Combined treatment with sitagliptin and vitamin D in a patient with latent autoimmune diabetes in adults

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Summary

Latent autoimmune diabetes in adults (LADA) is a relatively new type of diabetes with a clinical phenotype of type 2 diabetes (T2D) and an immunological milieu characterized by high titers of islet autoantibodies, resembling the immunological profile of type 1 diabetes (T1D). Herein, we report a case of a young male, diagnosed with LADA based on both clinical presentation and positive anti-glutamic acid decarboxylase antibodies (GAD-abs), which were normalized after combined treatment with a dipeptidyl peptidase-4 inhibitor (DPP-4) (sitagliptin) and cholecalciferol.

Learning points:
• Anti-glutamic acid decarboxylase antibodies (GAD-abs) titers in young patients being previously diagnosed as type 2 diabetes (T2D) may help establish the diagnosis of latent autoimmune diabetes in adults (LADA).
• Sitagliptin administration in patients with LADA might prolong the insulin-free period.
• Vitamin D administration in patients with LADA might have a protective effect on the progression of the disease.

Background

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes mellitus characterized by older age at diagnosis compared with type 1 diabetes (T1D) and the presence of pancreatic islet cell autoantibodies (1).

This results in the development of glucose intolerance and overt clinical disease when the majority of pancreatic cells are not functional due to the chronic autoimmune inflammation. This pathophysiological process is characterized by the presence of circulating antibodies against pancreatic islet cells and islet cell infiltration by mononuclear lymphocytes. Commonly, patients with LADA present with a relatively preserved beta-cell function compared with patients with T1D, they manifest a progressive deterioration of beta-cell function necessitating basal and prandial insulin therapy early after diagnosis (1).

Although, LADA is genetically associated with T1D, it shares some clinical features with type 2 diabetes (T2D). Usually, LADA patients are older than 30 years, have higher BMI in comparison with T1D patients, and because initially they maintain residual insulin production are often misdiagnosed as T2D. However, in clinical practice, LADA patients are younger at diagnosis than T2D, they tend to have worse glycemic control, lower BMI, and frequently insulin treatment is initiated much earlier than...
T2D (1). Hence, in rare instances, LADA patients present solely with diabetic ketoacidosis (2; Table 1).

In this report, we describe the case of a young male diagnosed with LADA based on both clinical presentation and positive anti-glutamic acid decarboxylase antibodies (GAD- abs), which were normalized after combined treatment with a dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitor (sitagliptin) and cholecalciferol.

Case presentation
A 31-year-old Caucasian male was referred to the emergency department with symptoms of vomiting and nausea. He had a 3 month history of polyuria and polydipsia, accompanied by a 15 kg weight loss and blurred vision.

He reported no remarkable previous medical conditions, except being a heavy smoker since adolescence. He was obese with a BMI of 32.8 kg/m². His family history revealed the presence of autoimmune disorders, since his sister had been diagnosed with T1D at the age of 5, autoimmune hemolytic anemia and autoimmune thyroiditis during puberty and had undergone thymoma resection at the age of 22.

Investigation
On initial physical examination, the patient’s arterial blood pressure was systolic: 105 mmHg/diastolic: 65 mmHg, with a pulse rate of 104 b.p.m and a respiratory rate of 24 breaths per minute. Axillary temperature was 37.1°C, but no obvious clinical signs of infection were found on the physical examination. Arterial pH was within normal range (7.36), urine analysis was negative for leukocytes, white blood cells (WBC) count was normal, and no radiologic signs of infection were found. Laboratory investigation demonstrated the following pathologic findings: blood glucose level of 300 mg/dL with traces of ketones in urine and glycosylated hemoglobin (HbA1c) at 9.6%.

The patient declined insulin therapy and was initially treated with gliclazide once daily and metformin 1000mg twice daily with the suggestion of regular consultation in an outpatient diabetes clinic.

