



Luis Bujanda, PhD, Professor, Series Editor

Alcohol consumption on pancreatic diseases

Marta Herreros-Villanueva, Elizabeth Hijona, Jesus Maria Bañales, Angel Cosme, Luis Bujanda

Marta Herreros-Villanueva, Schulze Center for Novel Therapeutics, Division of Oncology Research, Department of Medicine, Mayo Clinic, Rochester, MA 55905, United States

Marta Herreros-Villanueva, Elizabeth Hijona, Jesus Maria Bañales, Angel Cosme, Luis Bujanda, Department of Gastroenterology, Center for Biomedical Research in Digestive and Liver Diseases Network (CIBERehd), Donostia Hospital, University of the Basque UPV/EHU, 20010 San Sebastian, Spain

Author contributions: Herreros-Villanueva M, Hijona E, Bañales JM, Cosme A and Bujanda L designed and wrote the review.

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Correspondence to: Luis Bujanda, MD, PhD, Professor, Department of Gastroenterology, Center for Biomedical Research in Digestive and Liver Diseases Network (CIBERehd), Donostia Hospital, University of the Basque UPV/EHU, Avda Sancho El Sabio 17-2, 20010 San Sebastian, Spain. medik@telefonica.net
Telephone: +34-94-3007173 Fax: +34-94-3007065

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Abstract

Although the association between alcohol and pancreatic diseases has been recognized for a long time, the impact of alcohol consumption on pancreatitis and pancreatic cancer (PC) remains poorly defined. Nowadays there is not consensus about the epidemiology and the beverage type, dose and duration of alcohol consumption causing these diseases. The objective of this study was to review the epidemiology described in the literature for pancreatic diseases as a consequence of alcoholic behavior trying to understand the association between dose, type and frequency of alcohol consumption and risk of pancreatitis and PC. The majority of the studies conclude that high alcohol intake was associated with a higher risk of pancreatitis (around 2.5%-3% between heavy drinkers and 1.3% between non drinkers). About 70% of pancreatitis are due to chronic heavy alcohol consumption. Although this incidence rate differs between countries, it is clear that the risk of

developing pancreatitis increases with increasing doses of alcohol and the average of alcohol consumption vary since 80 to 150 g/d for 10-15 years. With regard to PC, the role of alcohol consumption remains less clear, and low to moderate alcohol consumption do not appear to be associated with PC risk, and only chronic heavy drinking increase the risk compared with lightly drinkers. In a population of 10%-15% of heavy drinkers, 2%-5% of all PC cases could be attributed to alcohol consumption. However, as only a minority (less than 10% for pancreatitis and 5% for PC) of heavily drinkers develops these pancreatic diseases, there are other predisposing factors besides alcohol involved. Genetic variability and environmental exposures such as smoking and diet modify the risk and should be considered for further investigations.

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Key words: Acute pancreatitis; Chronic pancreatitis; Alcohol consumption; Alcohol metabolism; Genetic variability; Pancreatic cancer; Risk

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INTRODUCTION

Alcohol causes different diseases and they are considered an important medical and social burden on society. Alcohol has been identified as a leading risk factor for death and disability globally, accounting for 3.8% of death and 4.6% of disability adjusted life years lost in 2004^[1].

Pancreas is one of the most important organs adversely affected by alcohol consumption. An association between alcohol abuse and pancreatic injury was reported by Friedrich^[2] as early as 1878. Freidreich recognized an

association of alcohol abuse with chronic pancreatic injury.

Since Friedreich's initial observation, many studies have confirmed that excessive alcohol intake is associated with pancreatic damage. Nowadays it is widely recognized that pancreatic injury due to alcohol consumption ranges from isolated episodes of acute pancreatitis (AP) to chronic manifestations that with time could move to pancreatic cancer (PC). However, there is not a consensus in the epidemiology and it is not clear how different drinks or dose of alcohol affect to the development of pancreatic diseases and finally, how drinking trigger pancreatic injury only in a minority of alcoholics.

