ORIGINAL ARTICLE

Gut and Liver, Vol. 6, No. 4, October 2012, pp. 501-504

Short and Long-Term Outcomes of Diabetes Mellitus in Patients with Autoimmune Pancreatitis after Steroid Therapy

Yuji Miyamoto*,†, Terumi Kamisawa*, Taku Tabata*, Seiichi Hara*, Sawako Kuruma*, Kazuro Chiba*, Yoshihiko Inaba*, Go Kuwata*, Takashi Fujiwara*, Hideto Egashira*, Koichi Koizumi*, Ryoko Sekiya*, Junko Fujiwara‡, Takeo Arakawa‡, Kumiko Momma‡, and Toru Asano†

Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, †Department of Internal Medicine, Tokyo Metropolitan Bokutoh Hospital, and ‡Department of Endoscopy, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Background/Aims: Autoimmune pancreatitis (AIP) is frequently associated with diabetes mellitus (DM). This study evaluated the effect of steroid therapy on the course of DM in AIP. **Methods:** Glucose tolerance was examined in 69 patients with AIP. DM onset was classified as either a simultaneous onset with AIP or an exacerbation of pre-existing DM. Based on the changes in the HbA1c levels and insulin dose, the responses of DM to steroids were classified as improved, no change, or worsened. **Results:** Thirty (46%) patients were diagnosed as having DM (simultaneous onset, n=17; pre-existing, n=13). Three months after starting the steroid treatment, the DM improved in 13 (54%) of 24 DM patients. The DM improved in 55%, had no change in 36%, and worsened in 9% of the 11 simultaneous onset DM patients, and it improved in 54%, had no change in 31%, and worsened in 15% of the 13 pre-existing DM patients. At approximately 3 years after starting the steroid treatment, the DM improved in 10 (63%) of 16 patients. The pancreatic exocrine function improved in parallel with the changes in the DM in seven patients. **Conclusions:** Because approximately 60% of DM associated with AIP is responsive to steroids in the short- and long-terms, marked DM associated with AIP appears to be an indication for steroid therapy. **(Gut Liver 2012;6:501-504)**

Key Words: Autoimmune pancreatitis; Diabetes mellitus; Steroids

INTRODUCTION

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology. It is characterized radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct; serologically by elevation of serum IgG4 levels; pathologically by lymphoplasmacytic sclerosing pancreatitis; and clinically by responsiveness to steroid.[1,2]

Diabetes mellitus (DM) is sometimes associated with AIP. DM is diagnosed simultaneously with onset of AIP in some cases, and pre-existing DM is exacerbated in some cases. DM also improves after steroid therapy in some cases. Although there are some published reports on the short-term effect of steroid therapy on the course of DM,[3-9] the long-term outcome of DM after steroid therapy in AIP patients remains unknown. This study aimed to compare the course of the two different onset types of DM in AIP patients after steroid therapy and clarify its long-term outcome.

MATERIALS AND METHODS

A total of 69 patients with AIP in the Tokyo Metropolitan Komagome Hospital from 1992 to 2011 were retrospectively examined. The diagnosis of AIP was made according to the Asian diagnostic criteria for AIP.[10] To make the diagnosis of AIP, the imaging criterion, consisting of enlargement of the pancreas and irregular narrowing of the main pancreatic duct, must be present, together with the serological criterion (elevated serum IgG or IgG4 levels, or detection of autoantibodies) and/or the histopathological criterion (lymphoplasmacytic sclerosing pancreatitis). AIP can also be diagnosed with fulfillment of both the imaging criterion and a good response to steroid treatment.

DM was diagnosed according to the following criteria:[11] 1) early-morning fasting serum glucose ≥126 mg/dL; 2) serum glucose 2 hours after the oral glucose tolerance test ≥200 mg/dL; 3) casual serum glucose ≥200 mg/dL; and 4) glycosylated

Correspondence to: Terumi Kamisawa
Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo, Tokyo 113-8677, Japan
Tel: +81-3-3823-2101, Fax: +81-3-3824-1552, E-mail: kamisawa@cick.jp
Received on January 6, 2012. Accepted on February 4, 2012.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2012.6.4.501

hemoglobin values (HbA1c) ≥6.5%. One of the first three items and item 4 lead to the diagnosis of diabetes. DM onset was divided into simultaneous onset with AIP and exacerbation of pre-existing DM. Clinical findings, including age at diagnosis, sex, body mass index (BMI), alcohol intake, and obstructive jaundice as an initial symptom, and pancreatic imaging findings (diffuse or segmental enlargement) on computed tomography were compared between AIP patients with and without DM.

