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Review Article

Latent autoimmune diabetes of the adult: current knowledge and uncertainty

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Abstract

Patients with adult-onset autoimmune diabetes have less Human Leucocyte Antigen (HLA)-associated genetic risk and fewer diabetes-associated autoantibodies compared with patients with childhood-onset Type 1 diabetes. Metabolic changes at diagnosis reflect a broad clinical phenotype ranging from diabetic ketoacidosis to mild non-insulin-requiring diabetes, also known as latent autoimmune diabetes of the adult (LADA). This latter phenotype is the most prevalent form of adult-onset autoimmune diabetes and probably the most prevalent form of autoimmune diabetes in general. Although LADA is associated with the same genetic and immunological features as childhood-onset Type 1 diabetes, it also shares some genetic features with Type 2 diabetes, which raises the question of genetic heterogeneity predisposing to this form of the disease. The potential value of screening patients with adult-onset diabetes for diabetes-associated autoantibodies to identify those with LADA is emphasized by their lack of clinically distinct features, their different natural history compared with Type 2 diabetes and their potential need for a dedicated management strategy. The fact that, in some studies, patients with LADA show worse glucose control than patients with Type 2 diabetes, highlights the need for further therapeutic studies. Challenges regarding classification, epidemiology, genetics, metabolism, immunology, clinical presentation and treatment of LADA were discussed at a 2014 workshop arranged by the Danish Diabetes Academy. The presentations and discussions are summarized in this review, which sets out the current ideas and controversies surrounding this form of diabetes.

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Introduction

Diabetes is a complex disease and the clinical classification into Type 1 and Type 2 fails to capture the range of diseases incorporated within the diagnosis [1]. Type 1a diabetes (henceforth Type 1 diabetes) is believed to be an autoimmune disease characterized by genetic, immunological and metabolic features. These features include an association with genes within the major histocompatibility complex (HLA), the presence of diabetes-associated autoantibodies (DAA) and severe loss of insulin secretion, which can lead to severe hyperglycaemia and ketoacidosis. The incidence is highest in children, but adults also get the disease. In adult-onset autoimmune diabetes, metabolic changes at diagnosis reflect a broad phenotype ranging from diabetic ketoacidosis to mild non-insulin-requiring diabetes. Alternative terms that have been used to describe adult-onset autoimmune Type 1 diabetes when it is not insulin dependent include: latent autoimmune diabetes in adults (LADA), Type 1.5 diabetes, slowly progressive insulin-dependent diabetes mellitus or double diabetes. Recently, adult-onset autoimmune diabetes with a positive T–cell response, but lacking DAA has been described. Adult-onset autoimmune diabetes thus encompasses a number of diabetic subgroups, Table 1. Challenges regarding classification, epidemiology, genetics, metabolism, immunology, clinical presentation and treatment of adult-onset autoimmune diabetes with a focus on LADA were discussed at a 2014 workshop arranged by the Danish Diabetes Academy. The presentations and discussions are summarized in this review, which sets out the current ideas and controversies surrounding this form of diabetes.

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What's new?

- Latent autoimmune diabetes of the adult (LADA) is an autoimmune diabetes defined by adult-onset, presence of diabetes associated autoantibodies, and no insulin treatment requirement for a period after diagnosis.
- Immunologically, glutamic acid decarboxylase 65 autoantibodies are by far the most common autoantibody in adult-onset diabetes.
- LADA is the most prevalent form of adult-onset autoimmune diabetes and probably the most prevalent form of autoimmune diabetes in general.
- LADA shares genetic features with both type 1 and type 2 diabetes.
- Phenotypically, LADA patients are often misdiagnosed as having type 2 diabetes.
- LADA patients generally have worse HbA1c levels than type 2 diabetes patients.
- Clinically, LADA patients tend to have a lower mean age at diabetes onset, lower body mass index and more frequent need for insulin treatment than patients with type 2 diabetes.
- Management of LADA may require a dedicated strategy, yet currently there is a paucity of randomized controlled trial data.

How does adult-onset autoimmune diabetes differ from Type 2 diabetes?

