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Pancreatic diabetes in a follow-up survey of chronic pancreatitis in Japan

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Background. We aimed to determine the cumulative rate of diabetes mellitus (DM) and the risk factors for DM in patients with chronic pancreatitis (CP) in Japan. ***Methods.*** We conducted a follow-up survey of CP in 2002 in patients registered as having CP in 1994, and confirmed 656 patients to be checked in regard to the survey items concerning diabetes. We analyzed the cumulative rate of DM and the risk factors for DM over an 8-year follow up period. ***Results.*** In 1994, 35.1% of 656 CP patients had DM, and the incidence of diabetes had increased to 50.4% in 2002. Of 418 patients without diabetes in 1994, 28.9% (121/418) were newly diagnosed with DM in 2002. Alcoholic CP was the most common type of CP in patients with newly developed diabetes, accounting for 67.8%. The incidence of DM was highest in those with alcoholic CP (34.3%) followed by idiopathic CP (23.0%). The risk of diabetes increased 1.32-fold after the onset of pancreatic calcification. Of 121 patients with newly diagnosed DM in 2002, 37 (30.6%) had pancreatic stones in 1994 and 49 (40.5%) had a stone in 2002. The highest incidence of newly diagnosed DM was observed in patients with continuous alcoholic intake (40.9%). Patients treated with camostat mesilate developed DM less frequently than those without camostat mesilate. ***Conclusions.*** The present study showed that the incidence of DM in patients with CP increased with time. Of 418 CP patients without DM in 1994, 28.9% developed DM over a period of 8 years. Continuous alcoholic intake aggravated CP and increased the risk of DM in those with CP.

Key words: chronic pancreatitis, pancreatic diabetes, nationwide survey, follow-up study

Introduction

Pancreatic diabetes, which is diabetes mellitus (DM) that develops from the impairment of pancreatic endocrine function due to the progression of pancreatic diseases, is closely related to the progression of the primary pancreatic disease such as pancreatitis, pancreatic surgery, or pancreatic carcinoma.[1–3] The epidemiological and clinical manifestations of pancreatic diabetes are often different from those of primary diabetes, because the synthesis and secretion of insulin from β-cells as well as that of glucagon from α-cells are affected by the primary disease.[2–5] Previous studies have investigated the pathophysiology, clinical features, and treatment of DM resulting from chronic pancreatitis (CP).[3,6–8] However, there is little information on the long-term prognosis of pancreatic diabetes in patients with CP.[6,9] In the present study, we investigated the clinical features of patients with CP who were alive in 2002 after being surveyed in 1995 and followed-up in 1998 and 2003.[10,11]

Patients and methods

Among the patients with CP who were registered in 1994 and were investigated in the secondary survey conducted in 1995 by The Research Committee of Intractable Diseases of the Pancreas in Japan, those patients who were also reviewed in 1998 were mainly investigated in 2003.[10,11] Of the 665 patients with CP who were alive in 2002, 656 patients (501 men and 155 women, mean 65.2 years, age range 24–94 years) who were checked in the survey items concerning diabetes were analyzed.

