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CASE SERIES

Islet Autoantibodies in the Patients with Sjogren's Syndrome and Thyroid Disease and Risk of Progression to Latent Autoimmune Diabetes in Adults: A Case Series

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Abstract: The glutamic acid decarboxylase 65 antibody (GAD65-Ab) is an autoimmune marker in some diseases such as diabetes or autoimmune disorders of the central nervous system such as stiff-man syndrome. It can appear with other pancreatic autoantibodies, such as insulin autoantibodies (IAA), presenting as early signs of pancreatic islet β-cells impairing, and play roles in the pathogenesis of type1 diabetes (T1D) and latent autoimmune diabetes in adults (LADA). Positive GAD65-Ab is rarely observed in insulin-dependent diabetic patients with other acquired autoimmune diseases, such as Sjogren's syndrome (SS). Besides, LADA revealed by islet autoantibodies such as GAD65-Ab can also be complicated with Hashimoto's thyroiditis (HT), another autoimmune thyroid disease. To date, whether GAD65-Ab positive in patients with autoimmune diseases predicts the onset or progression to T1D or LADA remains unknown. Herein, two unique cases of middle-aged Chinese Han women free from diabetes for three years are described despite their blood tests persistently testing positive for GAD65-Ab or IAA. Both patients suffered from HT and SS. Follow-up OGTTs (oral glucose tolerance test) for three years revealed that the patients had a well-controlled glycemic level and normal pancreatic function. However, one of the patients had a temporary increase of postprandial glucose after a short-term loss of diet control. The presence of auto-immune antibodies in these patients had little impact on glucose tolerance or insulin secretion in 3 years. The study postulate that both the primary immune injury caused by serum GAD65-Ab positive, an autoimmune marker, and increased body weight contribute to the progression of LADA.

Keywords: latent onset autoimmune diabetes in adults, LADA, Hashimoto's thyroiditis, HT, Sjogren's syndrome, SS, autoimmune diseases, glutamic acid decarboxylase 65 antibody, GAD65-Ab, insulin autoantibody, IAA-Ab

Introduction

Patients suffering from one type of an autoimmune disease are often at an increased risk of developing another autoimmune disease.[1] Latent autoimmune diabetes in adults (LADA) accounts for 5.9% of ketosis-free diabetic patients with GAD-Ab positive.[2] The prevalence of LADA is also reported low in other countries.[3] LADA is associated with other autoimmune diseases, such as HT,[4] SS,[5,6] and dermatomyositis,[7] These diseases share autoimmune components, including the common associated genetic loci such as HLA-DR (human leukocyte antigens

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class DR), the CTLA-4 (cytotoxic T-lymphocyte associated protein 4), CD25, PTPN22 (protein tyrosine phosphatase nonreceptor 22), and FOXP3 (forkhead box P3) genes.[8–10] However, recent studies postulate that specific variants in these genes, such as in PTPN22, determine the onset of different diseases with distinct phenotypes and clinical characteristics.[11] The gene variants for T2D have been reported to increase the susceptibility for LADA, especially in overweight individuals.[12] LADA development is initially predicted by the expression of serum markers including GAD65-Ab, ICA (Insulin cell antibody), IAA (Insulin antibody), and ZnT8 (Zinc transporter 8), which may be present for years before the diagnosis of diabetes.[13,14] Some studies also report that islet cell autoantigen 69 (ICA69) autoantibodies are expressed in salivary gland tissues of SS patients or murine model.[15] A previous case report affirmed that SS could be detected in an insulin-dependent diabetic patient, where the GAD65-Ab tested positive.[16] Another case reported the coexistence of LADA and SS in polyglandular syndrome type 3 (APS), where both GADA and ICA tested positive.[17] In recent years, numerous studies investigating the role of GADAb in other diseases, such as stiff-man syndrome and ketosis-prone diabetes, have been done.[18,19] This study aimed to determine whether GAD65-Ab and IAA-Ab positive patients with HT and SS progressed to LADA within a 3-year OGTT testing period.

