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Statin intake can decrease acute pancreatitis severit

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ABSTRACT

Background/Objectives: Acute Pancreatitis (AP) is one of the leading gastrointestinal conditions requiring hospitalization. It has been suggested that statins could exert a protective role in the natural history of AP; however, their influence is not entirely clear. Our objective was to investigate the relationship between statin intake and AP.

Methods: Retrospective analysis of a prospective registry of patients diagnosed with AP. Statin intake on admission as well as clinical, analytical, demographic and radiological data were recorded. Outcome parameters: Severity of AP, SIRS development, organ failure, local complications, intensive care admission, collection drainage, hospital length of admission, and death. Univariate and multivariate analyses as well as a propensity score logistic regression were conducted.

Results: From March 2014–October 2018 we studied 356 patients. 101 patients (28%) were taking statins. 55 (15%) suffered from moderate/severe pancreatitis. Multivariate analysis showed a 50% less risk of suffering from moderate/severe AP (OR 0.50 *95% CI* 0.22–1.0, *p* 0.50) and 33% less risk of developing local complications (OR 0.33 *95%CI* 0.15–0.80, *p* 0.014) among statin consumers, with a tendency towards less SIRS. Propensity score analysis confirmed that patients on statins suffering from AP had a lower risk to have a moderate/severe episode (OR 0.409 *95%CI* 0.192–0.872, *p* 0.031), to develop local complications (OR 0.47 *95%CI* 0.20–1.06, *p* 0.11) and SIRS (OR 0.516 *95% CI* 0.28–0.93, p 0.041).

Conclusions: Patients taking statins who suffer from an episode of AP are more likely to follow a mild course and have a lower risk of developing local complications and SIRS.

Introduction

Acute pancreatitis (AP) is an inflammatory process of the pancreas with a multifactorial pathogenesis in which pancreatic enzyme activation causes local pancreatic damage, resulting in systemic and peripancreatic tissues involvement [1].

Acute pancreatitis (AP) is the most common gastroenterology-related reason for hospital admission throughout the world [2]. Admissions have increased by at least 20% over the past decade with 275.000 patients hospitalized in the US annually [2,3]. Health care burden is around $ 2.5 billion with a steady tendency to increase [4]. 80% of patients admitted with acute pancreatitis have mild, self-limited disease and are discharge in a few days; however, up to 20% of patients suffer from a severe disease. The overall mortality rate in AP is around 2% but it approaches 30% among patients with persistent organ failure [1].

Current treatment for AP remains the same as in the previous decades and is based mainly on fluid resuscitation, analgesics, early feeding, and antibiotics if needed [1]. Nevertheless, great advances in the knowledge of the pathophysiology of AP have recently been achieved which, undoubtedly, will allow us to develop more accurate strategies to face this disease [5]. The intra-acinar activation of the nuclear factor *k*B (NF-*k*B) results in the upregulation in the expression of mayor proinflammatory cytokines (tumor necrosis factor, IL6.LI1,LI8, platelet activation factor) and chemokines [6]; as a consequence, activated neutrophils and macrophages are recruited which further amplify the systemic inflammatory reaction and the extent of pancreatic and extra-pancreatic injury [7].

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However, although several attempts using drugs to treat this disease have been carried out, none of them have succeeded [8–10].

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are the major group of lipid-lowering drugs [11]. In addition to their hypolipidemic properties, it has been suggested that statins could exert additional effects, the so-called "pleiotropic" effects. These benefits are due to the inhibition of isoprenoid intermediates by statins. Statins abolish over expression of toll-like receptors (TLRs) in inflammatory processes. Thus, the TLR4/Myd88/NF-*k*B signaling pathway is down-regulated and a slow in the progression of several inflammatory diseases is generated, as shown in literature [12,13]. In addition, the immunomodulatory and anti-inflammatory effects of statins have proven to be of great benefit in several other disorders such as neoplasms [14,15] and HIV [16].

