Nonalcoholic fatty pancreas disease as an endogenous alcoholic fatty pancreas disease

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Abstract

Nonalcoholic fatty pancreas disease (NAFPD) is closely linked to nonalcoholic steatohepatitis (NASH), suggesting that the two conditions share a common etiopathogenetic background. In Addition, growing evidence indicates that endogenous ethanol (EE) plays a fundamental role in NASH pathogenesis. Accordingly, it is intuitively appealing to assume that EE plays also a causative role in NAFPD development. This connection is further supported by the finding that NAFPD shares with alcoholic fatty pancreas disease (AFPD) similar metabolic signaling pathways and histopathological features. However, low blood alcohol concentrations (BAC) along with the alleged inability of gut microbiota to produce toxic amounts of ethanol are the main obstacles to validate the idea of an endogenous alcoholic fatty pancreas disease (EAFPD). Here, we provide a mechanistic explanation reconciling the EAFPD hypothesis with these apparently conflicting observations. The key conclusions of our investigation are as follows. First, ethanol is a prodrug, implicating that under extensive presystemic metabolism BACs can be low and/ or absent. Second, oro-gastrointestinal microbiota may produce higher amounts of ethanol than those required to cause AFPD. Last, livers of NASH/NAFPD individuals overexpress all genes encoding alcohol-metabolizing enzymes identically to livers of patients with alcoholic hepatitis. Even more importantly, the up-regulation of these genes is higher in the early steatotic stage of nonalcoholic fatty liver disease than in alcoholic hepatitis. This suggests a greater exposure of the liver, and by extension, of the pancreas, to ethanol in the former than in the latter condition. In summary, this paper provides a mechanistic framework for how NAFPD indeed may be an EAFPD.

Introduction

Nonalcoholic fatty pancreas disease (NAFPD) is a broad-spectrum disorder ranging from simple pancreatic steatosis to acute and chronic fibrosing nonalcoholic steatopancreatitis (NASP) and pancreatic cancer [1–4]. There are two distinct forms of this disease: primary or obesity-associated NAFPD, and secondary forms, which are linked to congenital syndromes, toxic agents, medications, viruses, and severe malnutrition [5]. Its risk factors include insulin resistance, prediabetes, diabetes, hyperferritinemia, central obesity, and hypertriglyceridemia [6,7]. Additionally, body mass index, HbA1c, total cholesterol, LDL-cholesterol, platelet count and systolic blood pressure are also a putative risk for NAFPD [8]. Based on these findings, it is clear that NAFPD and NAFLD share very similar environmental-related risk factors, suggesting a common etiological background between them. Agreeing with this observation, hepatic steatosis increases by nearly 14-fold the odds of having NAFPD [9], whereas ~70% of the individuals with NAFLD concurrently had NAFPD [10]. Moreover, interlobular and total pancreatic fat are positively correlated with NAFLD activity score [11], whereas pancreatic intralobular fat and impaired pancreatic β-cell function are heralds of NASH [11,12].

It is known that NAFPD shares with alcoholic fatty pancreas disease (AFPD) similar metabolic pathways [3,13–16], as well as histopathological features [1,3,4,17–25]. In addition, NAFLD patients produce significantly more endogenous ethanol (EE) than controls, suggesting that it plays an important role in its pathogenesis [26–32]. Thus, as NAFPD is closely linked to NAFLD and NAFLD-related conditions [1,5,10,33–35], it follows that EE can also exert a relevant role in the pancreatic injury. Taken together, these data allow us to hypothesize that NAFPD and AFPD are the same disease with different clinical presentations.

Currently, there is no study investigating a causal relationship between EE and NAFPD. Hence, the main focus this article is to provide a mechanistic explanation of how NAFPD may indeed be an endogenous alcoholic fatty pancreas disease (EAFPD). In this context, we will demonstrate how subjects with NAFLD/NAFPD can produce higher amounts of ethanol than those required for causing AFPD [36] without inducing significant blood alcohol concentration (BAC).

The hypothesis

Ethanol is a prodrug

Similarly to other prodrugs, ethanol must be metabolized to

acetaldehyde (ACD) and/or fatty acid ethyl esters (FAEEs) for exerting the most of its injurious effects. Compelling evidence comes from the finding that inhibitors of oxidative and nonoxidative metabolism of ethanol abrogate its cytotoxic effects [37–43]. The obvious implication of this is that an endogenous alcoholic disease may develop concomitantly with low/negligible BACs.

