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Commentary

Uncommon appearance of concurrent liver cirrhosis and chronic pancreatitis: The alcohol metabolism theory

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Chand et al. recently reported the frequency of liver diseases (LD) in pancreatitis. In an analysis of 20,931 patients, it was concluded that the incidence rate of LD in chronic pancreatitis (CP) is approximately 5%, whereas that of the end-stage liver disease, liver cirrhosis (LC), is around 2% [1]. Since more than 50% of CP develops due to alcohol consumption [2], we can estimate an incidence rate of LD and LC that is no more than two times higher in alcoholic CP.

Although the rate of LC is variable in each published national cohort of alcoholic CP (2% in a Spanish cohort [3], 16.7% in a Czech one [4], 8.4% in an Indian one [5] and 12.5% in an Italian one [6]), the incidence rate of LC is approximately 10–20%. Further, the incidence of CP is even lower in LC. It was 2.5% in the Czech cohort [4] and 5.3% in the Spanish one [3]. Since the proportion of CP in LC is lower than that of LC in CP and patients with CP are younger than those with LC [6,7], it seems more than likely that alcohol damages the pancreas earlier than it does the liver.

90% of alcohol is metabolized via the oxidative pathway by acetaldehyde dehydrogenase (ADH), whereas 10% is metabolized via the non-oxidative pathway mostly by fatty acid ethyl ester synthase and carboxyl ester lipase. The end product of the oxidative pathway, acetaldehyde, is rather toxic to the liver; however, the end product of the non-oxidative pathway, fatty acid ethyl ester (FAEE), is rather toxic to the pancreas [8–10]. Pharmacological suppression of the oxidative pathway exacerbates ethanol-induced mitochondrial dysfunction and acute pancreatitis, while pharmacological inhibition of the non-oxidative pathway prevents FAEE formation and ameliorates exocrine pancreatic damage and the outcome of acute pancreatitis in experimental models [9]. The same outcomes were observed in genetically altered conditions. In ADH-deficient mice, alcohol administration causes severe pancreatic injury [11]; moreover, mutations of carboxyl ester lipase in humans also increases the risk for alcoholic chronic pancreatitis [12].

Therefore, we hypothesize that in patients in whom alcohol is mostly metabolized via the oxidative pathway, LC develops first and pancreatitis presents in only a minority of patients. This may be due to the fact that (1) non-oxidative metabolism is suppressed and the formation of FAEE is low or (2) since mortality is high in LC, there is no time for CP to develop. Conversely, in patients in whom alcohol is mostly metabolized via the non-oxidative pathway, CP develops first and in some patients LC occurs later. (1) This may be due to the lower activity of oxidative metabolism or (2) since mortality is lower in CP, LC has time to develop (Fig. 1).

All in all, we have at least three independent mechanisms playing a role in the rare incidence of concurrent LC and CP: (1) a patient's genotype does not change during his or her lifetime; therefore, the characteristics of alcohol metabolism remain similar with aging; (2) after one of the diseases develops, the patient's alcohol consumption decreases; and (3) the patient's survival is diminished if comorbidities occur.

Conflict of interest

None declared.

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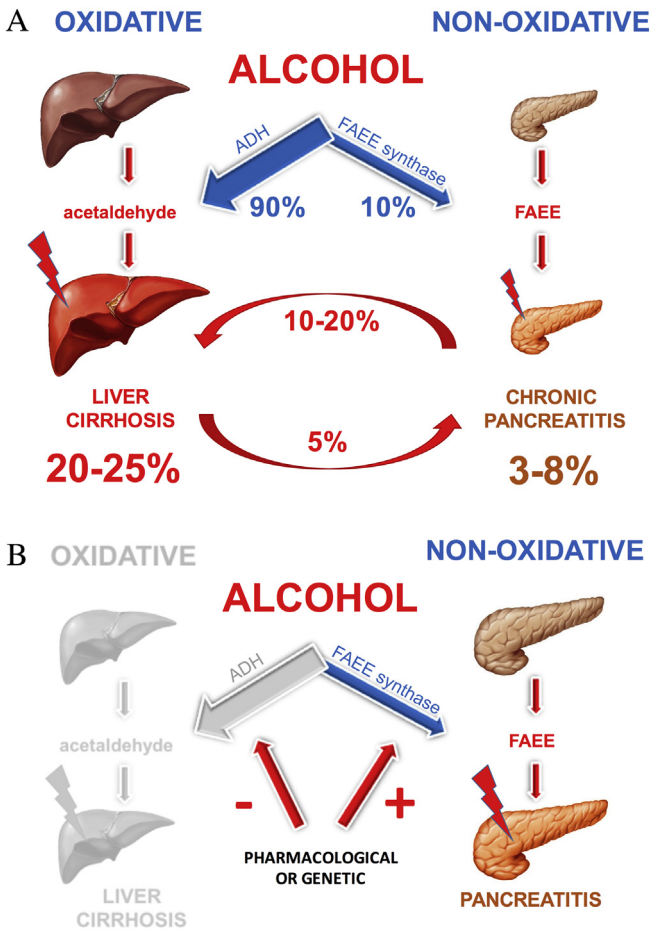