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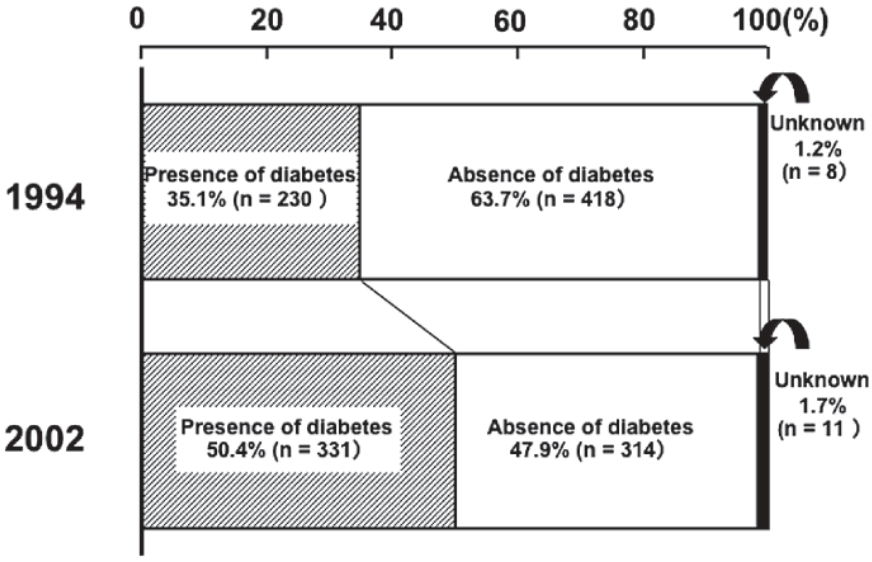

Fig. 1. Incidence of diabetes mellitus in 1994 and 2002 in 656 patients with chronic pancreatitis

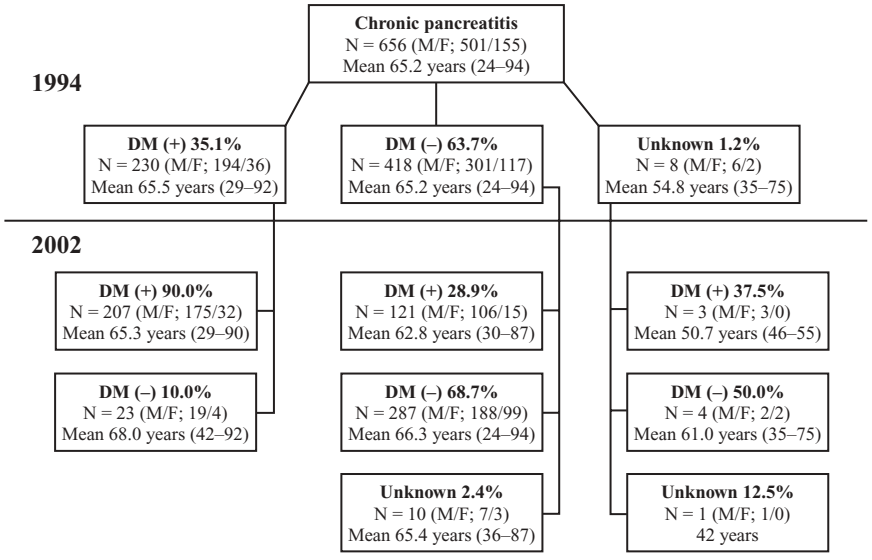

Fig. 2. Incidence of diabetes mellitus in 656 patients with chronic pancreatitis in 1994 and 2002. Of the 656 patients with CP, 230 patients (35.1%) had diabetes mellitus in 1994. The number of patients with diabetes mellitus had increased to 331 (50.4%) in 2002. Of the 230 patients who had diabetes mellitus in 1994, as many as 207 (90%) patients still suffered from pancreatic diabetes in 2002, but 23 (10.0%) patients showed improvement in diabetes. Of 418 patients without diabetes mellitus in 1994, 121 (28.9%) were newly diagnosed with diabetes mellitus in 2002. *M/F*, number of males and females; *mean*, mean age; *figures in parentheses*, age range

Consideration of ethics issues

This research was conducted in accordance with the Ethical Guidelines for Epidemiological Research (enacted on July 1, 2002, by the Ministry of Education, Culture and Sports, Science and Technology and the Ministry of Health, Labour, and Welfare in Japan), after being approved by the ethics committee of the University of Occupational and Environmental Health to which the lead researcher of this study belongs.