Epidemiology

Around 4–14% of patients classified with Type 2 diabetes have DAA (Table 2 and Fig. 1) The frequency of GADA-positive Type 2 diabetes is high in studies from northern Europe (7–14% with decreasing prevalence by increasing patient age) [2–5]. It appears to be lower in southern Europe, Asia and North America (4–6%) [6–10] and, within China, lower in the south than the north [8]. The frequency of DAA positivity is higher in hospital settings than from a population-based ascertainment. These discrepancies are dependent on biases including: selection criteria, patient age at diagnosis, assays and disease duration at study entry. In the Action LADA 7 study in which adult patients with diabetes were tested, autoimmune diabetes was prevalent and those initially non-insulin-requiring for six months (i.e. LADA) were far more frequent than those requiring insulin treatment within a month of diagnosis (i.e. 'classic' Type 1 diabetes; odds ratio 3.3) [11]. By implication, adult-onset autoimmune diabetes, including LADA, is more prevalent than childhood-onset Type 1 diabetes in Europe. In China, where childhood-onset Type 1 diabetes is rare, the frequency of LADA was found to be comparable with that in Europe [8].

Table 1 Diabetes classification

	Adult-onset autoimmune diabetes			
Diabetes subtype	Type 1	Latent autoimmune diabetes of adults	Autoimmune antibody-negative	Type 2 diabetes
Autoantibodies	Yes	Yes	No	No
Islet-reactive T cells	Yes	Yes	Yes	No
Insulin required at diagnosis	Yes	No	No	Variable

The three criteria conventionally used to define adult-onset autoimmune diabetes are non-specific; namely, age at diagnosis, autoantibody positivity and need for insulin treatment. Definitions of adult age range from 15 to 30 years, extending to all ages or up to 70 years. Even children aged less than 15 years with phenotypic Type 2 diabetes can have DAA and would be designated autoimmune diabetes. Autoantibody criteria lack specificity because they are based on autoantibodies associated with childhood-onset Type 1 diabetes, which lack 100% specificity, even in the best laboratories [12]. These DAA include autoantibodies to glutamic acid decarboxylase 65 (GADA), insulinoma-associated antigen IA–2 (IA-2A), islet cells (ICA) and zinc transporter 8 (ZnT8A). The definition of autoantibody positivity is not unequivocal and different cut-off points have been applied in different studies. Technically, false positives may be limited by setting a higher cut-off or by repeating positive measurements. Longitudinal studies observe changing autoantibody status over time [3,13], and even though the majority of patients are positive for only one type of autoantibody, existing autoantibodies may be lost and other autoantibodies may develop. The fluctuating autoantibody status remains incompletely understood, but potentially time-varying anti-idiotypic antibodies might interfere in DAA assays [14]. The clinical significance of borderline positivity remains unsettled. However, the term 'false positive' applied to changing autoantibody status might be misleading, as even transient autoantibody positivity indicates a predisposition to autoimmunity. Recent data even indicate that in some antibody-negative patients, the diabetes may be autoimmune as defined by an islet-cell-reactive T–cell response [15].

The need to start insulin treatment is usually physician dependent given the infrequency of diabetic ketoacidosis, now only found in the minority of children at diagnosis [16]. Although there is no consensus regarding diagnostic criteria, patients are generally designated as having adult-onset autoimmune diabetes in the presence of DAA with an

Table 2 Prevalence of patients with glutamic acid decarboxylase antibodies (GADA) among patients diagnosed with Type 2 diabetes.

	Patients with Type 2 diabetes (*n*)	Number of patients positive for GADA (%)	Number of patients designated LADA (%)	Antibody used in definition LADA definition	Mean age (years)	Specified age range recruited (years)
Hawa *et al.*, *Diabetes Care* 2013 [11]	6156	541 (8.8)	598 (9.7)	1 or more antibodies (GADA, IA-2A, ZnT8A)	54.4	30–70
Maioli *et al.*, *Eur J Endocrinol* 2010 [7]	5568	276 (5)	276 (5)	GADA	NA	35–70
Zhou *et al.*, *Diabetes* 2013 [8]	4880	287 (5.9)	287 (5.9)	GADA	51.3	30 or above
Tiberti *et al. Diabetes* 2008 [45]	4250	191 (4.5)	191 (4.5)	GADA	NA	NA
Zinman *et al. Diabetes* 2004 [10]	4134	174 (4.2)	174 (4.2)	GADA	Weighted 56.5	30–75
Turner *et al. Lancet* 1997 [3]	3672	361 (9.8)*	430 (11.7)	GADA or ICA (not clearly defined)	52.6	25–65
Tuomi T Diabetes 1999 [4]	1122	104 (9.3)	104 (9.3)	GADA	Weighted 69.7	NA
Radtke *et al. Diabetes Care* 2009 [2]	1049	106 (10.1)	106 (10.1)	GADA	Weighted 67.8	20 or above

*Overall prevalence among age groups. Age: 34–44 years (14%), 45–54 years (9%), 55–65 years (7%). LADA, latent autoimmune diabetes in adults; IA-2A, insulin antibodies 2A; ZnT8, zinc transporter 8 antibodies). NA, Not Available.