Oro-gastrointestinal production of ethanol and acetaldehyde

Gut microbiota of healthy individuals produces trace quantities of ethanol from unabsorbed dietary carbohydrates [44–47]. Next, it is converted in the liver to acetaldehyde, which in turn is oxidized to non-toxic concentrations of acetate [47]. The demonstration that the baker's yeast elicits a 4-fold increase in gastric EE concentration supports this view. Further, pharmacological blockade of alcohol dehydrogenase (ADH) elicits a 130-fold rise in EE content of hepatic venous blood in rats [47].

On the other hand, in patients with NAFLD/NAFPD the emergence of small intestinal bacterial overgrowth (SIBO) [48–53] is associated with significantly increased body concentrations of EE compared to controls [27,32,54,55]. Further, concurrent obesity-related hypochlorhydric/achlorhydric conditions may also contribute to EE production [56–61]. Thereby, in dysbiotic disorders gut concentrations of EE may be even higher than those found after moderate drinking [62–64]. In line with this, genomic studies suggest that alcohol-metabolizing enzymes are differentially expressed in livers of NAFLD/NAFPD patients [28,30,65–68]. These up-regulated enzymes can work at 500 to 3000 mM (~23 to 138 g) ethanol concentrations [69].

Of note, gut microbial makeup of these dysbiotic conditions includes both alcohol-producing [26,51,62,64,70–79] and alcohol-degrading microorganisms [62,80–85]. In this setting, both host and microbial enzymes of the oro-gastrointestinal tract produce ethanol and oxidize it into acetaldehyde in a dose-dependent manner [70,83,86–91]. Interestingly, on the one hand, exposure to ethanol stimulates alcohol-degrading enzymes [67,92], and on the other, it inhibits the catalytic action of aldehyde dehydrogenase (ALDH), thereby contributing to acetaldehyde accumulation [93–98]. This, coupled with hepatic first-pass metabolism (FPM) of ethanol may reduce substantially BACs. A study has clearly demonstrated this extensive metabolism of ethanol in chronic alcohol abusers. According to it, to maintain a steady-state BAC between 1.5 to 4.5 mg/dL, it was necessary performing a constant intravenous infusion of ethanol at a rate of 57.6 to 115.2 g/d [99]. In this setting, blood ethanol diffuses rapidly into liver and gastrointestinal tract, where it undergoes extensive first-pass metabolism by both host and microbial enzymes. For comparison purposes, mean BAC was 7.1 mg/dL 12-h after an overnight fast in obese patients with NAFLD [32]. For maintaining this BAC level, each patient would have to produce 114 g of EE or receiving continuous intravenous ethanol infusion at a rate of ~9.5 g/h.

A remarkable exception to this metabolic pattern is frequently observed in the auto-brewery syndrome. This disorder, in addition to SIBO, is accompanied by fungal overgrowth of alcohol-producing organisms such as *Candida* sp and/or *Saccharomyces cerevisiae* [62,71,72,76,100–102]. Characteristically, auto-brewery syndrome patients produce massive quantities of EE from dietary carbohydrates. In this scenario, the first-pass metabolism of ethanol is insufficient to avoid drunkenness and BACs can reach 250-350 mg/dL [76].

Endogenous production of fatty acid ethyl esters (FAEE)

Presently, there is no study investigating the role of FAEEs in NASH/NAFPD pathogenesis. Notwithstanding, it is known that healthy subjects not exposed to exogenous ethanol have endogenous trace of FAEEs in body fluids [103,104]. As the two substrates required for FAEEs biosynthesis, ethanol [68][77] [105] and free fatty acids [13,106–109], are significantly elevated in NASH/NAFPD body fluids, it is quite possible they are formed in toxic amounts in the pancreas and oro-gastrointestinal tract.

Harmful effects of acetaldehyde and fatty acid ethyl esters on the pancreas

The ALDH activity in the pancreas is nearly fivefold lower than that of the liver, contributing in this way to acetaldehyde glandular accumulation [110]. Despite this fact, data from animal studies have shown that acetaldehyde by itself does not elicit directly acute pancreatitis [111,112]. Conversely, some studies support the involvement of acetaldehyde in both pancreatic fibrosis and carcinogenesis [16,113–117]. Dysbiotic gut microbiota is able to convert both exogenous and endogenous ethanol to acetaldehyde in a dose-dependent manner [70]. This extrahepatic acetaldehyde (generated outside the liver) is about 30 to 330-fold more hepatotoxic than that formed in the liver [118,119]. Accordingly, it is reasonable to assume that extrahepatic acetaldehyde may play a protagonist role in more advanced stages of NAFPD pathogenesis.

