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EDITORIAL

Progression of recurrent acute to chronic pancreatitis: More questions than answers!

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Acute pancreatitis (AP) continues to pose a substantial challenge to clinicians and researchers. It has been proposed that an index episode of AP could progress to recurrent AP (RAP) and may finally culminate into chronic pancreatitis (CP). This is the sentinel acute pancreatitis event (SAPE) hypothesis that defines pancreatitis as a disease spectrum [1]. Even though several clinical and bench studies have provided insights into the pathophysiology of the disease [2–5], there is still no modality to accurately predict the progression of RAP to CP. This gap in understanding has likely, at least in part, precluded development of any specific interventions that could prevent progression of RAP to CP or reverse the changes of CP.

In the current *issue*, Kalaria and colleagues have reported their observations on the progression of RAP to CP in a tertiary care private hospital in western India [6]. They observed the development of features of CP during a median period of 32 months in five out of 72 patients who had a single episode of AP. 27.8% had RAP of which 13 (48.1%) developed features of chronicity after a median of 47 months from the index or sentinel episode. Chronicity was observed with a higher frequency among patients with alcoholic and idiopathic subtypes. In a meta-analysis by Sankaran et al. in 2015 [7], the crude prevalence of RAP based on 11 studies ($n = 8017$) was estimated to be 22% (95% CI 18% to 26%). However, on analysis of the prospective studies only (nine studies, $n = 1869$), the pooled prevalence of RAP turned out to be 20% (95% CI 15% to 25%). Five studies ($n = 6826$) in this meta-analysis reported the subsequent diagnosis of CP after RAP, which was reported to be 36% (95% CI 20% to 53%). On the other hand, 10% of patients who had a single episode of AP subsequently developed CP. Unpublished data from an ongoing study from our institute also reveals that 10% of patients with a single episode of AP and 28% with RAP eventually developed CP.

Since only a proportion of RAP progresses to CP, it becomes speculative as to what determines the progression of RAP to CP. A recent study from the Dutch group involving 669 patients who survived the first episode of AP defined independent risk factors for the development of CP after an index and recurrent AP [8]. RAP conferred an odds of 2.90 (95% CI 2.07 to 4.05) per episode for progression to CP. Among patients who had RAP as a risk factor, the other independent risk factors for progression to CP were alcohol as the etiology (OR 4.85 [95% CI 2.04 to 11.52]) and development of necrotizing pancreatitis (OR 8.78 [95% CI 4.09 to 18.86]). On the other hand, among patients who did not have RAP, the independent risk factors were alcohol (OR 4.22 [95% CI 1.83 to 9.73]; $p = 0.001$) and idiopathic etiology (OR 3.98 [95% CI 1.64 to 9.65]; $p = 0.002$), current smoker (OR 2.90 [95% CI 1.42 to 5.93]; $p = 0.004$), and necrotizing pancreatitis (OR 6.65 [95% CI 3.40 to 13.01]; $p < 0.001$).

It is now clearly established that the pathological hallmark of CP is progressive fibrosis that is mediated by the activated pancreatic stellate cells (PSCs). PSC activation could be triggered by several mediators including alcohol, smoking, and inflammatory cytokines such as interleukins, TGF-β, TNF-α, and PDGF, to name a few [9]. It was also shown in an experimental setting that application of pressure on PSCs could result in the generation of oxidative stress, which is known to result in inflammation [10]. This observation could have an implication in patients with CP, in whom ductal and interstitial hypertension due to pancreatic ductal obstruction could result in PSC activation. Interestingly, it has been shown in experimental models of AP using L-arginine that there could be PSC activation and early fibrosis even after the first episode of AP [11]. In our recent studies using human pancreatic acini, we could show that PSC activation could occur even after bile acid-mediated injury [4]. However, clinical acute biliary pancreatitis does not progress to CP. This implies that for

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progressive fibrosis to occur, PSC activation needs to be repetitive and persistent and should reach a certain threshold after which the process becomes irreversible. This is possible in RAP related to alcohol and smoking (both of which are known to be independent risk factors of acute and chronic pancreatitis) [12, 13] since the pancreatic acini are subjected to persistent multiple insults with these agents. This is also likely in idiopathic AP or RAP where multiple genetic polymorphisms could lead to premature intrapancreatic zymogen activation and recurrent pancreatic injury. These recurrent acinar insults may not always result in clinical RAP as a proportion of patient progress to CP even after one episode of AP and some with alcohol-related and idiopathic pancreatitis even present as CP without any index or recurrent episodes of AP.

The foregoing speculations raise more questions than providing solutions to the enigma of progression from AP to RAP and to CP. Even though the present study by Kalaria et al. provides important data in the Indian context, the sample size was small and the patient population was restricted to a specific geographic location. In order to get more precise estimates, similar studies need to be conducted with a multicenter population-based design involving a huge sample size. More importantly, independent risk factors for the development of RAP need to be carefully defined. Even though several genetic polymorphisms have been associated with the development of RAP and CP, the results need to be interpreted with caution. While the high penetrance pancreatitis-associated PRSS1 R122H gene is rare in India [14, 15], the other implicated genes such as the SPINK1, CTSB, Claudin2, CASR, and CTRC have lower penetrance and confer only a slightly increased odds ratio for development of RAP and CP [16, 17]. A whole gene or exome sequencing could unravel novel genetic polymorphisms involving a wide range of pathogenic functions, but again, the strength of association will have to be critically analyzed. Rather than focusing on one risk factor, it would be prudent to evaluate interactions between different genes or between genes and environmental factors such as alcohol, smoking, and metabolic (hypertriglyceridemia) and structural anomalies (e.g. pancreas divisum). Of note, the strength of association between RAP and pancreas divisum gets significantly higher in the presence of PRSS1 (rs10273639), CTSB (rs12338), and the combination of both [18]. This risk increases even further in patients who develop the index episode of pancreatitis during childhood. The other area that requires intense study is the behavior of PSC activation. It is still not clear at what time point in the natural history of RAP does PSC activation reach the threshold of irreversibility. Besides prospective clinical studies, which could be time, cost, and labor exhaustive, controlled experimental studies also need to be conducted to uncover this enigma of irreversibility of PSC activation.

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