Results

Incidence of diabetes mellitus in patients with chronic pancreatitis

Of the 656 patients with CP, 230 patients (35.1%) had DM in 1994, and the number of patients with DM had increased to 331 (50.4%) in 2002 (Fig. 1). Of the 230 patients who had DM in 1994, as many as 207 (90%) patients still suffered from pancreatic diabetes in 2002, while 23 (10.0%) patients showed improvement of diabetes (Fig. 2). On the other hand, 121 (28.9%) of the 418 patients without DM in 1994 were newly diagnosed with diabetes in 2002 (Fig. 2).

Etiology of chronic pancreatitis and risk factors for diabetes mellitus

We examined the etiology of CP, the incidence of pancreatic stones, and alcohol consumption in the 121 patients who had normal glucose tolerance in 1994, but had developed DM over the 8-year follow up.

Etiology of chronic pancreatitis

The distribution of CP by etiology among the 121 patients is shown in Fig. 3. Alcoholic CP was the most

common etiology, followed by idiopathic CP, accounting for 67.8% and 25.6% of the cases, respectively. Two miscellaneous cases were reported; one was hereditary pancreatitis and the other was intraductal papillary mucinous neoplasm (IPMN). The incidence of DM by etiology in the 418 patients with CP who were without glucose intolerance in 1994, but who had developed DM in 2002 is shown in Fig. 4. The highest rate of appearance of DM 8 years after the diagnosis of CP was in patients with alcoholic CP, accounting for 34.3% (82/239) of the cases (Fig. 4); the cumulative risk of alcoholic CP to develop DM over the 8 years was higher than that in patients with nonalcoholic CP, which accounted for 21.7% (39/179).

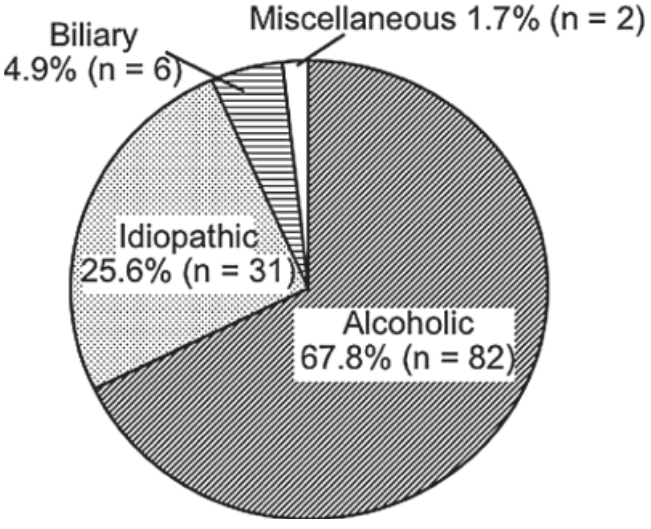

Fig. 3. Etiology of diabetes mellitus in the 121 patients with normal glucose tolerance in 1994 but who were newly diagnosed with diabetes mellitus in 2002

Prevalence of pancreatic stones and risk of pancreatic diabetes after onset of pancreatic calcification

Pancreatic stones were detected in 37 of the 121 CP patients (30.6%) in 1994, and in 49 patients (40.5%) in total in 2002. Of 418 patients with chronic pancreatitis who were without DM in 1994, 408 patients could be analyzed with or without DM in 2002. Over the 8-year follow up period, pancreatic diabetes developed in 49 of 139 (35.3%) CP patients with pancreatic calcification, and in 72 of 269 (26.7%) CP patients without pancreatic calcification, indicating that the onset of pancreatic calcification resulted in a 1.32-fold increase in the risk of pancreatic diabetes.

Alcohol consumption

Of the 121 patients with CP who did not suffer from DM in 1994 but who had developed DM in 2002, 52 (43.0%) patients continued drinking alcohol. Of the 287 CP patients with normal glucose tolerance both in 1994 and 2002, only 26.1 % continued drinking (Fig. 5).

Of 408 CP patients with normal glucose tolerance in 1994, 127 patients continued drinking alcohol, 81 patients quit drinking alcohol, and 149 patients were nondrinkers. In terms of alcohol consumption, the incidence of newly diagnosed DM was 40.9% (52/127), 30.8% (25/81), and 20.8% (31/149), respectively, in these three groups (Table 1).