There is great deal of controversy over the role that statins can play in AP. Traditionally, case control reports and observational studies have claimed an association between prolonged use of statins and development of AP [17–19]. Nevertheless, recent research has suggested that statins [1,20] play a protective role, either because of a diminished incidence of AP in statin consumers [21,22], or because of a decrease in the severity of episodes of AP [23]. On the other hand, several other publications have not found a true benefit effect from statins in mortality and outcome parameters in AP [24,25].

The aim of our study was to ascertain whether prior use of statins has any influence in the clinical outcome of patients admitted for acute pancreatitis in our institution.

Methods

Study subjects and data collection

Our study is a single-centre cohort study performed at the Gastroenterology Department of the Hospital Clínico Universitario in Valladolid, Spain. It is a tertiary, University Centre which serves a population of around 250.000 inhabitants. Data were analyzed retrospectively using our prospectively collected database on acute pancreatitis which started on March 2014. The diagnosis of AP was carried out according to the revised Atlanta Classification by the International Consensus of 2012 [26]. The diagnosis of AP required two of the three following criteria: 1.- acute onset of severe epigastric pain, 2.- serum amylase or lipase activity at least three times greater than the upper limit of normal, 3.- characteristic findings of acute pancreatitis on radiology (abdominal ultrasonography, contrast enhanced tomography or magnetic resonance imaging).

The exclusion criteria were the following: 1.- Patients who did not accept the inclusion in our previous database or did not sign the informed consent. 2.- Patient admission more than 5 days after the pain onset or patients referred from other hospitals. 3.- Patients who could not be followed up.

Clinical, analytic, radiologic and demographic data were recorded, which included age sex, abdominal perimeter, body mass index (BMI), Charlson Comorbidity Index, and smoking and alcoholic status on admission. The presence of high blood pressure (HBP), diabetes mellitus (DM) and dyslipidemia was also registered. Previous statin intake was obtained through the patients' medical record. The etiology of the episode of AP was attributed to one of the following: gallstones, alcohol, post-endoscopic retrograde cholangiopancreatography, idiopathic and others. The presence of single of multiple organ failure (respiratory, cardiovascular and renal) was registered according to the modified Marshall score system [27] and was defined as a score of 2 or more for one of those three organs. Local complications included acute pancreatic or peripancreatic fluid or necrotic collections (infected or sterile), pancreatic pseudocyst and walled-off necrosis. Radiological findings were analyzed by a specialized radiologist on abdominal imaging. Systemic complications were considered exacerbations of pre-existing co-morbidities precipitated by the AP.

The episodes of AP were classified according to the Modified Atlanta classification [26] into mild pancreatitis (no organ failure and no local or systemic complications), moderately severe pancreatitis (organ failure that resolves within 48 h and/or local or systemic complications) and severe pancreatitis (single or multiple organ failure which persists more than 48 h).

Ethics

The study was performed in accordance with the declaration of Helsinki and it was approved by the Research and Ethical Board of our institution (CEIC PI-19-1335). The research is reported following the Strengthening reporting of observational studies (STROBE) guidelines [28]. Participants provided signed informed consent to be included in our database. All data were coded.

Outcome measures

The primary outcome measure was the severity of the episode of AP according to the Atlanta modified classification.

Secondary outcome variables were the following: Systemic Inflammatory Response Syndrome (SIRS) development, in-hospital mortality, length of hospitalization, need for intensive care unit (ICU) admission, presence of local complications, organic failure and need of drainage of collections during the hospital admission (CT-guided percutaneous drainage, surgical or endoscopic necrosectomy).

Statistical analysis

The association between statin intake and the main and secondary outcome measures was studied by means of univariate and multivariate analysis. Firstly, a univariate logistic regression model was carried out to identify the factors associated with the analyzed outcome variables. Secondly, a multivariate regression model taking into account the statin intake of patients was performed. Thirdly, a propensity-matched cohort was created in an attempt to reduce the bias due to confounding variables; each patient on statin (case) was matched 1:1 to a non-statin patient (control); a subsequent logistic regression analysis was carried out. Quantitative variables are presented with mean and standard deviation and qualitative variables according to their frequency of distribution. D'Agostino's K-squared test was used to verify normality. Using Pearson's Chi-square test, the exact Fisher test or the Reason for Verisimilitude test the association of qualitative variables was analyzed. Comparisons of quantitative values were carried out using Student's T test or the ANOVA test for independent samples, depending on whether the number of groups to be compared were two or greater. The nonparametric alternatives were Mann Whitney's *U* test and Kruskal Wallis, respectively. The statistical calculations were performed using IBM SPSS Statistics version 24.0 for Windows (SPSS Inc. Armonk NY). $P < 0.05$ values were considered statistically significant.