Case Report 1

A 52-year-old Chinese woman was hospitalized with dry mouth and eyes, which reduced her quality of life. She attended the ophthalmology clinic because of her symptoms and was diagnosed with keratoconjunctivitis sicca. She had not experienced or had a history of vaginal dryness. The patient was not experiencing joint or muscle pains. Physical examinations revealed dryness and cracking in her lips, and multiple dental cavities. Table 1 outlines her laboratory data upon admission. The patient had several notable analytical parameters, including antinuclear antibodies (ANA)+, anti-histone antibodies (AHA)+, Sjogren's Syndrome A antibody (SSA+), Sjogren's Syndrome B antibody (SSB+), and Glutamic Acid Decarboxylase Antibody (GAD65-Ab+). Her labial gland biopsy was performed, and diagnosed with SS and HT (Figure 1).

The presence of GAD65-Ab represents a sign of autoimmunity directed towards the pancreatic islet β-cells (chemiluminescence assay: Linear range: 5IU/mL-250IU/mL; Minimum detection limit: no little than 0.2 IU/mL; maximum detection limit: no more than 2000IU/mL; Accuracy: the relative deviation was within ± 10.0%; Repeatability: the coefficient of variation (CV) of repeatability test was not more than 10.0%; Inter batch difference: the coefficient of variation (CV) of three batches of reagents was not more than 15.0%). Cognizant of this, hemoglobin A1c (HbA1c), oral glucose tolerance test (OGTT), C-peptide, and insulin release tests were performed upon admission (Figure 2). The HbA1c and the initial OGTT ($OGTT_0$) values were "technically normal" based on the ADA criteria.[20] Follow-up laboratory examinations after discharge were recommended because the fasting C-peptide (0.2 nmol/L) and insulin (17.66 pmol/L) levels were borderline low during the $OGTT_0$ (normal: fasting C-peptide, 0.27–1.28 nmol/L; fasting insulin, 35–145 pmol/L). The fasting plasma glucose levels were within the normal range during the follow-up examinations in the $OGTT_{1.5y}$ and $OGTT_{3y}$ despite the 180 min glucose levels (2.82 mmol/L) in the $OGTT_{1.5y}$ being below the normal range (3.36 mmol/L). The patient had no hypoglycemia-related symptoms. The patient's response to glucose stimulation of C-peptide levels during the three years was stable in the normal range (peak time: 30min-1h, response: 5-6-fold to fasting level) despite the fasting C-peptide and insulin levels being relatively low. These findings strongly suggested a relatively preserved pancreatic function. The HOMA-IR value in the patient was within the normal range, suggesting that insulin resistance and insulin sensitivity at the $OGTT_{1.5y}$ and $OGTT_{3y}$ were similar to that of the $OGTT_0$. However, the HOMA-β values were higher at the $OGTT_{1.5y}$ than the $OGTT_0$, but identical to those of the $OGTT_{3y}$. Nevertheless, the relatively low HOMA-β values were not attributed to insulin secretion dysfunction because the patient's HOMA-IS index showed intact insulin sensitivity. The small amounts of insulin were able to maintain normal blood glucose levels (Figure 2).

Case Report 2

A 51-year-old Chinese Han woman visited Shanghai Pudong Hospital because of unknown anemia, aleukemia, and infections. She had not experienced or had a history of vaginal dryness. She also had no joint or muscle pain. Physical examinations revealed no distinct abnormal signs and were thus subjected to relevant laboratory examinations upon admission. Her laboratory data is outlined in Table 1. Positivity for SSA and SSB indicates the