Medications for diabetes and chronic pancreatitis

Of 408 CP patients with normal glucose tolerance in 1994, 287 had normal glucose tolerance in 2002, whereas 121 patients were diagnosed with DM in 2002. The frequency of medication with camostat mesilate, with or without digestive enzyme, was higher in patients who continued to show normal glucose tolerance compared

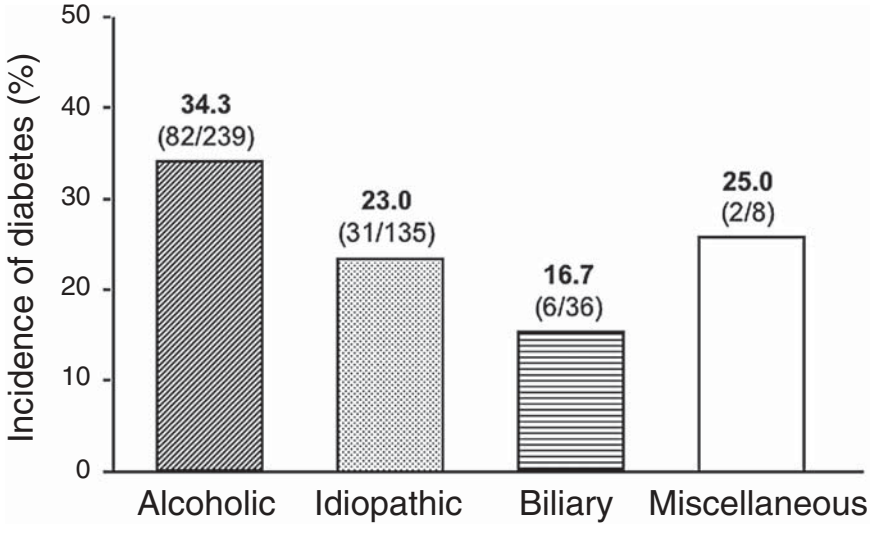

Fig. 4. Incidence of diabetes mellitus by each etiology in 418 patients with chronic pancreatitis who were without diabetes in 1994. Of these 418 patients, 121 were newly diagnosed with diabetes mellitus in 2002

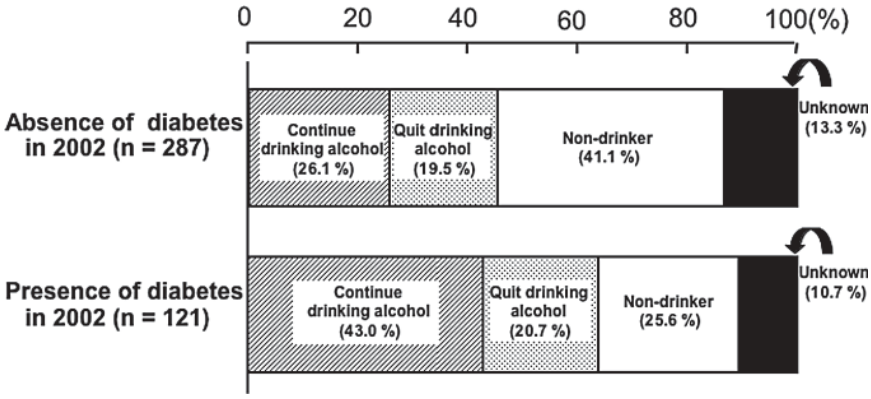

Fig. 5. Status of alcohol drinking in patients with chronic pancreatitis and normal glucose tolerance in both 1994 and 2002 (*top bars*) and this status in those who developed diabetes mellitus in 2002 (*bottom bars*)

