Acute Pancreatitis – Beyond Gallstones and Alcohol

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Abstract

Acute pancreatitis is the most common disorder of the pancreas. The incidence of the disease has increased markedly during the past decades. Whilst alcohol abuse and gallstone disease might explain a large proportion of the disease etiology, in one quarter of the patients, the cause remains unknown. Life-style and pharmaceutical drug use are potential risk factors for the disease. This brief review highlights the recent research on the role of these factors in the etiology of acute pancreatitis.

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Epidemiology

Acute pancreatitis is the most common disorder of the pancreas. In 10–20% of patients the disease progresses to multi-organ failure with high mortality. During the past decades there has been a steady rise in the incidence of acute pancreatitis, particularly the non-severe acute pancreatitis, in many industrialized countries.[1-6] The incidence of acute pancreatitis was increased by 30% in the United States between 2000 and 2009,[6] 50% in Ireland between 1997 and 2004[1] and 75% in the Netherlands between 1992 and 2004.[2] In the United States, acute pancreatitis resulted in more than 270,000 hospital discharges in 2009 to a cost of 2.6 billion dollars.[6] Although a more frequent use of computerised tomography and pancreatic enzymes might have contributed to such an increase in the incidence, changes in life-style factors and pharmaceutical drug use might also be involved.

Lifestyle and acute pancreatitis

The pathophysiology of acute pancreatitis is complex and not fully understood.[7] The disease is initiated by uncontrolled activation of proteolytic enzymes and an autodigestive process that progresses to an inflammatory cascade.[7] Alcohol abuse and gallstone disease are acknowledged risk factors for the disease.[8] However, during recent years several other risk factors for the development of acute pancreatitis have been identified.

Smoking

Smoking is an acknowledged risk factor for the development of chronic pancreatitis.[9] In an autopsy study, pancreatic fibrosis was more common in smokers compared to non-smokers.[10] Smoking accelerates the progress of acute alcoholic pancreatitis to chronic pancreatitis[11] whereas smoking cessation seems to postpone this development.[12] The role of smoking in the development of acute pancreatitis has been investigated in a few studies.[13-15] Smokers have between 2–3 fold increased risk of acute pancreatitis. In the most recent report, current smokers with ≥20 pack-years of smoking had more than 2-fold (HR=2.29; 95% CI: 1.63, 3.22) increased risk of first attack of acute non-gallstone-related pancreatitis compared to never-smokers.[15] Smoking duration rather than number of cigarettes smoked per day seemed to be more influential in the development of acute pancreatitis. Interestingly, 20 years of smoking cessation decreased the risk of acute pancreatitis to the levels comparable to never-smokers. The same risk reduction was seen among individuals

who consumed <400 g of alcohol per month, corresponding to one standard drink of alcohol or less, after 10 years of smoking cessation.

Obesity

The rise in the incidence of acute pancreatitis has occurred alongside an increase in the prevalence of obesity in the Western World.[16-17] Therefore, it is intriguing to clarify the role of obesity in the development of acute pancreatitis. It is known that obesity is an independent predictor for the severity of acute pancreatitis. Apart from an increased risk of complications confined to the pancreas, i.e. pancreatic necrosis, abscess or pseudocysts, and systemic complications, i.e. circulatory shock, respiratory- or renal insufficiency, obese patients with acute pancreatitis have higher risk of death compared to non-obese patients.[18] However, these associations do not necessarily imply causality in the development of this disease. A recent meta-analysis indicated that obesity was an independent, although weak, risk factor for the development of acute pancreatitis.[19] However, none of the included studies distinguished between abdominal and total adiposity.[19] Fat tissue, particularly abdominal fat, is associated with a systemic inflammatory state.[20] Intra-pancreatic unsaturated fat has been shown to promote inflammatory response and oxidative stress resulting in cell necrosis.[21] In a recent study, the association between abdominal adiposity, assessed as waist circumference, and total adiposity, assessed as body mass index (BMI), and the risk of acute pancreatitis was clarified.[22] In this cohort study, 68,158 Swedish men and women were followed for mean 12 years. During this period 424 persons had a first attack of acute pancreatitis. The risk of acute pancreatitis was two-fold increased among individuals with a waist circumference >105 cm (HR= 2.37; 95% CI: 1.50, 3.74) compared to individuals with a waist circumference of 75.1–85.0 cm adjusted for potential confounders including BMI. This increased risk remained virtually unchanged when stratifying the analyses for sex or the severity of acute pancreatitis. Importantly, there was no such association between BMI and the risk of acute pancreatitis, when mutually adjusting for waist circumference.

