SUNTEXT REVIEWS

SunText Review of Endocrine Care

ISSN: 2771-5469

Open Access
Commentary Article
Volume 3:1

Stable Glucose Variability in a Patient with Slowly Progressive Type 1 Insulin-Dependent Diabetes Mellitus (SPIDDM) with Low-Carbohydrate Diet (LCD)

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Received date: 18 December 2023; **Accepted date:** 29 December 2023; **Published date:** 05 January 2024

Citation: Wood M, Ebe K, Bando H (2024). Stable Glucose Variability in a Patient with Slowly Progressive Type 1 Insulin-Dependent Diabetes Mellitus (SPIDDM) with Low-Carbohydrate Diet (LCD). SunText Rev Endocrine Care 3(1): 115.

DOI: https://doi.org/10.51737/2771-5469.2024.015

Abstract

The patient was a 46-year-old man who presented with hyperglycemia and positive urine glucose 7 years ago. Since then, he has continued a super-low carbohydrate diet (LCD) and kept stable glucose variability. In 2019, his diabetic situation worsened and he received further evaluation. He showed positive glutamic acid decarboxylase (GAD) antibodies and was diagnosed with slowly progressive type 1 insulin-dependent diabetes mellitus (SPIDDM). The standard guideline of SPIDDM was presented by the Japan Diabetes Society (JDS) in 2023. Elevated levels of ketone bodies (KB) were found such as total-KB 624 μM/L (26-122) and 3-hydroxybutyric acid (3-HB) 557 μM/L (0-76).

Keywords: Slowly progressive type 1 insulin-dependent diabetes mellitus (SPIDDM); Low-Carbohydrate Diet (LCD); Glutamic acid decarboxylase (GAD); Ketone bodies (KB); 3-hydroxybutyric acid (3-HB)

Commentary Article

In the area of diabetic practice, slowly progressive type 1 insulin-dependent diabetes mellitus (SPIDDM) has been one of the topics. It was first reported in 1993 [1], and several reports were observed after that [2]. SPIDDM is situated between type 1 and type 2 diabetes associated with various confusion. Few diagnostic criteria for SPIDDM have been observed until 2012 [3]. Related to SPIDDM, other medical terms were present including Latent autoimmune diabetes in adults (LADA) [4] and latent autoimmune diabetes in youth (LADY) [5]. For the latest trend, the Japan Diabetes Society (JDS) has established its criteria which can be used adequately for usual clinical practice. The presentation of the report of the committee of JDS was found for the diagnostic criteria of SPIDDM in 2023 [6]. For SPIDDM, several types of islet-related autoantibodies are known, such as glutamic acid decarboxylase antibody (GAD-Ab), Islet cell antibody (ICA), Insulinoma-associated antigen-2(IA-2), zinc transporter 8（ZnT8）and insulin autoantibody (IAA) [7,8]. 2023 SPIDDM diagnostic guidelines include the following: 1) Islet-related autoantibodies are positive at some point or period during the course of the disease, such as GAD-Ab, ICA, IA-2, ZnT8, and IAA, and 2) generally speaking, when diabetes is diagnosed, ketosis or ketoacidosis is not necessarily present and insulin therapy is not immediately required in order to correct hyperglycemia [6].

Our diabetes group has continued clinical research and practice for many patients with type 1, type 2 and SPIDDM at length. Furthermore, we have developed a low carbohydrate diet (LCD) medically and socially through the activity of the Japan LCD Promotion Association (JLCDPA) [9]. Among them, we reported a case with positive GAD-Ab, the effect of LCD, the honeymoon period, the effect of oral hypoglycemic agents (OHAs), pregnancy with hyperglycemia, multiple medical problems and so on [10-13]. Our activities have contributed to the development of correct and adequate information and practice of diabetology through

books, papers, workshops and internet sites [14]. Recently, we have experienced an impressive case with SPIDDM. The outline of the case associated with some perspectives is described in this article.

