

Prevention of The Progression of Chronic Pancreatitis

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ABSTRACT

Chronic pancreatitis (CP) is usually progressive but prevention of the progression can be done somehow by many ways. Specific treatment should be attempted for autoimmune pancreatitis and obstructive chronic pancreatitis. Recurrent attacks of pancreatitis should be minimized by alcohol abstinence (in alcoholic CP), antioxidants (in idiopathic CP) or surgery. The progression of CP can be attenuated by ceasing alcohol, quit smoking and performing surgery when indicated.

Key words : Chronic pancreatitis, prevention, progression

Abbreviations:

ACP, alcoholic chronic pancreatitis
AIP, autoimmune pancreatitis
AP, acute pancreatitis
CP, chronic pancreatitis
E-ICP, early-onset idiopathic chronic pancreatitis
ICP, idiopathic chronic pancreatitis
L-ICP, late-onset idiopathic chronic pancreatitis
OCP, obstructive chronic pancreatitis
PSC, pancreatic stellate cells
RAP, recurrent acute pancreatitis

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INTRODUCTION

Chronic pancreatitis (CP) is a chronic inflammatory condition of the pancreas resulting in chronic severe abdominal pain for many years, follows eventually by calcification, exocrine insufficiency (steatorrhea) and endocrine insufficiency (diabetes). Once it occurs, CP is likely progressive, unsatisfactory responsive to any current treatment and tremendously impairs the patients' quality of life^(1,2). Thus, to slow the progression, to cease the disease or, the best, to reverse the disease is the ultimate goal and will be summarized in this article.

Pancreatic fibrogenesis^(3,4)

Pancreatic fibrosis is the hallmark of chronic pancreatitis, thus pancreatic fibrogenesis is the key process in the development CP. It is now clear that pancreatic stellate cells (PSC) have major role in this process⁽⁴⁾.

In normal pancreas, PSC comprise about 4% of the total cells and locate in the interacinar spaces. Normally, all the PSC are in the quiescent stage and are characterized by the presence of vitamin A-containing fat droplets, absence of α -smooth muscle expression, little proliferation and do not produce extracellular matrix (ECM).

When quiescent PSC are activated by the external or paracrine factors i.e. alcohol (and metabolites), oxidative stress, inflammatory cytokines (e.g. from acute pancreatitis) and growth factors (e.g. from pancreatic cancer), they begin proliferating, having myofibroblast phenotype, losing their vitamin A-containing droplets, expressing the α -smooth muscle, and producing large amount of ECM. They now turn to activated PSC.

Normally, the process of PSC activation aims to heal the pancreas after injury. The process is, therefore, self-limited by the apoptosis of the activated PSC. CP is the consequence of pathologic pancreatic fibrogenesis due to the maintenance of the PSC activation. This is probably because activated PSC can excrete various autocrines e.g. TGF(1, activin A, ET1, CTGF, MCP-1, IL1, IL8, IL15 and RANTES that keep activating the PSC themselves, causing pathologic pancreatic fibrosis and eventually CP (Figure 1).

On the opposite side, there are some antagonists against the activated PSC and could be the targeted treatment against pancreatic fibrogenesis. These candidate anti-fibrotic agents include interferon- γ , PPAR γ and IL10.

Natural course of CP

Natural course of CP differs among common eti-

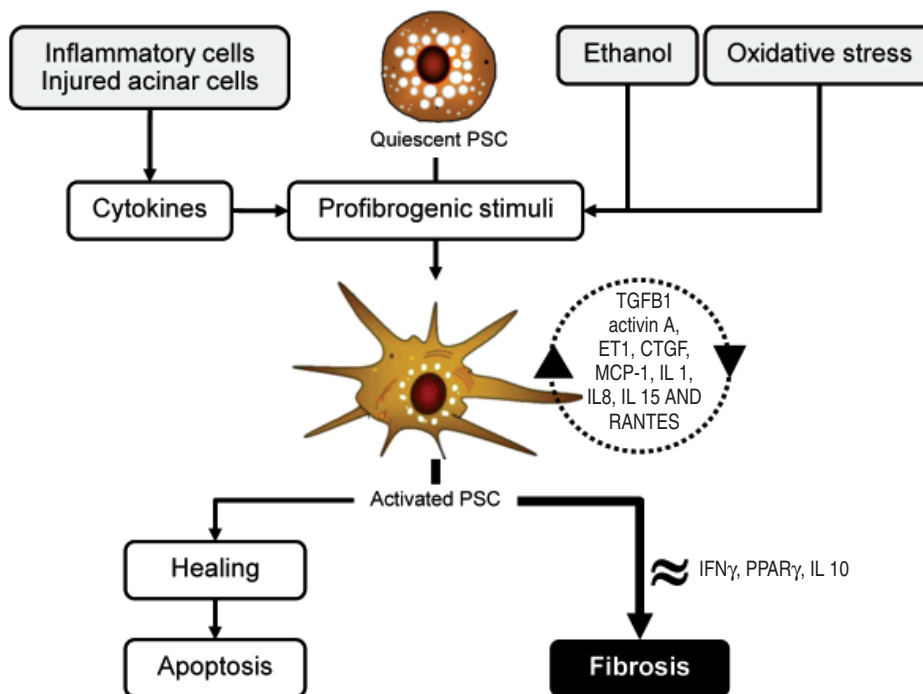


Figure 1. Pancreatic stellate cells activation and pancreatic fibrogenesis⁽⁴⁾.