Results

From March 2014 until October 2018 a total of 370 patients diagnosed with AP were admitted in our Institution. 14 patients were excluded (Fig. 1) thus a total of 356 were finally studied, 154 male (43%) and 202 female 57%), median age 68,19 ± 16,90. 55

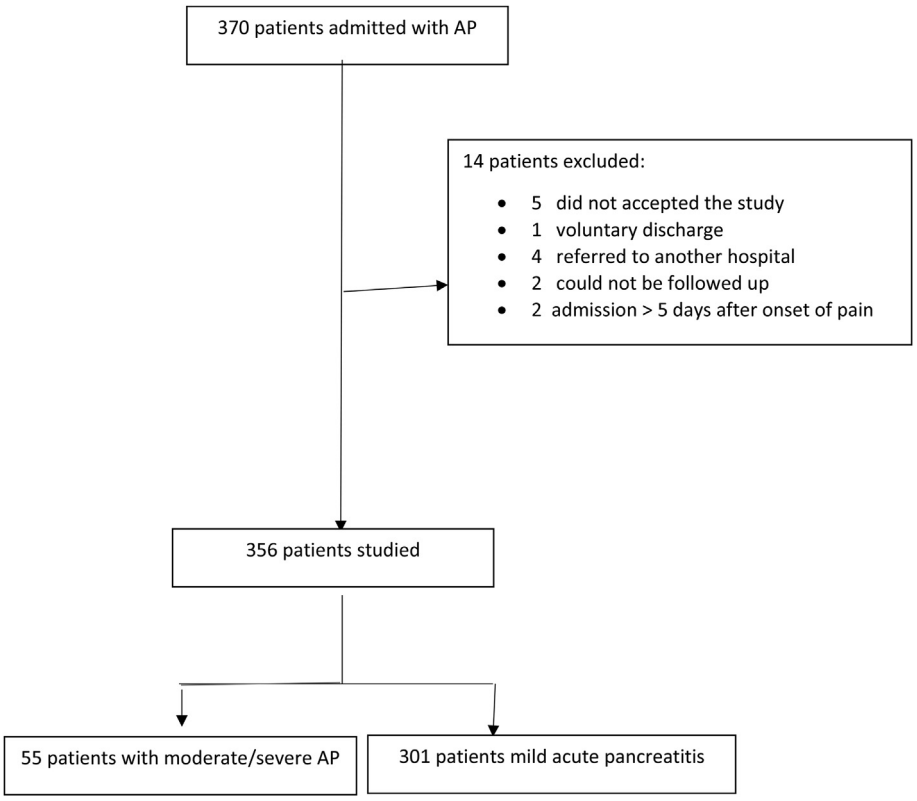

Fig. 1. Study flowchart with included patients after applying exclusion criteria.

Table 1
Demographic, analytic and clinic characteristics of patients studied.