Diet

The exocrine and endocrine functions of the pancreas are affected by the dietary components of food. Therefore, it is reasonable to assume that dietary habits could modulate the risk of acute pancreatitis, but very few studies have investigated this potential association. One study examined the association between vegetable and fruit consumption on the development of acute pancreatitis.[23] It is known that oxidative stress plays an important role in the pathogenesis of acute pancreatitis.[24] The high anti-oxidative content of vegetables and fruits could potentially protect against the development of non-gallstone-related acute pancreatitis. In this study, consumption of vegetables was found to reduce the risk of acute pancreatitis in a dose-response manner. Individuals with vegetable consumption in the highest quartile had almost 50% (HR=0.56; 95% CI: 0.37, 0.84) reduced risk of acute pancreatitis compared to the lowest quartile. This association was most clear among individuals who consumed >1 standard drinks of alcohol/ day and those with a BMI ≥25 kg/m2, i.e. individuals with higher baseline oxidative stress. Interestingly, there was no association between fruit consumption and acute pancreatitis. Although the anti-oxidative content of fruits is generally high, the high fructose content of fruits may counteract the protective effect of antioxidants.

Pharmaceutical drug use

Drug-induced acute pancreatitis has previously been considered as a rare cause of acute pancreatitis but recent reports have indicated that this form of acute pancreatitis might be the third most common cause of the disease, accounting for 3-5% of all cases.[25-26] More than 200 drugs have been proposed to induce acute pancreatitis.[27] The current knowledge is practically based on case-reports which cannot establish an association between a given drug and acute pancreatitis on the population level, since the disease being treated could be a risk factor for acute pancreatitis. Recently, a few population-based studies have been performed establishing an association between oral glucocorticoids,[28] tetracycline,[29] metronidazole,[30] and dismissing such association between antidopaminergic,[31] selective serotonin-reuptake inhibitors[32] and hormone replacement therapy[33]. Future population-based research will further clarify the role of different pharmaceutical drugs and acute pancreatitis.

Alcohol – unfinished business

Alcohol is an acknowledged risk factor for acute and

chronic pancreatitis. However, the role of drinking behaviour, amount and the type of alcohol consumed on acute pancreatitis is not fully studied. Among findings that tell against an association between alcohol and acute pancreatitis is the lack of an increased incidence of acute pancreatitis in conjunct to Munich Oktoberfest, during which 6.6 million litres of beer was sold.[34] In Stockholm County, the incidence of acute pancreatitis dropped between 1974 and 1987, during which sales of wine and beer increased while sales of spirit declined.[35] The overall alcohol sales were unchanged. Finally, consumption of spirit, but not wine or beer, was associated with increased risk of acute pancreatitis.[36] There was a dose-response association between the amount of spirit consumed on a single occasion and this risk. The average amount of alcohol consumption was not associated with acute pancreatitis. However, the average alcohol consumption was relatively low in the study population and may not be generalisable to individuals with high alcohol consumption. Future research should focus to clarify the role of alcohol type and drinking behaviour on the development of acute pancreatitis.

Clinical implications

The growing knowledge on the effect of lifestyle factors on the development of acute pancreatitis creates possibilities for both primary and secondary prevention of this disease. Acute pancreatitis shares similar risk factors for cancer and cardiovascular diseases. Therefore lifestyle change will provide general health benefits, including reduced risk of acute pancreatitis, to individuals with an unhealthy lifestyle. In patients who have already developed acute pancreatitis, it is reasonable to assume that continuous exposure to the risk factor will increase the risk of recurrent- and chronic pancreatitis. Yet, research on the secondary prevention of pancreatitis is scarce. Smoking cessation has been shown to reduce the progress of the pancreatic damage.[12] Therefore, as the least measure, smoking cessation should be provided to all smokers who have developed acute pancreatitis.

In conclusion, more knowledge on the risk factors of the disease will provide tools to improve the clinical management, particularly the secondary prevention, of acute pancreatitis.

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