ologies, *i.e.* alcoholic CP (ACP)⁽⁵⁻⁸⁾, early-onset idiopathic CP (E-ICP) and late-onset idiopathic CP (L-ICP)⁽⁶⁻⁸⁾.

In brief, almost all patients (80-100%) present with acute pancreatitis (AP) or recurrent acute pancreatitis (RAP) except patients with L-ICP, whose abdominal pain is present in only half of the cases^(7,8). Pain usually gradually declines over time and disappears (pain relief) within 10-12 years in ACP and L-ICP^(7,8), but 5-27 years in E-ICP^(7,8).

Pancreatic calcification develop in 6-8 years in ACP, 0-19 years in L-ICP (half of L-ICP are painless and have calcification as the first presentation), and 10-25 years in E-ICP^(7,8).

Exocrine and endocrine insufficiencies are late consequences of CP. In ACP, pancreatic exocrine insufficiency and diabetes occur in 5-13 years and 8-19 years, respectively. The correspondence numbers for L-ICP are 0-17 and 0-12 years (some L-ICP have exocrine insufficiency or diabetes as their first presentations) and for E-ICP are 14-26 and 27 years, respectively^(7,8).

Is it possible to stop or reverse the CP?

Until recently, it has been believed that once pancreatic fibrosis develops, it is irreversible and will eventually progress to CP sooner or later. However, 2 specific forms of CP are probably reversible, *i.e.* autoimmune pancreatitis (AIP) and obstructive chronic pancreatitis (OCP). For the other types of CP, though irreversible, slowing the progression is still feasible.

Autoimmune pancreatitis

AIP is a special form of CP presenting with pancreatic enlargement or mass mimicking pancreatic cancer but responsive to corticosteroid treatment⁽⁹⁾. Pancreatic calcification and CP can be the consequences of AIP^(10,11). With corticosteroid treatment, it has been shown that exocrine function⁽¹²⁻¹⁴⁾, endocrine function⁽¹²⁻¹⁵⁾ could be improved and pancreatic fibrosis was even regressed⁽¹⁶⁾.

Obstructive chronic pancreatitis

OCP is CP secondary from chronic obstruction of the pancreatic duct. The pancreas is characterized by marked pancreatic atrophy and diffuse fibrosis, however, pancreatic calcification are usually absent⁽¹⁷⁾. The etiologies of OCP include pancreatic neuroendocrine tumor (pNET)⁽¹⁸⁻²¹⁾, duodenal wall cyst⁽¹⁸⁾, duodenal diverticulum⁽²²⁾, benign pancreatic cyst⁽²³⁾, stricture from healed pseudocyst⁽²⁴⁾, and pan-

creatic trauma⁽²⁵⁾. Study in pig showed that OCP can occur within 4 weeks after pancreatic duct ligation⁽²⁶⁾ and OCP could be reversed after correcting the obstruction within 5 weeks in feline model⁽²⁷⁾.

It is unknown whether OCP will recover if obstruction lasts longer than a month and if it holds true for OCP in human. The author's personal experience found that most OCP from pancreatic cancer and IPMN do not recover after surgery.

The more controversial causes of OCP are pancreas divisum^(18,28) and sphincter of Oddi dysfunction (SOD)⁽²⁹⁾. It is unclear if pancreas divisum could cause OCP and or it is just an innocent bystander of idiopathic CP³⁰. Endoscopic therapy via minor papilla could reduce attack of RAP in some patients with pancreas divisum, but not all^(30,31). There is also no evidence that endoscopic therapy of pancreas divisum could stop or reverse the CP.

SOD is another controversial cause of RAP and CP^(32,33). Likewise, it is a debate whether SOD is the true cause or just a finding of idiopathic CP⁽³²⁾. An important recent study showed that even after dual sphincterotomy (biliary and pancreatic), the rate of developing CP were not reduced⁽³⁴⁾.

How to prevent the progression of CP?

The strategies to prevent the progression of CP are summarized in Table 1.