On the other hand, the critical role of FAEEs in acute pancreatic injury is already well-established [43,120–122]. In keeping with these data, the pharmacological blockage of FAEEs biosynthesis prevents [43,120], whereas the stimulation of its production promotes acute pancreatic damage [43,120,121]. By contrast, the role of FAEEs in pancreatic fibrosis is still far from being fully settled [123].

Estimating daily endogenous ethanol production and its first-pass metabolism

For the calculations, we use a validated physiologically-based pharmacokinetic model of body alcohol metabolism [124] and demographic data of patients taken from a published study [32]. According to this study, NAFLD patients had an average BAC of 7.14 mg/dL 12-h after an overnight fast [32]. We assume that the mean patient height was 1.74 m (68.8976 inches), and Watson's equation was used for total-body water calculation (*TBW*) [124].

Equation (1): calculating *TBW*

ΣVd = 2.44 – (0.09516 x age) + [0.1074 x (*height in inches*) x 2.54)] + [0.3362 x *weight in pounds* / 2.2045)]

ΣVd is *TBW* or volume of distribution in which alcohol will be dispersed according to the *age, weight, height*, and patient *gender* [124]. Inserting the figures from Menezes et al's study [32] (*age*, 48 *years, BMI*, 35 kg/m², and body *weight*, 107.20 Kg [236.3355 lb]), we obtain:

ΣVd = [2.44 – (0.09516 x 48)] + [0.1074 x (68.8976 x 2.54)] + [(0.3362 x 236.3355) /2.2045] = 52.70 *liters*. Then, we use the modified Widmark's equation.

Equation (2): calculating *total alcohol consumed/produced* (*TAC*)

$TAC = \Sigma Vd$ x (BAC_{obj} + $\beta 1n$ x t) / $B\ell H2O$

TAC means total alcohol endogenously produced; BAC_{obj} is the objective blood-alcohol concentration result; $\beta 1n$ is the range of the ethanol elimination rate (10 to 20 mg/dL/h for healthy individuals and 20 to 30 mg/dL/h for heavy drinkers); *t* is the time from the start of drinking (here meaning the start of carbohydrate intake) until the

time of the BAC test, and $B\ell H2O$ is the constant (80.65) approximate percentage of water in blood. It follows that TAC = 52.70 x (7.14 + 20 x 12)/80.65 = 161.49 g of ethanol [124].

This means each patient produces 161.49 g of ethanol after a 12-h overnight fast (Figure 1). Hence, by extrapolation, the daily production of ethanol should reach 484 g after eating three equicaloric meals (3 x 161g = 484g). Once the patients' BAC is consistently low, one concludes that ethanol has undergone extensive conversion to acetaldehyde in the gut-liver axis. The fist-pass metabolism (FPM) of ethanol in the gut-liver axis can also be accurately calculated. For this, we need initially to calculate the alcohol burden in the circulation utilizing some data we already described.

Equation (3): calculating *circulation alcohol burden* (*CAB*).

CAB = ($BACobj$ x ΣVd) / 80.65. Inserting the data into the equation, one obtains CAB = (7.14 x 52.70) / 80.65 = 4.60 g of ethanol.

FPM of ethanol can be estimated subtracting circulating alcohol burden (4.60 g) from total alcohol produced (161.49 g). We obtain the amount of ethanol metabolized (161.49-4.60 = 156.80 g) (Figure 1) [124]. This is consistent with the finding that blind-loop contents of a 0.3 kg rat oxidize ethanol at a rate of 123 mg/h [70]. If these data could be extrapolated to a SIBO patient weighing 107.20 kg, FPM of EE should reach about 43.90 g/h.