Before steroid therapy, blood glucose levels were usually controlled using insulin in patients with DM. Steroid therapy was started at 0.6 mg/kg/day of prednisolone and gradually tapered to a maintenance dose over a period of about 3 months. Biochemical and serological blood tests, such as liver enzymes and IgG4 levels, and imaging tests, such as CT, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography, were performed periodically after steroid therapy was started. To prevent relapse, maintenance therapy, usually with 5 mg/day of prednisolone, was performed for 1 to 3 years.[12,13] Changes in DM patients' glucose tolerance were examined at 3 months, 1 year, and about 3 years after starting steroid therapy. A decreased dose of insulin with a decrease of HbA1c by more than 0.5% in patients treated with insulin or a decrease of HbA1c by more than 0.5% in patients treated with diet therapy or oral antidiabetic agents was judged as improvement of glucose tolerance after steroid therapy. An increased dose of insulin or an increased HbA1c level by more than 0.5% percentage points in patients treated without insulin was considered an exacerbation. The other patterns were judged as no change.

N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion tests were performed to assess pancreatic exocrine function before and 3 months after steroid therapy in 11 AIP patients with DM. The normal limit of BT-PABA was ≥70%, and an increase >10% points on the BT-PABA test after steroid therapy was considered improvement. This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital.

Statistical analysis used Fisher's exact test and Mann-Whitney U test. A $p<0.05$ was considered a significant difference.

RESULTS

Thirty (46%) of 69 AIP patients were diagnosed as having DM. In 17 patients, the diagnoses of DM and AIP were made simultaneously, whereas the other 13 showed exacerbation of pre-existing DM with onset of AIP. Anti-gultamic acid decarboxylase antibody was negative in the 12 patients with DM in whom this test was performed. There were no significant differences in the age at diagnosis of AIP, male-to-female ratio, BMI, alcohol intake, and presence of obstructive jaundice between patients with and without DM (Table 1).

Twenty-four AIP patients with DM were treated with steroid, and all of them responded well to steroid radiologically and serologically. Three months after starting steroid therapy, DM improved in 13 (54%) of 24 DM patients. DM was improved in six (55%), no change in four (36%) and worse in one (9%) of 11

Table 1. Clinical Characteristics and Radiological Findings of the Study Population

Characteristic	All patients	Diabetes (+)	Diabetes (-)	p-value
No.	69	30	39	
Age, median, yr	64.7	65.5	62.7	NS
Male/Female	50/19	22/8	28/11	NS
BMI, median, kg/m^2	22.3	22.5	21.9	NS
Alcohol intake, +, n (%)		4 (13)	7 (18)	NS
Jaundice, +, n (%)		22 (73)	22 (56)	NS
Type, diffuse/segmental (%)	35/34 (51)	14/16 (47)	21/18 (54)	NS

Data are presented as median or number (%).
NS, not significant.

Table 2. The Effect of Steroid Therapy on the Clinical Course of Diabetes by the Type of Onset in the Patients with at Least 3 Months of Treatment (n=24)

Onset of diabetes	Course of diabetes		
	Improved	No change	Worse
Simultaneous onset (n=11)	6 (55)	4 (36)	1 (9)
Pre-existing (n=13)	7 (54)	4 (31)	2 (15)

Data are presented as number (%).

Table 3. Effect of Steroid Therapy in the Patients with at Least 3 Years of Treatment on the Clinical Course of Diabetes by Type of Onset (n=16)

Onset of diabetes	Course of diabetes		
	Improved	No change	Worse
Simultaneous onset (n=6)	4 (66)	2 (34)	0
Pre-existing (n=10)	6 (60)	4 (40)	0

Data are presented as number (%).

Table 4. Comparison of Pancreatic Endocrine and Exocrine Functions before and after the Steroid Therapy (n=11)

Course of diabetes	Pancreatic exocrine function		
	Improved	No change	Worse
Improved	7	0	0
No change	0	2	1
Worse	1	0	0

Data are presented as number.

simultaneous onset DM patients, and it was improved in seven (54%), no change in four (31%), and worse in two (15%) of 13 pre-existing DM patients (Table 2).

