

Slowly Progressive Type 1 Diabetes Treated with Metformin for Five Years after Onset

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Abstract

A 52-year-old man was diagnosed with slowly progressive type 1 diabetes (SPIDDM). We expected him to quickly progress to an insulin-dependent state due to a high anti-glutamic acid decarboxylase antibody titer (23.9 U/mL). At SPIDDM diagnosis, he was in a non-insulin-dependent state, with a fasting serum C-peptide immunoreactivity level of 2.5 ng/mL. Therefore, we prescribed metformin. His glycemic control remained stable, and his intrinsic insulin secretion capacity was maintained for five years. Although one case is insufficient to draw firm conclusions, this report suggests that metformin is a therapeutic choice for SPIDDM when the insulin secretion capacity is maintained.

Key words: slowly progressive type 1 diabetes, metformin, diabetes treatment

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Introduction

Slowly progressive type 1 diabetes (SPIDDM) is generally considered to progress to insulin dependence at a high rate (1, 2), although the insulin secretion capacity is maintained at the time of diagnosis. Islet-associated autoantibodies are detected in patients with SPIDDM (3), and it has been previously reported that progression to insulin dependence is evident, particularly in patients with a high anti-glutamic acid decarboxylase antibody (GADAb) titer (4, 5). We previously reported that early insulin administration reduces the rate of progression to insulin dependence compared with sulphonylurea (SU) in SPIDDM patients with a high GADAb titer (6).

However, it is unknown whether treatment with other oral hypoglycemic agents reduces the progression to insulin dependence in patients with SPIDDM. We herein report a case of SPIDDM involving a high GADAb titer in which the insulin secretion capacity was maintained for five years with metformin alone.

Case Report

A 52-year-old man was initially diagnosed with diabetes in 2004 at Saitama Social Insurance Hospital. His parents had type 2 diabetes; however, none of his relatives had type 1 diabetes or any autoimmune diseases.

His body mass index (BMI) was 26.3 kg/m² and his total cholesterol and triglyceride levels were high (Table). However, he did not have hypertension, and no other abnormalities were detected on a physical examination. His HbA1c (NGSP value) (7) level was 7.8%, his fasting plasma glucose level was 160 mg/dL and his fasting serum C-peptide immunoreactivity (CPR) level was 2.5 ng/mL. He was diagnosed with SPIDDM based on the detection of a high GADAb titer (23.9 U/mL; normal range, <1.3 U/mL, RSR, UK) and his clinical course. Other islet-associated autoantibodies, such as anti-insulinoma antigen-2 antibodies (IA-2 Ab), insulin autoantibodies (IAA) and zinc transporter 8 autoantibodies (ZnT8Ab), were negative. Although his thyroid function was normal, the patient's level of anti-thyroid peroxidase antibodies (TPOAb) was positive. He carried the human leukocyte antigen (HLA)-DR4 allele. He had no diabetes-related complications, such as diabetic retinopathy,

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Table. Laboratory Results

Cell blood counts		Glycemic control and insulin secretion	
WBC	7,300 / μ L	FPG	160 mg/dL
Hemoglobin	15.8 g/dL	HbA1c	7.8 %
Platelet	$26.3 \times 10^4/\mu$ L	CPR	2.5 ng/mL
Chemistry		Autoantibodies	
TP	7.9 g/dL	GADAb	23.9 U/mL
AST	22 IU/L	IA-2Ab	negative
ALT	26 IU/L	IAA	negative
γ -GTP	114 IU/L	ZnT8Ab	negative
Creatinine	0.8 mg/dL	TPOAb	>50.0 U/mL
UA	6.0 mg/dL	TgAb	negative
TC	261 mg/dL	HLA	
TG	185 mg/dL	A2, A24, B46, B54, Cw1	
HDL-C	73 mg/dL	DRB1*04:05/DQB1*04:01	
		DRB1*08:03/DQB1*06:01	

FPG: fasting plasma glucose, CPR: C-peptide immunoreactivity, GADAb: anti-glutamic acid decarboxylase antibody, IA-2Ab: anti-insulinoma antigen-2 antibody, IAA: insulin autoantibody, ZnT8Ab: zinc transporter 8 autoantibody, TPOAb: anti-thyroid peroxidase antibody, TgAb: anti-thyroglobulin antibody, HLA: human leukocyte antigen
The value for HbA1c (%) was estimated as an NGSP equivalent value (%) calculated by the formula: HbA1c (%) = HbA1c (JDS) (%) + 0.4% (7).

nephropathy or neuropathy.

The patient's clinical course is shown in Figure. Initially, he was treated with diet therapy alone (1,600 kcal/day). However, a biguanide (metformin at a dose of 500 mg/day) was prescribed after six months. Although the patient's BMI did not change, his HbA1c level was controlled at 7% for five years after onset. His GADAb titer decreased following the administration of metformin. Moreover, his insulin secretion capacity was maintained with a fasting serum CPR level of approximately 2 ng/mL for five years. He did not progress to insulin dependence.

