Letters

Alcohol consumption and smoking dose-dependently and synergistically worsen local pancreas damage

Chronic pancreatitis (CP) is characterised by irreversible damage to the pancreas causing endocrine and exocrine dysfunction which results in decreased quality of life and reduced life expectancy.[1]

Adam *et al* recently published an interesting study on a possible diagnostic tool for CP based on metabolomic profiles of patients and controls.[2]

Our previous international cohort analysis showed that the proportion of patients developing CP is exponentially and directly associated with the number of acute pancreatitis (AP) episodes, thus strengthening the focus on the challenging task of diagnosing CP early.[3 4] However, in addition to diagnosing early, we should also focus on preventive interventions, before the damage becomes irreversible.

Alcohol is the main aetiological factor for CP and both alcohol consumption and smoking increase the risk for recurrence of AP and the development of CP. According to Ahmed Ali *et al*, in a follow-up study of 669 AP patients, smoking represented the dominant risk factor for recurrent AP (RAP) and a combination of alcohol consumption and smoking was the main risk factor for the progression to CP.[5] Therefore, cessation programmes and patient education are extremely important means to intervening and lowering the recurrence of AP and the progression to CP.[6 7] However, total cessation and abstinence often seems impossible for patients and they do not even try. Is it also possible to reduce recurrence and progression by decreasing the amount consumed?

Basic research evidence clearly suggests that alcohol and smoking amplify each other's harmful effects.[8 9] However, large cohorts are lacking to determine whether smoking and alcohol consumption dose-dependently, mutually exacerbate the damage to the pancreas caused by each.

We have used the international cohort in the Acute Pancreatitis Registry initiated by the Hungarian Pancreatic Study Group. Data were collected from 13 countries and 30 medical centres, with 2441 cases included in the analysis. Further characteristics of the cohort and information on methods are available in online supplemental file 1.

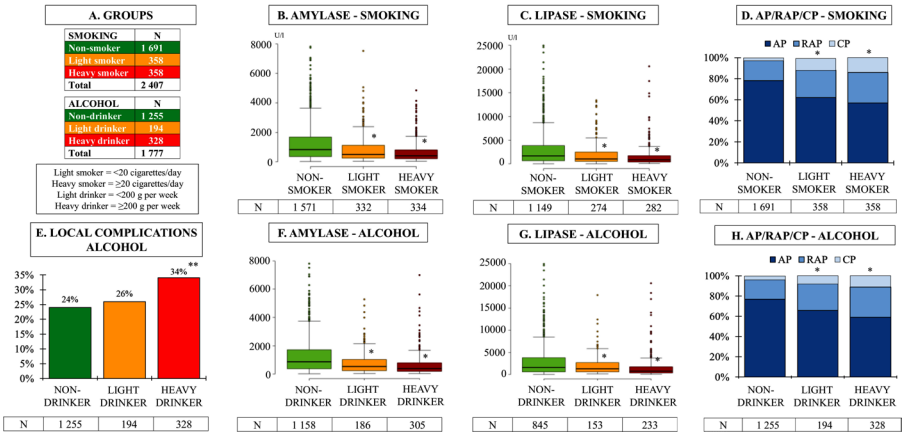

Figure 1 Dose dependency in alcohol consumption and smoking in AP. (A) Light and heavy alcohol consumption and smoking groups and definitions. (B, C) Amylase and lipase levels on admission. (D) Prevalence of RAP and CP (%). (E) Proportion of local complications (%). (F, G) Amylase and lipase levels on admission. (H) Prevalence of RAP and CP (%). *P<0.001, **p=0.003. Pearson's χ^2 test and the Kruskal-Wallis rank sum tests were used. AP, acute pancreatitis; CP, chronic pancreatitis; RAP, recurrent AP.

The patient population was divided into groups according to current amounts of smoking and alcohol consumption. We found that both smoking and alcohol consumption are dose-dependently associated with amylase and lipase levels and with the prevalence of RAP and CP among AP patients. Alcohol consumption was also linked to a higher rate of local complications (figure 1).