Table 1 The Initial Hospitalization Laboratory Data of the Two Cases

Variable	Case #1	Case #2	Reference Range
Diabetes-related			
Plasma glucose (mmol/L)	4.58	5.89	4.1–6.1
HbA1c (%)	4.9	5.9	4.9–6.0
Glycated albumin (%)	14.3	7.22	11–16
Immunoreactive insulin (mU/L)	17.66	4.43	1.0–18
Serum C-peptide (nmol/L)	0.2	0.27	0.27–1.28
Urinary glucose	-	-	-
Urinary protein	-	-	-
Urinary ketones	-	-	-
Islet-related autoantibodies (chemiluminescence)			
GAD antibody(U/mL)	+	-	N:<10.00; P>10.00
ICA antibody (COI)	-	-	S: 0.90–1.10; N<0.90; P>1.10
IAA antibody (COI)	-	4.32	S: 0.90–1.10; N<0.90; P>1.10
Autoimmune-related antibodies			
Anti-SSA/Ro	+	+	-
Anti-SSB/La	+	±	-
Anti-Sm	-	-	-
AHA	+	-	-
Anti-HKL	1:320↑	1:320↑	-
Anti-BJKL	1:320↑	-	-
ANA	+	+	-
Anti-pANCA	-	-	-
Anti-cANCA	-	-	-
ACAG	<12	<12	<12RU/mL
CCP	-	-	-
ASO	81.95	17.31	<200IU/mL
RF	68.24	1.6	0–20IU/mL
ESR	24↑	10	0–20mm/h
Thyroid function			
TSH (mIU/L)	4.40	1.24	0.55–4.78
Free triiodothyronine (pmol/L)	3.55	5.29	3.50–6.50
Free thyroxine (pmol/L)	12.07	14.80	11.50–22.70
Anti-TPO (IU/mL)	>1300↑	171.20↑	0–60.00
Anti-Tg (IU/mL)	455.5↑	<15.0	0–60.00
TRAb (IU/L)	<1.5	1.34	<1.5

Notes: The significantly elevated Anti-TPO or the elevated Anti-Tg values suggest the existence of Hashimoto thyroiditis (HT); Positive Anti-SSA/Ro with Anti-SSB/La suggest the high suspicion of SSs. RF and ANA (>1:320) are the critical diagnostic standard for SS based on the 2012 ACR guideline for SS classification. Elevated ESR level suggests disease activity; The islet related autoantibodies were detected using the chemiluminescence assay, and were not affected by jaundice (bilirubin<30 mg/dl), hemolysis (hemoglobin<1500 mg/dl), lipidemia (lipid<1500 mg/dl), total serum protein (<10g/dl), RF (<2000IU/mL), HAMA (< 600ng/mL) and ANA (<500AU/mL).
Abbreviations: GAD, glutamic acid decarboxylase; ICA, islet cell antibodies; IAA, insulin autoantibody; S, suspective; P, positive; N, negative; TSH, thyroid-stimulating hormone; TPO, thyroid peroxidase; Tg, thyroglobulin; TRAb, thyrotropin receptor antibody.

existence of SS. This patient only had ANA+ and HKL+ autoimmune antibodies. Her RF, ESR, and AHA were normal. Only the islet autoantibody (IAA) was positive. The patient was thus diagnosed with SS.[21] She received the same treatment for the SS as the 1st case. Measurements of her thyroid function revealed the presence of HT with normal TRAb levels and high thyroperoxidase antibody levels (Table 1).

The sole presence of insulin auto-antibody (IAA-Ab) suggested potential immune injury to the pancreatic islet β-cells. Cognizant of this, blood examinations on hemoglobin A1c (HbA1c), oral glucose tolerance test (OGTT), C-peptide, and insulin release tests were performed (Figure 3). The initial OGTT ($OGTT_0$) showed no impaired glucose tolerance because the glucose levels were below the threshold. The patient's response to

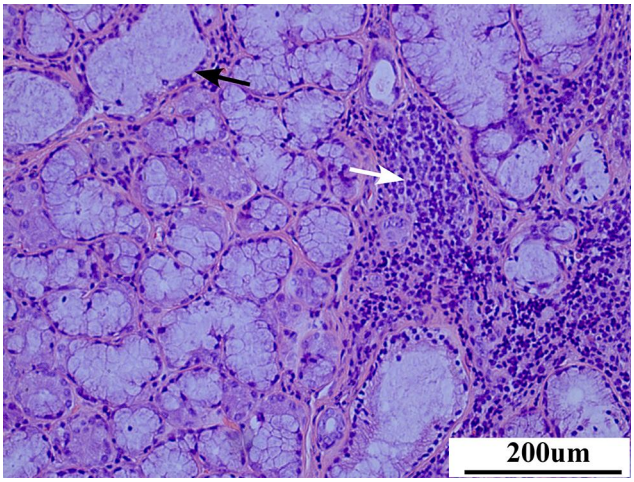

Figure 1 A biopsy of the labial gland. Haematoxylin and eosin stain of the labial gland biopsy (200× magnification). The right white arrow indicates focal lymph infiltration (several lymphocytic foci contained more than 50 lymphocytes). The left black arrow shows part of the glandular tube structure destroyed because of necrosis. Mild collagen hyperplasia and fibrosis are present.