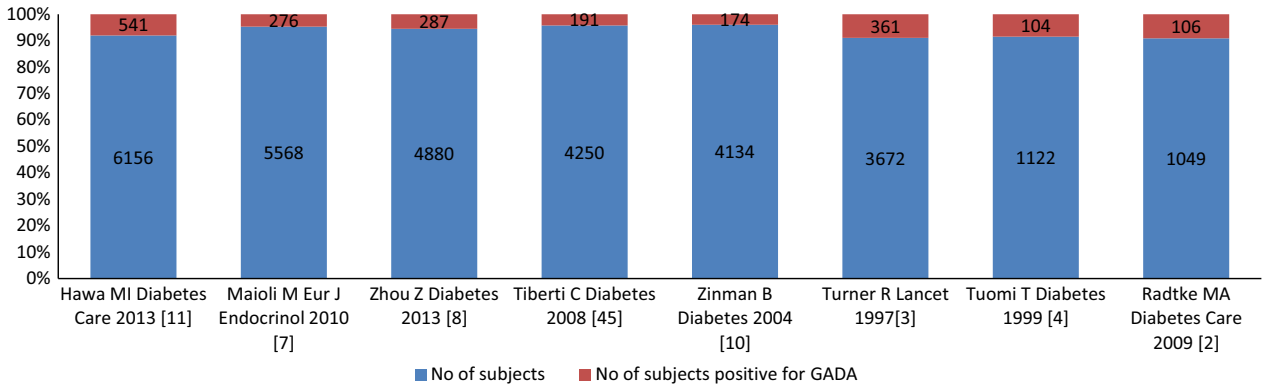

FIGURE 1 Prevalence of patients with glutamic acid decarboxylase antibodies (GADA) among total number of patients diagnosed with type 2 diabetes.

adult age at diagnosis, irrespective of insulin treatment [17]. When the patients have DAA but do not require insulin treatment for a period, usually six months, then they are designated to have LADA. Arbitrary definitions of LADA include a period without insulin treatment of at least six months and an age at diagnosis of more than 30 years [17,18].

Summary: knowledge and uncertainty

Adult-onset autoimmune diabetes is prevalent and likely far more prevalent than childhood-onset Type 1 diabetes. Most cases of adult-onset autoimmune diabetes are non-insulin requiring, i.e. LADA. By any of its definitions, LADA exists, the uncertainty is whether the underlying pathophysiology is distinct from childhood-onset Type 1 diabetes or is part of a clinical spectrum encompassing all forms of autoimmune diabetes. It is not known whether the burgeoning prevalence of Type 2 diabetes is associated with an increasing prevalence of LADA. The simplest position is to take all patients aged 18 years or more with Type 1 diabetes and DAA as having adult-onset autoimmune diabetes, although their clinical phenotype defines the clinical management.

Genetic features

Genome-wide association studies have identified many susceptibility loci predisposing to Type 1 diabetes [19–22] and Type 2 diabetes [23–26]. A commonality to the genetic basis of Types 1 and 2 diabetes has been suggested [27,28], but has not been confirmed.

The strongest Type 2 diabetes genetic association was identified within the transcription factor 7-like 2 (*TCF7L2*) gene by Grant *et al.* in 2006 [29] and later replicated by others

in patients of European, Asian and African descent [30–32]. Conversely, this locus is widely accepted as not being associated with 'classic' childhood-onset Type 1 diabetes [28]. However, the risk-conferring variant within *TCF7L2*, is similarly over-represented in adult-onset autoimmune diabetes and Type 2 diabetes [33]. Genotyping of patients with autoantibody-positive adult-onset autoimmune diabetes and population-based controls at childhood-onset Type 1 diabetes loci and the Type 2 diabetes/obesity risk markers *TCF7L2* and *FTO* has been performed. HLA, *PTPN22*, *STAT4*, *CTLA4*, *IL2RA* and *INS* were associated with autoimmune diabetes in adults, as previously reported for paediatric Type 1 diabetes [34]. HLA–DR3/4 was associated with a lower age at diagnosis, and DR3 and DR4 were associated with GADA and IA–2A positivity, respectively [34]. Phenotypically, it was reported that high/intermediate-risk HLA genotypes were associated with a significantly higher risk for the development of insulin dependence compared with the low-risk HLA genotype in patients with LADA [7]. However, even though prevalence of *HLA-DQB1* and *PTPN22* risk genotypes were increased in LADA, they were much less common than in childhood-onset Type 1 diabetes [35].