Second, we examined the possible synergistic effect of these two risk factors. We arranged the cohort population into four groups based on current smoking and alcohol consumption status (figure 2). Smoking and drinking together are associated with the male sex and linked to the first AP episode 15 years earlier than non-smoking and non-drinking are. Analysing on-admission and outcome parameters between groups, we found that amylase and lipase levels are the lowest and the proportion of moderately severe cases are the highest in the smoking–drinking group, suggesting the most pancreatic tissue damage and local complications here. The highest proportion of patients with RAP was found in both smoking groups, and the largest percentage of CP patients was observed in the smoking–drinking population, suggesting a clear synergising effect of alcohol consumption and smoking and

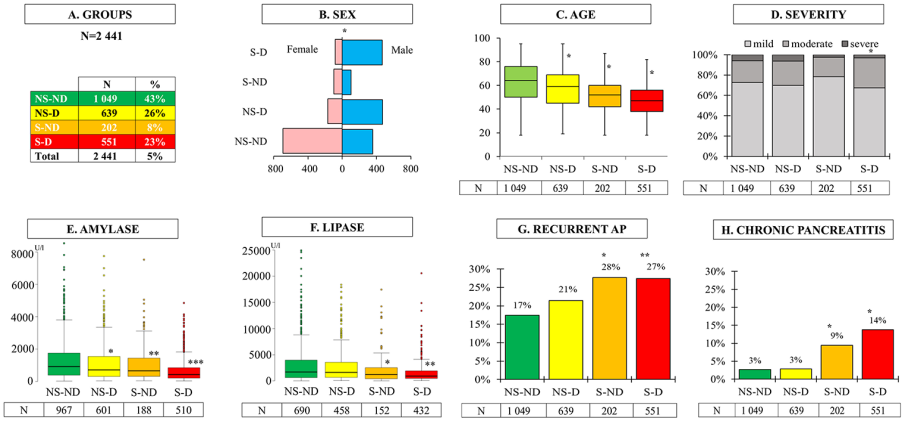

Figure 2 Combined alcohol consumption and smoking groups in AP. (A) Groups. (B) Sex. *P<0.001 in all comparisons. (C) Age. *P<0.001 or p=0.001 in all comparisons. (D) Severity. Moderately severe *p=0.003 vs NS–ND. P=0.022 vs S–ND. (E) On admission amylase level. *P<0.001 vs NS–ND. **P<0.003 vs NS–ND. ***p<0.001 vs NS–ND, NS–D and S–ND. (F) On-admission lipase level. *P<0.003 vs NS–ND, p<0.006 vs NS–D. **P<0.001 vs NS–ND and NS–D. (G) Prevalence of recurrent AP. *P=0.003 vs NS–ND. **p=0.04 vs NS–D. p<0.001 vs NS–ND. (H) Prevalence of chronic pancreatitis. *P<0.001 vs NS–ND, NS–D. Pearson's χ^2 test and the Kruskal-Wallis rank sum tests were used. AP, acute pancreatitis; NS–D: non-smoking–drinking; NS–ND: non-smoking–non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

a highlighted importance of smoking in progression.

Our analysis confirms in a clinical setting that both smoking and alcohol are dose-dependently associated with pancreatic tissue damage and the prevalence of RAP and CP. Moreover, they mutually exacerbate each other's harmful effect. In addition to the development of prognostic and therapeutic measures, further clinical trials on cessation programmes and patient education are needed. Communication to all stakeholders of the importance of at least quitting smoking or cutting the amount of smoking and alcohol consumption is crucial.