Case Presentation

The patient was a 46-year-old man in 2023, and his diagnosis was SPIDDM, dyslipidemia, and allergic rhinitis. When he was 20 years old he weighed 58 kg, but he gained weight up to 70 kg at 30 years old. When he was 39 years old, he was pointed out to have hyperglycemia and glucosuria in 2016. He visited Dr. Koji Ebe at Takao Hospital in Kyoto for further evaluation and treatment. He was advised to start and continue the super-low carbohydrate diet (LCD) for years. By super-LCD, he has maintained 61kg ever since.

Table 1: *Changes in laboratory data.*

	2019	2020		2021		2022		2023	
	Sept	Feb	Sept	May	Dec	Jun	Dec	Jul	Units
Lipids									
HDL	105	107	107	112	116	116	107	113	(mg/dL)
LDL	97	111	103	97	95	83	92	75	(mg/dL)
TG	53	58	62	31	59	33	33	28	(mg/dL)
Liver									
AST	15	20	14	16	21	14	14	16	(U/L)
ALT	2	34	20	29	36	25	17	20	(U/L)
GGT	18	16	15	14	16	14	18	16	(U/L)
Renal									
BUN	18	21	12	15	17	16	17	16	(mg/dL)
Cre	0.95	0.84	0.89	0.97	0.90	0.92	0.74	0.90	(mg/dL)
UA	2.5	2.7	3.2	2.7	2.8	2.3	2.1	2.1	(mg/dL)
Diabetes									
HbA1c	6.2	6.1	5.9	5.7	5.8	5.9	5.9	6.0	(%)
glucose	90	96	92	106	90	108	102	111	(mg/dL)
IRI		3.1		2.6					(μU/mL)
Ketone B.									
T-KB	157			624		581		(26-122)	(μM/L)
AcAc	36			67		46		(13-69)	(μM/L)
3-HB	121			557		535		(0-76)	(μM/L)

T-KB: Total Ketone Bodies, AcAc: acetoacetate, 3-HB: 3-hydroxybutyrate, normal ranges for green color.

During 2019, HbA1c was 6.2% in April and rose to 6.8% in June. Then, he was hospitalized in July for thorough evaluation and treatment. His physique was 172 cm, 61 kg, and BMI 20.6 m^2/kg. The exam results showed positive glutamic acid decarboxylase (GAD) antibody (18.4 U/mL, 0-0.5 as normal range), C-peptide immunoreactivity (CPR) 1.29 ng/mL (0.74-3.48), blood glucose 110 mg/dL, C-peptide index (CPI) = 1.17 (>1.2 for normal). The CPI value was borderline low. In September 2019, he was diagnosed with SPIDDM, and continued super-LCD. He has been an office worker and eaten a set meal at his company's cafeteria for lunch, but he does not eat rice. Until then, he had taken voglibose. However, he discontinued it because it was unnecessary while he was on super-LCD. He also took protein bars (5g carbohydrates, 20g protein) as supplements. Ketone bodies (KB) showed elevated values of total-KB and 3-hydroxybutyric acid (3-HB) [15] (Table 1).

For 2020-2021, HbA1c maintained 5.9-6.2% associated with super-LCD meal. For the KB study, 3-HB was remarkably

elevated at 557 μM/L (0-76). It indicated successful LCD continuation. Abdominal echogram showed fatty liver. Laboratory results revealed that zinc concentration was 92 μg/dL (80-130), cystatin C 0.65 mg/L (0.58-0.87), and urinary albumin 1.5 mg/gr･cre (<30), which were within the normal range.

During 2022-2023, 3-HB level showed remarkably elevated as 557.0 μM/L (0-76), associated with IRI 3.1 μU/mL, body weight 60kg, BMI 20.76 kg/m^2, stable A1c of 5.8-5.9%. Other results showed that NT-proBNP 30 (-126) pg/mL, TSH 3.93 μIU/mL, free T_3 2.8 pg/mL, free T_4 1.1 ng/dL, Cystatin 0.71 mg /L, urine Albumin 2.8 mg/gr･cre (< 30), IRI 2.2 μU/mL in September 2023. The patient has continued muscle training to strengthen his abdominal muscles and quadriceps nowadays.

