



New diagnostic criteria (2023) for slowly progressive type 1 diabetes (SPIDDM): Report from Committee on Type 1 Diabetes in Japan Diabetes Society (English version)

Akira Shimada¹ · Eiji Kawasaki² · Norio Abiru³ · Takuya Awata⁴ · Yoichi Oikawa¹ · Haruhiko Osawa⁵ · Hiroshi Kajio⁶ · Junji Kozawa⁷ · Kazuma Takahashi⁸ · Daisuke Chujo⁹ · Shinsuke Noso¹⁰ · Tomoyasu Fukui¹¹ · Junnosuke Miura¹² · Kazuki Yasuda¹³ · Hisafumi Yasuda¹⁴ · Akihisa Imagawa¹⁵ · Hiroshi Ikegami¹⁰

Received: 2 June 2023 / Accepted: 11 October 2023 / Published online: 8 January 2024
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Abstract

The diagnostic criteria for slowly progressive type 1 diabetes (slowly progressive insulin-dependent diabetes mellitus; SPIDDM) have been revised by the Committee on Type 1 Diabetes of the Japan Diabetes Society. All of the following three criteria must be met for “a definitive diagnosis of SPIDDM”: (1) presence of anti-islet autoantibodies at some point in time during the disease course; (2) absence of ketosis or ketoacidosis at the diagnosis of diabetes with no requirement of insulin treatment to correct hyperglycemia immediately after diagnosis in principle; and (3) gradual decrease of insulin secretion over time, with insulin treatment required at more than 3 months after diagnosis, and presence of severe endogenous insulin deficiency (fasting serum C-peptide immunoreactivity <0.6 ng/mL) at the last observed point in time. When a patient fulfills the only (1) and (2), but not (3), he/she is diagnosed with “SPIDDM (probable)” because the diabetes is non-insulin-dependent state.

Keywords Slowly progressive type 1 diabetes · SPIDDM · Type 1 diabetes · GAD antibody · Latent autoimmune diabetes in adults

This article is the English version of “New diagnostic criteria (2023) for slowly progressive type 1 diabetes (SPIDDM)—Report from Committee on Type 1 Diabetes in Japan Diabetes Society”(https://doi.org/10.11213/tonyoby.66.587) released in Japanese on Volume 66 Issue 7, 2023 on the official website of the Japan Diabetes Society, and has been jointly published in Journal of Diabetes Investigation(the official journal of AASD: https://doi.org/10.1111/jdi.14121) and Diabetology International (the official English journal of the Japan Diabetes Society).

Chairman: Prof. Hiroshi Ikegami. Reference items described in the Table of Japanese version is omitted in this English version because it is explained for the Japanese readers.

The authors have received approval from the editors of the Journal of the Japan Diabetes Society, Journal of Diabetes Investigation, and Diabetology International.

Extended author information available on the last page of the article

Introduction

Type 1 diabetes is characterized by beta-cell destruction and consists of three subtypes: fulminant type 1 diabetes, acute-onset type 1 diabetes (AT1D), and slowly progressive type 1 diabetes (SPIDDM). Kobayashi et al. [1] established the concept of SPIDDM. The diagnostic criteria for SPIDDM (2012) [2] were formulated according to Japanese data considering genetic and environmental factors. More than 10 years have passed since the diagnostic criteria for SPIDDM (2012) were formulated, and some problems have been pointed out in clinical practice; therefore, the diagnostic criteria have been revised.

Revision policy

The revision was based on accumulated and updated Japanese data, and the following points were considered: involvement of endogenous insulin secretory capacity, clarification of the relationship between SPIDDM in Japan [1, 3] and

latent autoimmune diabetes in adults (LADA) [4] or latent autoimmune diabetes in youth (LADY) [5], and establishment of consistency with the diagnostic criteria for AT1D [6] regarding anti-islet autoantibodies and endogenous insulin secretion. Notably, therapeutic intervention was not included in these new diagnostic criteria, and will be indicated in a statement to be published later.

Diagnostic criteria

The revised diagnostic criteria for SPIDDM are shown in Table 1. The points of revision are as follows: (1) “SPIDDM (definite)” is defined as progression to an insulin-dependent state, (2) “SPIDDM (probable)” is defined as suspicion of SPIDDM because of non-insulin-dependent state, (3) “In principle” has been added to “non-existence of ketosis” because of some exceptions, and (4) the relationship between SPIDDM and LADA (or LADY in youth) was considered.

Discussion

As per the previous diagnostic criteria for SPIDDM (2012) [2], the patients who had not yet progressed to an insulin-dependent state were diagnosed with SPIDDM if glutamic acid decarboxylase (GAD) autoantibody or islet cell antibodies (ICA) were detected, even if they were still in the non-insulin-dependent state. Based on evidence from the Tokyo study [7], many patients with anti-islet autoantibody-positive diabetes (SPIDDM as per the previous criteria) have been treated with insulin since the early stages of the disease course. Although the Tokyo study indicated that patients treated early with insulin were less likely to progress to an insulin-dependent state than those treated with sulfonylurea, the differences in the outcomes of early insulin treatment with anti-diabetic agents other than sulfonylurea treatment have not been studied.

Recently, it has been reported that some patients with GAD autoantibody-positive diabetes in the non-insulin-dependent state (SPIDDM as per the previous criteria) did not progress to an insulin-dependent state over time [8, 9]. Moreover, DPP4 inhibitors may inhibit the progression to an insulin-dependent state in patients with anti-islet autoantibody-positive diabetes with a non-insulin-dependent state (SPIDDM as per the previous criteria) as reported in a small-scale study (SPAN-S study) [10].

Based on these data, we revised the diagnostic criteria for SPIDDM (2012) so that patients in a non-insulin-dependent state that are unlikely to progress to insulin dependence are not diagnosed with SPIDDM. The revised diagnostic criteria for SPIDDM (2023) are as follows: SPIDDM is confirmed when a patient progresses to an insulin-dependent state. The criterion for progression to an insulin-dependent state was defined as fasting serum C-peptide immunoreactivity (CPR) < 0.6 ng/mL; this criterion is the same as that for AT1D [6].

Regarding anti-islet autoantibodies, only GAD autoantibodies and ICA were included in the previous criteria because, at the time, only these antibodies were considered as predictors of progression to an insulin-dependent state. However, some patients with single insulinoma-associated antigen-2 (IA-2) autoantibody positivity have been reported to progress to an insulin-dependent state, although the number of such cases is limited [9]. These patients were not diagnosed with SPIDDM using the previous diagnostic criteria for SPIDDM (2012).

Moreover, regarding the concept of LADA (overseas), the Immunology of Diabetes Society (IDS) indicates the following: (1) onset of diabetes after age 35, (2) positivity for either of the known anti-islet autoantibodies, and (3) insulin treatment required for more than 6 months after the diagnosis of diabetes. LADA is a concept that includes both insulin-dependent and non-insulin-dependent states with anti-islet autoantibody positivity, and the need to clarify the relationship between LADA and SPIDDM in

Table 1 Diagnostic criteria (2023) of slowly progressive type 1 diabetes (SPIDDM)

Required factors

- (1) Presence of islet-associated autoantibodies at some time point during the disease course^a
- (2) Principally, absence of ketosis or ketoacidosis at the time of diabetes diagnosis and unnecessary use of insulin treatment to correct hyperglycemia immediately after diagnosis
- (3) Gradual reduction in insulin secretion overtime, requirement of insulin treatment for more than 3 months^b after diagnosis of diabetes, and severe endogenous insulin deficiency (fasting serum C-peptide immunoreactivity < 0.6 ng/mL) at the last observed time point

Judgment

- When the patient fulfills all the three criteria described above, he/she is diagnosed with “slowly progressive type 1 diabetes (definite).”
- When the patient fulfills the only 1) and 2), but not 3), the case is diagnosed with “slowly progressive type 1 diabetes (probable).”

^aAnti-islet autoantibodies include glutamic acid decarboxylase (GAD), insulinoma-associated antigen-2 (IA-2), islet cells (ICA), zinc transporter 8 (ZnT8) autoantibody or insulin autoantibodies (IAA). IAA should be measured before initiating insulin treatment

^bMore than 6 months in a typical case

the Japanese population has been highlighted. Phenotype of progressive beta-cell dysfunction in SPIDDM occurred in age more than 30 years are similar with that of LADA, while the concept of SPIDDM is different from LADA in terms of age of onset and other endotypes [11].

Considering the criteria of LADA [4] mentioned above, anti-islet autoantibodies other than the GAD autoantibody and ICA, that is, IA-2 autoantibody, zinc transporter 8 (ZnT8) autoantibody, and insulin autoantibody, were included in the new diagnostic criteria of SPIDDM (2023). Moreover, we considered the diagnostic criteria for AT1D, which include all known anti-islet autoantibodies.

According to the IDS diagnostic criteria for LADA, insulin treatment is required for more than 6 months [4] after the diagnosis of diabetes. However, considering the diagnostic criteria of AT1D [6], we described the necessity of insulin treatment for more than 3 months in the new criteria of SPIDDM (2023) and added a comment on the necessity of insulin treatment for more than 6 months after diagnosis of diabetes in typical cases. Among patients in a non-insulin-dependent state within 3 months after the diagnosis of diabetes, some were treated with insulin because of clinical judgment; therefore, we can define those patients as having fulfilled the criterion 3 (“if endogenous insulin secretion [fasting C-peptide] is confirmed to be below 0.6 ng/mL, i.e., insulin-dependent state, at the last observed time point”).

Regarding ketosis, it has been reported that LADA is ketosis-resistant [4]; therefore, we believe ketosis is absent in typical cases of SPIDDM. However, in some cases, ketosis does exist, such as cases of soft drink ketosis and combined thyroidal disease. Therefore, we conclude that ketosis does not exist “in principle.”

Patients with SPIDDM (probable) as per the new diagnostic criteria are in the non-insulin-dependent state, even if they have anti-islet autoantibody-positive status; therefore, treatment choices other than insulin can be included. To clarify, patients with non-insulin-dependent state are considered to have suspected SPIDDM, i.e., “SPIDDM (probable).” However, the use of sulfonylurea should be avoided in cases of SPIDDM (probable) because it may cause progression to the insulin-dependent state, according to the Tokyo study [7]. The consensus statement of LADA [12] states that anti-diabetic agents, except sulfonylurea, are the treatment choice if the diabetes is non-insulin-dependent.

To formulate these new diagnostic criteria for SPIDDM (2023), we considered the academic background of the criteria, the relationship between the patient populations in Japan and overseas, and the usefulness of the criteria in clinical practice. We hope that the revised diagnostic criteria for SPIDDM (2023) will contribute significantly to clinical practice.

This is the English version of Diagnostic Criteria of SPIDDM (2023) in Journal of the Japan Diabetes Society [13].

Funding This study is funded by Japan Diabetes Society.

Declarations

Conflict of interest Akira Shimada: lecture fee (Sanofi, Novo, Lilly, Terumo, Sumitomo, Abbott). Norio Abiru: lecture fee (Novo, Lilly). Haruhiko Osawa: research funding (Sysmex), scholarship donation (Daiichi-Sankyo, Novo). Tomoyasu Fukui: research funding (Cosmic). Junnosuke Miura: lecture fee (Terumo). Kazuki Yasuda: scholarship donation (Ono). Akihisa Imagawa: research funding (Parexel International, Taiho, MSD, Ono). Hiroshi Ikegami: lecture fee (Sanofi, Sumitomo, Terumo, Novo), scholarship donation (Sumitomo, Taiho, Life Scan, Novo). Other authors: nothing to declare.

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Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Akira Shimada¹  · **Eiji Kawasaki²** · **Norio Abiru³** · **Takuya Awata⁴** · **Yoichi Oikawa¹** · **Haruhiko Osawa⁵** · **Hiroshi Kajio⁶** · **Junji Kozawa⁷** · **Kazuma Takahashi⁸** · **Daisuke Chujo⁹** · **Shinsuke Noso¹⁰** · **Tomoyasu Fukui¹¹** · **Junnosuke Miura¹²** · **Kazuki Yasuda¹³** · **Hisafumi Yasuda¹⁴** · **Akihisa Imagawa¹⁵** · **Hiroshi Ikegami¹⁰**

✉ Akira Shimada
asmd@saitama-med.ac.jp

¹ Department of Endocrinology and Diabetes, School of Medicine, Saitama Medical University, 38 Morohongo, Moroyama, Iruma, Saitama, Japan

² Diabetes Center, Shin-Koga Hospital, Fukuoka, Japan

³ Midori Clinic, Nagasaki, Japan

⁴ Pancreatic Islet Cell Transplantation Center, National Center for Global Health and Medicine, Tokyo, Japan

⁵ Department of Diabetes and Molecular Genetics, Ehime University Graduate School of Medicine, Ehime, Japan

⁶ Department of Diabetes, Endocrinology and Metabolism, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan

⁷ Department of Diabetes Care Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

⁸ Department of Basic Nursing Science, School of Nursing, Iwate Prefectural University, Iwate, Japan

⁹ Center for Clinical Research, Toyama University Hospital, Toyama, Japan

¹⁰ Department of Endocrinology, Metabolism and Diabetes, Kindai University Faculty of Medicine, Osaka, Japan

¹¹ Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Showa University School of Medicine, Tokyo, Japan

¹² Division of Diabetology and Metabolism, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

¹³ Department of Diabetes, Endocrinology and Metabolism, Kyorin University School of Medicine, Tokyo, Japan

¹⁴ Division of Health Sciences, Department of Public Health, Kobe University Graduate School of Health Sciences, Hyogo, Japan

¹⁵ Department of Internal Medicine (I), Faculty of Medicine, Osaka Medical and Pharmaceutical University, Osaka, Japan