Here, we review different studies and meta-analysis that have been published in the last years relating alcohol and pancreatic diseases as AP, chronic pancreatitis (CP) and PC. We summarize the effects of alcohol consumption in these diseases and at the end we present the possible mechanisms that have been proposed as a cause of this pancreatic pathogenesis.

Alcohol consumption measures

The incidence and prevalence of alcoholic pancreatic diseases are difficult to ascertain with precision, in part because of the variable considerations of drinking behavior and alcohol intakes measures.

Most of the studies in cohorts measures alcohol intake from wine, beer, and spirits separately. The final value of the daily alcohol intake is expressed in grams for each beverage based on the frequency of consumption, the alcohol content of the beverage, and the average quantity consumed. The United States Department of Agriculture established that alcoholic beverages are 12.8 g for 335 mL of alcohol for a bottle of beer (12-oz, 5% alcohol), 11.0 g for 118 mL (4-oz, 12% alcohol) glass of wine, and 14.0 g for 44 mL (1.5 oz, 40% alcohol) of 80-proof liquor.

The definition of a "standard drinker" differs between countries^[3,4]: in United States it is 14 to 15 g, in Great Britain is 8 g and 19.75 g of alcohol in Japan. In addition to the amount to alcohol in one drink, the cut points to define "moderate" and "heavy" drinking also vary. In general, and to simplify a "standard drink" can be considered equal to 10 g of alcohol. A glass of wine, beer or half a glass of liquor would equivalente a beverage. For example in United States the standards are as following: moderate drinking is for women less than 2 drinks per day and less than 3 drinks for men; Heavy drinking is more than 7 drinks per week or 3 per occasion and more than 14 drinks per week or 4 per occasion; Bingo drinkers is 4 or more drinks in a row for women and more than 5 for men^[5].

PANCREATITIS

Alcoholic pancreatitis is a potentially fatal illness that may be short term (*i.e.*, acute) or long term (*i.e.*, chronic). The relationship between acute and CP is complex. Symptoms are shared by acute and CP and include abdominal

pain and interference with normal pancreatic functions. Although the prevalence of alcoholic pancreatitis in the population is unknown, clinicians usually agree that both acute and chronic alcoholic pancreatitis are responsible for a significant amount of illness and death in the world. However, the proportion of cases of pancreatitis attributed to alcohol varies widely among countries and even among different studies in the same country.

There are not universally accepted criteria to assign alcohol as an etiology of patient's pancreatitis but experts defines that varying from consumption of over 50 to 80 g (4-7 drinks/d) with or without a minimum drinking duration^[6-9]. An international consensus defined alcoholic CP based on typical clinical history, threshold alcohol consumption (80 g or more of alcohol for a few years in males and less in females) and morphological evidence of CP on imaging studies or histology^[10].

Besides the alcohol intake, other list of etiologies have been described as factors that could increase the risk for pancreatitis as gallstones, cystic fibrosis, hyperlipidemia, hyperparathyroidism, pancreas divisum or traumas, infections, genetic factors and autoimmune disease^[11,12].

There is only a few numbers of epidemiological studies on the quantitative aspects of risk estimations for pancreatitis in relation to alcohol. In 2004, Corrao *et al*^[13] conducted a meta-analysis of case-control and cohort studies published between 1966 and 1995 that assessed the association between alcohol consumption and CP. Then, Irving *et al*^[14] in a review and meta-analysis published in 2009 analyzed studies published between 1980 and 2008 and assessed the association between alcohol consumption and the risk of pancreatitis. They concluded that the threshold between alcohol consumption and pancreatitis is 4 drinks daily.

However, about 70% of pancreatitis cases are believed to be attributable to chronic, heavy alcohol consumption but this percentage differs between countries^[13,15,16]. Autopsies done on alcohol abusers have shown that up to 75% of them present CP^[17]. On another hand, as less than 10% of consumers of alcohol in excess develop CP, other factors modify ethanol toxicity *in vivo*^[16].

ACUTE PANCREATITIS

Historically it has been well-known that the risk of developing AP increases with increasing doses of alcohol^[18] and with the duration of alcohol abuse^[19], although epidemiological studies have shown that only a minority of heavy drinkers develop evident pancreatitis episodes^[20,21]. This correlation shows again that besides of alcohol effects, additional factors are involved in AP develop.