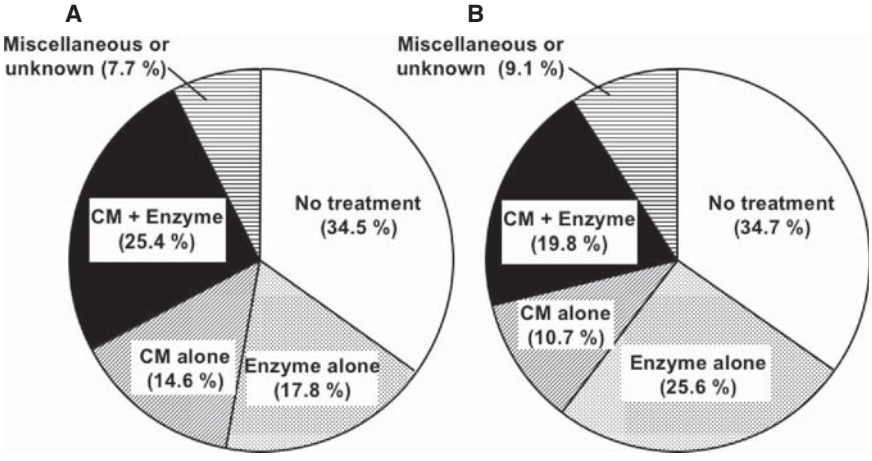

Fig. 6A,B. Treatment used for chronic pancreatitis. **A** Patients with chronic pancreatitis without diabetes mellitus in both 1994 and 2002 ($n = 287$). **B** Patients with chronic pancreatitis who were without diabetes mellitus in 1994 but who were newly diagnosed with diabetes mellitus in 2002 ($n = 121$). *CM*, camostat mesilate; *enzyme*, digestive enzyme

Table 1. Incidence of newly diagnosed diabetes mellitus in patients with chronic pancreatitis who had normal glucose tolerance in 1994, in terms of alcohol consumption

Newly diagnosed diabetes in 2002	Continue drinking alcohol ($n = 127$)	Quit drinking alcohol ($n = 81$)	Nondrinker ($n = 149$)	Unknown ($n = 51$)
Yes	52 (40.9%)	25 (30.8%)	31 (20.8%)	13 (25.5%)
No	75 (59.1%)	56 (69.2%)	118 (79.2%)	38 (74.5%)

Of the 408 chronic pancreatitis patients with normal glucose tolerance in 1994, 127 patients continued drinking alcohol, 81 patients quit drinking alcohol, and 149 patients were nondrinkers. The incidence of newly diagnosed diabetes mellitus in these three groups was 40.9%, 30.8%, and 20.8%, respectively

with those who developed DM (Fig. 6). Of the 121 patients who developed diabetes, 37 (30.5%) patients were treated with camostat mesilate with or without digestive enzyme, whereas 115 of the 287 (40.0%) patients who continued to exhibit normal glucose tolerance were treated with camostat mesilate with or without digestive enzyme. The incidence of newly diagnosed DM was lower in patients treated with camostat mesilate (24.3%) than in patients without camostat mesilate (32.7%; Table 2).

Of the 210 patients who were diagnosed with diabetes both in 1994 and 2002, 129 (61.4%) required insulin treatment (Fig. 7). On the other hand, only 42 of the 121 (34.7%) patients with CP who were newly diagnosed with DM in 1994 required treatment with insulin.

Discussion

CP is a chronic inflammatory disease characterized mainly by irreversible pancreatic morphological changes with progressive impairment of pancreatic exocrine and endocrine functions.[12–14] Typically, the first clinical manifestations of CP consist of abdominal pain and tenderness, frequently followed by symptoms of exocrine and endocrine pancreatic insufficiency with disease progression.[15,16] With regard to the mechanism of the develop-

Table 2. Incidence of newly diagnosed diabetes mellitus in patients with chronic pancreatitis who had normal glucose tolerance in 1994, in terms of treatment used for chronic pancreatitis