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Contributors PH conceptualised the study. ÁV, FI, AS and AP contributed to the data collection and quality assurance. AS, ZS, PM and NF extracted and analysed the data. PH, AS, AP and NF interpreted the data. AS and PH wrote the manuscript. All the authors reviewed and contributed to the manuscript before finalisation and submission. Hungarian Pancreatic Study Group (full names are available in the Contributors section and affiliations are detailed in online supplemental file 1: BE, PJH, SV, RN, KM, KO, FJ, MF, SK, BN, TT, LC, SG, JB, PS, LG, MP, JH, MV, MM, IT, JN, AM, ERM, SG, VS, BB, ATI contributed to the data collection. TN, NF contributed to the interdisciplinary evaluation of the cases. NG conducted preliminary analyses. BE, PJH, SV, RN, KM, KO, FJ, MI, MF, SK, NG, SB, TH, ML, AN, OU, DT, ST, DP, PV and NZ ensured professional data quality control.

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Supplementary file 1 2

Supplementary Table 1. CENTRE DISTRIBUTION

Institute	**City**	**Country**	**Number of cases**
First Department of Medicine, University of Pécs	Pécs	Hungary	877
Department of Medicine, University of Szeged	Szeged	Hungary	423
Szent György University Teaching Hospital of County Fejér	Székesfehérvár	Hungary	395
Department of Internal Medicine, University of Debrecen	Debrecen	Hungary	169
Bajcsy-Zsilinszky Hospital	Budapest	Hungary	152
Dr. Réthy Pál Hospital of County Békés	Békéscsaba	Hungary	67
County Emergency Clinical Hospital - Gastroenterology and University of Medicine, Pharmacy, Sciences and Technology	Tragu Mures	Romania	57
Pándy Kálmán Hospital of County Békés	Gyula	Hungary	31
Vilnius University Hospital Santariskiu Klinikos	Vilnius	Lithuania	31
General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes	Barcelona	Spain	28
Saint Luke Clinical Hospital	St. Petersburg	Russia	28
Helsinki University Central Hospital	Helsinki	Finland	25
Dr. Bugyi István Hospital	Szentes	Hungary	23
Hospital of Bezmialem Vakif University, School of Medicine	Istanbul	Turkey	20
Markusovszky University Teaching Hospital	Szombathely	Hungary	18
Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	Miskolc	Hungary	14
Bács-Kiskun County Hospital	Kecskemét	Hungary	11
Centrum péče o zažívací trakt, Vítkovická nemocnice a.s.	Ostrava	Czech Republic	11
Clinical Hospital Center Rijeka	Rijeka	Croatia	11
Csongrád County Health Center	Makó	Hungary	10
Gomel Regional Clinical Hospital	Gomel	Belarus	8
Bogomolets National Medical University	Kiev	Ukraine	8
Department of Surgery, University of Debrecen	Debrecen	Hungary	7
Gastroenterology, Hepatology and Nutrition Centre, Pauls Stradins Clinical University Hospital	Riga	Latvia	6
Polyclinic of Hospitaller Brothers of Saint John of God	Budapest	Hungary	4
Second Department of Medicine, Semmelweis University	Budapest	Hungary	2
Keio University	Tokyo	Japan	2
Central Military Emergency Hospital "Dr Carol Davila"	Bucharest	Romania	1
Heim Pál National Pediatric Institute	Budapest	Hungary	1
Medical Centre, Hungarian Defence Forces	Budapest	Hungary	1
Total			**2 441**

Supplementary Table 2. CHARACTERISTICS OF THE ANALYSED COHORT

Variable	**Value (n=2441)**
Age in years, median (IQR)	57 (44–69)
Male, n (%)	1 395 (57.1%)
Etiology, n (%)	
Biliary	972 (39.8%)
Alcoholic	475 (19.5%)
Alcoholic and hypertriglyceridaemia	57 (2.3%)
Hypertriglyceridaemia	77 (3.2%)
Post-ERCP	68 (2.8%)
Idiopathic	442 (18.1%)
Combined	89 (3.6%)
Other	261 (10.7%)
Revised Atlanta classification	
Mild, n (%)	1 738 (71.2%)
Moderate, n (%)	579 (23.7%)
Severe, n (%)	124 (5.1%)
Mortality, n (%)	67 (2.7%)
Length of stay in days, median (IQR)	8 (6–12)
Patients with local complication, n (%)	654 (26.8%)
Acute pancreatic fluid collection, n (%)	545 (22.4%)
Pseudocyst, n (%)	191 (7.8%)
Acute necrotic collection, n (%)	218 (8.9%)
Patients with systemic complication, n (%)	205 (8.4%)
Respiratory failure, n (%)	140 (5.7%)
Heart failure, n (%)	52 (2.1%)
Renal failure, n (%)	87 (3.6%)
New-onset diabetes, n (%)	77 (3.2%)

