

Practice guideline: Statement regarding treatment for suspected slowly progressive type 1 diabetes (SPIDDM; probable) cases (English version)

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Keywords

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ABSTRACT

Insulin treatment should be introduced in patients with slowly progressive type 1 diabetes (SPIDDM; definite), according to the revised diagnostic criteria of SPIDDM (2023). In contrast, SPIDDM (probable) patients are in a non-insulin-dependent state; therefore, a more flexible treatment can be considered, although sulfonylurea agents should be avoided. Insulin treatment has been shown to maintain endogenous insulin secretion capacity in SPIDDM (probable); however, this does not mean that all SPIDDM (probable) patients should use insulin from the early phase. Dipeptidyl peptidase-4 inhibitors and biguanides might be the treatment of choice for SPIDDM (probable), but no evidence exists for other hypoglycemic agents. In any case, careful monitoring of the endogenous insulin secretion capacity should be carried out, and if a decrease in insulin secretion capacity is suspected, a change in treatment should be considered to prevent progression to an insulin-dependent state.

In 2023, the diagnostic criteria of slowly progressive type 1 diabetes (SPIDDM) were revised (Table 1)^{1–3}. It has been more than 10 years since the diagnostic criteria for SPIDDM were

established in 2012, and problems in clinical practice have been pointed out. In the diagnostic criteria (2012)⁴, SPIDDM includes cases in a non-insulin-dependent state. Furthermore, regarding anti-islet autoantibodies, only glutamic acid decarboxylase (GAD) antibodies and islet cell antibodies, which are known to correlate with the risk of progression to an insulin-dependent state, were included in the previous diagnostic criteria. However, some cases progressed to an insulin-dependent state, even though they were positive for the insulinoma-associated antigen-2 antibody only⁵, raising the concern that these cases cannot be diagnosed as SPIDDM. Furthermore, it has been recognized recently that not all GAD antibody-positive cases with a non-insulin-dependent state,

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

Required factors:

- (1) Presence of anti-islet 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 at more than 3 months[†] 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 antibody, insulinoma-associated antigen-2 antibody, islet cell antibody, zinc transporter 8 antibody or insulin autoantibodies. Insulin autoantibodies should be measured before initiating insulin treatment. [†]More than 6 months in a typical case.

which were considered as SPIDDM in previous diagnostic criteria, progressed to an insulin-dependent state⁶.

Moreover, in Western countries, the concept of latent autoimmune diabetes in adults (LADA) includes both non-insulin-dependent and insulin-dependent states in anti-islet autoantibody-positive diabetes, and it has been discussed that the correlation between LADA and SPIDDM in Japan should be clarified.

The incidence of LADA among diabetes patients has been reported as 2–10% in Western countries, whereas SPIDDM, GAD autoantibody and/or islet cell antibodies-positive cases, according to previous diagnostic criteria in Japan, have been reported to be 2–4%, reaching approximately 10% if insulin autoantibody, insulinoma-associated antigen-2 antibody and zinc transporter 8 antibody are included, similar to those of LADA^{7,8}. Based on the aforementioned background, the diagnostic criteria for SPIDDM were revised.

In the new diagnostic criteria, the diagnosis of SPIDDM is made using the positivity of anti-islet autoantibodies, and despite a non-insulin-dependent state at diagnosis of diabetes, insulin secretion capacity gradually decreases until the insulin-dependent state (fasting C-peptide level <0.6 ng/mL). Patients diagnosed with SPIDDM (definite) are considered to be in an insulin-dependent state; therefore, insulin treatment is necessary.

In contrast, even though the anti-islet autoantibodies are positive, patients with preserved insulin secretion capacity are diagnosed with SPIDDM (probable), which cannot be diagnosed as SPIDDM at this stage; therefore, the patients will be treated as

suspected cases of SPIDDM. As these patients are in a non-insulin-dependent state, there are discussions on how to treat them.

These patients are at high risk of progressing to SPIDDM; however, they cannot be diagnosed with SPIDDM, as aforementioned. Hence, such patients are considered to have diabetes in a non-insulin-dependent state, previously designated as “non-insulin-dependent diabetes (NIDDM)”; therefore, it is not necessary to exclude the usage of hypoglycemic agents other than insulin. However, many patients in the non-insulin-dependent state with anti-islet autoantibody-positive diabetes (SPIDDM in previous diagnostic criteria) were treated with insulin from the early phase based on evidence from the Tokyo study⁹, with some cases treated with insulin despite the insufficient evaluation of pathophysiology. This leads to confusion regarding treatment in clinical practice; therefore, the current statement is established. Furthermore, recently, a consensus statement regarding the treatment for LADA has been published overseas¹⁰; therefore, this statement was established by considering the evidence in Japan and the consensus statement of LADA. LADA is a concept in adults, whereas similar pathophysiology in young patients, including children, is called latent autoimmune diabetes in youth; however, there is no consensus regarding latent autoimmune diabetes in youth¹¹.

EVALUATION OF THE RISK OF PROGRESSION TO INSULIN-DEPENDENT STATE IN SPIDDM (PROBABLE)

It is important to plan interventions for patients with SPIDDM (probable) by considering those who are at risk of progressing to an insulin-dependent state.

It has been shown that a high titer (>10 U/mL) of the GAD antibody in the radioimmunoassay method, which was used until 2015, predicts a high risk of progressing to an insulin-dependent state⁵. However, the prediction of insulin-dependent risk using GAD antibodies in enzyme-linked immunosorbent assays, which has been used in Japan since 2016, remains controversial.

In a previous report by Kawasaki *et al.*¹², it was shown that patients with two or more anti-islet autoantibodies were at a risk of progressing to an insulin-dependent state in SPIDDM (probable). However, it is noteworthy that we cannot measure insulinoma-associated antigen-2 antibodies under the current Japanese insurance system if GAD antibody positivity is confirmed, although it is possible to measure insulin autoantibodies. Similar results were also shown in the Ehime study¹³, which showed that positivity for anti-thyroid peroxidase antibody suggests a high risk of progressing to an insulin-dependent state.

Furthermore, it has been shown that patients with the following characteristics also show features of progression to an insulin-dependent state: low body mass index, younger onset age, short duration before diagnosis of GAD antibody-positive diabetes and low fasting C-peptide at diagnosis^{6,14,15}. In addition, in those aged <45 years¹⁶, SPIDDM (probable) cases

frequently progressed to an insulin-dependent state in the UK Prospective Diabetes Study.

Therefore, SPIDDM (probable) patients with the following characteristics are at a high risk of progressing to an insulin-dependent state: high GAD antibody titer, positivity of two or more anti-islet autoantibodies, anti-thyroid peroxidase antibody positivity in addition to GAD antibody positivity, low body mass index, relatively early onset of disease and low C-peptide at diagnosis.

SELECTION OF MEDICATION

Sulfonylurea agents

Even in the previous version of the diagnostic criteria, it was emphasized that sulfonylurea (SU) agents should be avoided in SPIDDM patients in the non-insulin-dependent state, based on the Tokyo study⁹. In the Tokyo study, it was suggested that patients with anti-islet autoantibody positivity (i.e., GAD antibody and/or islet cell antibodies positivity, SPIDDM (probable) in the current diagnostic criteria) progressed to an insulin-dependent state (i.e. decrease of endogenous insulin secretion capacity) when treated with SU agents, as compared with insulin therapy, irrespective of GAD antibody titer.

Although the precise mechanism is not defined, it has been suggested that the destruction of islets by lymphocytes might progress through the activation of antigen presentation in the islets by SU agents⁹.

In addition, it has been reported that SU agents are not the treatment of choice for LADA¹⁷, suggesting that the use of SU agents for SPIDDM (probable) is not the correct choice. Therefore, SU agents should be avoided when treating SPIDDM (probable).

In the Tokyo study, it was shown that early intervention with insulin therapy is more effective than SU agents; however, it is unknown whether insulin therapy is more effective than oral hypoglycemic agents other than SU agents. Therefore, care must be exercised not to select insulin therapy for all patients with SPIDDM (probable). However, it is noteworthy that insulin therapy is not excluded at the SPIDDM (probable) stage.

