

Epidemiology of Acute Pancreatitis in Southern Israel: A Retrospective Study

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ABSTRACT **Background:** There is a lack of information regarding acute pancreatitis in Israel. However, the most prevalent worldwide etiologic causes of acute pancreatitis are biliary stones and alcohol abuse.

Objectives: To delineate the prevalence, main causes, rate of recurrence, mortality, and complications of acute pancreatitis in southern Israel.

Methods: In this retrospective study medical files of all hospitalized patients diagnosed with acute pancreatitis during a 13-year period were reviewed.

Results: The study comprised 602 patients with acute pancreatitis (120/100,000 patients or 1.2/1000 admissions). The main causes were: biliary stones (41.5%), alcohol (8.8%), and drugs (8.3%). Disothiazide was the most common drug associated with acute pancreatitis followed by sitagliptin, angiotensin converting enzyme (ACE) inhibitors, and simvastatin. Undetermined etiology made up 33.6% of the cases. Recurrence rate was 33.8% (alcohol 3.7%, hypertriglyceridemia 1.8%). This finding had no implications on mortality rate, which was stable at 4.3%. Bilateral pleural effusion, advanced computed tomography severity index (CTSI) grading, older age, and being single were found to be poor prognostic predictive factors.

Conclusions: Biliary pancreatitis is the main cause of acute pancreatitis in southern Israel, similar to the rest of the world, and constitutes a much more common etiology than alcohol. Furthermore, drug-induced pancreatitis is a common etiology, with disothiazide being the most common drug associated with pancreatitis followed by ACE-Inhibitors, sitagliptin, and simvastatin. Recurrence of pancreatitis is common in this geographic area, and older age, advanced CTSI grading, bilateral pleural effusion, and being single are all poor prognostic predictive factors.

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KEY WORDS: acute pancreatitis, alcohol, disothiazide, drug-induced pancreatitis

Acute pancreatitis is a common disease, with an incidence rate of 4.8–38:100,000 in western Europe and the United States [1,2]. Both acute and chronic pancreatitis were the reasons for 327,000 admissions to hospitals in the United States and 531,000 physicians visits during the year 1998 alone [3]. Furthermore, during 2000 in the United States, 2834 cases of mortality due to acute pancreatitis were reported [4]. The main etiologies for acute pancreatitis are biliary stones and alcohol followed by drugs, trauma, hypertriglyceridemia, and hypercalcemia, endoscopic retrograde cholangio-pancreatography (ERCP). Nonetheless, in about 30% of the cases, the cause remains idiopathic.

During the past 2 decades there has been an increase in the rate of alcoholism in the western world, including Israel. Even though medical literature has shown biliary stones to be the main etiology for acute pancreatitis [5], our hypothesis was that alcohol has surpassed biliary stones as the main etiology for acute pancreatitis. This study was performed to delineate the main causes of acute pancreatitis in southern Israel, and to determine the main drugs that cause the disease in this region.

PATIENTS AND METHODS

Barzilai Medical Center is a secondary care rural community hospital that serves a population of over 500,000 in the towns of Ashkelon, Ashdod, and Kiryat-Gat, as well as related municipalities. The majority of the population is Jewish, most of whom are of North African descent or new immigrants from Russia.

In this retrospective study, all medical files of admitted patients during a 13-year period that were diagnosed as having "acute pancreatitis" were reviewed.

This study was conducted in compliance with the guidelines for human studies and was conducted in accordance with the Declaration of Helsinki. The study was approved by the local institutional review board.

STATISTICAL ANALYSIS

The comparison between demographic and epidemiological data with normal variation was performed using Student's

*The first and second authors contributed equally to this study

Table 1. Etiologic distribution in different ethnic groups

| Ethnic origin | Sex | Idiopathic | Trauma | Drug-induced | Biliary | Hypertriglyceridemia | Alcoholic |
|--------------------------|---------|------------|--------|--------------|---------|----------------------|-----------|
| Aschenazi | Males | 12 | 1 | 5 | 12 | 1 | 0 |
| | Females | 5 | 1 | 0 | 11 | 1 | 0 |
| Ethiopian new immigrants | Males | 3 | 0 | 0 | 4 | 1 | 2 |
| | Females | 3 | 0 | 0 | 5 | 0 | 0 |
| Israeli born | Males | 23 | 2 | 6 | 12 | 8 | 6 |
| | Females | 15 | 1 | 6 | 19 | 1 | 1 |
| Far East | Males | 8 | 0 | 5 | 3 | 0 | 3 |
| | Females | 4 | 0 | 0 | 11 | 1 | 0 |
| Russian new immigrants | Males | 42 | 2 | 9 | 43 | 7 | 33 |
| | Females | 44 | 0 | 7 | 89 | 5 | 7 |
| Sephardic | Males | 31 | 0 | 7 | 9 | 4 | 1 |
| | Females | 30 | 4 | 2 | 32 | 2 | 0 |
| All | Males | 119 | 5 | 32 | 84 | 21 | 45 |
| | Females | 91 | 6 | 15 | 166 | 10 | 8 |

t-test. Data with abnormal distribution were compared using the Mann-Whitney U test. Differences between categorical variables were analyzed with chi-square logistic regression, an analysis for estimating accumulating odds ratios. P values < 0.05 were considered significant. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences statistics software, version 19 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