Treatment used for chronic pancreatitis	Newly diagnosed diabetes in 2002 (Number)	Incidence of newly diagnosed diabetes (%)	Incidence of newly diagnosed diabetes with or without CM
CM + enzyme (n = 97)	24	24.7%	24.3%
CM alone (n = 55)	13	23.6%	(37/152)
Enzyme alone (n = 82)	31	37.8%	32.7%
No treatment (n = 141)	42	30.0%	(73/223)
Unknown (n = 33)	11	33.3%	

Of the 408 chronic pancreatitis patients with normal glucose tolerance in 1994, 97 patients were treated with camostat mesilate (CM) and digestive enzyme, 55 patients were treated with CM alone, 82 patients were treated with enzyme alone and 141 patients were without treatment. The incidence of newly diagnosed DM was 24.7%, 23.6%, 37.8%, and 30.0% in these four groups, respectively. The incidence of newly diagnosed DM was lower in patients treated with camostat mesilate (24.3%) than in patients without CM (32.7%)

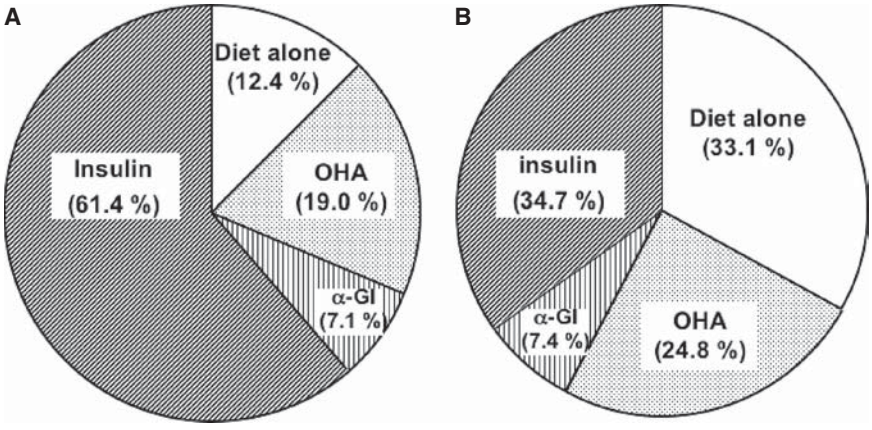

Fig. 7A,B. Treatment used for diabetes mellitus in patients with chronic pancreatitis. **A** Patients with chronic pancreatitis who were diagnosed with diabetes mellitus in both 1994 and 2002 (n = 210). **B** Patients who had chronic pancreatitis and normal glucose tolerance in 1994 but who were diagnosed with diabetes mellitus in 2002 (n = 121). *OHA*, Oral hypoglycemic agent; *α-GI*, α-glycosidase inhibitor

ment of diabetes in CP, the deficiency of insulin secretion (caused by reductions in both the number of islet cells and in their functional capacity), and the parallel spread of fibrosis inside the secretory part of the pancreas are considered to be the main causes.[17] In addition, impairment of circulation in islet cells, caused by reduced blood flow volume in the pancreas due to fibrosis, is also linked to the development of diabetes in CP.[18] Moreover, diabetes associated with CP is considered to be the result not only of impaired production of endogenous insulin, but also of insulin resistance.[19]

In the past, diabetes was known to occur as a complication of various pancreatic diseases. The incidence of diabetes in CP depends on several factors, such as etiology, the presence or absence of pancreatic calcification, and the duration of the disease.[1,6,20] With respect to patients with pancreatic calcification, it is reported that approximately 60%–70% of such patients have DM.[3,7,21] However, the number of patients with pancreatic diabetes caused by pancreatic diseases is less than 1% of all patients with diabetes.[22] Moreover, there are only few reports on the long-term prognosis of pancreatic diabetes among patients with CP.[6,9] Therefore, the present study focused on pancreatic diabetes in patients with CP who were followed up by the Research Committee of the Intractable Diseases of the Pancreas, and was financially supported by the Japanese Ministry of Health, Labour, and Welfare.