1. Treat the specific etiology

1.1 Autoimmune pancreatitis

As mentioned above, AIP can be reversed after corticosteroid treatment⁽¹²⁻¹⁶⁾. Thus, it is of importance to treat AIP patients who obviously have

Table 1. The strategies to prevent the progression of CP

Treat the specific etiology
Autoimmune pancreatitis
Obstructive chronic pancreatitis
Reduce the exacerbation of acute pancreatitis
Alcohol abstinence
Antioxidants
Surgery
Slow the progression of chronic pancreatitis
Alcohol abstinence
Quit smoking
Surgery
Novel therapy

symptoms, pancreatic mass or other organ involvement in order to ameliorate symptoms and prevent long-term consequence of pancreatitis⁽³⁵⁻³⁸⁾. However, it remains unclear whether we should treat asymptomatic AIP patients or patients who have only elevated IgG4 because the benefit of corticosteroid to prevent long-term consequences of AIP in such patients has not been proven and must be balanced with the side effects of treatment.

1.2 Obstructive CP

Reversible causes of OCP as mentioned above should be treated appropriately with surgery or endoscopic therapy.

2. Reduce the exacerbation of acute pancreatitis

Since the hypotheses of the pathogenesis of CP include the necrotic-fibrosis theory and sentinel acute pancreatitis event (SAPE), repetitive attacks of AP would likely accelerate the progression of CP. Study has shown that the more the number of attacks, the shorter the time to develop CP⁽³⁹⁾. One case series reported 4 patients who developed CP within 1.5-3.5 years after the first attack of acute pancreatitis. The numbers of attack among them were only 4-8 times⁽⁴⁰⁾. Therefore, the prevention of the attack of AP would logically slow the progression of CP.

2.1 Alcohol abstinence

Alcohol abstinence is the best way to reduce the attack of AP in alcoholic CP confirmed in a randomized study⁽⁴¹⁾. Thus, physician should put effort to encourage alcoholic CP patient to quit drinking.

2.2 Antioxidants

Antioxidants containing selenium, vitamin A, C, E and methionine has been shown to reduce attack of AP effectively in patients with ICP⁽⁴²⁾, but not ACP⁽⁴³⁾. Thus, it is a reasonable therapeutic option to reduce attack of AP in ICP.

2.3 Surgery

Although surgery is usually performed in CP patients with only intractable pain, one study showed that it could also reduce the exacerbation of AP in CP effectively⁽⁴⁴⁾. The most effective surgical technique reported to be the drainage surgery *i.e.*, lateral pancreaticojejunostomy⁽⁴⁴⁾.

3. Slow the progression of CP

3.1 Alcohol abstinence

Beside the main benefit to reduce exacerbation and severity of AP, alcohol abstinence would also slow the progression of CP because alcohol drives

the activation of PSC and the pancreatic fibrogenesis⁽⁴⁵⁾. Many cohort studies confirmed that alcohol abstinence slowed the progression of exocrine insufficiency⁽⁴⁶⁾ and the development of diabetes⁽⁶⁾. Thus, alcoholic abstinence is the must to do.

3.2 Quit smoking

Smoking is a well-established factor that accelerates the progression of ACP⁽⁴⁷⁾. In details, it increased the risk of pancreatic calcification for 4.6 folds and diabetes for 2.4 folds⁽⁴⁷⁾. In ICP, smoking accelerates the pancreatic calcification in L-ICP, but not that of E-ICP⁽⁴⁸⁾. In HP, smoking cessation reduced the incidence of pancreatic cancer⁽⁴⁹⁾ but there is no data on exocrine insufficiency and diabetes. Taken together, quit smoking is essential to slow the progression of CP.

3.3 Surgery

Landmark study by Nealon, *et al*⁽⁵⁰⁾ suggested that early surgery, particularly the drainage operation, could improve the pancreatic exocrine insufficiency of CP. Recent meta-analysis also supported that early surgery could reduce the risk of exocrine insufficiency with the odds ratio 0.4-0.6⁽⁵¹⁾. However, since the benefit is weak and pancreatic surgery does carry morbidity and mortality, it may not be good idea to perform surgery just for this purpose. Pain should be the primary indication for surgery and slowing the progression of exocrine insufficiency is just the complement.

3.4 Novel therapy

There is some progress on how to slow the progression of pancreatic fibrosis in animal studies. The potential therapy with positive results includes antioxidants (vitamin E⁽⁵²⁾ and allopurinol⁽⁵³⁾), TGF β inhibition⁽⁵⁴⁾, TNF α inhibition (TNF α antibody⁽⁵⁵⁾ and pentoxifylline⁽⁵⁶⁾), anti-protease (camostat mesilate⁽⁵⁷⁾), PPAR γ (troglitazone⁽⁵⁸⁾), lisinopril^(59,60), lovastatin⁽⁶⁰⁾ and pravastatin⁽⁶¹⁾. Currently, there is no study starting in human.

CONCLUSION

Although CP is usually a progressive disease, prevention of the progression and even reversal of the disease are not impossible. Specific treatment must be offered for AIP and OCP. Recurrent attack of AP should be prevented by alcohol abstinence (in ACP), antioxidants (in ICP) or surgery (if very frequent attacks).

Finally, attempt to slow the progression of CP can be done by ceasing alcohol, quit smoking and performing surgery if indicated.

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