		STATIN INTAKE		p-value
		NO (n = 255)	Yes (n = 101)	
AGE		65,8 ± 18 (17–96)	74,3 ± 11,7 (39–95)	<0,001
Gender	Male	104 (40,8%)	50 (49,5%)	0,134
	female	151 (59,2%)	51 (50,5%)	
Body Mass Index	≤25	80 (31,6%)	30 (29,7%)	0,033
	25–30	96 (37,9%)	52 (51,5%)	
	≻ 30	77 (30,4%)	19 (18,8%)	
Abdominal perimeter		98,4 ± 16,1 (44–174)	99,7 ± 12,6 (76–130)	0,431
Alcohol status	No	174 (68,2%)	65 (64,4%)	0,774
	Yes	69 (27,1%)	31 (30,7%)	
	Former (>6 months)	12 (4,7%)	5 (5%)	
Smoking status	No	172 (67,5%)	59 (58,4%)	0,044
	yes	46 (18%)	16 (15,8%)	
	Former (>6 months)	37 (14,5%)	26 (25,7%)	
Etiology	Gallstone related	155 (60,8%)	54 (53,5%)	0,632
	Alcohol	21 (8,2%)	12 (11,9%)	
	Post ERCP	6 (2,4%)	4 (4%)	
	Others	19 (7,5%)	9 (8,9%)	
	Idiopathic	54 (21,2%)	22 (21,8%)	
Charlson comorbidity index	0	150 (58,8%)	33 (32,7%)	<0,001
	1–2	52 (20,4%)	34 (33,7%)	
	>= 3	53 (20,8%)	34 (33,7%)	
High blood pressure	No	136 (53,3%)	33 (32,7%)	<0,001
	Yes	119 (46,7%)	68 (67,3%)	
Diabetes mellitus	No	232 (91%)	78 (77,2%)	<0,001
	Yes	23 (9%)	23 (22,8%)	
Albumin (mg/dl) median/SD		3,7 ± 0,5 (2–7)	3,6 ± 0,7 (0–5,9)	0,226
Calcium (mg./dl) median/SD		8,6 ± 0,7 (6–10,2)	8,5 ± 0,8 (3,8–10)	0,224
Triglycerides (mg./dl) median/SD		145 ± 432,9 (22–6747)	154 ± 281,4 (31–2775)	0,848
Thorax X-Ray	Normal	191 (74,9%)	76 (75,2%)	0,946
	Pleural effusion	64 (25,1%)	25 (24,8%)	

patients (15%) suffered from a moderate/severe disease while 301 (85%) had a mild acute pancreatitis. Baseline patients' characteristics are summarized in Table 1. 255 patients (72%) were taking statins and 101(28%) did not take the drug. Statin intake was higher among older patients, smokers, patients suffering from HBP and DM, with higher BMI and who were affected by more comorbidities. However, in propensity score matching each patient taking statins was matched 1:1 with a non-statin user according to their baseline characteristics (Table 2).

On univariate analysis no statistical association in terms of differences between statin users and non-statin users on outcome variables was found: Atlanta classification OR 0.74 (*95% CI* 0.38–1.46, *p* 0.39), Local complications OR 0.58 (*95% CI* 0.29–1.18, *p* 0.13), Mortality OR 1.71 (*95% CI* 0.47–6.17, *p* 0.40), SIRS OR 0.80 (*95% CI* 0.47–1.36, *p* 0.418), Organ failure OR 1.13 (*95% CI* 0.55–2.34, *p* 0.72), drainage of pancreatic collections OR 0.25 (*95% CI* 0.03–1.93, *p* 0.23), ICU admission OR 1.27(*95% CI* 0.31–0.18, *p* 0.74) and length of hospital stay OR 1.03 (*95% CI* 0.61–1.74, *p* 0.89). Nevertheless, in multivariate analysis (Table 3) the risk of suffering from a moderate/severe AP was 50% less among patients on statins (OR 0.50 *95% CI* 0.22–1.0, *p* 0.50). Similarly, statin users had a 33% less risk of developing local complications than non-users (OR 0.33 *95% CI* 0.15–0.80, *p* 0.014). There was also a tendency towards less SIRS evolution (*p* 0.089) for the patients on statins. Similar results were reached when the 2 matched groups were analyzed (Table 4). Again, statin users had a 40% less risk of suffering from a moderate/severe AP (OR 0.40 *CI 95%* 0.19–0.87, p 0.03) and SIRS development (OR 0.51 *CI 95%* 0.28–0.93, *p* 0.04) than non-users, with a tendency towards a lower rate of local complications (p = 0.11).

Table 3
Multivariate analysis including confounding variables for the outcomes between statin and non-statin users.