Supporting these observations, gene of all alcohol-metabolizing enzyme are differentially expressed in livers of NASH patients [30]. Also, intragastric administration of ethanol (1 g/kg) to rats with SIBO evoked a 10-fold increase in the portal concentration of acetaldehyde, whereas portal and systemic BACs reached negligible values [70]. Another study showed similar portal venous concentrations of ethanol in obese and lean mice, suggesting intraluminal FPM of ethanol in the obese group [125]. In addition, host ADH3 present in the stomach, small bowel, and liver may play a significant role in FPM of ethanol. It works at ethanol concentrations of 0.5 to 3 M (~23-138 g) [126]. Ultimately, adult human liver can metabolize ~240 g of ethanol per day [127,128].
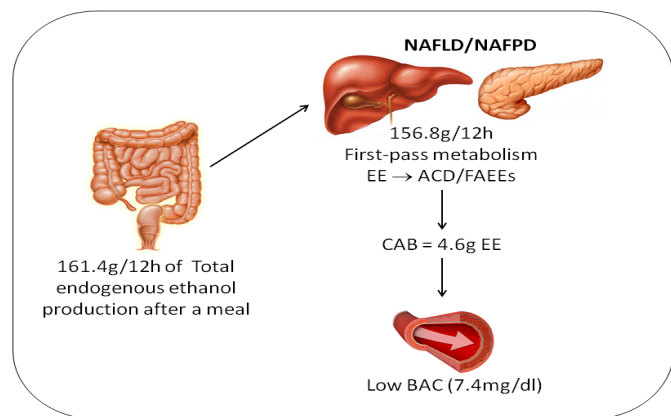

Figure 1. **Estimate of the production, metabolism, and circulation of endogenous ethanol according to a physiologically-based pharmacokinetic model of body alcohol metabolism.** The calculations are based in 20 NAFLD patients with the following average values: age: 48 years, BMI: 35 kg/m², height: 1.74m, weight: 107.2 Kg, and BAC: 7.1 mg/dL 12-h after an overnight fast [32]. The activity of aldehyde dehydrogenase (ALDH) in the pancreas is nearly fivefold lower than that in the liver, whereas non-oxidative metabolism of ethanol is 10 times higher in the pancreas than in the liver, contributing to accumulation of toxic acetaldehyde and fatty acid ethyl esters in the gland. EE = Endogenous Ethanol; ACD = Acetaldehyde; FAEEs = Fatty Acid Ethyl Esters; CAB = Circulating Alcohol Burden; BAC = Blood Alcohol Concentration.

Hepatic overexpression of genes encoding alcohol-metabolizing enzymes

Genomic studies demonstrated that all genes involved in oxidative metabolism of ethanol and acetaldehyde are up-regulated in the livers of NAFLD/NASH patients [28,30,65,66,68]. This suggests that the liver and, probably the pancreas, of these patients consistently metabolize high amounts of EE.

Discussion

Since ethanol is a prodrug, it becomes clear that an endogenous alcoholic disease may develop with low or even undetectable BACs. Yet, although NAFPD has the same histopathological features and metabolic pathways of AFPD, it is not recognized as an EAFPD. The underlying rationale for this is the purported inability of gut microbiota to produce toxic amounts of ethanol and the low BACs found in NAFLD/NAFPD [70,129].

As opposed to this, our calculations showed that an obese patient with NAFLD may produce larger amounts of ethanol than those required for causing AFPD [36] in the presence of low BAC. The finding that gene expression of alcohol-metabolizing enzymes in NAFLD livers is indistinguishable from that of alcoholic hepatitis supports this view [68]. Notably, hepatic ADH4 expression was shown to be ~40-fold higher in NASH livers than in controls [28]. This means that hepatic concentrations of EE can reach up to 1.5 M (6.9 g/dL) without enzyme saturation [69]. Even more surprisingly was the finding that the expression of alcohol-metabolizing genes was higher in livers with mild NAFLD than in alcoholic hepatitis [68].

It is known that as soon as EE is formed, it is dose-dependently converted to acetaldehyde and/or FAEEs. To illustrate, gut contents of rats with SIBO oxidizes ethanol at a rate of 0.99 to 1.99 μM/min/ml, respectively, in anaero- and aerobiosis [70]. Thus, a NAFPD patient with a dysbiotic small bowel contents around 2000 ml could metabolize ethanol at a rate of 3980 μM/min. This amounts to an ethanol elimination rate of 528 g per day, without including gastric, colonic, and hepatic FPM. This key role of gut microbiota in FPM of ethanol is supported by studies showing that oral antibiotics protect against both NAFLD/NAFPD [130–134] and alcoholic liver disease [135]. Furthermore, germ-free animals are also protected against diet-induced obesity-related disorders [136–138] as well as ethanol-induced liver injury [139].