Non-SU agents

1. Dipeptidyl peptidase-4 (DPP-4) inhibitors: In the SPAN-S study¹⁸ in Japan, it was suggested that DPP-4 inhibitors might preserve the insulin secretion capacity compared with pioglitazone in SPIDDM (probable), although the number of evaluated patients was limited. It has also been suggested that DPP-4 inhibitors might preserve endogenous insulin secretion capacity compared with SU agents¹⁷ or placebo¹⁹. In an animal model, it has been shown that a DPP-4 inhibitor suppresses the migration of lymphocytes to pancreatic islets²⁰. Furthermore, it has been suggested that DPP-4 inhibitors might promote pancreatic islet regeneration²¹. Based on the evidence described above, DPP-4 inhibitors might be a treatment choice for SPIDDM (probable).

2. Biguanides: It has been suggested that biguanides might preserve endogenous insulin secretion capacity compared with pioglitazone in the treatment of SPIDDM (probable)²², although these are preliminary data. It has been suggested that biguanides alter the characteristics of the gut flora and affect immune function²³. Overseas, there is no obvious evidence that biguanides preserve endogenous insulin secretion capacity in SPIDDM (probable); however, it is not necessary to exclude the use of biguanides¹⁰. Based on the evidence described above, it is not necessary to exclude biguanides as a treatment choice for SPIDDM (probable).

3. Others: It has been suggested that pioglitazone might not be able to preserve endogenous insulin secretion capacity as compared with DPP-4 inhibitors¹⁸ or biguanides²² in SPIDDM (probable), as aforementioned. In an animal model, it has been shown that pioglitazone might contribute to the improvement of islet β -cell function²⁴; however, it has been reported that the effectiveness of pioglitazone in treating type 1 diabetes is not conclusive²⁵. Although this is the case for other thiazolidinediones, it has been reported that a combination of thiazolidinedione and insulin therapy might be more effective than insulin therapy alone²⁶, although reproducibility warrants confirmation¹⁰. Based on the evidence described above, pioglitazone is not recommended for SPIDDM (probable). Regarding glucagon-like peptide-1 (GLP-1) receptor agonists, there is little evidence so far, although they have been reported to improve HbA1c levels in LADA²⁷. There is no statement regarding sodium-glucose cotransporter 2 inhibitors, α -glucosidase inhibitors, glinides and imeglimin, as there is currently no evidence regarding the effectiveness of those agents for SPIDDM (probable). There is limited evidence regarding the effectiveness of glucagon-like peptide-1 receptor agonists in the treatment of SPIDDM (probable), and there is no statement regarding the usage of sodium-glucose cotransporter 2 inhibitors, α -glucosidase inhibitors, glinides and imeglimin, as aforementioned. Hence, coming to a definite conclusion is difficult at this point.

CAREFUL OBSERVATION AFTER INTERVENTION

Irrespective of the choice of intervention, it is necessary to carefully monitor plasma glucose levels and β -cell function (through the measurement of C-peptide). If worsening plasma glucose levels and a decrease in endogenous insulin secretion capacity are suspected, it is necessary to switch to another treatment, such as prompt intensive insulin therapy, that can maintain appropriate plasma glucose levels and reduce the risk of progression to an insulin-dependent state. Currently, the evaluation of medication is based on plasma glucose control and progression to an insulin-dependent state in the midterm; however, it is necessary to include the evaluation of diabetic vascular complications in the future.