Fig. 1. (A) Alcohol is 90% metabolized via the oxidative pathway; liver cirrhosis is therefore more frequent in alcoholics than chronic pancreatitis (20–25% versus 3–8%, respectively). In patients in which LC develops first, CP is less frequent, whereas the chance for LC is higher in patients where CP develops first. (B) If the non-oxidative pathway is stimulated or the oxidative pathway is inhibited, the pancreas damage is greater, while if inhibited it is less severe.

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References

[1] Chand SK, Pendharkar SA, Bharmal SH, Bartlett AS, Pandol SJ, Petrov MS. Frequency and risk factors for liver disease following pancreatitis: a population-based cohort study. Dig Liver Dis 2018;18:31220–9.
[2] Szucs A, Marjai T, Szentesi A, Farkas N, Parniczky A, Nagy G, et al. Chronic pancreatitis: multicentre prospective data collection and analysis by the Hungarian Pancreatic Study Group. PLoSOne 2017;12:e0171420.
[3] Aparisi L, Sabater L, Del-Olmo J, Sastre J, Serra MA, Campello R, et al. Does an association exist between chronic pancreatitis and liver cirrhosis in alcoholic subjects. World J Gastroenterol 2008;14:6171–9.
[4] Spicak J, Pulkertova A, Kralova-Lesna I, Suchanek P, Vitaskova M, Adamkova V. Alcoholic chronic pancreatitis and liver cirrhosis: coincidence and differences in lifestyle. Pancreatology 2012;12:311–6.
[5] Soni A, Singh B, Nijhawan S, Mathur A, Gupta G. Chronic liver disease in alcohol-related chronic pancreatitis patients: does lightning strike twice? Indian J Gastroenterol 2015;34:345–6.
[6] Angelini G, Merigo F, Degani G, Camplani N, Bovo P, Fratta Pasini A, et al. Association of chronic alcoholic liver and pancreatic disease: a prospective study. Am J Gastroenterol 1985;80:998–1003.
[7] Gullo L, Casadei R, Campione O, Grigioni W, Marrano D. Alcoholic liver disease in alcoholic chronic pancreatitis: a prospective study. Ital J Gastroenterol 1995;27:69–72.
[8] Criddle DN, Raraty MG, Neoptolemos JP, Tepikin AV, Petersen OH, Sutton R. Ethanol toxicity in pancreatic acinar cells: mediation by nonoxidative fatty acid metabolites. Proc Natl Acad Sci U S A 2004;101:10738–43.
[9] Huang W, Booth DM, Cane MC, Chvanov M, Javed MA, Elliott VL, et al. Fatty acid ethyl ester synthase inhibition ameliorates ethanol-induced Ca^{2+}-dependent mitochondrial dysfunction and acute pancreatitis. Gut 2014;63:1313–24.
[10] Judak L, Hegyi P, Rakonczay Jr Z, Maleth J, Gray MA, Venglovecz V. Ethanol and its non-oxidative metabolites profoundly inhibit CFTR function in pancreatic epithelial cells which is prevented by ATP supplementation. Pflugers Archiv Eur J Physiol 2014;466:549–62.
[11] Kaphalia BS, Bhopale KK, Kondraganti S, Wu H, Boor PJ, Ansari GA. Pancreatic injury in hepatic alcohol dehydrogenase-deficient deer mice after subchronic exposure to ethanol. Toxicol Appl Pharmacol 2010;246:154–62.
[12] Fjeld K, Weiss FU, Lasher D, Rosendahl J, Chen JM, Johansson BB, et al. A recombined allele of the lipase gene CEL and its pseudogene CELP confers susceptibility to chronic pancreatitis. Nat Genet 2015;47:518–22.