The data suggest a genetic susceptibility continuum in autoimmune diabetes extending from a marked effect in childhood-onset Type 1 diabetes to a significant, but far less pronounced effect of the same genes in LADA [18]. The lack of HLA–DR3 and -DR4 heterozygotes in Chinese patients might explain the very low incidence of childhood-onset diabetes with HLA genes in this population, although Chinese patients with LADA have moderate risk or protective HLA disease-associated variants [8].

Summary: knowledge and uncertainty

LADA has been associated with the same genetic features as childhood-onset Type 1 diabetes (HLA, *INS VNTR* and *PTPN22*) and Type 2 diabetes (*TCF7L2*) [36], which suggest that it may represent a genetic admixture of the two types of diabetes, especially when non-insulin requiring. The question is whether such genetic admixture represents a distinct disease syndrome or is part of an autoimmune continuum. Genome-wide association studies targeting exome sequencing or whole-genome exome sequencing remain to be conducted in large cohorts of adult-onset autoimmune patients.

Metabolic features

Multiple studies have found that patients with LADA require insulin treatment more frequently and earlier post diagnosis than those with antibody-negative Type 2 diabetes. GADA positivity in adult patients with non-insulin-requiring diabetes is associated with decreased fasting C–peptide and a decreased C–peptide response to oral glucose [2–4,8]. The magnitude of this insulin response is inversely related to the GADA titre [37]. Interestingly, in two large studies, insulin secretion was similar in recently diagnosed patients with LADA and Type 2 diabetes [10,38]. A detailed smaller metabolic study of insulin secretion and insulin sensitivity confirmed the lack of difference in weight-matched groups with LADA and Type 2 diabetes [39]. However, despite these early features, over time, the increased propensity for reduced β–cell function in LADA becomes evident [2–4].

Patients with adult-onset autoimmune diabetes generally have a better metabolic profile than those with Type 2 diabetes, with lower triglyceride, higher HDL cholesterol levels, and lower BMI, waist-to-hip ratios and blood pressure [6,8,11,37,40]. Within GADA-positive patients, these altered metabolic parameters tend to be significantly better in those with high-titre GADA compared with low-titre GADA, but without a clear distinction between the groups [4,6,8,11]. These broad differences in metabolic parameters translate into GADA-negative patients having more signs of metabolic syndrome than GADA-positive patients, irrespective of whether the latter have LADA or adult-onset Type 1 diabetes [5,8,11]. Formal examination of insulin resistance indicates that patients with LADA are more insulin insensitive than healthy controls, but their insulin insensitivity is comparable with or less than that of patients with Type 2 diabetes and is dependent of BMI [10,39,41,42].

Summary: knowledge and uncertainty

Adult patients with DAA are more likely to have lower C–peptide, fewer signs of metabolic syndrome, higher HbA_{1c}, progress to insulin therapy more rapidly and require insulin treatment more often than do adult patients with Type 2 diabetes without DAA. It remains unclear how DAA is associated with the loss of insulin secretory capacity. Our recommendation is not to manage diabetes based on the knowledge of DAA alone.

Immunological features

Adult-onset Type 1 autoimmune diabetes is characterized by less aggressive β–cell loss than childhood-onset autoimmune diabetes, less HLA-associated genetic susceptibility and fewer multiple autoantibodies.

Serum islet autoimmunity characterized by ICA in patients classified with Type 2 diabetes was first described in 1977 [43]. Several studies have compared autoantibodies in childhood- and adult-onset autoimmune diabetes. In general, ICA, IAA, IA–2 and ZnT8 were more frequent in childhood-onset than adult-onset autoimmune diabetes, whereas GADA and IA–$2_{256–760}$ were equally common [3,44–47]. GADA is by far the most common autoantibody in adult-onset diabetes (90% of positive cases) even in China where GADA is less dominant [4,6,8,11]. After diagnosis of adult-onset autoimmune diabetes, autoantibodies tend to disappear, especially IA–2A and ZnT8A [3,13,48,49]. However, GADA can still be detected in patients with apparent 'Type 2' diabetes some 12 years post diagnosis [5].

