisenbarth, *Genetic susceptibility factors of Type 1 diabetes in Asians.* Diabetes Metab Res Rev, 2001. **17**(1): p. 2-11.

106. Hossein, G.M., et al., *The prevalence of latent autoimmune diabetes in adults and its correlates in patients with type 2 diabetes in Kerman, Iran [2011].* Diabetes Metab Syndr, 2015. **9**(2): p. 104-7.

107. Shaltout, A.A., et al., *Incidence of type 1 diabetes has doubled in Kuwaiti children 0-14 years over the last 20 years.* Pediatr Diabetes, 2017. **18**(8): p. 761-766.

108. Pihoker, C., et al., *Autoantibodies in diabetes.* Diabetes, 2005. **54 Suppl 2**: p. S52-61.

109. Huang, G., et al., *Zinc transporter 8 autoantibody (ZnT8A) could help differentiate latent autoimmune diabetes in adults (LADA) from phenotypic type 2 diabetes mellitus.* Diabetes Metab Res Rev, 2013. **29**(5): p. 363-8.

110. Buzzetti, R., S. Zampetti, and E. Maddaloni, *Adult-onset autoimmune diabetes: current knowledge and implications for management.* Nat Rev Endocrinol, 2017. **13**(11): p. 674-686.

111. Groop, L., et al., *Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects.* Diabetes, 1996. **45**(11): p. 1585-93.

112. Liu, L., et al., *Latent autoimmune diabetes in adults with low-titer GAD antibodies: similar disease progression with type 2 diabetes: a nationwide, multicenter prospective study (LADA China Study 3).* Diabetes Care, 2015. **38**(1): p. 16-21.

113. Redondo, M.J., et al., *Dissecting heterogeneity in paediatric Type 1 diabetes: association of TCF7L2 rs7903146 TT and low-risk human leukocyte antigen (HLA) genotypes.* Diabet Med, 2017. **34**(2): p. 286-290.

114. Xiang, Y., et al., *Glutamic acid decarboxylase autoantibodies are dominant but insufficient to identify most Chinese with adult-onset non-insulin requiring autoimmune diabetes: LADA China study 5.* Acta Diabetologica, 2015. **52**(6): p. 1121-1127.

115. Siraj, E.S., et al., *Islet cell-associated autoantibodies in Ethiopians with diabetes mellitus.* Journal of Diabetes and its Complications, 2016.

116. Nambam, B., S. Aggarwal, and A. Jain, *Latent autoimmune diabetes in adults: A distinct but heterogeneous clinical entity.* World J Diabetes, 2010. **1**(4): p. 111-5.

117. Sachan, A.A., *Low prevalence of latent autoimmune diabetes in adults in northern India.* Diabetic medicine, 2015. **32**(6): p. 810-813.

118. Fourlanos, S., et al., *A clinical screening tool identifies autoimmune diabetes in adults.* Diabetes Care, 2006. **29**(5): p. 970-5.

119. Bingley, P.J., *Clinical applications of diabetes antibody testing.* J Clin Endocrinol Metab, 2010. **95**(1): p. 25-33.

120. American Diabetes, A., *Standards of medical care in diabetes--2009.* Diabetes Care, 2009. **32 Suppl 1**: p. S13-61.

121. Garg, S.K., et al., *Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes.* N Engl J Med, 2017. **377**(24): p. 2337-2348.