# 5 Pancreatic Endocrine and Exocrine Functions in Patients with Autoimmune Pancreatitis

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## Introduction

Autoimmune pancreatitis (AIP) is a distinctive type of pancreatitis, and it is considered that the pathogenesis of AIP involves autoimmune mechanisms [1–6]. Recently, AIP has been considered as a systemic disease because it is often accompanied by various extrapancreatic lesions including cholangitis, sialadenitis, retroperitoneal fibrosis, hilar lymphadenopathy, and chronic thyroiditis [7–11]. Furthermore, AIP is often associated with pancreatic exocrine and endocrine dysfunction. Recently, AIP is known to have two clinical and histological subtypes [12, 13], and the international consensus diagnostic criteria (ICDC) published in 2012 [14] enabled us to classify these subtypes into type 1 and type 2. Patients with type 1 AIP often show accompanying extrapancreatic lesions but seldom reveal abdominal pain. On the other hand, patients with type 2 AIP commonly have abdominal pain and sometimes accompany acute pancreatitis. In the present manuscript, we focus on the endocrine and exocrine functions associated with type 1 AIP according to the revised Japanese consensus guideline for management of AIP [15–17].

## Endocrine Dysfunction Associated with Type 1 AIP

Diabetes mellitus with pancreatic disorders (pancreatic diabetes) is closely related to the progression of a primary disease such as pancreatitis or pancreatic cancer because diabetes mellitus occurs due to pancreatic endocrine dysfunction caused by the progression of a pancreatic disorder [18–21]. From endocrinologic aspects, both insulin and glucagon synthesis/secretion are affected by the primary disease [20, 21]. Therefore, the pathology and clinical features of pancreatic diabetes are often different from those of types 1 and 2 diabetes, and its treatment method should be different [20].

A nationwide epidemiological survey on pancreatic diabetes to determine the incidence, pathology, clinical features, and current treatment status was conducted in Japan [22]. According to this survey, the causal factors of pancreatic diabetes were chronic pancreatitis (40.0 %), pancreatic cancer (24.6 %), pancreatectomy (10.2 %), acute pancreatitis (7.5 %), and AIP (6.1 %) (Table 5.1) [22]. On the other hand, 77.0 % of patients with AIP were reported to be associated with diabetes mellitus [23]. Studies by individual medical facilities reported that 83–88 % of the cases were associated with secretion dysfunction and 42–78 % with diabetes mellitus [11, 24, 25]. The diabetes mellitus accompanying AIP was analyzed in detail in the nationwide survey conducted in Japan in 2006 [26]. Among those AIP patients who sought

**Table 5.1** Prevalence of pancreatic diabetes by causal factor and relationship with onset of diabetes

| Etiology | Number of patients | (%) | Onset of diabetes secondary to pancreatic disorder (%) |
|---|---|---|---|
| Chronic pancreatitis | 684 | 40.0 | 46.3 |
| Acute pancreatitis | 129 | 7.5 | 47.6 |
| Autoimmune pancreatitis | 105 | 6.1 | 43.3 |
| Pancreatic injury | 13 | 0.8 | 66.7 |
| Pancreatic cancer | 421 | 24.6 | 33.7 |
| Pancreatic endocrine tumor | 18 | 1.1 | 38.9 |
| Pancreatic cystic tumor | 117 | 6.8 | 38.6 |
| Other tumors | 15 | 0.9 | 60.0 |
| After pancreatectomy | 174 | 10.2 | 65.2 |
| Pancreatic hemochromatosis | 8 | 0.5 | 71.4 |
| Pancreatic hypoplasia | 1 | 0.1 | 0 |
| Others | 25 | 1.5 | 45.8 |
| Total | 1,710 | 100 | 44.5 |

Modified from Ref. [22]

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medical attention during the 1-year period of 2002, 66.5 % of cases were found to be associated with diabetes mellitus; of those, 33.3 % had diabetes mellitus prior to the onset of AIP, and 51.6 % started developing diabetes mellitus around the same time as the onset of pancreatitis. Among those patients having diabetes mellitus, 14 % developed diabetes after steroid treatment [26], suggesting that such diabetes may be caused by long-term steroid treatment. There are some cases where pancreatic endocrine dysfunction was improved by steroid treatment; however, since not all cases improved, it can be stated that medical conditions that have progressed far enough to cause some degree of organic change cannot be reversed.