OUTCOME	OR	95% Confident interval	p-value
Atlanta classification (mild/severe)	**0.5**	**0.22–1.0**	***0.050***
Local complications	**0.33**	**0.15–0.80**	***0.014***
SIRS development	**0.59**	**0.31–1.09**	**0.089**
Mortality	1.07	0.23–3.72	0.910
Organ failure	0.67	0.39–1.51	0.337
Drainage of pancreatic collections	0.24	0.03–19.60	0.084
ICU admission	1.27	0.31–5.26	0.743
Length of hospital stay	0.93	0.20–4.16	0.924

Table 4
Logistic regression for the propensity score matching for the outcomes between statin and non-statin users.

OUTCOME	OR	95% Confident interval	p-value
Atlanta classification (mild/severe)	**0.409**	**0.192–0.872**	***0.031***
Local complications	**0.471**	**0.208–1.066**	***0.11***
SIRS development	**0.516**	**0.285–0.935**	**0.041**
Mortality	0.75	0.188–2.993	1
Organ failure	0.571	0.246–1.328	0.286
Drainage of pancreatic collections	0.25	0.038–1.663	0.371
ICU admission	0.75	0.188–2.993	1
Length of hospital stay	0.625	0.331–1.179	0.278

Discussion

Our research shows a protective effect of statins in AP, in terms of severity, development of local complications and SIRS. Non-statin intake patients who develop an acute pancreatitis episode have a two-fold risk of developing a moderate-severe pancreatitis than non-users. Similarly, the odds of development local complications were three times higher among non-statin users than in those patients on the drug. Our findings go in the same direction as some other published research [21–23], in which patients under previous statin exposure suffered from milder episodes of AP. In our study statin intake was associated both in individual and in propensity score matching analyses with a decrease in the severity of AP.

This protective effect of statins was previously shown by Wu et al. in their wide cohort study in Southern California [22]. They found that users of simvastatin and atorvastatin had a reduced risk of AP (RR 0.29 *95% CI* 0.27, 0.31).

Statins are widely prescribed drugs and orally administered. Although several mild side effects have been described [29] they have a good safety profile and are safe and well tolerated. There are several potential mechanisms regarding the action of statins. Based on experimental and clinical studies, it has been shown that statins exert an anti-inflammatory activity in different ways. Firstly, statins would modulate migration of monocytes to the site of inflammation by down regulating expression of pro-inflammatory cytokines (TNF-α, IL6 and chemokines) [11]. Secondly, statins activate diverse integrins such as lymphocyte function associated antigen 1 (LFA-1) and thus modify lymphocyte adhesion and migration. And thirdly, they abolish over expression of toll-like receptors (TLRs) in

Table 2
Case-control groups matched according to baseline parameters.

Baseline characteristics	Statin users N = 101	Non-statin users N = 101	*p-value*
Age (ms)	74 (11.7%)	73.8 (14.7%)	0.804
Etiology (n)			0.868
Biliary	54 (53.5%)	56 (55.4%)	
Alcohol	12 (11.9%)	9 (8.9%)	0.646
Post ERCP	4 (4%)	3 (3%)	1
Others	9 (8.9%)	9 (8.9%)	1
Idiopathic	22 (21.9%)	24 (23.8%)	0.845
Gender (n)	51 (50.5%)	56 (55.4%)	0.59
Smoker (n)	16 (15.8%)	15 (14.9%)	1
Alcohol intake (n)	31 (30.7%)	24 (23.8%)	0.36
Charlson Comorbidity Index (md, ir)	1 (3)	1 (2)	0.952
High blood pressure (n)	68 (67.3%)	62 (61.4%)	0.47
Diabetes mellitus (n)	23 (22.8%)	17 (16.8%)	0.327
Abdominal perimeter (ms, sd)	99.7 (12.6)	99.6 (17.3%)	0.988
Albumin (ms, sd)	3.6 (0.6)	3.6 (0.6)	0.791
Calcium (ms), sd	8.5 (0.7)	8.5 (0.6)	0.927
Glucose on admission (md, ir)	102 (48)	110 (51)	0.131
Triglyceride (md, ir)	110 (70)	108 (68)	0.549
Body mass index (ms, sd)	27 (3.6)	28.3 (5.8)	0.069