At about 3 years after starting steroid therapy, DM improved in 10 (63%) of 16 DM patients. DM was improved in four (66%), including two patients in whom insulin became unnecessary, and no change was seen in two (34%) of six simultaneous onset DM patients, and it was improved in six (60%), with no change in four (40%) of 10 pre-existing DM patients (Table 3). Each simultaneous onset and pre-existing DM patients who was worse after 3 months of steroid therapy was improved 3 years later.

Pancreatic exocrine function was reduced in 10 (91%) of 11 AIP patients with DM. In all seven patients whose glucose tolerance improved after steroid therapy, pancreatic exocrine function also improved. In three patients whose glucose tolerance was not changed after steroid therapy, pancreatic exocrine function was not changed in two and worse in one. In one patient whose glucose tolerance was worse after steroid therapy, pancreatic exocrine function improved (Table 4).

DISCUSSION

DM was seen in 30 (46%) of 69 AIP patients in this series. Of the 30 DM patients, 57% were diagnosed as having DM simultaneously with the onset of AIP, and the remaining 43% showed exacerbation of pre-existing DM with onset of AIP. According to a nationwide survey in Japan,[8] DM was present in 67% of 167 AIP patients, and about half of the patients started DM simultaneously with AIP, and one-third of the patients had DM before AIP. A lower incidence of DM in AIP patients in the present study might be due to the fact that DM was diagnosed strictly according to the diagnostic criteria of DM. Onset of DM during the course of AIP was similar to that reported in the nationwide survey.

AIP responds well to steroid therapy symptomatically, radiologically, and serologically. Pancreatic enlargement began to improve 1 to 2 weeks after the start of steroid therapy, and the pancreas returned to almost normal size after 3 to 4 weeks. If a biliary stent is placed when biliary strictures are present, the stent can be removed 1 to 2 months after starting steroid. Serum IgG4 levels decreased in all cases after steroid administration.[12,14]

It has been reported that DM associated with AIP sometimes improved after steroid therapy. Nishino *et al*.[7] reported that the HbA1c level improved in 30% of 10 AIP patients with DM after steroid therapy. According to the report of Ito *et al*.,[6] in seven AIP patients with simultaneous onset DM, five (71%) showed improvement of DM control, and two (29%) showed no change after steroid therapy; and in four AIP patients with early-onset DM, three (75%) showed aggravation of DM, and one (25%) showed no change. According to the National survey,[8] in the 31 AIP patients with simultaneous onset DM, 17 (55%) showed improvement of DM, nine (29%) showed no change, and five (16%) showed worsening after steroid therapy; and in 22 AIP patients with early-onset DM, eight (36%) showed improvement, 10 (45%) showed no change, and four (18%) showed worsening. In the present study, at 3 months after starting steroid, 55% showed improvement, 36% showed no change, and 9% showed worsening of the 11 simultaneous onset DM patients, whereas it was improved in 54%, no change in 31%, and worse in 15% of 13 pre-existing DM patients. From these data, it can be seen that more than half of simultaneous onset DM patients improved after steroid therapy. Although pre-existing DM showed less responsiveness to steroid than simultaneous onset DM, some patients with steroid-responsive pre-existing DM might have had subclinical AIP.

There are few data about long-term changes in DM associated with AIP, and the present study may be the first reporting such changes. At about 3 years after starting steroid therapy, DM improved in 63% of 16 DM patients, although the incidence of improvement was 54% at 3 months. A fair number of DM associated with AIP appears to respond well to steroid over the short- and long-terms, although 13% showed worsening of DM control at 3 months after starting steroid. Each simultaneous onset and pre-existing DM patients who showed worsening at 3 months after steroid improved 3 years later. Even though the negative effect of steroid to counter the effect of insulin may be greater in some cases in the short-term, the long-term positive effect of steroid therapy on glucose tolerance and pancreatic inflammation might be greater in such cases.