Previously, we demonstrated for the first time that endocrine pancreas showed the dysfunction of both insulin secretion from beta cells and glucagon secretion from alpha cells in patients with AIP [27]. These findings mean that endocrine dysfunction in AIP is a secondary pancreatic diabetes mellitus, unlike primary diabetes mellitus, in which glucagon secretion is preserved [27]. Furthermore, the results of histological findings in AIP showed markedly that fibrosis and lymphoplasmacytic cell infiltration were observed strongly around the islet cell, but the islet cell was revealed to be almost intact [27]. Therefore, the onset mechanism of endocrine dysfunction in AIP is considered to be as follows: At first, rapid inflammatory cell infiltration and fibrosis induce the reduction in blood flow in exocrine pancreas, and subsequently, islet cells fall into ischemia because of the reduction in blood flow, and then circulation failure causes the dysfunction of hormone secretion from islet cells, such as alpha cells and beta cells. However, interestingly, Tanaka et al. [28] reported that the volume of beta cells was reduced in patients with AIP, but the volume of alpha cells in AIP did not differ from that of type 2 diabetes by immunohistologic examination. Accordingly, exocrine dysfunction in AIP, especially insulin secretion from beta cells, may be induced not only by circulation failure in islet cells but also by the reduction in the number of beta cells. However, details need to be clarified in the future. After all, the mechanism of pathogenesis of diabetes mellitus is assumed to be affected by both of the following disorders [11, 28]: obstructed blood flow to the endocrine glands (islets of Langerhans) associated with the fibrosis of the exocrine glands and damaged islets of Langerhans due to the spreading of inflammation [11, 28].

## Exocrine Dysfunction Associated with Type 1 AIP

AIP is in many cases associated with pancreatic exocrine dysfunction. According to the nationwide survey conducted in Japan in 2000, 80.6 % of patients with AIP showed abnormal pancreatic exocrine function in which the abnormality is defined as 70 % or lower secretion in the BT-PABA (PFD test), and 70.0 % of the cases showed exocrine dysfunction (as determined by the secretin test), comparable to that in confirmed cases of chronic pancreatitis [15]. From our detailed examination of secretin test, differences of results between chronic pancreatitis and AIP were clarified [27]. Patients with chronic pancreatic exocrine dysfunction examined by secretin test revealed especially the reduction in bicarbonate concentration, whereas main reductions in patients with AIP were in volume and amylase output. The reason for these differences between chronic pancreatitis and AIP was determined by histological examination as follows: Destruction of the basement membranes of the pancreatic duct in chronic pancreatitis was observed. Therefore, as pancreatic ducts assume the responsibility of bicarbonate secretion, bicarbonate secretion in chronic pancreatitis by secretin test may be reduced. On the other hand, most basement membranes in AIP were intact, so bicarbonate secretion was preserved. However, stenoses of pancreatic ducts cause disturbances in pancreatic juice flow in AIP, and therefore, volume and amylase output by secretin test may be reduced. Of course, if the basement membranes were destroyed, bicarbonate secretion would diminish even in AIP. On this point, Otsuki et al. [29] and Yamaguchi et al. [30, 31] reported certain interesting facts. They examined 2 models of pancreatitis in rats – irreversible pancreatitis induced by intraductal infusion of oleic acid and reversible pancreatitis induced by retrograde intraductal infusion of sodium taurocholate – and noted that the difference between irreversible pancreatitis and reversible pancreatitis depended on the degree of injury of the pancreatic duct, especially injury of the pancreatic ductal basement membranes [29–31]. These experimental studies have clearly indicated that the difference between reversible and irreversible pancreatitis depended on the degree of damage of the duct epithelium where pancreatic progenitor cells exist. If the epithelial cells were severely injured, the pancreas could not regenerate [29–31]. Furthermore, Song et al. [32] reported that the pattern of fibrosis was mainly loose fibrosis with stromal edema in AIP, whereas it was dense fibrosis in CP. Taken together, it is considered that exocrine function in AIP is reversible to some extent by steroid therapy if the basement membranes of the pancreatic ducts are not destroyed, because the pancreatic ducts are compressed and stenosed by lymphoplasmacytic cell infiltration, which extended from the pancreatic parenchyma to the ducts in most AIP.

After all, in AIP, the mechanism of pathogenesis of pancreatic exocrine dysfunction is assumed to involve the following: decreased secretion of pancreatic enzymes associated with collapsed acinar cells caused by pronounced cellular infiltration mainly of plasmacytes and fibrosis and obstructed flow of pancreatic juice due to inflammatory cell infiltration around the pancreatic ducts and subsequent

narrowing of the pancreatic ducts [11, 25, 26, 28]. A recent study suggested that mislocalization of cystic fibrosis transmembrane conductance regulator (CFTR), which plays a central role in pancreatic duct $HCO_3$– secretion, and upregulation of aquaporin-1 (AQP1) on the plasma membrane and in the cytoplasm of pancreatic duct cells may be involved in the development of AIP [33]. Corticosteroids reduce inflammation and restore both digestive enzyme and $HCO_3$– secretion in patients with AIP by regenerating acinar cells and correcting CFTR localization in pancreatic duct cells [33].

## Pancreatic Exocrine and Endocrine Functions After Steroid Therapy in AIP

Many AIP patients have associated pancreatic exocrine and endocrine dysfunction [11, 24–27, 34]. It has been reported that improvement of pancreatic exocrine and endocrine function was detected after steroid therapy in 38 % [25]–50 % [11] and 25 % [25]–45 % [11] of AIP patients, respectively. It has also been suggested as a mechanism of improvement in pancreatic exocrine and endocrine functions after steroid therapy that steroid suppresses lymphoplasmacytic cell infiltration and fibrosis, permitting the attenuation of blood flow [27] and further regenerating islet cells by suppression of cytokine production [28]. A recent study about the changes in pancreatic tissue before and after steroid therapy in AIP patients revealed regeneration of acinar cells by steroids and suggested that acinar cell regeneration might be associated with CD133-positive pancreatic progenitor cells [33]. Diabetes mellitus control worsens in 75 % of AIP patients with type 2 diabetes mellitus before AIP onset after steroid therapy [11]. DM also develops after steroid therapy in some AIP patients [11, 26]. We should therefore take occurrence of DM into consideration in patients who continuously undergo steroid therapy.