Alcohol is the second most common cause of AC after gallstones^[22]. The clinical features at the time of initial presentation are abdominal pain, jaundice, distal common bile duct obstruction and exocrine or endocrine insufficiency. Generally, the onset of alcoholic pancreatitis occurs in the 4th decade of males with an average of alcohol consumption around 150 g/d for a period of

Table 1 Alcoholic pancreatitis epidemiology in the different countries

Ref.	Country	Alcoholic etiology
Layer <i>et al</i> ^[7]	United States	56%
Coté <i>et al</i> ^[31]	United States	45%
Yadav <i>et al</i> ^[32]	United States	51%
Lin <i>et al</i> ^[36]	Japan	56%
Cavallini <i>et al</i> ^[6]	Italy	43%
Frulloni <i>et al</i> ^[37]	Italy	79%
Lankisch <i>et al</i> ^[9]	Germany	78%
Nøjgaard <i>et al</i> ^[29]	Denmark	44%
Dite <i>et al</i> ^[33]	Czech Republic	60%
Ammann <i>et al</i> ^[38]	Switzerland	71%
Robles-Díaz <i>et al</i> ^[39]	Mexico	68%
Dani <i>et al</i> ^[40]	Brazil	90%
Marks <i>et al</i> ^[41]	South Africa	80%
Balakrishnan <i>et al</i> ^[42]	India	33%

10-15 years^[23]. Initially patients present acute abdominal pain, elevated serum levels of pancreatic enzymes and evidence of pancreatic damage in imaging studies.

These acute toxic effects of alcohol on the pancreas are considered AP but the progression of acute episodes (potentially reversible) leads to chronic disease with irreversible changes in the pancreas.

Traditionally, AP has been classed as fundamentally different from CP as the first one is characterized by restoration of normal pancreatic histology after full clinical recovery^[24]. However, acute, recurrent acute and CP are now regarded as a disease continuum^[25,26]. For this reason, the majority of the epidemiologic studies of alcoholic pancreatitis are referred to CP.

There is no data in the literature showing whether the heavy alcohol intake (> 80 g/d) in abstainers or moderately drinkers is a risk factor for AP. Also it is unknown whether this risk would be the same for all alcoholic beverages (wine, beer or spirits).

CHRONIC PANCREATITIS

CP is an inflammatory disorder of the pancreas typically associated with heavy alcohol consumption. Clinical features of CP consist of abdominal pain, recurrent attacks of clinical AP, and exocrine and/or endocrine insufficiency^[27].

Alcohol is the most common cause for CP^[22]. Clinical and experimental studies analyzing alcoholic CP development have concluded that alcoholic pancreatitis begins as a acute process that progresses to chronic irreversible pancreatic damage as a consequence of repeated acute attacks^[23,28].

The overall survival in patients with alcoholic pancreatitis is significantly lower compared with the background population, but most of the patients die from causes unrelated to pancreatitis^[29,30].

Dufour *et al*^[16] concluded that CP development is proportional to the dose and duration of alcohol consumption (minimum, 6-12 years of approximately 80 g of alcohol per day).

The incidence rates of CP and the proportion of cases attributed directly to alcohol etiology differ based on geographic distribution (see Table 1).

In United States alcohol etiology accounts around 50%-55% depending on the study. Layer *et al*^[7] published a study with patients obtained since 1976 to 1982 and they found that 56% were heavy drinkers (> 50 g/d) and present alcoholic etiology. Coté *et al*^[31] published their results from a multicenter study (2000-2006) in 2010 concluding that alcohol contributes to CP in 45% of the patients. In 2011, Yadav *et al*^[32] published a population-based study with patients from Mayo Clinic in Olmsted County, MN concluding that 51% presented alcoholic CP. In these studies patients with alcohol consumption of > 50 g/d were defined as alcoholic CP.

In general this percentage is lower than Europeans series^[6,9,33,34] or other regions^[35] (67%-89%) but similar to those from Japan (56%)^[36].