In 1994, 230 of 656 patients (35.1%) with CP were diagnosed with pancreatic diabetes. In 2002, however, the number of patients with pancreatic diabetes increased to 331 (50.4%). In addition, among the CP patients with normal glucose tolerance in 1994, 121 (28.9%) were newly diagnosed with diabetes in 2002. We divided the etiology in these 121 patients into alcoholic, idiopathic, and biliary, accounting for 67.8%, 25.6%, and 4.9% of the cases, respectively. This distribution of the etiology was almost the same as that found in a nationwide survey of CP.[11] Furthermore, the percentage of newly diagnosed diabetic patients with CP was 34.3%, 23.0%, and 16.7%, respectively, for alcoholic, idiopathic, and biliary etiologies. It has been reported that endocrine function is more disturbed in alcoholic CP than in nonalcoholic CP,[1,3] and that the incidence of overt diabetes was only 36.1% in nonalcoholic CP, compared with 53.7% in alcoholic CP.[3] Thus, the high ratio can be attributed to alcohol intake.

It has been reported that the secretion of both insulin and glucagon is disturbed more strongly in calcified CP than in noncalcified CP.[23] Indeed, pancreatic diabetes is

observed in 70% patients with calcified CP, whereas the development of pancreatic diabetes in noncalcified CP is only 30%.[6] In addition, Malka et al.[9] reported a more than threefold increase in the risk of diabetes after the onset of pancreatic calcification in a follow-up study of CP over a mean period of 7.7 years. In the present study, however, the incidence of pancreatic stone in the 121 patients with CP who were normoglycemic in 1994 but who were diagnosed with DM in 2002 was already 30.6% in 1994 but only 40.5% in 2002. Moreover, the risk of diabetes in Japan was increased approximately 1.32-fold after the onset of pancreatic calcification. It is unlikely, therefore, that the development of DM in CP is closely related to pancreatic stones.

In the present study, we showed that 67.8% of CP patients who were newly diagnosed with DM over an 8-year observation period had alcoholic CP and that 34.3% of those with alcoholic CP developed DM over the 8-year period. Moreover, 43.0% of patients with newly developed diabetes were continuous drinkers. Taken together, these data suggest that alcohol intake aggravates CP and increases the risk of development of DM in CP.

The frequency of appearance of DM in patients with CP treated with camostat mesilate was lower than that in those without such treatment. In this regard, we have recently shown that camostat mesilate can inhibit not only the proteolytic activity of trypsin but also the development of fibrosis in CP by inhibiting the generation of various cytokines from monocytes and the growth of pancreatic stellate cells.[24] These results, therefore, suggest that camostat mesilate, which is used clinically for the treatment of CP in Japan,[25] may inhibit the development of DM by suppressing the progression of CP.

Insulin treatment for the control of DM was provided to 34.7% (42/121) of the patients with newly developed diabetes. As for the patients who were diagnosed with diabetes in both 1994 and 2002, as many as 61.4% (129/210) received insulin treatment. Thus, the longer the duration of diabetes, the higher the number of patients who require insulin treatment. Investigation of the duration of diabetes after the development of CP will be necessary for more detailed analysis.

In conclusion, we have described an 8-year follow-up study of 656 patients with CP, extending from 1994 to 2002, and found that the incidence of DM increased from 35.1% in 1994 to 50.4% in 2002. Of the 418 patients without diabetes in 1994, 28.9% developed DM over the period of 8 years. Alcoholic CP is the most common type of CP for the development of DM. It seems that continuous alcoholic intake aggravates CP and increases the risk of DM in CP. Because the patients who could be analyzed over the 8-year follow-up may have been a group whose compliance to going to hospital regularly was better than the compliance of patients who dropped out of follow-up or those who died during the follow-up period, further investigation must be performed in order to clarify the incidence and the current status of treatment of pancreatic diabetes.

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