## The Management of Pancreatic Exocrine Insufficiency in Patients with AIP Associated with Pancreatic Diabetes

Pancreatic diabetes is frequently complicated with lack or insufficiencies in pancreatic enzymes because of the destruction and reduction of pancreatic exocrine cells due to pancreatic exocrine diseases. Consequently, patients with pancreatic diabetes suffer from excessive malnutrition, such as hypoglycemia, hypoproteinemia, hypoalbuminemia, hypocholesterolemia, and hypotriglycemia, caused by insufficiencies in digestion and absorption of fat, protein, and carbohydrates (Fig. 5.1) [20]. This condition is one of the reasons for the unstable glycemic control and poor prognosis in patients with pancreatic diabetes. Therefore, patients with pancreatic diabetes need to receive sufficient pancreatic exocrine replacement therapy for the supplementation of pancreatic enzymes. The clinical management of pancreatic diabetes is divided into two parts: one is the adequate supplementation of pancreatic diges-

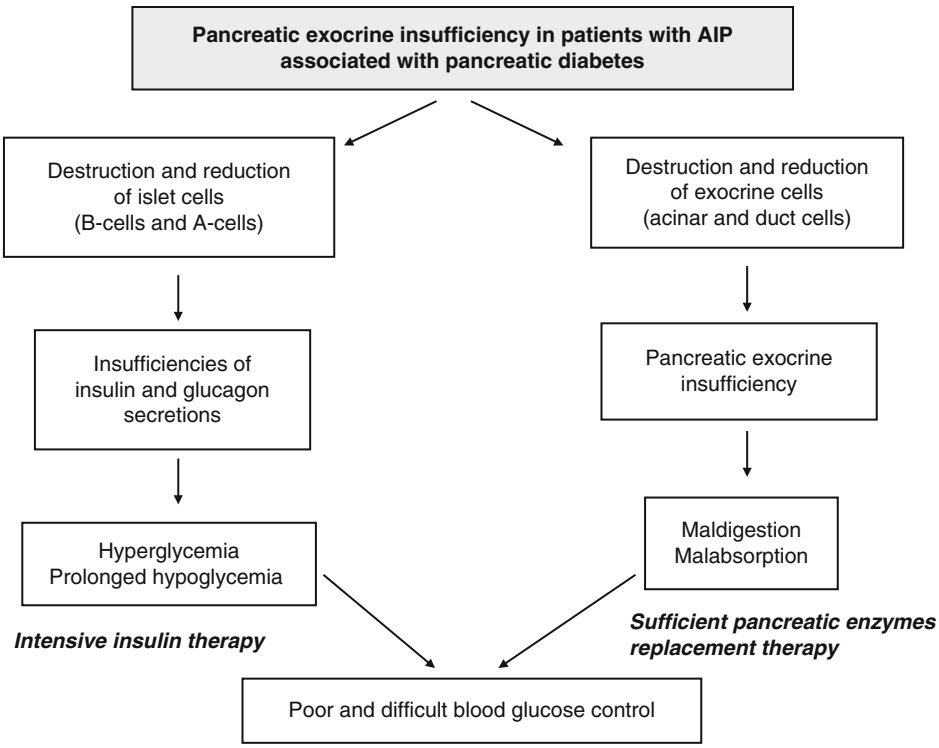


**Fig. 5.1** Management of pancreatic exocrine insufficiency in patients with AIP-associated pancreatic diabetes

tive enzymes and the other is the achievement of appropriate glycemic control. The appropriate and sufficient pancreatic exocrine replacement therapy is important for the maintenance of better nutrient conditions for patients with pancreatic diabetes. Furthermore, the intensive insulin therapy combined with short- or ultrashort-acting insulin and long-acting insulin can be achieved for the stable glycemic control and reduction of severe frequent hypoglycemia in patients with pancreatic diabetes. To mimic physiological insulin secretion and achieve appropriate glycemic control in patients with pancreatic diabetes, we should recognize that sufficient basal insulin supplementation is important [20]. These current advanced management techniques against insufficiencies of pancreatic exocrine endocrine functions are beneficial for improving and maintaining the quality of life in patients with AIP-associated pancreatic diabetes.

### Conclusion

In this chapter, we focus on the endocrine and exocrine functions associated with type 1 AIP according to the revised Japanese consensus guideline for management of AIP [15–17]. In conclusion, AIP is often associated with pancreatic exocrine and endocrine dysfunctions (diabetes mellitus); occurrence ratios are about 80 % and 70 %, respectively. Pancreatic exocrine and endocrine functions improve after steroid therapy in some AIP patients. Many AIP patients with type 2 diabetes mellitus before AIP onset showed worsening of diabetes mellitus control after steroid therapy [35].

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