Factors affecting glycemic control in diabetes mellitus complicated by autoimmune pancreatitis

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ABSTRACT

Aims/Introduction: To investigate factors influencing glycemic control in diabetes mellitus complicated by autoimmune pancreatitis.

Materials and Methods: This retrospective cohort study investigated 33 patients with diabetes mellitus complicated by autoimmune pancreatitis who had received steroid therapy at Toranomon Hospital between January 1, 2011, and December 31, 2020. The course of glycemic control at 12 months after starting steroids was classified into three groups: Improved, Unchanged, or Worsened. Factors affecting these groups were investigated. Furthermore, we created two scores: (1) time of diabetes mellitus onset and baseline body mass index; (2) time of diabetes mellitus onset and baseline C-peptide index. Diabetes mellitus occurring at the same time as autoimmune pancreatitis, body mass index $\geq 22$ kg/m$^2$, and C-peptide index $\geq 1.1$ were each worth 1 point. Scores were summed and totals of 0–2 were compared between groups.

Results: Ten patients were in the Improved group, 10 were in the Unchanged group, and 13 were in the Worsened group. The baseline body mass index and baseline C-peptide index were lower in the Worsened group than in the Improved group ($P < 0.05$ each). In addition, the scores were lower in the Worsened group than in the other groups ($P < 0.05$).

Conclusions: Patients with a lower baseline body mass index and a decreased baseline C-peptide index may experience worse glycemic control on steroid therapy.

INTRODUCTION

Autoimmune pancreatitis (AIP) was first proposed by Yoshida1 in 1995 and was considered a pancreatic lesion of immunoglobulin (Ig)G4-related disease. Multiple-organ diseases such as sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, lymphadenopathy, chronic thyroiditis, and interstitial nephritis may also be seen with this pathology. Autoimmune pancreatitis is reportedly associated with diabetes mellitus (DM) in about 40–80% of cases2–5.

The standard treatment for autoimmune pancreatitis is steroid therapy. Indications for steroid therapy can include jaundice, abdominal pain, back pain, and multiple-organ diseases6,7.

A nationwide survey conducted by the Ministry of Health, Labor and Welfare in Japan reported that the remission rate of AIP with steroid treatment was about 98%, and the mean time to remission was 98 days8.

Although steroids can have a side effect of hyperglycemia, the course of glycemic control complicated by autoimmune pancreatitis varies from case to case. Glycemic control improves after steroid therapy in about 55% of cases and deteriorates in about 9–15%4,9. Two factors have been reported to improve glycemic control after steroid therapy: autoimmune pancreatitis and diabetes mellitus occurring at the same time2,4,5,9, and the absence of pancreatic atrophy after steroid therapy10,11. This latter factor can only be determined after treatment and thus cannot be used before treatment to predict glycemic control. In the absence of other factors, predicting the course of glycemic control is difficult12.
control before steroid therapy remains difficult. Identification of factors predictive of the course of glycemic control before steroid therapy might contribute to better treatment strategies for diabetes mellitus. We therefore investigated factors influencing glycemic control in diabetes mellitus complicated by autoimmune pancreatitis.

MATERIALS AND METHODS
Study design and patients
This study used a retrospective cohort design. Patients with diabetes mellitus complicated by autoimmune pancreatitis who had visited Toranomon Hospital between January 1, 2011, and December 31, 2020, and had received steroid therapy were included in this study. Two patients for whom steroid doses were increased within a year due to autoimmune pancreatitis relapse were included. One patient on a steroid trial was also included. Two patients who were not followed up for more than 1 year were excluded, and the data from a total of 33 patients were analyzed. Autoimmune pancreatitis was treated by the Department of Biliary and Pancreatic Medicine at Toranomon Hospital. Prednisolone (PSL) was started at 30–40 mg/day (0.3–0.7 mg/kg body weight). The timing of dose reduction depended on the attending physician, but in most cases, the initial dose was continued for 2–4 weeks, then the dose was reduced by 2.5–5 mg/day every 2–6 weeks, and the maintenance dose was 5 mg/day. Diabetes mellitus was treated by the Department of Endocrinology and Metabolism at Toranomon Hospital.