inflammatory processes [13]. The anti-inflammatory, anti-oxidant and immunomodulatory properties of statins (pleiotropic effects) have also been evaluated to assess their potential benefit in the treatment of some other inflammatory processes such as heart diseases [13], atherosclerosis, chronic osteomyelitis [30], lives abscesses [31] and neoplasms [14,15,32]. There is currently an interesting prospective study to analyze the use of statins for acute post ERCP pancreatitis [33]. Furthermore, we suggest that statins may lower the severity of acute pancreatitis by decreasing circulating inflammatory mediators.

The relationship between statins and AP has been a very controversial issue for a long time. Badalov et al. [18] included statins as Class Ia drugs in relation with acute pancreatitis based only on case reports of AP on re-challenging with the drug. Research from Europe [24] and Asia [25] could not find a beneficial effect of statins in clinical outcomes of AP. On the other hand, the meta-analysis on almost 40 randomized clinical trials and case-control studies performed by Preiss et al. clearly demonstrates [21] a lower risk of acute pancreatitis in patients on statin consumption. An elegant propensity score analysis carried out by Lee et al. where patients were matched 1:1 in relation to statin intake, showed convincing evidence of the benefits that previous statin use can exert on AP outcomes [23]. Another recently published European meta-analysis claims that published isolated clinical cases report an increased risk of AP in statin consumers; however, case-control studies, less prone to bias, exhibit a trend towards a protective effect of statins in AP [34].

In the current and challenging issue of the role of statins in so many inflammatory processes, our research adds more positive information about statins' benefits on acute pancreatitis. Many other questions are raised. Is only chronic statin intake beneficial or otherwise, could statins be prescribed on admission for patients with AP in order to develop a less severe episode? Could statins be added to patients after biliary AP discharge previous to cholecystectomy to prevent further severe episodes? Are there any other advantages to be obtained from statin intake in AP? There is, undoubtedly, important research to be done in the field of statins and AP, and many questions to be answered in large controlled studies. It is of note to mention that we have recently enrolled on a multicenter trial to investigate whether simvastatin is effective in decreasing the incidence of new episodes of AP in recurrent idiopathic AP [35].

The strength of our research is that our results are established not only by means of multivariate analyses but also by a propensity score matching logistic regression. This statistical technique, introduced by Rosembaum and Rubin in 1983 [36], attempts to reduce selection bias by equating groups based on confusing covariates and thus simulate a randomized control trial.

However, our study has several limitations. Firstly, we were unable to find out the exact dose and the total duration of statin exposure; the use of the drug was ascertained by the patients' electronic chronic prescription. Secondly, we did not separately study the different types of HMG-CoA reductase inhibitors, all of them were considered as the same group; however, as WU et al. address [22] the benefits of stains are probably class-effect ones. And finally, we did not take into account other drugs that patients were on and could subsequently influence the evolution of the disease.

In conclusion, our unicenter data shows clear evidence that previous use of HMG-CoA reductase inhibitors can modify the clinical course of AP. Large prospective multicenter randomized controlled trials are warranted in order to assess similar results. Even more, further research should be carried out to define whether statin type, dosage or treatment duration would account for any difference in terms of anti-inflammatory properties not only in AP but in several other clinical scenarios (e.g. recurrent acute pancreatitis, acute pancreatitis on chronic pancreatitis). With no specific treatment currently available for AP, a further challenging issue would be to consider whether statins could even be administered to patients on admission for AP, in order to decrease severity.

Conflicts of interest

The authors declare no conflict of interest. Agustin Mayo-Íscar has been partially supported by the Spanish Ministero de EconomíaEd y Competitividad grant MTM 2017-86061-C2-1-P and by Consejeruía de Educacicón de Castilla y León and FEDER grant VA005P17 and VA 002G18; these sources are not related with any kind of conflict os interests as they are public agencies devoted to funding research in all areas of knowledge.

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