glucose was generally normal despite the fasting C-peptide level being relatively lower than the normal level. The OGTT was repetitively checked at 1.5 years ($OGTT_{1.5y}$) and 3 years ($OGTT_{3y}$). The patient's BMI at 1.5 years was high with high postprandial glucose at 120 min. Fasting and response to glucose challenge of C-peptide levels were generally stable at the $OGTT_{1.5y}$ and $OGTT_{3y}$ than $OGTT_0$. However, the higher peak of C-peptide response at $OGTT_{1.5y}$ appeared after 120 min. The patient had a slight increase in HOMA IR and decreased HOMA-β at $OGTT_{1.5y}$ (Figure 3A–C and E and F). The $OGTT_{3y}$ returned to the normal range after controlling the patient's body weight for 3 years (Figure 3).

Discussion

Pancreatic islet autoimmunity is commonly observed in the pathogenesis of T1DM and LADA, in which autoantibodies circulate in the patient's body. These autoantibodies, including GAD65-Ab, IAA, IA-2, and ZnT8, have diagnostic values in differentiating autoimmune diabetes from type 2 diabetes (T2D). GAD65-Ab has stable properties and strong sensitivity to diagnose T1DM and LADA,[22] and predict the insulin requirements of patients with other positive islet autoantibodies.[23] When GAD65-Ab is combined with islet autoantibodies, the exceptional diagnosis of T1DM or LADA has a low probability. It is also postulated that GADA levels predict insulin dependence.[24] GADA positive combined with the lower level of fasting C-peptide in the first patient suggested the existence of pancreatic immune injury. However, the patient had a well-controlled blood glucose level, indicating relatively slow pathological alterations to the pancreatic islet cell. Insulin replacement was therefore postponed. Differentiating LADA from T2D is important in that the treatment of Sulfonylurea applied to LADA induce the more autoantibodies to the β-cell, thereby deteriorating pancreatic function.[25,26] However, the clinical diagnosis of LADA may be difficult without the reference of pancreatic autoantibodies because of its progression heterogeneity in different individuals.[27] The precursors of LADA and β-cell hyposecretion are unclear. As such, the clinical manifestations of LADA are diverse. Herein, the two middle-aged Chinese women showing either GAD65-Ab or IAA-Ab positive, and with SS and HT, did not progress immediately to LADA in 3 years. This study is inconsistent with the reports of other studies. It was thus concluded that there exist other critical promoting factors such as obesity in the pancreatic islet β-cell to LADA besides the GAD65-Ab and IAA-Ab positive.

GAD-65 is found in pancreatic islets and the thyroid, brain, pituitary glands, kidneys, liver, adrenal glands, ovaries, and testes.[28,29] As such, these tissues may trigger anti-GAD antibody production, based on the polyclonal B-lymphocyte response seen in patients with autoimmune thyroid disease (AITD).[30] There are a few cases of SS reported in insulin-dependent diabetic patients with GAD65 positive.[16] Several clinical and basic studies also report that ICA69 autoantibodies are expressed by the pancreatic islet β-cell and the salivary gland. The antibodies can be detected in patients or murine model with SS, but are absent in patients with Systemic lupus Erythematosus(SLE),[15] suggesting the internal immune relationships between the two diseases. A rare case of APS, where LADA and SS coexist, has also been reported.[17] Studies further postulate that the risk of thyroid disease is increased in SS patients.[31] Adult-onset T1DM and LADA patients with different epitopes of GAD65 have an increased risk of developing thyroid autoimmunity.[32] A previous study reported that epitopes specific for GAD65-Ab associated with T1D are located in the middle region (between amino acids 221 and 359) and the COOH-terminal (between amino acids 453 and 569) of the GAD65 protein.[33] Nonetheless, it has been reported that there are similarities and differences in the humoral response to GAD65 in AITD and T1DM.[34] This study reveals the coexistence of multiple autoimmune diseases which upholds the hypothesis that GAD65-Ab is an