A bimodal distribution of GADA titres has been reported in several studies in patients with LADA diabetes, although formal analysis for bimodality has not been made [6–8]. Other studies did not find such a bimodal distribution [4]. These apparent discrepancies may reflect differences in the character of LADA in different populations and certainly in China, the proportion of patients with high-titre GADA is lower than in Europe [8]. Patients with high-titre GADA tend to have high-affinity GADA and it appears that the β cell loss is more rapid than in those with low-affinity GADA [50].

Data from the European Action LADA cohort (Action-LADA) showed that adult-onset autoimmune patients, whether they have 'classic' Type 1 diabetes or LADA, have similar changes in systemic cytokines, chemokines and adhesions molecules [51,52]. A large Chinese study reported higher C–reactive protein and lower adiponectin in LADA compared with adult-onset Type 1 diabetes [53]. In both Chinese and European populations, there was a hierarchy of differences in systemic inflammation (e.g. interleukin–6) such that serum levels were highest in Type 2 diabetes compared with autoimmune diabetes (whether LADA or 'classic' Type 1), and lowest in healthy controls [51,53].

Small studies have described differences in LADA with regard to abnormal DNA methylation in CD4 + T cells in LADA [54], altered T–regulatory cells [55], NK cells [56], gene expression profiles of monocytes [57] and some antigen-reactive T cells [58,59]. However, these data require confirmation and other studies have not shown differences in T cells upon stimulation with different islet-associated antigens [60]. It is generally accepted that T cells are largely responsible for the inflammatory pancreatic β–cell destruction in autoimmune diabetes. Yet we know little of this response and even less in LADA. A T–cell assay of cellular immunoblotting measuring reactivity to human islet antigens using peripheral blood demonstrated excellent specificity and sensitivity, comparable with DAA, in distinguishing between blood from patients with childhood-onset Type 1 diabetes and normal controls [61,62]. Intriguingly, using this T–cell assay, a proportion of patients with phenotypic Type 2 diabetes showed T–cell reactivity comparable with that seen in patients with Type 1 diabetes [63]. The implications were emphasized by confirmation that a percentage of patients with autoantibody-negative 'Type 2' diabetes have distinct T–cell reactivity to islet antigens and that T–cell reactivity was more closely associated with reduced C–peptide than DAA [15]. These observations need to be confirmed in other laboratories and there is no evidence that the T cells are strictly autoimmune. However, they certainly challenge the conventional perception that only Type 1 diabetes is due to an 'autoimmune' process.

Summary: knowledge and uncertainty

Adult-onset autoimmune diabetes and childhood-onset Type 1 diabetes are barely distinguishable immunologically, although the latter has a greater immunogenetic load with more multiple DAA, more frequent IA–2A and ZnT8A, plus lower C–peptide and more rapid C–peptide loss. High-titre GADA in the former is associated with multiple DAA, high-affinity GADA and with greater loss of C–peptide. In adult-onset autoimmune diabetes, the dominant autoantibody is GADA [50,64]. In childhood, GADA tends to appear later (about age 5 years) than IAA (about age 2 years) [65]. It is not known when GADA associated with LADA first appears and whether GADA found in childhood might predict autoimmune diabetes developing 20 or more years later. The pathophysiological significance of patients with Type 2 diabetes having T–cell islet immunoreactivity, even when they are negative for GADA and other DAA, is not known.