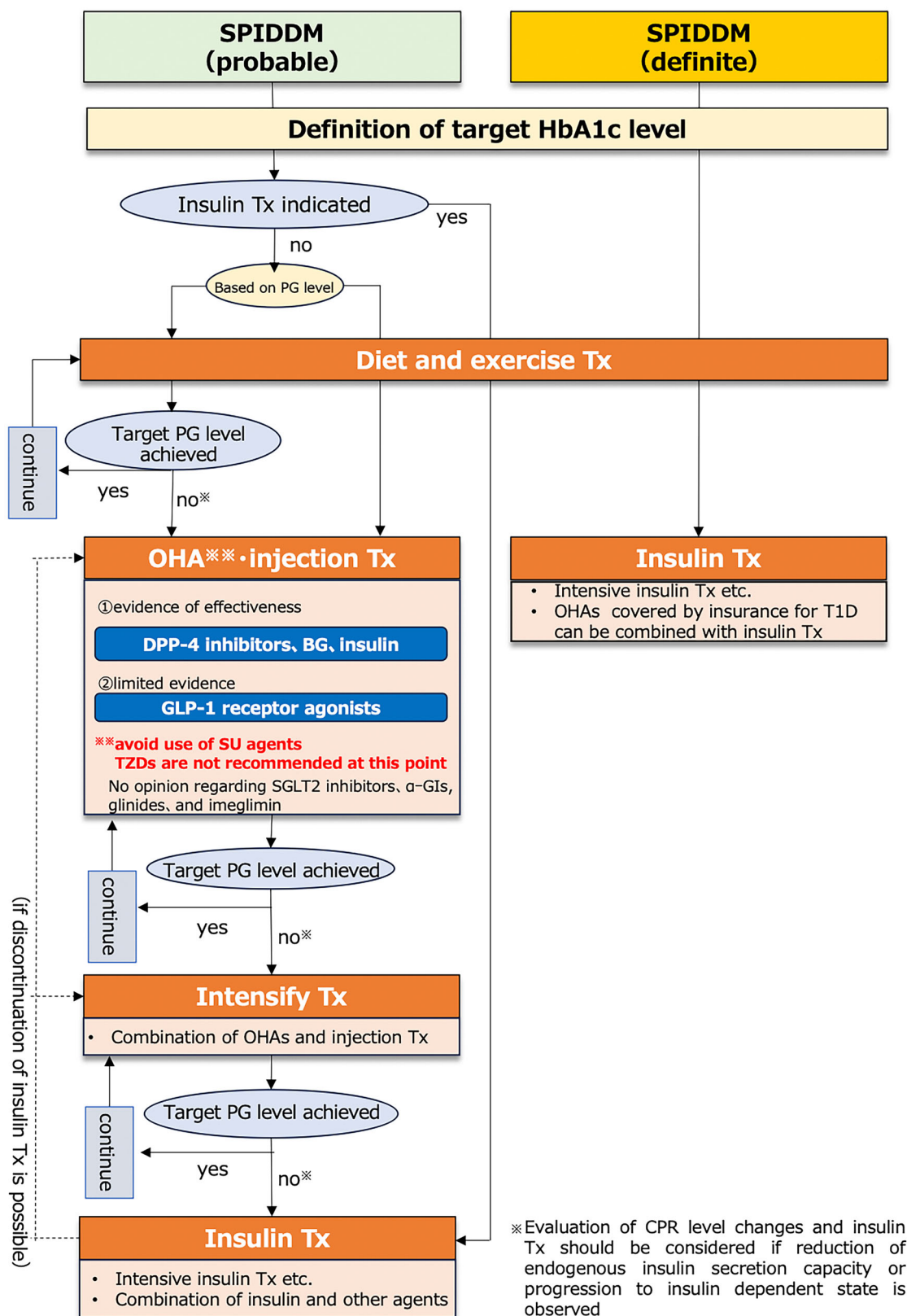


Figure 1 | Therapeutic intervention for patients with slowly progressive type 1 diabetes (SPIDDM; probable). α -GI, α -glucosidase inhibitor; BG, biguanides; CPR, C-peptide immunoreactivity; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; OHA, oral hypoglycemic agents; PG, plasma glucose; SU, sulfonylurea; T1D, type 1 diabetes; Tx, therapy; TZD, thiazolidinedione.

SUMMARY

Figure 1 summarizes the description above. Insulin therapy is the treatment of choice for patients diagnosed with SPIDDM (definite) according to the revised diagnostic criteria (2023; Table 1), by fulfilling criteria 1, 2 and 3. For cases with SPIDDM (probable) that fit only criteria 1 and 2; that is, only those who are still in a non-insulin-dependent state, the treatment choice is more flexible. This statement is described as a reference for treating these cases, and the important points are as follows.