In European series there is some variability between countries. For example in Italy the described percentage was 43%-79%^[6,37], Germany 78%^[9], Denmark 44%^[29], Czech Republic 60%^[33] and Switzerland 71%^[38].

The series published in Mexico show 68%^[39] of patients with alcoholic etiology, while alcohol is the responsible factor in 90%^[40] of patients in Brazil, 80%^[41] in South Africa and 33%^[42] in India.

Taken together the data presented above, independently of the region it has been shown that 50% or more of AP or CP are associated with alcohol consumption.

Besides of the geographic distribution, CP due to alcohol consumption could be different based on the race but not on the sex. Lowenfels *et al*^[43] determined that at equal levels of consumption the rates of alcoholic pancreatitis are similar for males and females although patients with alcoholic pancreatitis are more likely males. This is due to the overrepresentation of males among patients with alcoholic pancreatitis, showing a higher prevalence of alcohol consumption than sex-based differences in susceptibility.

Also, regardless to the race it was initially described by Lowenfels *et al*^[30] and then confirmed by other authors^[44-46] that blacks have two to three folds higher rates of alcoholic pancreatitis. Other authors have described that polymorphisms associated to specific populations and races are associated with functional differences in alcohol metabolizing enzymes leading to variation in pancreas damage^[47].

However, detailed reasons for geographic or racial differences in susceptibility to alcoholic pancreatitis are still unknown and most likely are because differences in alcohol intake influenced by habits and genetic susceptibility. Further investigations are needed to confirm that or look in detail for cofactors associated to alcohol consumption.

Based on alcohol consumption, Kristiansen *et al*^[48] estimated that the risk of any pancreatitis among non drinkers (abstainers) is 1.33% while it is among 2.5% (1.6% acute and 1.6% chronic) in heavy drinkers (> 35 drinks/wk or > 5 drinks/d). Lowenfels *et al*^[30] concluded that the risk of pancreatitis among heavy drinkers (> 5

drinks/d) is about 2%-3%.

Also, some studies have been made to evaluate whether the type of beverage (beer, wine or spirits) or the frequency of drinking (daily, almost daily, weekly or monthly) is associate with the risk of pancreatitis^[48]. This study concluded that consumption (> 14 drinks/wk) of beer but not wine or spirits increase the risk of pancreatitis. However this analysis was limited by the number of cases at high levels of consumption. These authors did not find an independent association between the frequency of consumption and risk. In addition some experimental studies carried out in animals conclude that prolonged ethanol feeding does not induce CP although causes little histological changes and variation in pancreatic enzymes^[49,50].

Although it has been well established that pancreatic inflammation appears to increase the risk of PC^[51] and it could be that alcoholic pancreatitis could leads also to PC, future epidemiological studies are needed to analyze this correlation in population.

Some studies have indicated that CP can result in type 2 diabetes, and with a time (up to 20 years) 2%-4% of these pancreatitis cases will develop PC^[52]. Also, long-standing type 2 diabetes is a risk factor for PC^[53]

Even in heavy alcoholics, CP and alcoholic cirrhosis seldom occur together in the same patient^[54,55], despite a few contradictory reports. The mechanisms or factors determining this dichotomy of some alcoholics developing pancreatitis and others developing liver cirrhosis have not been adequately explained. Whether this can be explained by the quantity, duration, and pattern of drinking, or by other cofactors, tobacco smoking, genetic predispositions or dietary factors is debatable.

Veena *et al*^[56] showed that a longer duration of use and bigger amounts of alcohol consumption are necessary before cirrhosis disease compared with CP.

PANCREATIC CANCER

Looking at the risk factors of PC, cigarette smoking represent one of the most important contributing lifestyle risk factor accounting around 20% of the patients. Other factors include CP, diabetes, *Helicobacter pylori* infection, obesity, family history of PC and also heavy alcohol consumption^[57].

While the association between alcohol abuse and pancreatitis is well established the association between alcohol consumption and PC is less clear and remains controversial.

Historical studies in different cohorts have shown that patients with CP have an increased risk of PC; the excess risk was observed in men and women^[52].