ERCP: endoscopic retrograde cholangiopancreatography
IQR: interquartile range

Supplementary Table 3. DATA QUALITY OF THE ANALYSED COHORT

Synergistic effect	**Total cohort**	**Uploaded data**	**%**
Age	2 441	2 441	**100.0%**
Sex	2 441	2 441	**100.0%**
Etiology	2 441	2 441	**100.0%**
Severity (mild/moderate/severe)	2 441	2 441	**100.0%**
Mortality	2 441	2 441	**100.0%**
Local complications	2 441	2 421	**99.2%**
Fluid collection	2 441	2 422	**99.2%**
Pseudocyst	2 441	2 422	**99.2%**
Necrosis	2 441	2 421	**99.2%**
Diabetes as complication	2 441	2 441	**100.0%**
Systemic complications	2 441	2 433	**99.7%**
Respiratory failure	2 441	2 432	**99.6%**
Heart failure	2 441	2 433	**99.7%**
Renal failure	2 441	2 433	**99.7%**
Smoking status	2 441	2 441	**100.0%**
Alcohol consumption status	2 441	2 410	**98.7%**
Smoking amount	2 441	2 407	**98.6%**
Alcohol consumption amount	2 441	1 777	**72.8%**
Amylase	2 441	2 266	**92.8%**
Lipase	2 441	1 732	**71.0%**
RAP	2 441	2 441	**100.0%**
CP	2 441	2 441	**100.0%**
Overall	**53 702**	**51 978**	**96.8%**

Smoking dose dependency	**Total cohort**	**Uploaded data**	**%**
Local complications	2 407	2 386	**99.1%**
Amylase	2 407	2 237	**92.9%**
Lipase	2 407	1 705	**70.8%**
RAP	2 407	2 407	**100.0%**
CP	2 407	2 407	**100.0%**
Overall	**12 035**	**11 142**	**92.6%**

Alcohol dose dependency	**Total cohort**	**Uploaded data**	**%**
Local complications	1 777	1 762	**99.2%**
Amylase	1 777	1 649	**92.8%**
Lipase	1 777	1 231	**69.3%**
RAP	1 777	1 777	**100.0%**
CP	1 777	1 777	**100.0%**
Overall	**8 885**	**8 196**	**92.2%**

RAP: recurrent acute pancreatitis, CP: chronic pancreatitis

Supplementary Table 4. STATISTICAL RESULTS – DOSE DEPENDENCY

SMOKING DOSE DEPENDENCY	NON-SMOKER	LIGHT SMOKER	HEAVY SMOKER	p*
AMYLASE (N=2237)				
N	1 571	332	334	<0.001
Mean (SD)	1 206 (1 188)	851 (952)	692 (788)	
Median (IQR)	831 (343, 1 681)	496 (240, 1 112)	398 (195, 808)	
Minimum; Maximum	13; 8 544	30; 7 532	32; 4 852	
LIPASE (N=1705)				
N	1 149	274	282	<0.001
Mean (SD)	2 916 (3 523)	1 962 (2 398)	1 587 (2 459)	
Median (IQR)	1 675 (635, 3 846)	1 027 (499, 2 508)	822 (376, 1 692)	
Minimum; Maximum	10; 24 940	14; 13 398	31; 20 569	
RAP AND CP (N=2407)				
RAP, n (%)	321 (19%)	94 (26%)	105 (29%)	<0.001
CP, n (%)	46 (2.7%)	41 (11%)	50 (14%)	<0.001
LOCAL COMPLICATIONS (N=2386)	438 (26%)	92 (26%)	109 (31%)	0.200