Besides, individuals chronically exposed to ethanol convert it to its metabolites at a rate 3 to 4 fold higher than that of healthy controls [124,140]. A plausible explanation is that chronic exposure to ethanol leads to hyperinsulinemia [125], which shifts energy supply from glucose to ketone bodies [65]. In turn, high ketone bodies alongside oxidized carbohydrates and iron overload shift ethanol metabolism from low Km ADH1 (that works in the millimolar range) to high Km alcohol-metabolizing enzymes (that work in the molar range) [65,141] such as cytochrome P450 2E1 (CYP2E1), ADH4, and ADH3 [28,30,66,69,126,142,143]. The net result is that large amounts of ethanol may cause organ damage concurrently with negligible BACs (Figure 2) [28,30,65–68].

Big differences between BACs and orally administered ethanol in healthy individuals are found only when it is ingested with a large meal [144]. It may delay for several hours gastric delivery of ethanol to small bowel absorption [145,146]. Seen from this perspective, the pharmacokinetics of EE in patients with NAFPD is likely even more erratic than the above-mentioned.
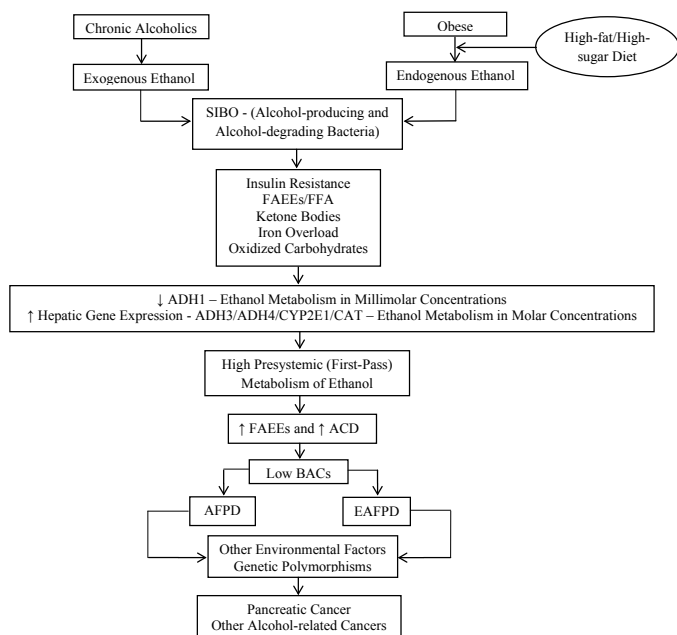
Figure 2. **Possible common pathways in the pathophysiology of exogenous and endogenous Alcoholic Fatty Pancreas Disease**. Chronic alcoholics and obese individuals are respectively exposed to high concentrations of exogenous and endogenous ethanol formed from dietary carbohydrates. This leads to SIBO rich in both alcohol-producing and alcohol–degrading microorganisms. Then, IR and hyperinsulinemia shift energy supply from glucose to ketone bodies. Ketones along FFA, FAEEs, Iron Overload, and Oxidized Carbohydrates inhibit low Km ADH1 activity and induce gene expression of high Km ADH3, ADH4, CYP2E1, and Catalase activities. As a result, the ability to metabolizing ethanol is shifted from millimolar to molar range. The extensive presystemic (first-pass) metabolism of molar quantities of ethanol generates ACD/FAEEs, leading to AFPD/ EAFPD and to the consequent insignificant BACs. Other environmental factors such as obstructive sleep apnea, LPS, glyceraldehyde, methylglyoxal, AGEs, RAGEs, nitric oxide/ peroxynitrite, and ALEs may also contribute to both AFPD and EAFPD development. Importantly, genetic polymorphisms of alcohol-metabolizing enzymes as well as genetic mutations specifically linked to chronic pancreatitis such as CFTR, SPINK1, PRSS1, (CTR)C, and (CLDN)2 confer increased risk of developing disease progression and pancreatic cancer. Of note, obese individuals with NAFPD share with alcoholics the same increased risk of alcohol-related cancers, reinforcing the hypothesis that they are also exposed to abnormally high concentrations of endogenous ethanol. SIBO = Small Intestinal Bacterial Overgrowth; IR = Insulin Resistance; FAEE = Fatty Acid Ethyl Ester; FFA = Free Fatty Acid; ADH = Alcohol Dehydrogenase; CYP2E1 = Cytochrome P-450 2E1; CAT = Catalase; ACD = Acetaldehyde; BAC = Blood Alcohol Concentration; AFPD = Alcoholic Fatty Pancreas Disease; EAFPD = Endogenous Alcoholic Fatty Pancreas Disease; Km = Michaelis Constant; LPS = Lipopolysaccharide (Endotoxin); AGE = Advanced Glycation End Products; RAGE = Receptor for Advanced Glycation End Products; ALE = Advanced Lipid Peroxidation End Products; CFTR = Cystic Fibrosis Transmembrane Conductance Regulator; SPINK1 = Kazal-type Serine Protease Inhibitor-1; PRSS = Protease Serine 1; (CTR)C = Chymotrypsin C; (CLDN)2 = Claudin 2;