1. Avoid the use of SU agents.
2. There is clear evidence that insulin therapy preserves endogenous insulin secretion capacity as compared with SU agents; therefore, it is the preferred treatment choice; however, there is no evidence for comparison with agents other than SU agents. Therefore, there is no evidence supporting the use of insulin therapy to treat all SPIDDM (probable) cases.
3. DPP-4 inhibitors can be one of the treatment choices.
4. It is not necessary to avoid the usage of biguanides.
5. Regarding other agents, the use of pioglitazone is not recommended at this point, and evidence is lacking regarding glucagon-like peptide-1 receptor agonists, sodium–glucose cotransporter 2 inhibitors, α -glucosidase inhibitors, glinides and imeglimin; therefore, the use of these agents should be evaluated in the future.

Even if any medication is selected, close observation should be carried out to evaluate the plasma glucose control state and endogenous insulin secretion capacity (measurement of C-peptide) over time. If worsening of plasma glucose levels or a decrease in endogenous insulin secretion capacity is suspected, a change in treatment, such as prompt introduction of insulin therapy to suppress the progression to an insulin-dependent state, should be considered.

For reference, SPIDDM (probable) patients are in a non-insulin-dependent state; as aforementioned, it is necessary to treat those patients as NIDDM in the Japanese insurance system; however, we should discuss making the use of the agents described above for SPIDDM (probable) in the insurance system possible.

This is the English version of the statement regarding treatment for suspected slowly progressive type 1 diabetes cases in the *Journal of the Japan Diabetes Society*²⁸.

DISCLOSURE

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Approval date of Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

REFERENCES

1. Shimada A, Kawasaki E, Abiru N, *et al.* Diagnostic criteria of SPIDDM (2023). *J Jpn Diabetes Soc* 2023; 66: 587–591 (Japanese).
2. Shimada A, Kawasaki E, Abiru N, *et al.* New diagnostic criteria (2023) for slowly progressive type 1 diabetes (SPIDDM): Report from committee on type 1 Diabetes in Japan Diabetes Society (English version). *Diabetol Int* 2024; 15: 1–4.
3. Shimada A, Kawasaki E, Abiru N, *et al.* New diagnostic criteria (2023) for slowly progressive type 1 diabetes (SPIDDM): Report from committee on type 1 diabetes of the Japan Diabetes Society (English version). *J Diabetes Investig* 2024; 15: 254–257.
4. Tanaka S, Ohmori M, Awata T, *et al.* Diagnostic criteria for slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM) (2012): Report by the committee on slowly progressive insulin-dependent (type 1) diabetes mellitus of the Japan diabetes society. *Diabetol Int* 2015; 6: 1–7.
5. Nishimura A, Matsumura K, Kikuno S, *et al.* Slowly progressive type 1 diabetes mellitus: Current knowledge and future perspectives. *Diabetes Metab Syndr Obes* 2019; 12: 2461–2477.
6. Yasui J, Kawasaki E, Tanaka S. *Et al*; Japan diabetes society committee on type 1 diabetes mellitus research. Clinical and genetic characteristics of non-insulin- requiring glutamic acid decarboxylase (GAD) autoantibody-positive diabetes: A Nationwide survey in Japan. *PLoS One* 2016; 11: e0155643.
7. Tanaka S, Awata T, Shimada A, *et al.* Clinical characteristics of slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM): 1st subcommittee report on SPIDDM, committee on type 1 diabetes, Japan diabetes society and committee on type 1 diabetes. *J Jpn Diabetes Soc* 2011; 54: 65–75 (Japanese).