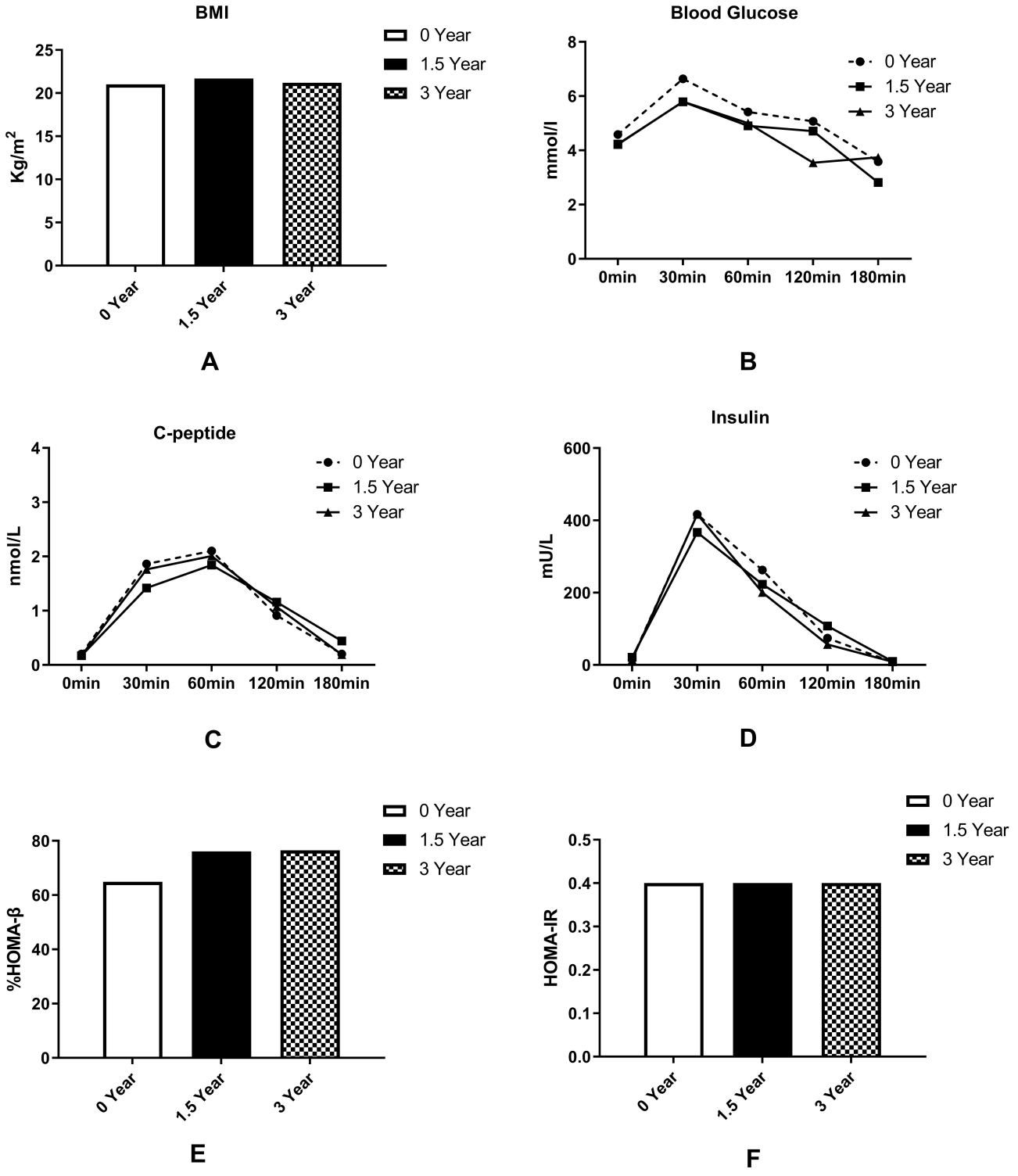

Figure 2 The 1st case (**A**) the body mass index (BMI) showed no significant change at $OGTT_{1.5y}$ and $OGTT_{3y}$ when compared to the $OGTT_0$. (**B**) Glucose levels were lower at the oral glucose tolerance test at 1.5 years ($OGTT_{1.5y}$) and 3 years ($OGTT_{3y}$) compared to the initial OGTT ($OGTT_0$); fasting blood glucose and postprandial blood glucose levels were within the normal range. (**C**) C-peptide was similar at the $OGTT_{3y}$ than the $OGTT_0$, whereas the $OGTT_{1.5y}$ demonstrated a reduced C-peptide response in $OGTT_{1.5y}$. All fasting C-peptide levels were distinctly lower than the normal level (normal range: 0.27–1.28 nmol/L), but the response to C-peptide's glucose challenge is the normal range in 3 years. (**D**) Insulin levels showed no significant change at the $OGTT_{1.5y}$ and $OGTT_{3y}$, compared to the $OGTT_0$. The fasting insulin levels in all tests were relatively low (normal values: 5–10 μU/mL). (**E**) Homeostatic Model Assessment (HOMA) of β-cell function (HOMA-β) was improved at the $OGTT_{1.5y}$ and $OGTT_{3y}$ compared to the $OGTT_0$. (**F**) HOMA index of insulin resistance (HOMA-IR) revealed identical insulin resistance at the $OGTT_{1.5y}$ and $OGTT_{3y}$ compared to the $OGTT_0$.