INCIDENCE

Between the years 2000 and 2012, 602 patients were diagnosed as having acute pancreatitis out of approximately 500,000 admissions to the hospital. The incidence of admissions was found to be 1.2:1000 or 0.124% of all admissions.

PATIENT ETHNIC CHARACTERISTICS

Of the patients, 50.8% were male, 92.4% were married, and the mean age was 60.7 ± 19.8 years. Half of the patients were new immigrants from the former USSR, the rest were Israeli born (16.4%), of north African origin (18.6%), new immigrants from Ethiopia (3%), or born in Europe or North America.

ETIOLOGY

Biliary stones were the most common cause of acute pancreatitis (41.5% of the patients) and alcohol was the cause in only 8.8% of the cases. Drug-induced pancreatitis was almost as common as alcohol-induced (8.3%, including solitary drug etiology), in particular disothiazide (64% comprising 5% of all cases of pancreatitis) [Table 1]. It is important to note that disothiazide was prescribed to an overall 12.8% of patients, but most of them had other more likely causes, such as biliary

Table 2. Drugs associated with pancreatitis

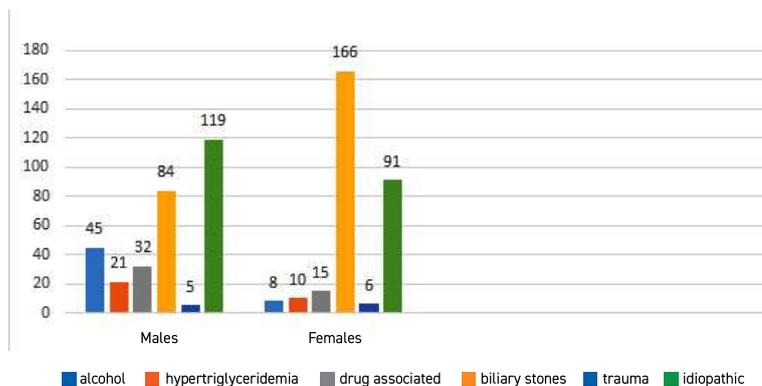
| Name of the drug | Number of cases |
|--|-----------------|
| Disothiazide | 30 |
| Angiotensin converting agents | 6 |
| Sitagliptin | 6 |
| Simvastatin | 5 |
| Birth control pills | 1 |
| Mirtazapine | 1 |
| Imuran | 1 |
| Angiotensin converting agents + disothiazide | 1 |
| Angiotensin converting agents + alcohol | 1 |
| Angiotensin converting agents + hypertriglyceridemia | 1 |

stones. The overall incidence of patients who were prescribed disothiazide among patients who were admitted to either the internal medicine departments or surgical departments was 5% among the 602 patients whose medical files were reviewed. The odds ratio [OR] for acute pancreatitis, with the use of disothiazide on admission, was 2.5. Additional drugs that were associated with acute pancreatitis were angiotensin-converting enzyme (ACE) inhibitors (6 patients), sitagliptin (6 patients), simvastatin (5 patients), and other drugs (6 patients) [Table 2].

Hypertriglyceridemia was associated with 5.1% of acute pancreatitis while trauma was associated with only 1.5% of the cases. "Idiopathic acute pancreatitis" comprised a third of the patients (33.6%), as a result of no clear etiology being found [Figure 1].

DEPARTMENTS OF ADMISSION

In total, 50.9% of the patients were admitted to the internal medicine wards, 42% were admitted to the general surgery department, and 7% of patients were admitted directly from the

Figure 1. Etiologies of acute pancreatitis in males and females

emergency department to the intensive care unit.

RECURRENCE OF ACUTE PANCREATITIS

The recurrence rate of pancreatitis stood at 33.8%. The highest recurrence rate was found to be in patients with alcohol-induced pancreatitis (68.3%, OR 3.715, 95%CI 1.81–7.64), and hypertriglyceridemia-induced pancreatitis (67.8%, OR 1.86, 95%CI 1.41–2.46). Despite this rate, the recurrence of pancreatitis was not found to be associated with an increased mortality in the patients.