On presentation to the diabetes outpatient setting 3 weeks later, he had poor glycemic control, with fasting blood glucose values of approximately 180 mg/dl and a BMI of 28.6 kg/m². As LADA was suspected due mainly to the family history, GAD-abs titer was measured since islet autoantibodies and IA-2 antibodies are rarely detected in LADA (3). Results demonstrated a positive titer at 32U/mL (six times the upper limit) (GAD-abs normal values <5 U/mL) (Table 2). HLA genotyping for DR- and DQ-encoding loci were performed and results were HLA-DRB1*04:01/03:01 and HLA-DQB1*02:01/03:02. By combining all available clinical and laboratory data including patient’s age, increased GAD-abs titer, and the haplotype of DQB1*02:01/03:02, which has been reported to be positively associated with T1D, the diagnosis of LADA was supported (4). Further biochemical workup revealed normal findings with the exception of profound vitamin D hypovitaminosis (25-OH-D): 11 ng/mL (vitamin D normal values >30) (Table 2). The patient was referred to an ophthalmologist for funduscopy, which revealed no signs of diabetic retinopathy.

Treatment
As the patient declined insulin therapy again, he was advised to discontinue gliclazide treatment and a combination of metformin 850mg/sitagliptin 50mg twice daily along with vitamin D supplementation (cholecalciferol p.o., 2000IU/daily) was prescribed.

Outcome and follow-up
Upon completion of the first month of treatment, the patient started to show a significant decrease in his blood glucose values, until complete glycemic control 8 weeks

Table 1  Clinical presentation of T1D, T2D, and LADA.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>T1D</th>
<th>LADA</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibodies</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Autoimmune destruction of pancreatic beta-cell</td>
<td>Autoimmune destruction of pancreatic beta-cell</td>
<td>Increased insulin resistance, reduced insulin production</td>
</tr>
<tr>
<td></td>
<td>From the time of diagnosis</td>
<td>Soon after diagnosis</td>
<td>Late after diagnosis, when oral antidiabetic agents no longer maintain adequate glycemic control</td>
</tr>
<tr>
<td>Insulin requirements</td>
<td>Usually with diagnosis</td>
<td>When patient is insulinopenic</td>
<td>Usually absent, aggravated by other comorbidities</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>


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after diagnosis, reaching fasting plasma glucose concentrations between 70 and 120mg/dL and an HbA1c of 7.3%. Being able to comply with diet and exercise consultation, he presented 6 months later with an excellent glycemic profile and an HbA1c of 6.1%. By this time, the patient had lost another 7 kg of weight and his BMI was 24.9 kg/m².

One year after diagnosis he underwent a clinical and laboratory examination, which revealed a decline to his GAD-abs levels by 86% falling within the normal range (4.2 U/mL) and his HbA1c was 5.4% (Table 2). Currently, 2 years from initial diagnosis, under the same treatment he has negative GAD-abs, his HbA1c is 5.2%, and he maintains an excellent glycemic profile.

### Discussion

LADA is manifested with the same genetic and immunological profile as T1D, but it also shares common clinical features with T2D. Although our patient presented with hyperglycemia and traces of ketones in the urine, his arterial pH excluded the diagnosis of ketoacidosis and made the LADA diagnosis more probable. In the literature, there have occasionally been described cases of LADA patients presenting with severe insulinopenia and diabetic ketoacidosis (2), which was not the case in our patient. On the other hand, some T1D patients after initiation of insulin treatment and despite disease progression transiently regain insulin production from pancreatic cell. During, this period, which is frequently referred as a ‘honeymoon period’, patients present with improved glycemic control and their requirements in medication are diminishing. The incidence of remission in T1D almost always follows initial insulin treatment, is highly variable regarding the degree and the duration, and is more common in the adult population within the first year of diagnosis (5). In this case although insulin was never administered, a notable and fast improvement was evident soon after treatment initiation and was maintained for 2 years thereafter.

The pathogenesis of LADA involves the presence of autoantibodies and the progressive deterioration of the beta-cell function (6). Diagnosis is primarily based on three criteria: (i) age of disease onset ≥30 years, (ii) detection of high titers in at least one of anti-islet antibodies and (iii) no need of insulin treatment early after diagnosis (4, 7).

Our patient was diagnosed with LADA based on his age, positive GAD-abs, and HLA alleles that are linked to T1D. Although 10% of patients with presumed T2D at diagnosis, in fact, have positive antibodies, therapeutic guidelines regarding this have not yet been established (4, 7). An ideal therapeutic approach would aim not only at diminishing the acute and chronic complications associated with diabetes, but also at preserving beta-cell residual function.

Sitagliptin is a potent DPP-4 inhibitor which results in the delay of degradation of incretin hormones (glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)), thereby improving beta-cell function and resulting in better glycemic control in patients with T2D. Nevertheless, this DPP-4 inhibitor was prescribed to our patient due to a growing body of evidence that attributes immunomodulatory effects to this pharmaceutical compound. Recent studies demonstrate that the use of sitagliptin in individuals with T1D improved overall the glycemic control and reduced insulin requirements.