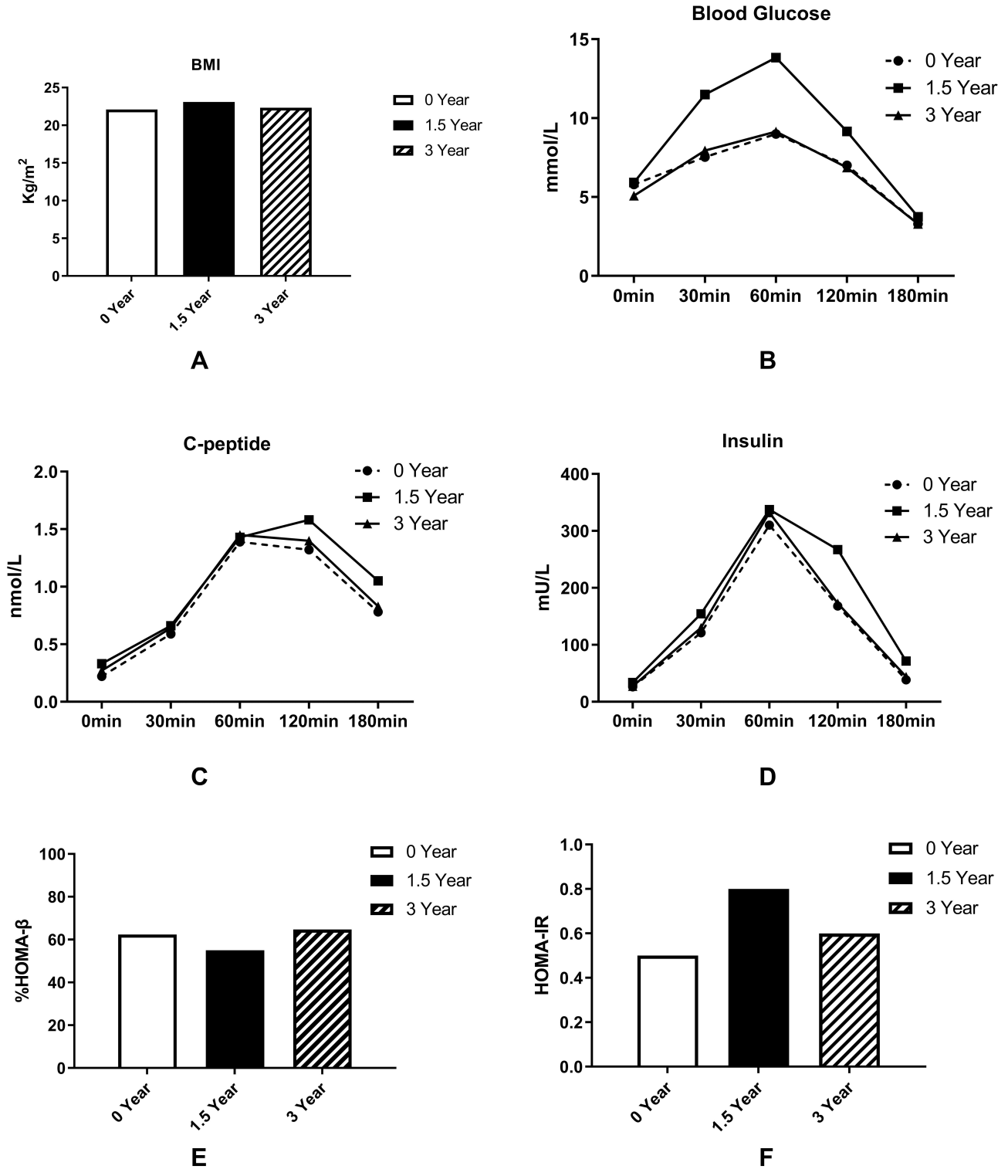

Figure 3 (**A**) The body mass index (BMI) showed slight elevation at $OGTT_{1.5y}$ but returned at $OGTT_{3y}$ to the level of $OGTT_0$. (**B**) Glucose levels were higher at $OGTT_{1.5y}$ than the $OGTT_0$, but this change normalized at the $OGTT_{3y}$ to the normal level; all fasting blood glucose levels were in normal range, but 2h postprandial blood glucose levels of $OGTT_{1.5y}$ reached IGT standards. (**C**) C-peptide levels were generally stable at the $OGTT_{1.5y}$ and $OGTT_{3y}$ than the OGTT0, while the 2h responses to the glucose challenge of $OGTT_{1.5y}$ enhanced when compared with the $OGTT_0$. (**D**) Insulin levels showed an enhanced release of insulin at 120min of $OGTT_{1.5y}$ than that at $OGTT_{1.5y}$ and $OGTT_{3y}$. (**E**) Homeostatic Model Assessment of β-cell function (HOMA-β) slightly decreased at $OGTT_{1.5y}$ compared to the $OGTT_0$ and $OGTT_{3y}$. (**F**) HOMA index of insulin resistance (HOMA-IR) revealed an increase at $OGTT_{1.5y}$.

antibody for general immunity rather than a pre-condition for diabetes.

In both cases, the fasting C-peptide, insulin levels, and HOMA-β were relatively low. The BMIs were far lower than the overweight range (normal weight <25 kg/m^2, overweight 25–29.9 kg/m^2, and obese ≥30 kg/m^2, based on the World Health Organization (WHO) criteria. In the second case, there was an enhanced response of C-peptide and insulin because of BMI and HOMA-IR increase, and HOMA-β decrease. The patient's IGT was reversible, and thus did not progress to LADA after controlling the bodyweight for three years. Cognizant of this, BMI may also be a critical promoter of the onset of LADA. Recently, it has been reported that obesity is a major risk of LADA.[35] Controlling the patient's BMI may be the reason why they did not develop hyperglycemia in 3 years. Besides, alleviating the immune and secondary injury processes to the pancreatic β-cell potentially delays the onset of diabetes. For instance, using low doses of nicotinamide has been demonstrated to reduce β-cell dysfunction in T1D clinical trials with no side effects.[36,37] Such strategies can therefore be adopted to prevent the further loss of pancreatic β-cell function, and the onset of diabetes in SS patients.

Conclusion

Patients with autoimmune diseases and positive islet autoantibodies, but with a BMI laying within the normal range, rarely progress to diabetes unless they gain weight. However, it is essential to explore the immune disease backgrounds and the relationships between different autoimmune diseases to identify their precursors accurately. T1DM and LADA diagnosis may require a combination of lab testing for SS immune markers and islet autoantibodies, and clinical manifestations.

Ethical Statement

The publication of this case series was approved by Shanghai Pudong Hospital affiliated to Fudan University (Shanghai, China). Informed written consent was obtained from the patients for publication of this case series and accompanying images.

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Disclosure

The authors declare that they have no conflicts of interest.

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