Ethical Considerations

This patient complied with ordinary ethical guidelines for the Helsinki Declaration. Further, certain comment was observed for personal information. The related principle is found in ethical rules for medical practice and research. This guideline has been regulated by the Japanese government. It is included in both the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science Technology. The authors and collaborators have established our ethical committee about the case. It exists in Takao Hospital, Kyoto, Japan. The committee has several hospital staffs, including the president, physician in charge, registered nutritionist, registered nurse, pharmacist, laboratory staff and legal professional. These committee staffs discussed the case enough in a satisfactory manner. The informed consent was taken from the case by the written data.

Discussion

The standard guidelines for SPIDDM were announced in 2023 [6]. The first criterion is required for a diagnosis of SPIDDM, which is met when islet-related autoantibodies (GAD-Ab, etc.) are detectable. The second criterion is met when ketosis and ketoacidosis are absent on initial diagnosis and insulin is not necessary for glycemic correction. The third criterion is met when at least three months have passed since the diagnosis of diabetes and endogenous insulin production decreases enough that exogenous insulin is required. Fasting serum C peptide would be less than 0.6 ng/ml. Probable SPIDDM is defined as meeting only the first two criteria, while definite SPIDDM is defined as meeting all three of the criteria mentioned above.

In this case, GAD antibody was positive and SPIDDM was suspected. As a result of continuing super-LCD meal for several years, general status has been stable in the light of glucose variability. In other words, the length of the honeymoon period seems to have been extended. During his clinical progress, the levels of total KB and 3-HB were elevated, evidence of increased fatty acid utilization and LCD diet adherence. KB and 3-HB presence has been long associated with LCD adherence. SPIDDM is characterized by autoantibodies such as GAD-Ab. A case has been reported in which the GAD-Ab value increased from 6.9 U/mL to 1600 U/mL during the course of the disease, and the amount of insulin required decreased when entering the honeymoon period [16]. For 3 years, GAD-Ab remained positive (40 U/mL) and HbA1c levels remained below 7%.

As to former management for SPIDDM cases, insulin treatment was introduced at an early stage as a therapeutic intervention. It was recommended because the data was compared with both therapies of insulin and SU agents at that time [17]. In recent years, the following recognition has been found. Even if GAD-Ab is positive, not all diabetes that is insulin-independent SPIDDM by previous criteria will progress to insulin-dependent status [18]. Furthermore, impressive reports of a few cases with SPIDDM are found. DPP-4 inhibitors have been shown to slow the progression to insulin dependence as a therapeutic intervention for SPIDDM by conventional standards [19]. These phenomena have been suggested by the SPAN-S study [20].

Recent studies clarified pathologic findings in the pancreas of patients with SPIDDM [3]. They include markers of type 1 diabetes such as T-cell-mediated insulitis and pseudoatrophic islets, a lack of amylin deposition to the islet cells and a pathologic marker of type 2 diabetes. From the consensus statement of an international expert panel, autoimmune diabetes such as LADA seems to account for 2-12% of adult-onset diabetes cases [21]). They have endotype heterogeneity with a personalized approach. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus 2020 have proposed deviations for LADA from these guidelines. They showed the recommended measurements of random C-peptide levels and large clinical trials. If insulin secretion is maintained, treatment with oral antidiabetic drugs other than SU drugs would be an option.

In summary, an impressive case of SPIDDM with a longer honeymoon period was shown in this article with certain perspectives. JDS presented a standard guideline for SPIDDM in 2023 that helps the diagnosis and treatment [6]. Further, ADA/EASD consensus showed the guidelines for recommending measurement of C-peptide and large clinical trials [21]. We expect that this article will serve as a meaningful reference for diabetic practice and research in the future.

Conflict of Interest

The authors declare no conflict of interest.

Funding

There was no funding received for this paper.

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