### Table 2 Laboratory investigation from initial diagnosis to 2 years later.

<table>
<thead>
<tr>
<th></th>
<th>Day of diagnosis</th>
<th>Diabetes clinic visit</th>
<th>One year after diagnosis</th>
<th>Two years after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9.6%</td>
<td>5.4%</td>
<td>5.2%</td>
<td></td>
</tr>
<tr>
<td>GAD-abs (U/mL)</td>
<td>32</td>
<td>4.2</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1</td>
<td>1.2</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.9</td>
<td>4.5</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>142</td>
<td>139</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>19</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>27</td>
<td>20</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>241</td>
<td>194</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>157</td>
<td>85</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>TSH (μIU/mL)</td>
<td>1.01</td>
<td>1.3</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td>Insulin (μIU/mL)</td>
<td>10.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-peptide (mg/mL)</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>16.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>Ketone traces</td>
<td></td>
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</table>

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TSH, thyroid-stimulating hormone.
without altering the amount of endogenous insulin production (8). Although great controversy exists in available data (8, 9), it has been proven that DPP-4 (also known as adenosine deaminase complexing protein 2 or CD26) is a transmembrane glycoprotein encoded by the DPP4 gene. CD26 is expressed by many cell types including lymphocytes and is associated with immune regulation. Sitagliptin by inhibiting DPP-4/CD26 decreased the incidence of T1D in the non-obese diabetic (NOD) mouse by reducing CD4 T-cell migration (10). Recently, case reports have described DPP-4 inhibition effects on patients speculating an immunomodulatory pathway. A patient diagnosed with T1D attained an excellent glycemic control without insulin, only by administration of 100 mg of sitagliptin daily 15 months after initial diagnosis (11). In another recent report in a T2D patient with a 17-year history of psoriasis, a gradual remission of his skin lesions was reported after sitagliptin treatment initiation (12). A prospective study of 1-year duration demonstrated maintenance of beta-cell function through the administration of sitagliptin in patients with recent-onset LADA (13). A similar study proved that c-peptide secretion and glycemic control was improved by the use of another DPP-4 inhibitor, saxagliptin, versus placebo in LADA patients (14). All these accumulating evidences support the hypothesis that this may be a class effect; however, further studies are required.

In our case, the patient received additional oral supplementation with vitamin D, due to a deficiency that was revealed in laboratory investigation. The active form of vitamin D, [1,25(OH)₂D₃], regulates not only calcium metabolism, but also modulates the activity of different defense and immune cells, including lymphocytes, monocytes, macrophages and epithelial cells. Since vitamin D₃ promotes phagocytosis by triggering macrophages and affects immune response, it is potentially involved in the pathogenesis of several diseases. A positive correlation between T1D mellitus prevalence and hypovitaminosis D has been demonstrated in several epidemiological trials (15). Taking into consideration these findings, researchers tested the hypothesis that similar results will emerge from the use of vitamin D in LADA patients. Positive correlation was found between 1-alpha(OH)D₃ plus insulin and the preservation of beta-cell function in early onset LADA (16). Moreover, findings from animal trials suggested that low levels of vitamin D may cause a reduction in the secretion of insulin by the beta-cell. Supplementation with 1,25(OH)₂D₃ in patients with T1D with hypovitaminosis D has been shown to improve their glycemic profile (17, 18). In our case, the patient experienced a remarkable decline in GAD-abs titer, which contributed to his excellent glycemic profile for two consecutive years. In the literature, only few data exist to correlate the use of vitamin D with the reduction of GAD-ads in children with T1D. Further investigation in larger cohorts has been advocated to draw safer conclusions (19).

Both vitamin D analogs and DPP-4 inhibitors have been shown to improve beta-cell function and attenuate autoimmunity in diabetes. To our knowledge, this is the first case of combined treatment in a patient with LADA that resulted in reverting the phenotype and preserving excellent glycemic control without the use of insulin 24 months after initial diagnosis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent was obtained from the patient for publication of this case report.

Author contribution statement
E Rapti is a trainee doctor in Endocrinology, who treated the patient and prepared the initial manuscript. K Kotsa is the Assistant Professor of the department, who supervised the care of the patient and edited the manuscript. All other authors have provided significant contribution toward patient care.

References
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