Definitions
Autoimmune pancreatitis was diagnosed according to the Japanese consensus guidelines for autoimmune pancreatitis12. Diabetes mellitus was diagnosed according to the flowchart for clinical diagnosis presented by the Japan Diabetes Society.13 Specifically, patients with diabetes mellitus were defined as those with: (1) fasting blood glucose ≥126 mg/dL; (2) blood glucose ≥200 mg/dL at any time; (3) hemoglobin (Hb) A1c ≥6.5%, who fulfilled (1) or (2) and (3), or who fulfilled (1) or (2) at least twice, or who were already on pharmacotherapy for diabetes mellitus. Concerning the time of onset of diabetes mellitus, patients with diabetes mellitus within 12 months before or after the diagnosis of autoimmune pancreatitis were defined as showing contemporaneous onset of autoimmune pancreatitis11,14. The C-peptide index (CPI), calculated as CPI = fasting C-peptide immunoreactivity (CPR) [ng/mL] × 100/fasting blood glucose [mg/dL], was used to assess insulin secretion15,16. Imaging evaluation of the pancreas was performed by CT or MRI. The maximum anteroposterior diameter of the pancreatic body was measured in front of the vertebral body in axial sections. A pancreatic body of <10 mm was defined as atrophic10,17. According to previous reports, the course of glycemic control at 12 months after starting prednisolone was classified into three groups: Improved group; Unchanged group; and Worsened group9,10,18. The Improved group was defined as patients for whom the HbA1c decreased by at least 0.5% at 12 months after starting prednisolone and for whom diabetes mellitus treatment was not intensified. Intensification of diabetes mellitus treatment was defined as an initiation of or an increase in the dose of oral hypoglycemic agents (OHAs) or insulin compared with diabetes mellitus treatment just before the start of prednisolone. The Worsened group was defined as patients for whom the HbA1c increased by ≥0.5% at 12 months after starting prednisolone or with intensified diabetes mellitus treatment. The Unchanged group was defined as any patient not assigned to either the Improved group or the Worsened group.

Methods and statistical analysis
The dependent variable was the course of glycemic control at 12 months after starting prednisolone (Improved, Unchanged, or Worsened group). Analysis of continuous variables was performed using the Shapiro-Wilk test for normality followed by analysis of variance (ANOVA) when a normal distribution was followed and the Kruskal-Wallis test when a non-normal distribution was followed. When significance was confirmed, multiple comparisons were performed using the Steel-Dwass test. Analysis of nominal variables was performed using the Fisher’s exact test. When significance was confirmed, multiple comparisons were performed using the Holm test. Analyses of the amount of change in blood test data at the time of AIP diagnosis and 12 months after the initiation of prednisolone were performed using the paired t-test when a normal distribution was followed and the Wilcoxon signed-rank sum test when a non-normal distribution was followed. Missing values were excluded. We created two scores, comprising: (1) time of onset of diabetes mellitus and baseline body mass index (BMI); (2) time of onset of diabetes mellitus and baseline CPI. Time of onset of diabetes mellitus has previously been reported as a factor affecting glycemic control14,15,9. Baseline BMI and baseline CPI were items that showed significant differences in the present study. Because a significant correlation exists between baseline BMI and baseline CPI, we examined these two scores separately. Diabetes mellitus occurring at the same time as AIP, BMI ≥22 kg/m², or CPI ≥1.1 were each scored as 1 point. These three items were then summed and total scores (range, 0–2) were compared between groups. Missing values in any of the three items were excluded from scoring. The dependent variable was the course of glycemic control at 12 months after initiation of prednisolone (Improved, Unchanged, or Worsened groups). The independent variable was the total score. The Kruskal-Wallis test was performed. When significance was confirmed, multiple comparisons were performed using the Steel-Dwass test.

Spearman’s rank correlation analysis was performed to examine the correlation between BMI and CPI.

EZR version 1.5219 was used to analyze the data. EZR is statistical software that extends the functionality of R and R Commander20. Values of $P < 0.05$ were considered statistically significant.
RESULTS

Clinical characteristics
Table 1 shows the clinical characteristics of all patients. The Improved, Unchanged, and Worsened groups comprised 10 patients (30.3%), 10 patients (30.3%), and 13 patients (39.4%), respectively. The BMI and the time of diabetes mellitus onset differed significantly among the three groups. Multiple comparisons of these items showed significant differences in BMI, which was significantly lower in the Worsened group than in the Improved group.