Clinical features

At diagnosis, the clinical phenotype in patients with autoimmune diabetes is remarkably broad, ranging from diabetic ketoacidosis to diabetes that can be controlled with diet alone. The classification of these patients also covers a range that can appear arbitrary; for example, in the European Action LADA study, patients with GADA and started on insulin within one month of diagnosis were designated classic Type 1 diabetes, those started on insulin within six months were unclassified and those started on insulin at six months or later were designated LADA. By comparison with those with Type 2 diabetes, patients with adult-onset autoimmune diabetes, even when non-insulin requiring (LADA), tend to have a lower age at diabetes onset, lower BMI and waist-to-hip ratio, but a more pronounced loss of C–peptide and an increased likelihood of insulin treatment [2,8,11]. Substantial heterogeneity is also observed within patients who are GADA positive. Phenotypically, high-titre GADA patients tend to have these same characteristics, but these are more marked and more similar to classic Type 1 diabetes, patients being younger at diagnosis, leaner with a high risk of progression to insulin treatment. Low-titre GADA patients are phenotypically more similar to those with Type 2 diabetes. These differences are also captured by the metabolic syndrome, which is more prevalent in Type 2 diabetes than Type 1 diabetes and LADA, and more prevalent in low-titre than high-titre GADA patients [2,4,6,8,11]. Because high-titre GADA tends to be associated with multiple DAA, it is not surprising that the NIRAD study found that among patients with adult-onset diabetes, the more DAA were detected the more these patients needed insulin treatment and had younger age at onset [47]. However, there is sufficient overlap for these clinical parameters between groups of patients to make it impossible to accurately distinguish adult-onset autoimmune diabetes from Type 2 diabetes on clinical features alone when considering individual patients [66,67].

Summary: knowledge and uncertainty

There are no clear clinical features that distinguish autoimmune diabetes from Type 2 diabetes. However, there is a

tendency for adult patients with GADA, even when non-insulin requiring, to be younger at diagnosis and leaner with a greater tendency to progress to insulin treatment. Within a cohort of GADA-positive adult patients, the GADA titre and the number of DAA impact the clinical and biochemical differences from Type 2 diabetes. Clinical phenotype should drive management strategy.

Does it matter that LADA is different from Type 2 diabetes?

Clinical presentation

It is highly debatable if GADA should be measured in all patients with diabetes. Screening strategies differ widely, both internationally and regionally, ranging from mandatory screening at some university hospitals to patient-driven or sponsored screening at other sites.

In favour of general screening of adult patients with diabetes, patients with Type 2 and LADA cannot be identified by any single clinical feature short of diabetic ketoacidosis. However, the data are conflicting regarding the predictive value of GADA positivity for incident diabetes [14,38,68–71].

Disease progression

Need for insulin treatment

GADA positivity is strongly associated with subsequent insulin requirement [72]. In the UKPDS, 84% of GADA-positive patients vs 14% of GADA-negative patients received insulin treatment by six years after diagnosis [3]. In the Nord-Trøndelag Health Study (HUNT) the numbers were 40% vs 22% 14 years after diagnosis [2]. In the Collaborative Atorvastatin Diabetes Study (CARDS) 56% and 17% of GADA-positive and -negative patients, respectively, received insulin at baseline, and 16% vs 5% insulin-naïve patients at baseline began insulin treatment during 3.9 years of follow-up [5]. Awareness of patients having LADA might result in more frequent and focused follow-up and an earlier start for insulin treatment if metabolic decompensation develops. Data from studies with the available newer, second-line antidiabetic drugs suggest that these may postpone loss of β-cell function [73–75].

Blood glucose control

Despite greater use of insulin, patients with LADA tend to have worse glycaemic control than those with Type 2 diabetes [5,76,77], although this difference in China this difference was not evident [8]. More patients with LADA (68%) than patients with Type 2 diabetes (53%) had poor glycaemic control — defined as $HbA_{1c} > 52$ mmol/mol (> 6.9%) — during 107 months of follow-up [76]. Early insulin therapy does not seem to improve control [78].

Diabetes microvascular and macrovascular complications

The prevalence of microvascular complications in LADA is broadly similar to that seen in patients with Type 2 diabetes, although a lower risk of nephropathy was reported in the small Freemantle study [5,79–81].

Patients with LADA generally have a more favourable cardiovascular risk profile than those with Type 2 diabetes. However, studies to date have not found evidence for a lower risk of macrovascular disease in patients with LADA [5,79,80]. Despite the fact that these studies were small, there is no evidence to support a less-aggressive treatment policy for cardiovascular risk factors in patients with LADA.

Summary: knowledge and uncertainty

Because it is not possible to identify patients with LADA without screening, there might be value in routine GADA screening. However, even in Europe where awareness of the issue is relatively high, screening is not performed consistently. A substantial proportion of patients with LADA do not require insulin after many years of disease, which calls into question the strategy of initiating all GADA-positive patients on insulin at diagnosis. Conversely, in patients on insulin, glycaemic control is suboptimal, suggesting that insulin alone may not be sufficient. So before clinical trial data are available to direct specific therapy, it is important to identify autoimmune diabetes cases to focus on their quality of control.