Discussion

In patients with SPIDDM, various factors, such as a male gender (8), high GADAb titer (3-5, 9) and the presence of multiple islet-associated autoantibodies (GADAb/IA-2Ab/IAA) (10) and / or thyroid-related autoantibodies (TPOAb) (10) can predict the progression to an insulin-dependent state. In our case, we initially expected that the patient would progress to insulin dependence within a short period of time due to his high GADAb titer and positive TPOAb status. Surprisingly, his insulin secretion capacity was maintained for five years with biguanides alone.

We speculate that the biguanide (i.e. metformin) preserved the patient's intrinsic insulin secretion and resulted in a lower insulin concentration at the local lesion; this may have resulted in less T-cell activation. Previous reports have indicated that metformin suppresses the toll-like receptor activity by activating adenosine monophosphate (AMP)-activated protein kinase (11) and inhibiting T-cell-mediated immune responses in an animal model of multiple sclerosis (12). Furthermore, metformin increases the glucagon-like peptide (GLP)-1 level following the ingestion of an oral glucose

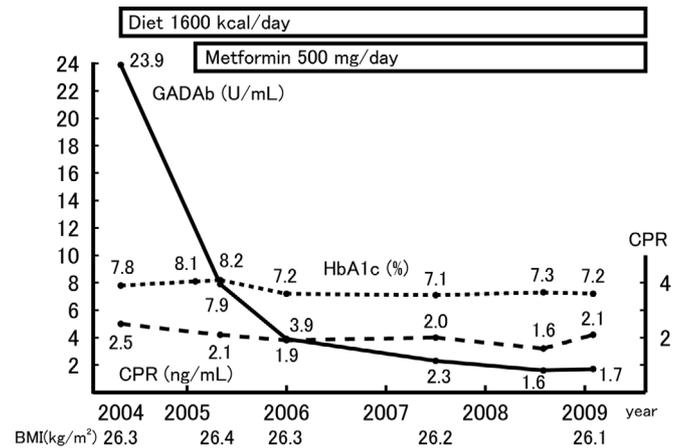


Figure. Clinical course of slowly progressive type 1 diabetes in our patient. GADAb: anti-glutamic acid decarboxylase antibody, CPR: C-peptide immunoreactivity, BMI: body mass index

load, and GLP-1 receptor signaling regulates lymphocyte proliferation and the maintenance of peripheral regulatory T-cells (13, 14). We speculate that the present patient's insulin secretory capacity was maintained for five years due to immunological modification via metformin administration through the mechanisms discussed above, although further investigation is required to prove this hypothesis. At this point, we can suggest that biguanides should not be excluded as a treatment option for SPIDDM, but rather should remain a treatment choice.

Insulin therapy is usually recommended for SPIDDM patients with a high GADAb titer due to the high insulin requirement within a short period of time (15). We previously reported that early insulin therapy significantly reduces the progression to insulin dependence in SPIDDM patients compared with SU therapy (6). We need to compare insulin and metformin directly in a future study to confirm whether metformin really reduces the progression to an insulin-dependent state in SPIDDM patients. Regarding thiazolidinediones, which improve insulin resistance, several previous studies have reported the use of this drug in patients with SPIDDM (16-18); however, there is no consensus to date. Biguanides also improve insulin resistance and may preserve the insulin secretion capacity, although there are no reports regarding the clinical course of SPIDDM after using this class of drug.

As we previously described, the existence of TPOAb in SPIDDM patients has been shown to predict progression to an insulin-dependent state. However, the present patient did not progress to an insulin-dependent state, even though he had a high titer of TPOAb. We speculate that metformin has favorable effects in "overcoming" the influence of TPOAb on the disease course of SPIDDM; however, the mechanism is thus far unknown. Although the thyroid function of the present patient has remained normal, we must follow it closely in addition to the glucose status.

While the patient's insulin secretory capacity was main-

tained in this case, there is a limitation in evaluating this parameter. A recent study reported that the level of stimulated C-peptide is more appropriate than that of fasting C-peptide for assessing the insulin secretory capacity in patients with type 1 diabetes (19). We used only the fasting C-peptide level to evaluate the patient's insulin secretory capacity because we were unable to acquire consent from the patient to perform a glucagon stimulation or mixed-meal tolerance test. We would like to measure the stimulate C-peptide level in order to evaluate the patient's insulin secretory capacity more correctly in the future.

In conclusion, we treated an SPIDDM patient with a high GADAb titer in whom insulin independence was maintained with metformin (a biguanide) for five years. We suggest that a biguanide such as metformin is a therapeutic option for treating SPIDDM patients with insulin independence. However, to reach a firm conclusion, a prospective clinical study with a large number of cases is required.

The authors state that they have no Conflict of Interest (COI).

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