COMPLICATIONS

Disease complications included: acute respiratory distress syndrome (4.5% of patients), hypovolemic shock (4.2%), sepsis (2.7%), pseudocyst (1.8%), and abscess (1.3%). Laparotomy/laparoscopy was performed in 10.5% of patients, and ERCP during hospitalization was performed in only 4.5% of the cases.

MORTALITY AND MORTALITY PREDICTING FACTORS

A patient's death as a result of acute pancreatitis was observed in only 4.3% of the cases. Diabetes mellitus (OR 3.026, 95%CI 0.9–10.2) and chronic renal failure (OR 3.534, 95%CI 1.48–8.8) were found to be associated with increased mortality in pancreatitis. Dyslipidemia, malignancy, hypertension, and ischemic heart disease were seen as factors increasing the rate of mortality. Surprisingly, the strongest risk factor for mortality was marital status; being single was correlated with an OR of mortality 19.83 ($P < 0.001$, 95%CI 8.48–46.38).

DISCUSSION

Just as it is in the rest of the world, acute pancreatitis is a common disease in the southern region of Israel. The incidence in our area was found to be 15:100,000 per year, somewhere halfway between American and European incidences [1,2].

Similar to the rest of the world, biliary stones were found

to be the most common cause of acute pancreatitis, much more common than any other cause (41.5% of the patients) with about the same incidence as in the United States [6]. However, compared to the western world, the incidence of alcohol-induced pancreatitis in our area was found to be much lower (8.8%) [1], while in many areas it is the second most common cause of acute pancreatitis. This finding is probably due to the fact that alcoholism prevalence is lower in Israel than in western Europe and the United States, especially when comparing the amounts of alcohol consumed [7]. However, both the high incidence of cryptogenic acute pancreatitis (33.6%) and the high incidence of recurrence (25.7% of our patients), may represent an actual hidden alcoholic etiology especially since cryptogenic etiology was found to be much more common among males who are known to consume more alcohol than women [8]. Acute pancreatitis was found to be idiopathic in 10–30% of cases [8].

Drug-induced pancreatitis was found to be a much more common cause of acute pancreatitis in Israel, when compared to European studies (8.3% vs. 0.3–1.4%) [9,10]. The pathogenesis of drug-induced pancreatitis is an allergic reaction (e.g., 6-mercaptopurines, sulfonamides), or related to direct toxicity (diuretics and sulfonamides) [1]. However, the main problem regarding drug-induced pancreatitis is that it has no distinguishing clinical features. For this reason, meticulous drug history is critical for the diagnosis of drug-induced pancreatitis. The time course for the development of pancreatitis depends on the drug. Unlike pancreatitis associated with an immunologic reaction, acute pancreatitis associated with direct toxicity (following the use of valproic acid, pentamidine, and other drugs) may not develop until after a few months of use because their pathogenesis is due to the accumulation of toxic metabolites [1]. Disothiazide is a drug that has been known for years to cause acute pancreatitis [11–13], and the incidence of acute pancreatitis due to the drug was found to be surprisingly high. In our study, the drug was found to be the main cause of drug-induced pancreatitis. We were slightly skeptical regarding this association, attributing the high incidence of disothiazide-induced acute pancreatitis to the fact that it is a popular and common drug for the treatment of hypertension in Israel. We evaluated the incidence of disothiazide use in the general population and found it to be 5% among the 600 patients admitted to the departments of surgery and internal medicine (compared to 12.8% among the patients with pancreatitis).

It is noteworthy that our study found that the use of ACE inhibitors was associated with only a few cases of acute pancreatitis ($n=6$). The use of both ACE inhibitors and calcium channel blockers was associated with an increased risk of acute pancreatitis in a large study done by Eland et al. [14]; while loop and thiazide diuretic use were not associated with an increased risk of acute pancreatitis in the same study. Potassium-sparing diuretics elevated the risk of acute pancreatitis; however, this finding was not statistically significant. The

medical literature is conflicted regarding gliptins and pancreatic toxicity (probably since it is a relatively new drug). In our study, an association with an increased risk of pancreatitis (6 cases) was found. Faillie and colleagues [15] showed that the use of incretin-based drugs is associated with an increased risk of reported pancreatitis, contrary to Zhang et al. [16], who did not note an increased risk. Most others have found that the use of gliptins is not associated with an increased incidence of acute pancreatitis [17-21]. We believe that the association between sitagliptin and acute pancreatitis should be of some concern due to the increasing use of this popular and "benign" medication in the treatment of diabetes.

More than half of the patients were admitted to the internal medicine department. Most of them were patients with milder disease.

The lack of autoimmune pancreatitis is surprising; however, the disease is quite rare, 1.24:100,000 vs. 1.24:1000 admissions in cases of acute pancreatitis [22].