Epidemiological data on alcohol and PC are difficult to interpret due to several reasons as: the small sample size (and limited power to detect a possible weak effect of a rare exposure), variability in dose and time of alcohol exposure and other causes influencing (genetic or environmental).

Since 2009 three pooled data analysis and one meta-analysis have been performed. The first pooled study published in 2009 was adjusted for age, smoking status, diabetes, weight, food intake and time of exposure. The control group was no drinkers (0 g ethanol/d). The authors showed a moderate effect of heavy drinking (> 30 g ethanol/d or approximately more than 2-3 alcoholic beverages/d) in women but not in men although the difference in the results by gender was not statistically significant. No associations were observed for the different types of beverage (beer, wine or liquor). This finding is consistent with a modest increase in risk of PC for alcohol intakes of at least 30 g/d^[58].

The second pooled analysis^[59] was performed using PanScan study. Analysis was adjusted for age, study, race, smoking status, diabetes and body mass index. The control group was a very light drinkers (> 0-4.99 g ethanol/d) for the total alcohol intake and non-drinkers (0 ethanol/d) for the beverage type group. The author concluded that heavily consumption of alcohol from liquor (> 45 g ethanol/d) was associated with PC in men but not in women and not in men and women combined.

The third pooled analysis^[60] included a big number of PC cases. Analysis was adjusted for age, sex, race, area, smoking status, education, body mass index and diabetes. The study concluded that heavy drinkers (> 9 drinks/d) have a moderately increased risk of PC compared with lightly drinkers (< 1 drink/d).

The meta-analysis of alcohol consumption and PC includes 21 case-control studies and 11 cohort studies published since 2009^[61]. The results obtained indicate that heavy drinkers (> 3 drinks/d) but not moderate or low drinkers, have an increased risk of PC. This result is valid for both men and women.

In summary, these analysis and meta-analysis suggest that heavy drinkers (>30-40 g ethanol/day or > 3 drinks/d) can result in an increased risk of PC. The authors conclude that in a population of 10%-15% of heavy drinkers, 2%-5% of all PC cases could be attributed to alcohol consumption.

Most of the data published in the literature indicate that alcohol drinking at the levels typically consumed by the general population is probably not a risk factor for PC, however heavy alcohol drinking may be related to PC risk^[62]. As an extreme case, Gupta *et al*^[63] conclude that men binge drinkers (> 5 drinks/episode or > 70g ethanol/episode) leads to a 3.5-fold increased risk of PC and this risk is higher with the numbers of drinks per binge episode. This effect is greater in current smokers than in former or never smokers.

In contrast, most previous epidemiological studies could not demonstrate an excess risk for PC associated with moderate alcohol intake. Velema *et al*^[64] did not find sufficient evidence for a causal relationship. Ye *et al*^[65] concluded that the excess risk for PC among alcoholics was small, and may be totally attributable to a mix of causes, for example also increased by smoking.

Some of these studies demonstrated no significant

elevation in risk of PC was observed among alcohol consumers less than 55 years old; however, no similar elevation in risk was observed among those 55 or more years old^[66].

In conclusion, there is several difficulties to evaluate the association between alcohol and PC and in epidemiological studies the small sample size has probably contributed to the problem of limited power to detect a possible weak effect of a rare exposure (*i.e.*, chronic heavy alcohol drinking). Also causes like exposure measurement error, limited number of cases under study and competing causes have made difficult study the potential effects of alcohol consumption on the risk of PC^[67].

Compared with the general population, alcoholic drinkers without alcoholic CP or alcoholic liver cirrhosis have a modest 40% excess risk to develop PC. Even patients diagnosed with alcoholic CP or liver cirrhosis, have only two folds risk for PC. In addition, it has been shown that non-alcoholic CP patients have a markedly greater excess risk for PC, and this risk is higher than that among alcoholic CP patients^[65]. These data suggest that in some circumstances, pancreatitis may be an early manifestation of an as yet undiagnosed PC. Also Kudo *et al*^[68] concluded that alcohol drinking was not significant risk factor for developing PC in CP patients. So far, no studies have demonstrated that alcoholic pancreatitis leads to an increased risk of PC compared with non-alcoholic pancreatitis.