Unlike chronic alcoholics, NAFPD patients endogenously and gradually produce ethanol from dietary carbohydrates over meals instead of ingesting it. Moreover, both EE production and metabolization are dose-dependent phenomena which happen simultaneously. Lastly, delayed gastric emptying [147] coupled with SIBO-induced prolonged small bowel transit time [148] allow efficient intraluminal production and metabolization of molar amounts of ethanol. In this way, intraluminal ethanol cannot reach saturating concentrations as well as arrive at the liver in saturating quantities [144]. This process is made easier by the fact that increased concentrations of ACD reduce portal blood flow, causing a decrease in ethanol absorption and, consequently lower portal and systemic BACs [149,150]. This is consistent with a study in chronic alcoholics in which to maintain a steady-state BAC between 1.5 to 4.5 mg/dL, it was necessary performing a constant intravenous infusion of ethanol

at a rate of 57.6 to 115.2 g/d [99]. Briefly, our analysis suggests that the ability of obese patients with NAFLD/NAFPD and SIBO to produce and metabolize ethanol is greater than that of chronic alcoholics.

The non-oxidative metabolism of ethanol is about 10 times higher in the pancreas than in the liver [151], whereas pancreatic ability for oxidizing ethanol is relatively low [16], favoring net build-up of FAEEs within the gland. In addition, chronic alcohol exposure induces overexpression of FAEE synthase-related genes in the pancreas and liver [152]. Thus, given the evidence that FAEEs are synthesized by individuals not exposed to exogenous ethanol [103,104] and that NAFLD/NAFPD subjects are exposed to high concentrations of EE [26–32,65–68], it is unsurprising that FAEEs play a causative role in NAFPD pathogenesis. It is worth mentioning that the pharmacologic blockage of the hydrolysis of FAEEs to free fatty acids prevents pancreatic necrosis [153]. So, FAEEs are sufficient but not necessary for pancreatic injury. Given that free fatty acids are significantly increased in NAFPD/NASH, it is plausible that they may also mediate the pancreatotoxic effects of EE [13,106–109].

Several genetic polymorphisms, including those of alcohol-metabolizing enzymes, are positively associated with an increased occurrence of chronic alcoholic pancreatitis [154–158]. Based on this and in the chronic long-term exposure to EE, we postulate that NAFPD patients carrying these polymorphisms are at increased risk of developing disease progression [159,160] and alcohol-related cancers [61,160–164].

Our analysis indicates that together, endogenous acetaldehyde and FAEEs/free fatty acids may recapitulate the full clinical-pathologic spectrum of NAFPD. Yet, we cannot rule out the involvement of others toxic compounds, particularly during NAFPD progression. Indeed, some studies suggest a possible causal relationship between NAFLD/ NAFPD-related disorders with chronic intermittent hypoxia elicited by obstructive sleep apnea [165,166], bacterial endotoxin [167–169], glyceraldehyde [170], methylglyoxal [171–173], advanced glycation end products (AGE)s [174], receptor for advanced glycation end products (RAGE) [175], nitric oxide/peroxynitrite [176], and lipid peroxidation end products [177,178].

Conclusion

In conclusion, seen from this perspective becomes easier to understand how huge amounts of ethanol (ingested or endogenously produced) may elicit organ injury with insignificant BACs. The EAFPD hypothesis reconciles the apparently contradictory development of an endogenous alcoholic disease concomitantly with low BACs. It can be easily tested in both humans and animal models by conventional laboratory and histopathological technics. Its main limitation is that much of the supporting evidence comes from in vitro, observational, and preclinical studies.

Ultimately, NAFPD is a worldwide public health problem whose causative agents remain to be identified. Therefore, it is expected that if the EAFPD hypothesis is validated by further studies, it might help to implement effective preventive and therapeutic approaches.

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