8. Kawasaki E. Anti-islet autoantibodies in type 1 diabetes. *Int J Mol Sci* 2023; 24: 10012.
9. Maruyama T, Tanaka S, Shimada A, *et al.* Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus. *J Clin Endocrinol Metab* 2008; 93: 2115–2121.
10. Buzzetti R, Tuomi T, Mauricio D, *et al.* Management of latent autoimmune diabetes in adults: A consensus statement. From an International Expert Panel. *Diabetes* 2020; 69: 2037–2047.
11. Zachariah S, Sharfi MO, Nussey SS, *et al.* Latent autoimmune diabetes in the young. *Clin Med* 2008; 8: 552–553.
12. Kawasaki E, Nakamura K, Kuriya G, *et al.* Autoantibodies to insulin, insulinoma-associated antigen-2, and zinc transporter 8 improve the prediction of early insulin requirement in adult-onset autoimmune diabetes. *J Clin Endocrinol Metab* 2010; 95: 707–713.
13. Murao S, Kondo S, Ohashi J, *et al.* Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict beta cell failure in patients with latent autoimmune diabetes in adults (LADA)—A 5-year follow-up of the Ehime study. *Diabetes Res Clin Pract* 2008; 80: 114–121.
14. Tanaka S, Okubo M, Nagasawa K, *et al.* Predictive value of titer of GAD antibodies for further progression of beta cell dysfunction in slowly progressive insulin-dependent (type 1) diabetes (SPIDDM). *Diabetol Int* 2015; 7: 42–52.
15. Wada E, Onoue T, Kinoshita T, *et al.* Adult-onset autoimmune diabetes identified by glutamic acid decarboxylase autoantibodies: A retrospective cohort study. *Diabetologia* 2021; 64: 2183–2192.
16. Turner R, Stratton I, Horton V, *et al.* UKPDS 25: Autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. *Lancet* 1997; 350: 1288–1293.
17. Johansen OE, Boehm BO, Grill V, *et al.* C-peptide levels in latent autoimmune diabetes in adults treated with linagliptin versus glimepiride: Exploratory results from a 2-year double-blind, randomized, controlled study. *Diabetes Care* 2014; 37: e11–e12.
18. Awata T, Shimada A, Maruyama T, *et al.* Possible long-term efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for slowly progressive type 1 diabetes (SPIDDM) in the stage of non-insulin-dependency: An open-label randomized controlled pilot trial (SPAN-S). *Diabetes Ther* 2017; 8: 1123–1134.
19. Zhao Y, Yang L, Xiang Y, *et al.* Dipeptidyl peptidase 4 inhibitor sitagliptin maintains beta-cell function in patients with recent-onset latent autoimmune diabetes in adults: A one year prospective study. *J Clin Endocrinol Metab* 2014; 99: E876–E880.
20. Kim SJ, Nian C, McIntosh CH. Sitagliptin (MK0431) inhibition of dipeptidyl peptidase IV decreases nonobese diabetic mouse CD4+ T-cell migration. *Diabetes* 2010; 59: 1739–1750.
21. Tian L, Gao J, Hao J, *et al.* Reversal of new-onset diabetes through modulating inflammation and stimulating beta-cell replication in nonobese diabetic mice by a dipeptidylpeptidase IV inhibitor. *Endocrinology* 2010; 151: 3049–3060.
22. Shimada A, Shigihara T, Okubo Y, *et al.* Pioglitazone may accelerate the disease course of slowly progressive type 1 diabetes. *Diabetes Metab Res Rev* 2011; 27: 951–953.
23. Ursini F, Russo E, Pellino G, *et al.* Metformin and autoimmunity: A “new Deal” of an old drug. *Front Immunol* 2018; 9: 1236.
24. Maganti AV, Tersey SA, Syed F, *et al.* Peroxisome proliferator-activated receptor- γ activation augments the β -cell unfolded protein response and rescues early glycemic deterioration and β -cell death in non-obese diabetic mice. *J Biol Chem* 2016; 291: 22524–22533.
25. Shigihara T, Okubo Y, Kanazawa Y, *et al.* Thiazolidinediones may not reduce diabetes incidence in type 1 diabetes. *Ann N Y Acad Sci* 2006; 1079: 365–368.
26. Zhou Z, Li X, Huang G, *et al.* Rosiglitazone combined with insulin preserves islet beta cell function in adult-onset latent autoimmune diabetes (LADA). *Diabetes Metab Res Rev* 2005; 21: 203–208.
27. Pozzilli P, Leslie RD, Peters AL, *et al.* Dulaglutide treatment results in effective glycaemic control in latent autoimmune diabetes in adults (LADA): A post-hoc analysis of the AWARD-2, -4 and -5 trials. *Diabetes Obes Metab* 2018; 20: 1490–1498.
28. Shimada A, Kawasaki E, Abiru N, *et al.* Statement regarding treatment for suspected slowly progressive type 1 diabetes cases. *J Jpn Diabetes Soc* 2023; 66: 807–814 (Japanese).