Taking these data together, although the role of alcohol consumption in PC remains unclear, it appears that low to moderate alcohol consumption is not associated with PC risk, but chronic heavy drinking (and perhaps prolonged binging, although available data are confusing) may increase risk of PC^[58,59,61,63]. Heavy alcohol consumption may increase PC risk by potentiating the effects of other risk factors such as tobacco smoking, poor nutrition, and inflammatory pathways related to CP, but also may have independent genetic and epigenetic effects.

Overall alcohol intake is only one dimension of drinking behavior. Other considerations such as spacing of drinking occasions, quantity of alcohol consumed, type of alcoholic beverages, ways in which beverages are mixed and commodities consumed in conjunction with alcoholic beverages as salt^[69], coffee or tobacco or food^[70] are important of pancreatic disease and were described many years ago.

POTENTIAL MECHANISMS OF ALCOHOL CONSUMPTION AND PANCREATIC DISEASES

Over the last decades there have been numerous efforts to elucidate the mechanisms by which alcohol damages the pancreas.

The injurious effects of ethanol on the pancreas are mediated through different mechanisms^[71] as (1) sensitization of acinar cells to cholecystokinin (CCK) inducing

premature activation of zymogens^[72]; (2) potentiation of the effect of CCK on the activation of transcription factors, nuclear factor- κ B and activating protein-1^[73,74]; (3) generation of toxic metabolites such as acetaldehyde and fatty acid ethyl esters; (4) sensitization of the pancreas to the toxic effects of coxsackievirus B3^[75]; and (5) activation of pancreatic stellate cells by acetaldehyde and oxidative stress and subsequent increased production of collagen and other matrix proteins^[76].

Chronic alcohol exposure leads to impaired exocytosis mediated by acetaldehyde-induced microtubular dysfunction and apical cytoskeleton reorganization in acinar cells, with a subsequent accumulation of intracellular enzymes^[77]. In addition, alcohol decreases the stability of zymogen and lysosomal membranes and enhances acinar cell sensibility to CCK further increasing susceptibility to pathological enzyme activation^[78,79]. Some theories also show that physiologically ethanol leads to the formation of protein secretory plugs that obstruct pancreatic ducts, spasm of the sphincter of Oddi or decreased tone of the sphincter causing reflux^[80-82].

Ethanol and its major metabolite, acetaldehyde, are classified by the International Agency for Research on Cancer as group 1 carcinogens^[83].

Alcohol metabolism depends on enzymes that transform ethanol. Genes for these modifying enzymes have specific polymorphisms that differ between subjects and races leading to differences in susceptibility to alcohol effects and alcohol dependence^[47].

Although the liver is the major ethanol-metabolizing organ in the body, the pancreas can metabolize alcohol both via oxidative and non-oxidative pathways.

The oxidative pathway is catalyzed by the enzyme alcohol dehydrogenase (ADH) and the cytochrome P450 and produces the metabolite acetaldehyde. Finally, the oxidative alcohol metabolism results in the generation of oxygen species (ROS)^[84] and a depletion of the ROS scavenger glutathione^[85]. The increased ROS production (which damage DNA and proteins) and a reduction of proteins that eliminate this ROS (glutathione and enzymes related) lead to oxidant stress and resultant damage in tissue. This stress could be responsible for induce alcoholic pancreatitis as has been demonstrated by several models^[86-88].

But in pancreas, the non-oxidative pathways may be more important than oxidative metabolism, generating fatty acid ethyl esters (FAEE) by fatty acid ethyl ester synthases (FAEE synthases)^[89]. It has been shown that pancreas exhibits higher FAEE synthase activity than liver^[90] and FAEEs accumulation have been observed in human and rat pancreas after alcohol intake^[91-93].