The mechanism of pancreatic endocrine dysfunction and its recovery are undefined at present. Histopathologically, dense infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis is seen in the pancreas, and ectopic expression of the MHC class II molecule is seen in pancreatic cells. Rapid inflammation and fibrosis may induce reduction in blood flow in the exocrine pancreas, resulting in ischemia of islet cells, which causes dysfunction of hormone secretion. It is also estimated that elevated cytokine production and fibroblast proliferation occurs in the pancreas. The steroid therapy inactivates inflammatory cells and fibroblast function, and it is estimated that the functional disorder is improved by control of a series of autoimmune mechanisms, including cytokine production.[15]

Nishino *et al*.[7] reported that the BT-PABA test showed reduced pancreatic exocrine function in six (67%) of nine AIP pa-

tients, and it improved in three (50%) after steroid therapy. According to a study of Ito *et al*.[5] of pancreatic exocrine function in AIP using the secretin test, 92% of 12 AIP patients showed reduction in volume and amylase output, but a reduction in bicarbonate secretion was observed in only 42%, whereas a reduction in bicarbonate secretion was observed in all 25 patients with ordinary chronic pancreatitis. They explained this discrepancy based on the fact that most of the basement membrane where pancreas progenitor cells exist was preserved in AIP patients, whereas the basement membrane was destroyed in chronic pancreatitis. In the present series, pancreatic exocrine function was reduced in 91% of 11 AIP patients with DM, and in all seven patients whose glucose tolerance improved after steroid therapy, pancreatic exocrine function also improved. Given that pancreatic exocrine and endocrine function improved in parallel, initiation of steroid therapy in the early stage when pancreatic islets and the basement membrane are preserved appears to be important. Although the major indication for steroid therapy for AIP is clinical symptoms such as obstructive jaundice,[12,13] marked DM requiring insulin associated with AIP also appears to be an indication for steroid therapy.

In conclusion, about half of AIP patients had DM. Since around 60% of DM associated with AIP is responsive to steroid in the short- and long-terms, marked DM associated with AIP appears to be an additional indication for steroid therapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported in part by the Research Committee of Intractable Pancreatic Diseases (Principal investigator, Tooru Shimosegawa) provided by the Ministry of Health, Labour, and Welfare of Japan.

REFERENCES

1. Okazaki K, Kawa S, Kamisawa T, et al. Japanese clinical guidelines for autoimmune pancreatitis. Pancreas 2009;38:849-866.
2. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010;7:401-409.
3. Tanaka S, Kobayashi T, Nakanishi K, et al. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. Lancet 2000;356:910-911.
4. Kamisawa T, Egawa N, Inokuma S, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. Pancreas 2003;27:235-238.
5. Ito T, Kawabe K, Arita Y, et al. Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis. Pancreas 2007;34:254-259.
6. Ito T, Nishimori I, Inoue N, et al. Treatment for autoimmune pancreatitis: consensus on the treatment for patients with autoimmune pancreatitis in Japan. J Gastroenterol 2007;42 Suppl 18:50-58.
7. Nishino T, Toki F, Oyama H, Shimizu K, Shiratori K. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med 2006;45:497-501.
8. Nishimori I, Tamakoshi A, Kawa S, et al. Influence of steroid therapy on the course of diabetes mellitus in patients with autoimmune pancreatitis: findings from a nationwide survey in Japan. Pancreas 2006;32:244-248.
9. Frulloni L, Scattolini C, Katsotourchi AM, et al. Exocrine and endocrine pancreatic function in 21 patients suffering from autoimmune pancreatitis before and after steroid treatment. Pancreatology 2010;10:129-133.
10. Otsuki M, Chung JB, Okazaki K, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol 2008;43:403-408.
11. Seino Y, Nanjo K, Tajima N, et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus: the Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Diabetol Int 2010;1:2-20.
12. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut 2009;58:1504-1507.
13. Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M. Japanese consensus guidelines for management of autoimmune pancreatitis: III. treatment and prognosis of AIP. J Gastroenterol 2010;45:471-477.
14. Kamisawa T, Takuma K, Hara S, et al. Management strategies for autoimmune pancreatitis. Expert Opin Pharmacother 2011;12:2149-2159.
15. Tanaka S, Kobayashi T, Nakanishi K, et al. Evidence of primary beta-cell destruction by T-cells and beta-cell differentiation from pancreatic ductal cells in diabetes associated with active autoimmune chronic pancreatitis. Diabetes Care 2001;24:1661-1667.