As for the course of treatment for autoimmune pancreatitis, an improvement of pancreatic swelling was observed in all patients who were followed up. Atrophy was observed in about 18% of patients (6/33).

Comparison before and after initiation of PSL
Table 2 shows a comparison of blood test data at the time of diagnosis of autoimmune pancreatitis and 12 months after initiation of prednisolone. Lipase and IgG4 improved significantly in all groups. A significant difference in the amount of change among the three groups was only identified for HbA1c. Data at the time of diagnosis of autoimmune pancreatitis showed significant differences in HbA1c and CPI. HbA1c tended to be higher in the Improved group than in the Unchanged group. Baseline CPI tended to be lower in the Worsened group than in the Improved group.

AIP and DM treatment
Table 3 shows treatments for autoimmune pancreatitis and diabetes mellitus. The treatment of autoimmune pancreatitis did not differ significantly between the three groups. At 12 months after initiation of prednisolone, about 9% of patients (3/33) were on 2.5 mg/day, 58% (19/33) were on 5 mg/day, 24% (8/33) were on 7.5 mg/day, and 9% (3/33) were on 15 mg/day.

A significant difference in the treatment of diabetes mellitus was evident between the groups. With multiple comparisons, significant differences were found only for insulin use and ‘no treatment’ just before initiation of prednisolone. Insulin use was more common in the Improved group than in the Unchanged group, whereas ‘no treatment’ was more common in the Unchanged group than in the Improved group. During this study, insulin was used in 64% of patients (21/33): 90% (9/10) in the Improved group, 77% (10/13) in the Worsened group, and 20% (2/10) in the Unchanged group. In terms of the timing of insulin introduction, all nine patients in the Improved group were just before initiation of prednisolone. In the Worsened group, three patients were just before initiation of prednisolone, two patients were on the same day as the initiation of prednisolone, and five patients were on the day after the initiation of prednisolone. In the Unchanged group, one patient was 6 days after the initiation of prednisolone and one patient was 3 months after the initiation of prednisolone. Among the insulin users, 78% of patients (7/9) in the Improved group, 10% (1/}

Table 1 | Clinical characteristics of patients

|                          | Improved (I) (n = 10) | Unchanged (U) (n = 10) | Worsened (W) (n = 13) | P value |
|--------------------------|-----------------------|------------------------|-----------------------|---------|
| Age, years               | 70 (56–73)            | 63 (60–70)             | 70 (66–73)            | 0.22    |
| Male                     | 10 (100%)             | 9 (90%)                | 11 (85%)              | 0.76    |
| BMI (kg/m²)              | 23.2 (21.3–25.3)      | 22.2 (20.2–22.9)       | 20.2 (18.6–21)        | 0.01    |
| Onset of DM              |                       |                        |                       |         |
| Before AIP diagnosis     | 1 (10%)               | 1 (10%)                | 7 (54%)               | 0.04    |
| Concurrent with AIP      | 9 (90%)               | 9 (90%)                | 6 (46%)               | 0.88    |
| Multiple-organ disease   | 4 (40%)               | 3 (30%)                | 3 (38%)               | 0.58    |
| Salivary gland inflammation | 2 (20%)           | 2 (20%)                | 1 (8%)                | 0.61    |
| Sclerosing lacrimal adenitis | 1 (10%)             | 0                      | 0                     | 0.35    |
| Sclerosing cholangitis   | 1 (10%)               | 0                      | 3 (23%)               | 0.32    |
| Retropertoneal fibrosis  | 0                     | 0                      | 2 (15%)               | 0.32    |
| Kidney disease           | 0                     | 1 (10%)                | 0                     | 0.22    |
| Pattern of pancreatic swelling | 6/4 (60%)/(40%) | 4/6 (40%)/(60%)        | 4/9 (31%)/(69%)       | 0.37/0.37 |
| Pancreatic atrophy after PSL | 1 (10%)           | 1 (10%)                | 4 (31%)               | 0.46    |