Co-morbidities with LADA

Patients with LADA, compared with those with Type 2 diabetes, are characterized by a higher prevalence of other autoimmune diseases, especially thyroid disease [82]. In the Italian NIRAD studies of LADA, patients had a higher frequency of thyroid peroxidase antibodies (TPO) (27%) compared with patients with GADA-negative diabetes (10.5%) [6]; those with a high GADA titre had a higher frequency of TPO antibodies compared with those patients with low GADA titre [83].

Summary: knowledge and uncertainty

The risk of thyroid autoimmunity and, by implication, thyroid disease is substantially higher in patients with LADA than in those with Type 2 diabetes. Monitoring thyroid function more closely in such patients, and potentially screening for other autoimmune diseases, may be important in their management.

Management strategies

There is a marked paucity of data regarding the treatment of patients with LADA.

Despite its widespread use as primary treatment in Type 2 diabetes, there are no controlled studies on the effects of

metformin alone in patients with LADA [84]. The theoretical risk of treating diabetic ketoacidosis-prone patients with biguanide is, in clinical practice, very low in adults. Glibenclamide and insulin were compared in patients with LADA in two randomized controlled Japanese trials. The sulfonylurea group in one pilot study had worse metabolic control and more rapid deterioration of C–peptide secretion compared with insulin treatment at 30 months follow-up [85]; this was confirmed by the second study [86]. Therefore, sulfonylureas should not be used as first-line therapy in patients with LADA. Insulin sensitizers, such as thiazolidinediones, might potentially be of interest. One small study in China supported their use when combined with insulin in preserving islet β–cell function in LADA, yet these agents are not currently widely used [87].

Instead attention has focused on the use of dipeptidyl peptidase–4 (DPP–4) inhibitors.

Three DPP–4 inhibitors (sitagliptin, linagliptin and saxagliptin) have been studied in patients with LADA in three trials, two of them reported as abstracts of retrospective analyses [73,75] and the other, a prospective study [74]. In the prospective study, Chinese patients with LADA were given insulin glargine and randomized to either sitagliptin or placebo. Sitagliptin-treated patients had a minimal and insignificant decline in C–peptide over one year, whereas the placebo-treated group had a significant decrease. The two-hour C–peptide level in the sitagliptin-treated patients was significantly higher than in the placebo-treated patients at 12 months [74]. Whether DPP–4 inhibitors alter β–cell function, independent of their acute insulin-stimulating action, remains unknown.

Summary: knowledge and uncertainty

To date, the evidence indicates that patients with LADA should be treated with insulin as a first choice when glycaemic control deteriorates to a level indicating need for antiglycaemic treatment. There is no evidence either for or against the use of metformin, although sulfonylureas are positively discouraged. The role of DPP–4 inhibitors remains to be determined. This strategy contrasts with the current treatment of non-insulin-requiring Type 2 diabetes. However, evidence is not strong and large prospective randomized trials are required.

Immune therapy

Theoretically, immunotherapy in antibody-positive patients might prevent or modify the underlying disease process. Yet, in childhood-onset Type 1 diabetes, immunological approaches have had limited success at reducing the loss of C–peptide secretion. Agents that have been shown to be of benefit include cyclosporine (an inhibitor of T–cell activation), Abatacept (a CTLA–4 inhibitor), Rituximab (anti-CD20) and anti-CD3 monoclonal antibodies. As reviewed by Larsson and Lernmark, these immunosuppressive drugs generally lose their disease-modifying capacities quite rapidly [88]. In addition, they have negative side effects, e.g. cyclosporine A can cause kidney damage [89].

In Type 1 diabetes, treatment with GAD had divergent results with a positive Phase 2 study antedating two unsuccessful Phase 3 studies [90–92]. A safety study of patients with LADA using the GAD-alum formulation, however, did show a relative preservation of C–peptide secretion in response to a mixed-meal, which was sustained after five years [93].

Summary: knowledge and uncertainty

In summary, an immunological approach is logical in LADA, but only one small study has been finished. In that study a GAD-alum formulation had a beneficial effect without adverse side effects, even after five years. Theoretically, a high GADA titre might be of the least benefit, for in that same GAD-alum study it was those patients with low GADA affinity, and by implication low GADA titre, who had prolonged preservation of C–peptide secretion [50]. This field is open to development and no immunotherapy is currently offered clinically to any patients with autoimmune diabetes outside research trials.

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Competing interests

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

S1 Contributors to the manuscript preparation are listed online.