The products of alcohol oxidation (acetaldehyde and ROS) and of non-oxidative metabolism have been reported to cause acinar cell injury. Acetaldehyde cause morphological changes in rat and dog's pancreas^[94] and it has been showed that inhibits CCK-simulated acinar cell secretion^[95]. Also, several studies have demonstrated that alcohol intake causes oxidant stress within the pan-

creas^[86-88] which may play a role in the alcohol-induced destabilization of zymogen granules and lysosomes. In addition, alcohol oxidation contributes to acinar damage altering the intracellular redox state (a reduced NAD/NADH ratio and increased lactate/piruvate ratio). Other results obtained in isolated mouse pancreatic acinar cells suggest that FAEEs leads to mitochondrial damage, loss of ATP and rise in cytosolic free calcium, which leads to acinar cell toxicity^[96]. Other authors have shown that acute application of ethanol at clinically relevant concentrations (1-50 nmol/L) of isolated acinar cells resulted in calcium influx due to the production of oxidative metabolites of alcohol^[97]. Together, these data show that the role of alcohol metabolites in acinar cell damage could be due to aberrant calcium signals^[98]. FAEEs can elevate Calcium greater than ethanol alone. In addition, FAEEs and their products, fatty acids induces necrosis in acinar cells and this process could be avoided by calcium chelation^[99].

These physiological changes leads to the pathobiology found in alcoholic pancreatitis including acute and chronic inflammation, elimination of parenchymal cells of the pancreas by a deregulation of apoptosis/necrosis and/or modification in cell proliferation^[49]. The hypothesis called “necrosis-fibrosis sequence” shows these pathological changes where in the early episodes of pancreatitis, patients present focal necrosis and mild fibrosis while patients evaluated years later of the onset of symptoms presents fibrosis and calcifications but not necrosis^[100].

But the fact that only a minority of heavily drinkers develops pancreatitis or PC indicates that other susceptibility factors as lipid tolerance, smoking or hereditary factors play an important role. In the last decades, genetic susceptibility has been considered between the factors that contribute mainly to the development to alcoholic pancreatic diseases.

One study showed an association between a polymorphism of the gene for one FAEE synthase enzymes, carboxylester lipase and risk of developing alcoholic pancreatitis^[101].

In addition, the G191R variant in the anionic trypsinogen gene *PRSS2*, has been shown to result in a form of trypsin that is easily degraded, is more infrequent in alcoholic pancreatitis patients compared with healthy controls^[102].

Other studies have demonstrated that mutation N34S in *SPINK1* gene is found in 5%-5.8% of patients with pancreatitis compared with 1% in healthy controls^[103,104]. But still the functional consequences of this mutation are unknown.

One of the enzymes that have been also related to alcoholism and drug dependence for decades is ADH. Li *et al*^[105] performed a recent meta-analyses and confirmed strong associations of the *ADH1B* and *ALDH2* genes with alcoholism and alcohol-related medical diseases^[106]. Recently, Celorrio *et al*^[107] demonstrated that some specific polymorphism in the genes *TH*, *ADH1B* increase the risk to develop diseases a consequence of excessive

consumption of alcohol.

Although it is clear that alcohol consumption is genetically influenced, but characterized by incomplete penetrance, phenocopies, heterogeneity, and polygenic inheritance.

In conclusion, nowadays it appears clear that alcohol consumption is the first or second most common cause of pancreatitis. Based on the different epidemiology studies published in the literature the percentage of pancreatitis cases attributable to alcohol abuse vary since 30% to 90% between countries. A statistical association has been shown with a threshold of ≥ 5 drinks per day with a dose of alcohol ≥ 50 g/d.

But despite that excessive alcohol consumption is primarily responsible for most cases of pancreatitis, alcohol intake alone is not sufficient to lead to this disease, as less than 10% of heavily drinkers develop pancreatitis.

Regarding to PC, the role of alcohol consumption remains less clear, and low to moderate alcohol consumption do not appear to be associated with PC risk, but only chronic heavy drinking increase the risk compared with lightly drinkers.

Genetic variability and environmental exposures such as smoking and diet could act synergistically with regard to pancreatitis and PC and should be considered for further investigations. Probably heavy alcohol consumption may increase pancreatic disease risk most likely potentiating the effects of these other risk factors, but also may have independent genetic and epigenetic effects.

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