Acute pancreatitis can lead to recurrence of acute pancreatitis if the underlying factor remains uncorrected [23]. It is most commonly caused by alcohol abuse or gallstone disease. When a regular evaluation fails to diagnose a cause for recurrent disease, a further evaluation that includes ERCP, endoscopic ultra sound (EUS), magnetic resonance cholangiopancreatography (MRCP), or manometry of the Sphincter of Oddi may reveal microlithiasis, Sphincter of Oddi dysfunction, pancreas divisum, and other causes of pancreatitis. Recurrence of acute pancreatitis was very common in our study, especially among patients with either alcoholic pancreatitis or pancreatitis due to hypertriglyceridemia. This observation was probably due to the chronicity and persistence of these two conditions, unlike biliary pancreatitis in which most of the patients underwent laparoscopic cholecystectomy, with or without ERCP.

Surprisingly, the best predicting factor of mortality was found to be neither chronic background diseases, nor the computed tomography severity index (CTSI) [24], but the marital status of the patient. Being single was correlated with higher mortality due to acute pancreatitis; whether it is because the patient arrived at the hospital later when he lives alone, or because his marital status influences his mood and motivation and ultimately his medical condition is unknown. Loneliness is known to be associated with both increased risk of alcoholism and increased risk of death. Advanced CTSI (grade D, E) was also associated with increased mortality and was found to be as a reliable predictor of mortality, just as in previous studies. A recent report found a prevalence of 1% of pancreas cancer among patients with acute pancreatitis [25]. We did not find such cases and further investigations are warranted.

LIMITATIONS

The main weakness of our study, being retrospective, is the lack of certainty as to whether the drug (or sometimes alcohol and

biliary stones) is really the cause of the disease or just a coincidental factor that happened to coexist with the real etiologic agent such as microlithiasis or a toxin that was mistakenly ingested. A good scale that is efficient in causality assessment of unexpected acute pancreatitis is necessary, such as the CIOMS/RUCAM scale [20] or the NARANJO scale [21] in drug-induced liver toxicity.

CONCLUSIONS

Acute pancreatitis is still a common disease in southern Israel. The most common etiology was found to be biliary stones, by far more common than alcohol. Medications are also a common etiology, with the most common drug being disothiazide, unlike the findings in other studies. Gliptins, although quite recently introduced in Israel, were found to be already a remarkable cause of acute pancreatitis.

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Capsule

Effects of underfeeding and oral vancomycin on gut microbiome and nutrient absorption in humans

Direct evidence in humans for the impact of the microbiome on nutrient absorption is lacking. **Basolo** and co-authors conducted an extended inpatient study using two interventions that they hypothesized would alter the gut microbiome and nutrient absorption. In each, stool calorie loss, a direct proxy of nutrient absorption, was measured. The first phase was a randomized cross-over dietary intervention in which all participants underwent in random order 3 days of over- and underfeeding. The second was a randomized, double-blind, placebo-controlled pharmacologic intervention using oral vancomycin or matching placebo. Twenty-seven volunteers (17 men and 10 women, age 35.1 ± 7.3 years, body mass index 32.3 ± 8.0 kg/m²), who were healthy other than having impaired glucose tolerance and obesity, were enrolled and 25 completed the entire trial. The primary endpoints were the effects of dietary and pharmacological intervention on stool calorie loss. The authors hypothesized that stool calories expressed as percentage of caloric intake would increase with underfeeding compared with overfeeding

and increase during oral vancomycin treatment. Both primary endpoints were met. Greater stool calorie loss was observed during underfeeding relative to overfeeding and during vancomycin treatment compared with placebo. Key secondary endpoints were to evaluate the changes in gut microbial community structure as evidenced by amplicon sequencing and metagenomics. The authors observed only a modest perturbation of gut microbial community structure with under- versus overfeeding but a more widespread change in community structure with reduced diversity with oral vancomycin. Increase in *Akkermansia muciniphila* was common to both interventions that resulted in greater stool calorie loss. These results indicate that nutrient absorption is sensitive to environmental perturbations and support the translational relevance of preclinical models demonstrating a possible causal role for the gut microbiome in dietary energy harvest.

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Capsule

Breaking down barriers in the brain

Strokes decrease the function of the microvascular endothelial cells in the blood-brain barrier. The resulting immune cell infiltration and solute leak exacerbate the neuronal death caused by ischemic injury. In a mouse model of stroke, **Ma** et al. found that endothelial cell-specific ablation of a microRNA cluster protected mice from ischemic brain damage. Analysis of cultured microvascular

endothelial cells showed that this microRNA cluster, which suppresses gene expression, targeted the gene encoding the tight junction protein claudin-5, which is critical for the barrier function of these cells.

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