Data are presented as median (interquartile range) or number (%). AIP, autoimmune pancreatitis; BMI, body mass index; DM, diabetes mellitus; PSL, prednisolone.
Table 2: Comparison of blood test data at the time of autoimmune pancreatitis diagnosis and 12 months after initiation of prednisolone

| Test         | Pre (median, IQR) | Post (median, IQR) | Δ Pre vs. Post | P-value Pre vs. Post | Δ Pre vs. Post | P-value Pre vs. Post |
|--------------|-------------------|--------------------|---------------|----------------------|---------------|----------------------|
| Amylase (U/L) | 76 (56–120)       | 73 (71–108)        | +Δ = -1 (10) 55 | 0.8                 | -Δ = 1 (14) 35 | 0.87                 |
| Lipase (U/L)  | 352 (122–478)     | 125 (85–126)       | +Δ = 337 (122 to 0) | 0.01; Improved vs. Improved | +Δ = 148 (127 to 0) | 0.03; Improved vs. Improved |
| IgG4 (mg/dL) | 380 (214–608)     | 147 (79–292)       | +Δ = -235 (122 to 0) | 0.01; Improved vs. Improved | +Δ = -80 (59 to 0) | 0.03; Improved vs. Improved |
| HbA1c (%)    | 7.5 (7.1–7.9)     | 7.3 (6.5–7.7)      | +Δ = 0.2 (0.5 to 0) | 0.89; Improved vs. Improved | +Δ = 0.1 (0.2 to 0) | 1.00; Improved vs. Improved |

**DISCUSSION**

In patients treated with prednisolone for autoimmune pancreatitis, those showing a decreased baseline CPI and lower baseline BMI were more likely to experience worsened glycemic control after treatment. In addition, the scores we created were significantly lower in the Worsened group. To the best of our knowledge, associations between glycemic control after prednisolone therapy and baseline CPI in patients with autoimmune pancreatitis have not been reported to date. In patients with type 2 diabetes mellitus, a decreased CPI is well known to be associated with worsened glycemic control[16,21]. Our present study therefore demonstrated that a decreased CPI was also associated with worse glycemic control in patients with autoimmune pancreatitis after steroid therapy. This result suggests that among the patients with autoimmune pancreatitis and decreased baseline CPI, intensive treatment such as multiple daily insulin injection will be needed even after improvements in pancreatic inflammation are obtained from steroid therapy.

Further, our study showed that a lower baseline BMI was associated with worse glycemic control. However, we consider a lower BMI to be a confounding factor for decreased CPI, because: (1) BMI and CPI showed a positive correlation in the present study (Figure 3); (2) several previous studies have shown that BMI correlates positively with fasting CPR in patients with type 2 diabetes mellitus[22,24].

Scores for predicting glycemic control

Figure 1 shows the numbers of patients and either the score for the time of diabetes mellitus onset and baseline BMI (Figure 1a) or the time of diabetes mellitus onset and baseline CPI (Figure 1b). The CPI values were missing for two cases in the Improved group, three cases in the Worsened group, and six cases in the Unchanged group. These cases were excluded from analysis.

Figure 2 shows box plots comparing scores among the three groups. The score comprising the time of diabetes mellitus onset and baseline BMI were significantly lower in the Worsened group than in the Improved and Unchanged groups (P < 0.01; Improved vs. Unchanged, P > 0.9; Improved vs. Worsened, P < 0.01; Unchanged vs. Worsened, P < 0.01) (Figure 2a). The score comprising the time of diabetes mellitus onset and baseline CPI tended to be lower in the Worsened group than in the Improved group (P < 0.01; Improved vs. Unchanged, P = 1.00; Improved vs. Worsened, P = 0.03; Unchanged vs. Worsened, P = 0.13) (Figure 2b).

Correlation between baseline BMI and baseline CPI

The correlation between baseline BMI and baseline CPI showed a correlation coefficient of 0.468 (P = 0.029; Figure 3).
| Table 3 | Steroid therapy and diabetes mellitus treatment for each group |
|--------|-------------------------------------------------|
|         | Improved (I) \((n = 10)\) | Unchanged (U) \((n = 10)\) | Worsened (W) \((n = 13)\) | \(P\) value |
| Steroid therapy | | | | |
| Period from symptom appearance to start of treatment (months) | 1.5 (1–2) | 1 (0.8–1) | 3.5 (1.5–6) | 0.18 |
| Initial dose (mg/kg body weight) | 0.5 | 0.5 | 0.6 | 0.12 |
| Maintenance dose (mg/day) | 5 | 5 | 5 | 0.1 |
| Period to maintenance dose (months) | 7.5 (7–9) | 10 (7–11) | 9 (6–12.5) | 0.76 |
| Dose at 12 months after initiation of PSL | | | | |
| Dose (mg/day) | 5 (2.5–7.5) | 5 (2.5–7.5) | 5 (2.5–15) | 0.34 |
| 2.5 mg/day | 1 (10%) | 1 (10%) | 1 (8%) | |
| 5 mg/day | 7 (70%) | 6 (60%) | 6 (46%) | |
| 7.5 mg/day | 2 (20%) | 3 (30%) | 3 (23%) | |
| 15 mg/day | 0 | 0 | 3 (23%) | |
| Total PSL dose up to 12 months after initiation of PSL (mg) | 3555 (3206–4878) | 3520 (3110–4005) | 4033 (3664–4351) | 0.5 |
| DM treatment | | | | |
| At time of AIP diagnosis | | | | |
| No treatment | 9 (90%) | 9 (90%) | 5 (38%) | <0.01 |
| OHA | 1 (10%) | 1 (10%) | 8 (62%) | <0.01 |
| Insulin | 0 | 0 | 0 | <0.01 |
| Just before initiation of PSL | | | | |
| No treatment | 0 | 8 (80%) | 5 (38%) | <0.01 |
| OHA | 1 (10%) | 2 (20%) | 5 (38%) | 0.04 |
| Insulin | 9 (90%) | 0 | 3 (23%) | <0.01 |
| At 12 months after initiation of PSL | | | | |
| No treatment | 5 (50%) | 8 (80%) | 1 (8%) | <0.01 |
| OHA | 3 (30%) | 2 (20%) | 3 (23%) | 0.58 |
| Insulin | 2 (20%) | 0 | 9 (69%) | 0.01 |

Data are presented as median (interquartile range) or number (%). AIP, autoimmune pancreatitis; DM, diabetes mellitus; OHA, oral hypoglycemic agent; PSL, prednisolone.
On the other hand, previous reports have shown that the time of diabetes mellitus onset and pancreatic atrophy after steroid therapy are factors affecting glycemic control\textsuperscript{2,4,5,9–11}, whereas our study found no such associations. The actual cause of this discrepancy is unknown, but we suppose that the small sample size may have affected the present results. Further investigation of a larger cohort is needed.

In addition, steroid dose, pattern and degree of pancreatic swelling, and the degree of elevated pancreatic enzymes at the time of diagnosis of autoimmune pancreatitis were not associated with glycemic control in the present study. In other words, these parameters cannot be used to predict future glycemic control after treatment with prednisolone.

According to the above mentioned results and previous findings, we created two scores for potentially predicting glycemic control, because: (1) the baseline CPI was not evaluated in some patients; (2) BMI is more convenient to check than CPI; (3) our study showed that BMI and CPI were positively correlated. In this study, both scores were significantly lower in the Worsened group. These scores are therefore useful to predict future glycemic control in patients with diabetes and autoimmune pancreatitis treated using prednisolone. No previous reports have examined the use of scores as meaningful values to compare disparate and qualitative data uniformly as quantitative data. Increasing the number of cases and generalizing the score would provide an objective, clinically useful, indicator. Further validation is needed, and future interventional studies need to be considered for cases showing lower scores.

Currently, worsening diabetes mellitus alone is not considered to be an indication for steroid therapy for autoimmune pancreatitis\textsuperscript{25}, but active treatment may be considered in patients who show improvement of diabetes mellitus on steroid therapy. Furthermore, such patients were more likely to be able
to discontinue insulin in the future, according to the present results. Since AIP-induced diabetes mellitus worsens mainly due to pancreatic endocrine dysfunction, the early introduction of insulin should be considered from the perspective of pancreatic protection.

Worsening of glycemic control in patients with autoimmune pancreatitis may have two possible causes: (1) AIP-induced mechanisms; (2) steroid-induced mechanisms.

AIP-induced mechanisms involve pancreatic endocrine dysfunction. Inflammation of the pancreas and fibrosis of exocrine glands cause ischemia and dysfunction of the islet cells, resulting in insufficient insulin secretion.25,9,26,27

Steroid-induced mechanisms include increased insulin resistance, decreased insulin secretion, increased glycogenesis, and amino acid release.28,29

The improvement of glycemic control after steroid therapy is reported to be due to improvements in pancreatic endocrine function. In detail, steroid therapy improves disturbances in the outflow of pancreatic juice due to the disappearance of inflammatory cells and fibroblasts, improves excessive cytokine production, and reduces apoptosis and regeneration of the islets of Langerhans.9,27,30

Through this study, we suggest three patterns in the course of diabetes mellitus complicated by autoimmune pancreatitis. The first involves cases in which glycemic control improves after steroid therapy. In the typical case, diabetes mellitus is worsened by autoimmune pancreatitis (with AIP and diabetes mellitus having occurred at the same time). In addition, BMI and insulin secretion are maintained. Glycemic control improves as a result of improvement of pancreatic endocrine function by steroid therapy. The second involves cases in which glycemic control worsened after steroid therapy. In the typical case, diabetes mellitus is present before the onset of autoimmune pancreatitis. Furthermore, BMI and insulin secretion are decreased. The improvement of pancreatic endocrine function after steroid therapy is insufficient to overcome the increased insulin resistance. As a result, glycemic control worsens. The third pattern is so-called ‘steroidal diabetes’. In the typical case, the patient displays good glycemic control at the diagnosis of autoimmune pancreatitis, which is temporarily aggravated by steroids. However, as a result, the reduction in steroid dose improves glycemic control to the same level as at the diagnosis of autoimmune pancreatitis. The BMI and insulin secretion are thus maintained.

Several limitations to this study should be considered. First, this study was a single-center, retrospective study. Due to the small number of cases, we judged that introduction of multivariate analysis was not statistically appropriate. More cases need to be accumulated in the future. Second, CPI data were missing for many patients in the Unchanged group. Since most of the Unchanged group had steroidal diabetes and good glycemic control both before and 12 months after initiation of prednisolone, fasting CPR was not measured. Third, treatment of diabetes mellitus and blood glucose levels can affect CPI. Fourth, insulin resistance after steroid use was not assessed in this study. An indicator of insulin resistance is HOMA-R (HOMA-R = fasting blood glucose [mg/dL] × fasting insulin level [μU/mL]/405). However, accurate insulin levels cannot be assessed in patients who are using insulin because the blood concentration of the drug is detected as the insulin level. In this study, insulin levels could not be measured due to the large number of insulin users. Fifth, some patients were not on a maintenance dose of steroids at 12 months after starting prednisolone. Non-maintenance dose cases were also included in the study, since the steroid dose is related to the disease activity of autoimmune pancreatitis, which in turn affects the course of diabetes. Sixth, regarding the determination of cutoff values for BMI and CPI in scoring, BMI was set at 22 kg/m², as recommended by the Japan Society for the Study of Obesity as an appropriate weight. CPI was set at 1.1 because CPI values of 1.0–1.1 have been reported to determine the need for insulin therapy.15,16,21 In the future, cases will be accumulated and cutoff values will be set to allow for more accurate determination.

In conclusion, in patients treated with prednisolone for autoimmune pancreatitis, those with a lower baseline BMI and decreased baseline CPI were more likely to experience worse glycemic control after treatment. In addition to the time of onset of diabetes mellitus, baseline BMI and baseline CPI are likely factors affecting glycemic control in patients with diabetes mellitus complicated by autoimmune pancreatitis.

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DISCLOSURE
The authors declare no conflict of interest.
This study was conducted in accordance with the Declaration of Helsinki.
Approval date of registry and the registration no. of the study/trial: This study was conducted after receiving approval from the Research Ethics Committee at Toranomon Hospital (approval no. 2020, approved on March 19, 2021).
Informed consent: N/A.
Animal studies: N/A.

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