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

ALCOHOL DOSE DEPENDENCY	NON-DRINKER	LIGHT DRINKER	HEAVY DRINKER	p*
AMYLASE (N=1649)				
N	1 158	186	305	<0.001
Mean (SD)	1 247 (1 216)	821 (892)	663 (846)	
Median (IQR)	863 (366, 1 719)	522 (230, 1 016)	379 (180, 782)	
Minimum; Maximum	13; 8 544	28; 5 283	30; 7 000	
LIPASE (N=1231)				
N	845	153	233	<0.001
Mean (SD)	2 864 (3580)	2 155 (2 575)	1 723 (2 862)	
Median (IQR)	1 571 (572, 3 756)	1 276 (570, 2 681)	736 (353, 1 730)	
Minimum; Maximum	10; 24 940	110; 17 904	19; 20 569	
RAP AND CP (N=1777)				
RAP, n (%)	239 (19%)	50 (26%)	98 (30%)	<0.001
CP, n (%)	47 (3.7%)	16 (8.2%)	36 (11%)	<0.001
LOCAL COMPLICATIONS (N=1762)	301 (24%)	51 (26%)	109 (34%)	0.003

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

SD: standard deviation, IQR: interquartile range, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis.

Supplementary Table 5. STATISTICAL RESULTS – SYNERGISTIC EFFECT

SYNERGISTIC EFFECT	NS-ND	NS-D	S-ND	S-D	p*
AGE (N=2441)					
N	1 049	639	202	551	<0.001
Mean (SD)	62 (18)	57 (15)	51 (14)	47 (12)	
Median (IQR)	64 (50, 76)	59 (45, 69)	52 (42, 60)	47 (38,56)	
Minimum;Maximum	18; 95	19; 95	18; 91	18; 82	
SEX (N=2441)					
Male, n (%)	356 (34%)	470 (74%)	102 (50%)	467 (85%)	<0.001
Female, n (%)	693 (66%)	169 (26%)	100 (50%)	84 (15%)	
SEVERITY (N=2441)					
Moderately severe, **n (%)**	225 (21%)	153 (24%)	39 (19%)	162 (29%)	0.002
Severe, n (%)	61 (5.8%)	40 (6.3%)	5 (2.5%)	18 (3.3%)	0.022
Mortality, n (%)	32 (3.1%)	23 (3.6%)	2 (1.0%)	10 (1.8%)	0.100
AMYLASE (N=2266)					
N	967	601	188	510	<0.001
Mean (SD)	1 285 (1 233)	1 079 (1 101)	1 056 (1 117)	692 (764)	
Median (IQR)	918 (381, 1 751)	705 (298, 1 537)	652 (309, 1 428)	414 (197, 844)	
Minimum; Maximum	13; 8 544	28; 7 750	33; 7 532	23; 4 852	
LIPASE (N=1732)					
N	690	458	152	432	<0.001
Mean (SD)	2 999 (3 684)	2 788 (3 268)	2 244 (3 024)	1 637 (2 191)	
Median (IQR)	1 690 (623, 3 964)	1 624 (678, 3 537)	1 213 (426, 2 524)	914 (454, 1 924)	
Minimum; Maximum	10; 24 940	19; 18 380	14; 17 450	22; 20 569	
RAP AND CP (N=2441)					
RAP, n (%)	183 (17%)	137 (21%)	56 (28%)	151 (27%)	<0.001
CP, n (%)	28 (2.7%)	18 (2.8%)	19 (9.4%)	76 (14%)	<0.001

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

NS–ND: non-smoking–non-drinking; NS–D: non-smoking–drinking; S–ND: smoking–non-drinking; S–D: smoking–drinking, SD: standard deviation, IQR: interquartile range, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis.