Acute Pancreatitis and Type 2 Diabetes

Vincenzo Neri
Department of Medical and Surgical Sciences
University of Foggia, Italy

1 Introduction

Acute Pancreatitis (AP) is an inflammatory disease of the pancreas with prevalence of biliary pathogenesis characterized by different degrees of severity from a mild edematous-interstitial inflammation, which is a self-limiting disease, to a severe type with local necrotizing inflammation and systemic complications (organ failure). Patients with severe acute pancreatitis (SAP) have a high mortality rate (20%) (Yadav & Lowenfels, 2006). The incidence of AP in western countries has been evidently increasing in the last decades (Kingsnorth & O'Reilly, 2006). The reasons behind this increase have not been clearly identified yet. However it may be noticed that a similar increase has occurred for type 2 diabetes (T2DM) and obesity; particularly in the latter it is evident the association with biliary lithiasis. T2DM and obesity present some clinical factors which can be considered risk factors for AP (Pagliarulo et al.,2004; Olokoba et al.,2007;Togerson et al.,2003). Several etiological factors can cause AP.

The most common etiological factors for AP in the global population are biliary lithiasis (biliary pancreatitis) and excessive alcohol consumption. Other causes of AP are hypertriglyceridemia, hypercalcaemia, obesity, trauma, obstruction of the main pancreatic duct and also drugs (Spanier et al.,2008). The frequency of AP induced by drugs in the global population is esteemed around 2% (Trivedi & Pitchumoni,2005). The possibility of recurrence of AP is an important element and the global frequency of a new attack is esteemed around 10-15% (Yadav & Lowenfels, 2006). Moreover as AP has many risk factors in common with T2DM it may be useful to evaluate the role of these risk factors in AP. T2DM may increase the risk of AP and may also adversely affect the evolution of AP.

Our purpose is to identify within severe forms, the critical or early severe acute pancreatitis (ESAP) and the prevalence of diabetic patients; also to illustrate their clinical features and therapeutic choices and finally to evaluate if diabetes is associated with a higher incidence of SAP and also of critical forms (ESAP). Detailed examination of an homogeneous series contributes to clarify the pathogenetic and clinical details.

2 Patients and Methods

In the period September 1997/December 2011, 924 patients with biliary lithiasis were hospitalized in our department of General Surgery: 555 gallbladder lithiasis, 276 acute biliary pancreatitis (ABP) and 93 choledocholithiasis without pancreatitis. The demographic data of the patients with ABP were: mean age 49 years (range 40-86 years) and female to male ratio 1.33:1. Biliary pathogenesis was confirmed in all patients:

cholecystic lithiasis or biliary sludge was present in 100% of cases, while common bile duct size was >8mm in 40.7% of cases.Alterations of the cholestasis indexes were present in more of 50% of the patients (Table 1). The majority of our patients presented with clinical features of mild/moderate forms. Mild pancreatitis are self limiting forms characterized by edema and normal enhancement of pancreatic parenchyma on contrast-enhanced CT. In moderate pancreatitis there are early acute fluid collections located in or near the pancreas without wall of fibrous tissue, almost always with spontaneous regression and minimal and transient organ dysfunction. Mild/moderate pancreatitis were 216/276 (78.2%), out of which 33/216 (15.2%) were moderate/severe. Moderate/severe forms are characterized by great peri-pancreatic and pancreatic involvement with fluid/necrotic collections but organ failure is transient or absent. Severe forms are characterized by diffuse or local areas of non viable pancreatic parenchyma, peri-pancreatic fat necrosis, non enhanced pancreatic parenchyma and/or fluid-necrotic peri-pancreatic collections with persistent or transient organ failure. Within the severe forms there are also critical or early severe forms with persistent or transient organ failure and infected pancreatic and peri-pancreatic collections.

SAP were 60/276 (21.7%), out of which 13/60 (21.6%) were critical forms (ESAP). The mean age in ESAP group was 52 years (range 39-71) and in the other 47 patients of the SAP group the mean age was 46 years (range 37-74) ; the prevalence of diabetes in all patients with severe forms was 31.6% (19/60) but in the patients of ESAP group was 38.46% (5/13), in the remnants of SAP group 29.78% (14/47); the patients with previous repeated episodes in all SAP group were 21.6% (13/60), but in ESAP group the incidence of recurrent pancreatitis was 30.7% (4/17), while 19.1% (9/47) in the other patients with SAP.

CT severity index with Balthazar scoring for the grading of acute pancreatitis and points for necrosis has been applied. This classification is based on morphological and functional features: focal or diffuse enlargement of the pancreas, pancreatic gland abnormalities, peri-pancreatic inflammation with pancreatic and peripancreatic fluid collection, areas of non enhanced parenchyma (Table 1).

Mean age	Sex	Dir. Bil < 2 mg	Dir. Bil 2-5 mg	AST/ALT x 3	G-GT >200	CBD size (US)> 8mm	Colecystic Lithiasis
49 (40-86)	F 158 M 118	60.4%	39.6%	26.8%	59.9%	40.7%	100%

Grade B1	183 (66.3%)
Grade C2	93 (33.6%)
Grade D3	47 (17.02%)
Grade E4	13 (4.7%)

Table 1 : Demographic data,percentage incidence of biliary lithiasis and cholestasis indexes. CT severity index : CT GRADE POINT + point for necrosis (Balthasar) 276 acute biliary pancretitis.

In both groups of patients, severe and critical forms, the therapeutic approach is the same and is based on intensive care, fluid resuscitation, correction of hypoxemia and enteral nutrition; the evolution is followed controlling and treating the infection of necrotic tissue and peri-pancreatic fluid collections. In biliary pancreatitis, the therapeutic program includes assuring papillary patency and common bile duct cleaning (Fan et al.,1993; Folsch et al.,1997; Neoptolemos et al.,1988; Kroh & Chand, 2008; Petrov,2009; Kopetanos,2010; Vitale et al.,2009; Petrov et al.,2008; Moretti et al.,2008; Acosta et al., 2006; van Santvoort et al., 2009) with endoscopic retrograde cholangiopancreatography/ endoscopic sphincterotomy (ERCP/ES). After ERCP/ES, it is necessary to perform laparoscopic cholecystectomy to complete gallstones treatment. The timing of laparoscopic cholecystectomy is connected with acute pancreatitis evolution because it is preferable to wait for the stabilization of the general conditions but in the same hospital stay. Treatment of the later phase of acute pancreatitis consists in control and treatment of local complications: infections, haemorrhage, pancreatic and peri-pancreatic fluid necrotic collections. It is useful to identify among severe acute pancreatitis the critical forms with particular early severity.

The data of these two groups of patients are compared by means of statistical analysis with chi-square test and t-student test, with c.i. 0.95. In addiction we have evaluated in all groups of AP, severe and critical forms, the prevalence of patients with T2DM. We have also considered in the patients subdivided according to each severity criteria the prevalence of diabetic patients. Peri-pancreatic fluid collection suggests the anatomical-clinical scenario of necrotizing acute pancreatitis. Acute fluid collections occur early in acute biliary pancreatitis and they are peri-pancreatic or localized in the pancreas (Hamm & Franzen, 1993; Vitas & Sarr, 1992; Baranyai & Jakab, 1997). Fluid collection has no surgical indication if it is not complicated (symptomatic or infected), and in the majority of cases it resolves spontaneously.

The intra-hepatic localization of fluid collection is very rare with less than 30 cases being described in literature (Mofredj et al.,2000; Balzan et al., 2005; Neri et al., 2009). We have observed 2 cases of rare voluminous intrahepatic fluid collections in 2 patients affected by acute biliary pancreatitis with T2DM.

The first case is that of a 68-year-old female with pathological obesity (BMI=47.5), arterial hypertension, and T2DM, with no alcohol problems. Ten days before admission to our institution, the patient was admitted to another hospital and diagnosed with acute biliary pancreatitis. On admission to our hospital, the patient was in fairly good general condition (ABP 150/80 mm Hg, HR 110 (BPM), spO2 65 mm Hg, sO2 90%, total bilirubin 3.12 mg/dL, direct bilirubin 2.65 mg/dL, GOT 87 U/L, GPT 90 U/L, alkaline phosphatase 548 U/L, gamma-GT 943U/L, lipasemia 1288U/L, pancreatic amylasemia 840 U/L, Hb 9.1g/dL, HCT 27%, MCV 62fL, WBC 12000 mm3, PLT 165000mm3). The other bio-humoral tests were normal. The standard chest X-ray showed left basal pleural effusion. The abdominal examination revealed right hypochondrium pain with negative Blumberg and Murphy signs. The cardiovascular examination was normal. Twenty-four hours after admission, the patient underwent an ultrasound that revealed abdominal gallbladder microlithiasis with mild dilation of the intra- and extra-hepatic biliary ducts without images of intraluminal lithiasis. This was within a scenario of necrotizing pancreatitis with disruption of the entire gland except a small part of the head, and there were several peri-pancreatic, peri-hepatic, peri-splenic, and pelvic fluid collections (Balthazar E grading). The patient continued NPO and the appropriate medical therapy. About 72 hours after admission, she was in good general condition and was scheduled to undergo ERCP because of the biliary cause of the pancreatitis and the persistence of an increase in cholestasis tests. However, ERCP was not performed because Vater's papilla could not be cannulated. Seven days after admission, the patient had fever that reached 40.5℃. She therefore underwent a chest-abdominal CT-scan that showed an intra-hepatic subcapsular fluid collection in the left lobe about 5cm in diameter with air inside. The intra-hepatic collection was successfully treated with percutaneous US/CT guided drainage with a pigtail tube. The chemical-physical and bacteriological examination revealed very high levels of lipase and pancreatic amylase, necrotic material, and Candida Albicans. Intravenous B Amphotericin and intradrainage washing of the collection with fluconazole were started. Forty-eight hours after positioning the drain, the patient's fever broke, and 10 days later the drain was removed after CT-scan control because the intra-hepatic collections had disappeared

Twenty-five days after admission, the patient was discharged with no major morbidity after the percutaneous treatment, and a cholecystectomy was planned for 30 days later.

A 72-year-old female with arterial hypertension, T2DM, previous acute myocardial infarction, chronic renal failure and with no alcohol problems, had undergone an aorto-bis-femoral by-pass 3 months earlier. She had experienced at least 2 episodes of acute biliary pancreatitis in the previous 6 months and was treated with medical therapy only. On admission, the patient had epigastric pain and vomiting but was in fairly good general condition (ABP 140/80 mm Hg, HR 90/m', spO2 72 mm Hg, sO2 95%, total bilirubin 1.15 mg/dL, direct bilirubin 0.6 mg/dL, GOT 45U/L, GPT 40 U/L, alkaline phosphatase 224 U/L, gamma-GT 94 U/L, lypasemia 320 U/L, pancreatic amylasemia 124 U/L, Hb 10.2 g/dL, HCT 31%, MCV 83 fL, BUN 70 U/L, creatinine 1.7 mg/dL, WBC 8000 mm3, PLT 221000 mm3). The other bio-humoral tests were normal, and the standard chest X-ray showed COPD. The abdominal examination revealed epigastric pain with negative Blumberg and Murphy signs. The cardiovascular examination was normal. Twenty hours after admission, the patient underwent an abdominal ultrasound that revealed a gallbladder microlithiasis without dilation of the intra- and extra-hepatic biliary ducts with lithiasic material inside. Several pancreatic necrotic collections were also reported within the head, body, and tail of the pancreas, as was a voluminous intra-hepatic subcapsular fluid collection in the left lobe about 10cm in diameter causing epigastric pain The patient underwent an ERCP/ES to remove the stone from the main biliary duct, with no major morbidity. Three days later, she successfully underwent percutaneous US/CT guided drainage of the intra-hepatic collection with a pigtail tube. The chemical-physical and bacteriological examination revealed very high levels of lypase and pancreatic amylase with a negative microbiological examination. After 12 hours, the pain was gone. The drain was removed 7 days later during a control CT-scan that showed that the intra-hepatic fluid collections had disappeared The patient was discharged in good general condition with no major morbidity after the percutaneous treatment, and a cholecystectomy was scheduled for 15 days later.

3 Results

The comparison between the patients with SAP (47) and ESAP (13) has shown the following data: the degree of pancreas impairment with Balthazar score was 2.3 in SAP vs 3.85 in ESAP, abdominal compartment syndrome (ACS) was demonstrated in only 1 patient with ESAP (7.6%), multiple organ dysfunction syndrome (MODS) in 6 patients with ESAP (46.1%), simple organ dysfunction in 24 patients with SAP (51%) vs 7 patients with ESAP (53.8%), pancreatic sepsis in 3 patients with SAP (6.3%) vs 3 patient with ESAP (23%), hypoxemia in 31 patients with SAP (65.9%) vs 10 patients with ESAP (76.9%). Mortality rate was 4.24% in SAP vs 15.4% in ESAP. The result of the comparison of critical, early severe forms and severe pancreatitis is showed in table 2.

	SAP (47)	**ESAP (13)**
Impairment degree of pancreas (Balthazar CT score)	2.3	3.85
Abnominal compartment syndrome ACS (%)	-	7.6% (1/13)
Multiple organ dysfunction syndrome	-	46.1% (6/13)
Single organ dysfunction	51% (24/47)	53.8% (7/13)
Pancreatic sepsis	6.3% (3/47)	23% (3/13)
Hypoxemia	65.9% (31/47)	76.9% (10/13)
Mortality	4.2% (2/47) late	15.4% (2/13) early

Table 2 : Comparison of the clinical appearance of ESAP and SAP.

The difference between SAP and ESAP has statistical significance for: degree of pancreas impairment (Balthazar CT score), abdominal compartment syndrome, treated in emergency with open approach, MODS and mortality (Table 3).

	SAP (47)	ESAP (13)	P =
Impairment degree of pancreas	2,3	3,85	0,003
ACS	0/47 (0%)	1/13 (7,6%)	0,055
MOF	0/47 (0%)	6/13 (46,1%)	0,000
single organ disfunction	24/47 (51%)	7/13 (53,8%)	0,859
Pancreatic sepsis	3/47 (6,3%)	3/13 (23%)	0,076
Hypoxemia	31/47 (65,9%)	10/13 (76,9%)	0,452
Mortality	2/47 (4,2%)	2/13 (15,4%)	0,155

Table 3 : Statistical evaluation of SAP-ESAP comparison.

In summary, in our experience, we have classified within severe acute pancreatitis, some patients with most severe forms, particularly at the onset of the disease, with high degree of pancreas impairment and great involvement of general conditions: ACS, multiorgan dysfunction, etc. Moreover in 225 cases (80%) out of our 276 patients with acute biliary pancreatitis, we performed ERCP/ES within 72 hours. This therapeutic procedure has been performed in the following cases: in 60 patients, 13 with ESAP and 47 with SAP; in 7 cases ERCP/ES was delayed for 10 days, and in 3 patients it was not possible; besides, in 73 patients with recurrent acute biliary pancreatitis; in 33 patients with moderate/severe acute pancreatitis; in 59 patients with mild/moderate AP with laboratoristic or US or MRCP confirmation of papillary or CBD lithiasis obstacle (Heider et al., 2006). In 225 patients undergoing ERCP/ES, CBD cleaning was confirmed in 161 cases (71.5%). In the later phases of the disease the preferred approach to fluid and necrotic collections is US/CT guided percutaneous drainage, although on this point there are works in literature demonstrating the results of aggressive approach as we did in the past (van Baal et al.,2011; Besselink et al., 2011).

In our experience, considering 60 patients (47 with SAP and 13 with ESAP), we intervened only in 8 patients: 3 US/CT guided percutaneous drainage of infected necrotic collections, 2 laparotomies with necrosectomy and drainage, 1 open approach for ACS, 2 US/CT guided percutaneous drainage of intra-hepatic fluid collections (Bradley,1993). In 2 cases with acute intra-hepatic fluid collection, the clinic and

laboratory study on admission showed gallbladder lithiasis and principal biliary duct dilation and a severe alteration in the patients' general condition. Thus, the usual therapeutic program for severe acute pancreatitis was started. The morphologic evaluation (US/CT after 48 hours) showed the anatomo-pathologic alterations of the pancreatic and peri-pancreatic area (necrotizing fluid collections). In both cases, intra-hepatic fluid collections were present also. Among 276 patients with AP, 54 were diabetics and 222 non diabetics. The prevalence of diabetes in AP was 19.5% (54/276). In the group of patients with SAP the prevalence was 31.6% (19/60). Within the patients with ESAP the prevalence was 38.46% (5/13), in the remnants patients of SAP group 29.78% (14/47). Overall the patients with diabetes have shown a higher risk of critical forms of AP than non diabetic patients. According to severity criteria, in ESAP group, diabetic patients had the prevalence 30.7% (4/13) in MODS, 38.46% (5/13) in single organ disfunction, 15.38% (2/13) in pancreatic sepsis, 38.46% (5/13) in hypoxemia and mortality rate was 15.4% (2/13). Within the other 47 patients of the SAP group diabetic patients had the prevalence 29.78% (14/47) in single organ disfunction, 4.25% (2/47) in pancreatic sepsis and 25.53% (13/47) in hypoxemia.

4 Discussion

Diabetes is a very frequent disease so much that it can be considered an endemic illness in western countries. In fact its prevalence in recent surveys reaches 3-4% and can rise to 6-11% if undiagnosed cases are included (Centers of Disease Control and Prevention Atlanta GA : US Department of Health and human services, 2003; Center for Chronic disease Prevention and health Promotion) . According to the WHO in the last decade the incidence of T2DM has tripled on a world scale. T2DM patients are prone to hypertriglyceridaemia and biliary lithiasis (Mentula et al., 2008; Kemppainen et al.,2007) which represent the major risk factors for AP. The association of AP with diabetes is in evidence: it seems that the risk of AP is increased by diabetes, but also that of SAP and severe critical forms. It is possible to detect a close connection between T2DM and AP which has rather complex aspects. For example, it must be considered that AP and T2DM have common risk factors: hypertriglyceridaemia, obesity, etc. Moreover, in T2DM there are concomitant conditions which require the use of drugs whose use has been associated to the onset of pancreatitis. In fact, glyburide, exematide (incretin based) and dipeptyldepeditidase-4 inhibitor (DPP-4 inhibitor), drugs recently introduced in the therapy and used to control T2DM, have been considered responsible of the onset of pancreatitis (Noel et al.,2009; Garg et al.,2010; Olansky,2012). Therefore diabetes can be considered a concomitant disease, a worsening factor in the evolution of AP and a metabolic illness which can cause AP. On the whole, AP risk can be considered higher in diabetic patients (Gonzalez-Perez et al.,2010) and AP evolution can be negatively influenced by diabetes.

Diabetes prevalence is probably underestimated in AP patients and moreover an ulterior element of confusion is represented by hyperglycemia which is present at the onset of AP also in non diabetic patients. In conclusion some patients do not know that they are diabetics until the onset of AP. The interconnection between diabetes and AP highlights some questions which are part of the aims of this study as how to assess diabetes prevalence in AP patients and the negative influence of the coexistence of diabetes on the evolution of AP. As a start, it is appropriate to consider that the relationship between the two diseases, AP and T2DM, can be presented, as shown in literature, in a twofold sense: prevalence of diabetic patients in AP series and in reverse higher risk for AP in diabetic patients. AP incidence considered on the whole shows, in many recent studies, an evident increase (Yadav & Lowenfels, 2006; Frey et al., 2006; Lankisch et al.,2009). Moreover AP incidence in T2DM patients is 2-3 times higher than in non diabetics (Girman et al., 2010). In Zhao's study (Zhao et al., 2012) the incidence of diabetic patients reaches almost 10% and increases up to 12.5% if patients in which diabetes has been diagnosed for the first time on the occasion AP onset are included.

Detailed data regarding a higher risk for AP in T2DM patients in recent literature (Noel et al., 2009; Garg et al., 2010) are very numerous. With some variations, they agree on an increased risk of about 20/30%.

However, these results are subject to variations considering that there are a number of AP in which diabetes had not been previously diagnosed: the incidence of AP in patients with T2DM 1.5 to 3 fold increase risk compared to non diabetic patients (Noel et al., 2009; Garg et al., 2010). We can assume valid and concrete the finding of a higher risk for AP and particularly of pancreatitis with biliary etiopathogenesis (Noel et al., 2009) in T2DM patients. Moreover diabetic patients have a higher risk for severe and also critical forms of pancreatitis characterized by functional organ impairment and pancreatic/peri-pancreatic necrosis with possible septic complications.

Of great interest is the study and the understanding of the elements and mechanisms on which the increased risk for AP (particularly ABP) in diabetic patients is founded. In diabetes diverse and numerous metabolic dysfunctions occur which manifest as hyperglycemia, alterations in insulin production and transport and onset of insulin resistance. In sum, the pancreatic endocrine/esocrine interactions, in which both hormones and polypeptides play a role (Lin & Sun, 2009; DeFronzo et al., 1992), are altered. The high level of blood glucose induces oxidative stress in different tissues as shown by the increase of mitochondrial oxidative stress (Kamboj & Sandhir, 2011). Moreover, many factors and hormones are associated to the development and the persistence of insulin resistance: tumour necrosis factor α (TNF-α), amylin, leptin, interleukin 6 (IL-6), etc. (Solanki et al., 2012). Also, there are medical conditions linked to the increased risk for AP in diabetic patients. Obesity, hypertriglyceridemia and the use of antidiabetic drugs are in evidence.

Obesity belongs only marginally to the risk factors for AP, while it is surely a risk factor for T2DM onset. In fact, obese patient have an hypercaloric diet and a genetic factor with metabolic syndrome due to insulin resistance. On the other hand, obesity is a condition associated to the most severe evolutions of AP for the necrosis of adipose tissue with liberation of high levels of inflammation mediators which start systemic inflammatory response syndrome (SIRS) (Franco-Pons et al., 2010; Martinez et al., 2006). High levels of triglycerides (>1000 mg/dl) have been considered to cause AP. In fact, pancreatic lipase can hydrolyze the excess of triglycerides forming great amounts of free fatty acids and free radicals which cause pancreatic ischemia through an impairment of small vessels circulation (Tsuang et al., 2009).

In diabetic patients though hypertriglyceridemia rarely reaches very high levels and moreover insulin therapy has a protective effect on lipids metabolism (Solanki et al., 2012). In fact, few diabetics patients with hypertriglyceridemia develop AP. Regarding this aspect, Solanki (Solanki et al., 2012) puts forward an interesting hypothesis. Oxidative stress in pancreatic cells caused by the exposition to high levels of blood glucose with factors and hormones which induce insulin resistance, contributes to reduce the possibility of AP onset. However, also etiological factors and the effects of T2DM complications must be considered: diabetic ketoacidosis, use of antidiabetic drugs, hypertriglyceridemia, excessive dietary fats, excessive alcohol consumption and cholesterol biliary lithiasis. These elements constitute a “critical mass” which damages the acinar cells and causes AP (Barreto & Saccone, 2010). In this complex scenario of metabolic alterations it may be concluded that insulin resistance and hyperglycemia can worsen pancreatitis evolution. Therefore, therapies controlling these alterations, as it happens in diabetic patients, have a protective effect against an evolution to severe forms of AP (Petrov & Zagainov, 2007).

A further consideration concerns the possible role of drugs as cause of AP. Badalov (Badalov et al., 2007) has offered a classification of drugs involved in AP onset. These drugs are divided in 4 classes, from I to IV, which include, progressively, drugs from the more implicated, like the angiotensin converting enzyme inhibitors (ACE), sinvastatin, etc, up to less involved drugs (metformin) (Badalov et al., 2007). Diabetic patients take numerous drugs: to control glucose blood levels especially but also for hypertension, hyperlipidemia, vasculopathies etc. ACE inhibitors are in evidence as they would cause angioedema of pancreatic ducts and alteration of pancreatic microcirculation (Balani & Grendell, 2008). A particular consideration must be given to the use of incretin-based antidiabetic therapies, as exenatide and sitagliptin. Dore (Dore et al., 2009) and Garg (Garg et al., 2010) have examined the coexistence of AP and diabetes

treated with incretin-based therapies. Dore (Dore et al., 2009) found for exenatide a relative risk of 1.0 (95% CI :0.6 – 1.7) for AP; also for sitagliptin the relative risk for AP was 1.0 (95% CI : 0.5-2.0). Therefore these data do not show a role for these drugs in causing AP. Garg (Garg et al., 2010), on the contrary found in diabetic patients treated with incretin-based therapies an incidence for AP of 5.6 per 1000 patients per year; in the control group (non diabetics) AP incidence was 1.9 per 1000 patients per year. In any case these are very wide analysis but retrospective. Exenatide is involved as causing AP in the studies of Anderson and Ayoub (Anderson & Trujillo, 2010; Ayoub et al., 2010). In conclusion the role of incretins, used in T2DM therapy, as causing AP remains uncertain and not well defined.

The increased incidence of biliary lithiasis in diabetics is due to metabolic and functional factors. There are references to the secretion of lithogenic bile linked to obesity, insulin resistance and dyslipidemia. In particular, this determines an alteration in bile composition with increased secretion of cholesterol and reduced secretion of biliary salts. The alteration in the balance of bile components (cholesterol, phospholipids, biliary salts) determines the precipitation of cholesterol chrystals. Moreover, symptoms of altered gallbladder function may appear also without the presence of evident stones (so called alithiasic cholecystitis), caused by the presence of biliary sludge. In conclusion the increase of the incidence of acute biliary pancreatitis in T2DM patients is evident. These are obese and dyslipidemic patients who present an increased incidence of biliary lithiasis which represent a further element for the increase of acute biliary pancreatitis in T2DM patients (Pagliarulo et al., 2004; Noel et al., 2009; Chapman et al., 1996). On the whole it is not clear the relantionship between T2DM and AP: risk factor of increased incidence of AP, concomitant diseases or worsening factor in the evolution of AP. In the Figure 1 (Solanki et., 2012; Franco-Pons et al, 2010; Martinez et al., 2006; Tsuang et al., 2009; barreto & Saccone, 2010) we summarize the pathogenetic connections between T2DM and AP. Our experience confirms the close connections between severe forms of AP and T2DM.

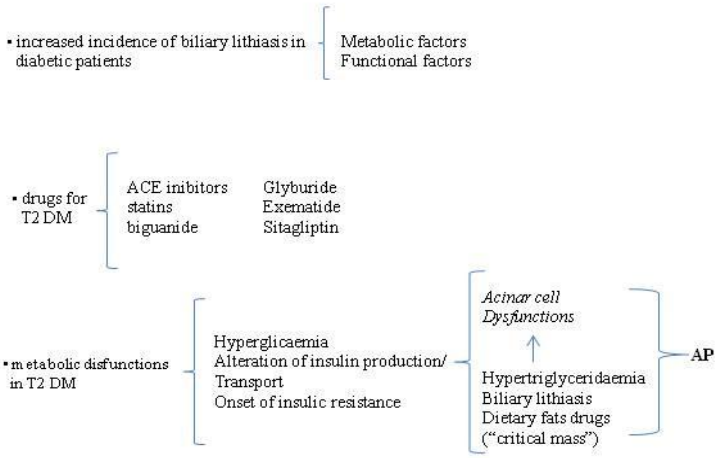

Figure 1 : T2DM and AP : pathogenetic connections

SAP can be seen as a biphasic disease, with the first phase (1^{st} - 2^{nd} weeks) characterized by early toxic-enzymatic injury (SIRS, MODS) and a later phase in the third and fourth week characterized by septic complications (infection of necrotic tissue and of peri-pancreatic fluid collections) (Al Mofleh, 2008; Carnovale et al., 2005; Toouli et al., 2002). Moreover the prolonged evolution of the disease can be increased by metabolic diseases as diabetes. Pancreatitis can present different severity in the first (toxic) phase: it can be self-limiting or quickly responsive to intensive care (especially rehydration), or it can quickly evolve in SIRS and multi-organ failure (MOF). In a new nosographic approach AP has a broad spectrum of clinical

manifestations. The most important changes in the clinical picture come from two elements: possible organ failure and complications of pancreatic and peri-pancreatic necrotic collections (Petrov & Windsor, 2010; Di Fabio et al., 2011). It is possible to identify four clinical manifestations of AP. Mild: no complications of pancreatic/peri-pancreatic collections, no organ failure; Moderate: sterile pancreatic/peri-pancreatic complications or transient organ failure; Severe: pancreatic/peri-pancreatic complications or persistent organ failure; Critical: pancreatic/peri-pancreatic complications and persistent organ failure. The response of the pancreatic tissue to an injury, like acinar cells necrosis, leads to production and liberation of proinflammatory cytokines, chemokines and other biological active compounds (Beger & Rau, 2007; Dugernier et al., 2003; Mayer et al., 2000; Makhija & Kingsnoth, 2002; Lipsett, 2001). In summary (Figure 2 (Pezzilli et al., 2003; Poch et al., 1999; Sakai et al., 2003; Guzman & Rudnicki, 2006; Deitch et al., 1991; Bonham et al., 1997; Kylanpaa-Back et al., 2001; Bhatnagar et al., 2003; Andersson et al., 2007). ESAP can develop by altered balance between pro-inflammatory reaction to pancreatic necrosis in the peritoneal compartment (positive effect) and systemic circulation and diffusion of high level of anti-inflammatory mediators (negative effect leading to SIRS and MODS).

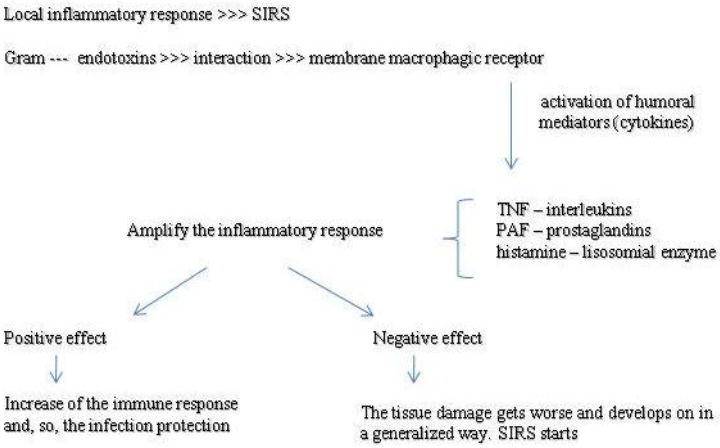

Figure 2 : Evolution of the severe acute pancreatitis

The results of the comparison between our two groups of patients, severe and more severe pancreatitis, have shown that the distinction is actual and useful. In fact, in the first phase of the disease (1-2 weeks), pancreas pathological alteration (CT severity index), multi-organ dysfunction and compartment syndrome are in evidence as discriminant data between severe and critical forms. In a late phase of pancreatitis evolution the septic complication of pancreatic and peri-pancreatic necrotic fluid collections assumes a discriminant role, even if in our study it is at the limit of statistical significance. Our experience, even if numerically very limited, shows that it is possible to identify within SAP clinical forms of particular severity. However, the clinical features which cause a pancreatitis to become very severe present a temporal sequence: in the first phase, the multi-organ impairment, while in a following phase the septic complication of the fluid collections, which is however possible also in the less severe forms where multi-organ dysfunction was at the beginning absent or transient.

According to our data the difference in mortality incidence between the two groups of patients (SAP and ESAP), even if evident, is not statistically significant ($p=0.155$). From a detailed analysis of our experience it is possible to notice that, in the group classified as critical, mortality is present in the initial phases when the most evident clinical aspect is represented by ACS and MODS which are the causes of death. On the contrary, mortality in the SAP group is present in the late phase and is connected to the septic complication which intervenes after the organ dysfunction has been controlled. Thus, according to the data gathered with

our analysis, even if within the limits deriving from schematizations, two phases in the evolution of SAP can be detected. The first phase, which can be limited to the 1st-2nd week from the onset in which severity is graduated by general conditions impairment: transient or stable organ or multi-organ dysfunction to the severe complication of abdominal compartment syndrome. Thus early mortality is linked to the severity of the systemic inflammatory syndrome. The extension and the degree of phlogistic-necrotic involvement of the pancreas and peri-pancreatic space, even if remaining an index of severity, does not seem to have a directly proportional relationship with multi-organ dysfunction (number of organs, transient or persistent dysfunction). Persistent dysfunction may worsen the extension of pancreatic necrosis because of reduced perfusion (Johnson & Abu-Hilal, 2004). Thus the connection between necrosis and organ failure, which are not necessarily correlated (Vege et al., 2009),is not clear.

Therapeutic approach in the first phase tries to control and treat general complications, i.e. SIRS and MODS, applying intensive care, preserving intestinal wall integrity and assuring papillary patency in biliary pancreatitis. Antibiotic prophylaxis and enteral feeding reduce significantly the infection rate of necrosis (Beger & Rau, 2007; Abou-Assi et al., 2002; Olah et al., 2002; Owens et al., 1997; Kalfarentzos et al., 1997; Gupta et al., 2003). The second, late phase is in the 3rd-4th week and beyond. It is characterized by the evolution of pancreatic and peri-pancreatic fluid-necrotic collections, resulting from the self-digesting inflammatory process. The collections may be reabsorbed generally over a long time or in infrequent cases (15%) they may cause the formation of post-necrotic pseudo-cysts. The most severe event is represented by the collections infection. So the septic complication characterizes the severity in the late phase of acute pancreatitis. The evacuation with US-CT guided percutaneous drainage of fluid-necrotic collections and of possibly infected collections represents the therapeutic standard. The new nosographic formulation proposed by Petrov (Petrov & Windsor, 2010) which identifies an increasing severity on the basis of the presence of transient or stable organ dysfunction and of septic complication of pancreatic and peri-pancreatic post-necrotic collections can be integrated by the temporal clarification of the two clinical elements of severity which generally are not simultaneous.

In our opinion it is necessary to clarify that there are critical or early severe acute pancreatitis characterized in the initial phase by SIRS with multi-organ dysfunction and equally severe forms in the late phase, after resolution or at least control of MODS which are instead characterized by septic complication of fluid-necrotic collections. Moreover, the septic complication can develop after some time (3-4 weeks). In fact fluid-necrotic collections may be considered the result of the pancreatic phlogistic process on which subsequently the septic complication, generally for bacteria translocation, superimposes.

Intra-hepatic fluid collections are rare entities in the course of necrotizing acute biliary pancreatitis. To date, only about 30 cases have been reported in the medical literature. However, with the routine use of imaging techniques more will be recognized and references in the medical literature should increase. This rare complication of acute biliary pancreatitis can be useful to confirm the role of T2DM as worsening factor in the evolution of acute pancreatitis.

Two etiopathogenetic methods for the development of the intra-hepatic fluid collections have been proposed (Pelletier, 1997; Mortele & Ros, 2001; Aguilera et al., 2003; Shibasaki et al., 2002). The first mechanism consists of pancreatic juice accumulation in the pre-renal space and thereafter of eroding through the posterior layer of the parietal peritoneum and into the lesser sac. Then the lesser sac collection tracks along the lesser omentum or gastrohepatic ligament toward the liver leading to the formation of left lobe subcapsular collections. The second mechanism consists of tracking the pancreatic juice along the hepatoduodenal ligament from the head of the pancreas to the porta hepatis, resulting in the formation of intraparenchymal fluid collection. In our patients, it seems that the intra-hepatic collections developed by means of the first mechanism because of the left lobe localization.

The complete therapeutic program in the 2 reported cases has followed the usual approach for severe acute biliary pancreatitis: control and support of the patient's general clinical condition, early removal (within 72 hours) of the papillary obstacle (in case of the presence of signs of cholestasis and principal biliary duct

dilation) by means of ERCP/ES. Following the stabilization of the patient's general condition, VLC was programmed for the treatment of gall-bladder lithiasis. The treatment rationale based on acute pancreatic and peri-pancreatic fluid collection observation and control was derived from the most frequent evolution. Fluid collections are bound to disappear spontaneously. The therapeutic indication, therefore, is only in case of complications (infection or pain). The intrahepatic localizations, in our experience and in literature reports, had an overlapping evolution like the most frequent peri-pancreatic collections: therefore, they need the same therapeutic approach. So, in the first phase (collections without a real neo-formed wall), only the infection or painful symptoms derived from compression of the most voluminous collections can justify therapeutic intervention. Moreover, only percutaneous external drainage can be successfully proposed (Scappaticci & Markowitz, 1995; Mehler et al., 1998; Shibasaki et al., 2002; Mofredj et al., 2000) in this phase where there is no stable fibrotic wall. So, only if necessary, the peri-pancreatic or intra-hepatic collections, as shown in our cases, undergo percutaneous US/CT guided drainage if they are infected or if pain is present due to hepatic capsula compression. The percutaneous drainage of the fluid collections in our patients was a safe and efficacious procedure, according to the conclusions derived from literature (Balzan et al., 2005; Mofredj et al., 2000). Furthermore, today there is a general trend toward reducing all invasive treatment of necrotizing acute biliary pancreatitis. It is a serious disease, dominated by systemic inflammatory response syndrome, where the main therapy (medical, or surgical, or both) is to support and check organic disorders until anatomical and functional recovery of the compromised systems is achieved.

5 Conclusion

Data from our experience confirm the prevalence of diabetic patients in AP. In particular it reaches 19.5% in pancreatitis globally considered, but becomes very evident reaching 31.6% in SAP and 38.46% in critical forms (ESAP).Within severity criteria prevalence of diabetics manifests in MODS (30.7%- 4/13), hypoxemia (28.33% - 17/60), single organ disfunction (31.6% that is all diabetic patients of SAP group : 19/60). The prevalence of diabetics was less evident in septic complications, in fluid/necrotic collections (11.66% - 7/60). We believe that this different result within severity factors is due to their differentiated temporal distribution. Metabolic alterations in diabetics are less controllable and negatively effective at the onset of severe pancreatitis with impairment of general conditions and organ dysfunction. They are instead more controllable and have less effect in the late phases of severe pancreatitis in relation to the possible septic infection of fluid-necrotic collections.

In conclusion, AP incidence in T2DM is higher (about 3 times more) than in non diabetics. AP presents in 20% of cases in acute and rapidly worsening form with multiple and persistent organ dysfunction in the critical form. It is therefore necessary the full awareness of the elevated risk for AP in T2DM patients and particularly in the ones with previous pancreatitis attacks.

References

Yadav D. & Lowenfels AB. (2006). Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 33, 323-330

Kingsnorth A. & O'Reilly D. (2006). Acute pancreatitis. *Br Med J* 332:1072-1076

Pagliarulo M., Fornari F., Fraquelli M. & Conte D. (2004). Gallstone disease and related risk factors in a large cohort of diabetic patients. *Dig Liver Dis* , 36,130-134

Olokoba A.B., Bojuwoye B.J., Olokoba L.B. & Inikori A.K. (2007). Gallstone disease and type-2 diabetes mellitus- the link. *J Coll Surgeons Pak,* 17, 594-597

Togerson J.S., Lindroos A.K. & Naslund I. (2003). Gallstones, gallbladder disease, and pancreatitis : croos-sectional and 2-year data from the Swedish Obese Subjects (SOS) and SOS Reference Studies. *Am J Gastroenterol* ,98, 1032-1041

Spanier B.W., Dijkgraaf M.G. & Bruno M.J. (2008) Epidemiology, aetiology and outcome of acute and chronic pacreatitis : an update. Best Pract Res ,22, 45-63

Trivedi C.D & Pitchumoni C.S. (2005) Drug-induced pancreatitis : an update. *J Clin Gastroenterol* , 39, 709-716

Fan S.T., Lai E.C., Mok F.P., & Wong J. (1993) Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* , 328 (4) , 228-32.

Folsch U.R., Nitsche R., Ludtke R. & Creutzfeuldt W. (1997) Early ERCP and papillotomy compared with conservative treatment of acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* , 336(4):237-242.

Neoptolemos J.P., Carr-Locke D.L., London N.J. & Fossard D.P. (1988) Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment of acute pancreatitis due to gallstones. *Lancet* , 2(8618), 979-983.

Kroh M. & Chand B. (2008). Choledocholithiasis, endoscopic retrograde cholangiopancreatography, and laparoscopic common bile duct exploration. *Surg Clin North Am* , 88(5) , 1019-1031.

Petrov M.S. (2009) Early use of ERCP in acute biliary pancreatitis with(out) jaundice: an unjaundiced view. *JOP* ,10(1):1-7

Kopetanos D.J. (2010) ERCP in acute biliary pancreatitis. *Word J Gastrointest Endosc* , 2(1), 25-28.

Vitale G.C., Davis B.R., Zavaleta C. & Fullerton J.K. (2009) Endoscopic retrograde cholangiopancreatography and histopathology correlation for chronic pancreatitis. *Am Surg* , 75(8), 649-653.

Petrov M.S., van Santvoort H.C., Besselink M.G. & Gooszen H.G. (2008) Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. *Ann Surg* , 247(2): 250-257.

Moretti A., Papi C., Aratari A. & Capurso L. (2008) Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. *Dig Liver Dis* , 40(5), 379-385.

Acosta J.M., Katkhouda N., Debian K.A. & Berne T.V. (2006) Early ductal decompression versus conservative management for gallstones pancreatitis with ampullary obstruction: a prospective randomize clinical trial. *Ann Surg* , 243(1), 33-40.

van Santvoort H.C., Besselink M.G., de Vries A.C. & van Erpecum K.J. (2009) Dutch Acute Pancreatitis Study Group. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. *Ann Surg* ,250(1), 68-75.

Hamm V.B. & Franzen N. (1993) Atypically located pancreatic pseudo-cyst in liver, spleen, stomach wall and mediastinum: their CT diagnosis. *Rofo.*, 159(6), 522–527.

Vitas G.J. & Sarr M.G. (1992). Selected management of pancreatic pseudocyst: Operative versus expectant management. *Surgery*, 111(2), 123–30.

Baranyai Z. & Jakab F. (1997) Pancreatic pseudocyst propagating into retroperitoneum and mediastinum. *Acta Chir Hung* , 36 (1–4), 16–17

Mofredj A., Cadranel J.F., Dautreaux M. & Harry G. (2000) Pancreatic pseudocyst located in the liver: a case report and literature review. *J Clin Gastroenterol*., 30, 81–83.

Balzan S., Kianmanesh R., Farges O. & Belghiti J. (2005) Right intrahepatic pseudocyst following acute pancreatitis: an unusual location after acute pancreatitis. *J Hepatobiliary Pancreat Surg.* , 12(2), 135–137.

Neri V., Ambrosi A., Fersini A. & Valentino T.P. (2009) Minimally Invasive Treatment of Acute Intrahepatic Fluid Collections With Acute Biliary Pancreatitis. *JSLS.* Apr-Jun; 13(2), 269–272.

Heider T.R., Brown A., Grimm I.S. & Behrns KE. (2006) Endoscopic sphincterotomy permits interval laparoscopic cholecystectomy in patients with moderately severe gallstones pancreatitis. *J Gastrointest Surg* , 10(1), 1-5.

van Baal M.C., van Santvoort H.C., Bollen T.L. & Gooszen H.G., (2011) Dutch Pancreatitis Study Group. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Br J Surg* ; 98(1), 18-27.

Besselink M.G., van Santvoort H.C., Bollen T.L. & Gooszen HG. (2011) Draining sterile fluid collections in acute pancreatitis? Primum non nocere! *Surg Endosc* , 25(1), 331-332.

Bradley E.L. (1993). 3rd A clinically based classification system for acute pancreatitis. Summary of the international symposium on acute pancreatitis. Atlanta, Georgia, September 11 through 13, 1992. *Arch Surg.* , 128, 586–590.

Centers of Disease Control and prevention Atlanta GA : US. Department of Health and human services. Centers for Disease Control AN Prevention ; National Diabetes factsheet : general information and national estimates on diabetes in the United States (2003)

Centers for disease control and prevention. Atlanta, GA:US; National Center for Chronic disease Prevention and health Promotion (2007)

Mentula P., Kylanpaa M.L., Kemppainen E & Pualakkainen P. (2008) Obesity correlates with early Hyperglycaemia in patients with acute pancreatitis who developed organ failure. *Pancreas* 36, e21-25

Kemppainen E. & Pualakkainen P. (2007) Non-alcoholic etiologies of acute pancreatitis – exclusion of other etiologic factors besides alcohol and gallstone. *Pancreatology* , 7,142-146

Noel R.A, Braun D.K., Patterson R.E. & Bloomgren GL. (2009) Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes : a retrospective cohort study. *Diabetes Care* , 32, 834-838

Garg R., Chen W. & Pendergrass M. (2010). Acute pancreatitis in type 2 diabetes trated with exenatide or sitagliptin. *Diabetes Care* , 33,11,2349-2354

Olansky L. (2012) Diabetes or Diabetes Drugs : A cause of acute pancreatitis. *INTECH Acute pancreatitis Ed. Luis Rodrigo* , 91-98

Gonzalez-Perez A., Schlienger R.G. & Garcia Rodriguez L.A. (2010) Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs. A population-based cohort study. *Diabetes Care* , 33, 13 , 2580-2585

Frey C.F., Zhou H., Harvey D.J. & White RH. (2006)The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas* ,33, 336-344

Lankisch P.G., Karimi M., Bruns A. & Lowenfels A.B. (2009). Temporal trends in incidence and severity of acute pancreatitis in Luneburg County, Germany : a population-based study. *Pancreatology* , 9, 420-426

Girman C.J., Kou T.D., Cai B. & Katz L. (2010) Patients with type2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes, Obesity and Metabolism* , 12, 766-771

Zhao X., Huangpu C., Chen L. & Hu R. Increased risk of severe acute pancreatitis in patients with diabetes. Accepted Article , doi: 10.1111/j.1464-5491.2012.03680.x

Lin Y. & Sun Z. (2009) Current views on type 2 diabetes. *J Endocrinol* , 204:1-11

DeFronzo R.A., Bonadonna R.C. & Ferrannini E. (1992) Pathogenesis of NIDDM. A bilance overview. *Diabetes Care* ; 15,318-68

Kamboj S.S. & Sandhir R. (2011) Protective effect of n-acetylcysteine supplementation on mitochondrial oxidative stress and mitochondrial enzymes in cerebral cortex of streptozotocin-treated diabetic rats. *Mitochondrion*;11:214-22

Solanki N.S., Barreto S.G. & Saccone G.T.P. (2012) Acute pancreatitis due to diabetes : the role of hyperglycaemia and insulin resistance. *Pancreatology* , 12, 234-239

Franco-Pons N., Gea-Sorli S. & Closa D. (2010). Release of inflammatory mediators by adipose tissue during acute pancreatitis. *J Pathol* , 221, 175-82

Martinez J., Johnson C., Sanchez-Paya J. & Perez-Mateo M. (2006) Obesity is a definitive risk factor of severity and mortality in acute pancreatitis : an updated meta-analysis. *Pancreatology* , 6 , 206-9

Tsuang W., Navaneethan U., Ruiz L. & Gelrud A. (2009) Hypertriglyceridemic pancreatitis : presentation and management. *Am J Gastroenterol* ; 104, 984-991

Barreto S.G. & Saccone GT. (2010) Alcohol-induced acute pancreatitis : the “critical-mass” concept. *Med Hypotheses* ; 75:73-6

Petrov M.S. & Zagainov V.E. (2007) Influence of enteral versus parental nutrition on blood glucose control in acute pancreatitis : a systematic review. *Clin Nutr* , 26 , 514-23

Badalov N., Baradarian R., Iswara K. & Tenner S. (2007) Drug-induced acute pancreatitis : an evidence-based review. *Clin Gastroenterol Hepatol* , 5 , 646-61

Balani A.R. & Grendell J.H. (2008) Drug-induced pancreatitis : incidence, management and prevention. *Drug Saf* , 31-823-37

Dore D.D., Seeger J.D. & Arnold Chan K. (2009) Use of claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* , 25, 1019-1027

Anderson S. & Trujillo J. (2010). Association of pancreatitis with glucagon-like peptide 1 agonist use. *Ann Pharmacother* , 44:904-9

Ayoub W., Kumar A., Naguib H. & Taylor H. (2010) Exenatide-induced acute pancreatitis. *Endocr Pract* , 16 : 80-3

Chapman B.A., Wilson I.R., Frampton C.M., & Allan R.B. (1996) Prevalence of gallbladder disease in diabetes mellitus. *Digestive Dis. And Sciences* , 41 , 2222-2228.

Al Mofleh I.A. (2008) Severe acute pancreatitis: Pathogenetic aspects and prognostic factors. *World J Gastroenterol.* ; 14(5):675-684.

Carnovale A., Rabitti P.G., Manes G. & Uomo G. (2005) Mortality in acute pancreatitis: is it an early or a late event? *JOP*; 6(5), 438-444.

Toouli J., Brooke-Smith M., Bassi C. & Tandon R. (2002). Working Party of the Committee of the Bangkok World Congress of Gastroenterology 2002. *J Gastroenterol Hepatol* , Suppl S15-39.

Petrov M.S. & Windsor J.A. (2010) Classification of the severity of acute pancreatitis : how many categories make senso? *Am J Gastroenterol* 2010 , 105 , 74-76.

Di Fabio F., Abu Hilal M. & Johnson CD (2011). Acute pancretitis : mild, severe or potentially fatal. *Pancreatogy* ,11:373–375

Beger H.G. & Rau B.M. (2007). Severe acute pancreatitis: Clinical course and management. *World J Gastroenterol* , 13(38), 5043-5051.

Dugernier T.L., Laterre P.F., Wittebole X. & Pugin J. (2003). Compartimentalization of the inflammatory response during acute pancreatitis: correlation with local and systemic complications. *Am J Respir Crit Care Med* ,168, 148-157.

Mayer J., Rau B., Gansauge F. & Beger H.G. (2000) Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. *Gut*; 47, 546-552.

Makhija R. & Kingsnorth A.N. (2002) Cytokine storm in acute pancreatitis. *J Hepatobiliary Pancreat Surg* , 9 , 401-410.

Lipsett P.A. (2001) Serum cytokines, proteins, and receptors in cute pancreatitis: mediators, markers, or more of the same? *Crit Care Med* , 29 ,1642-1644.

Pezzilli R., Maldini K., Morselli-Labate A.M. & Corinaldesi R. (2003). Early activation of peripheral lymphocytes in human acute pancreatitis. *J Clin Gastroenterol* , 36, 360-363.

Poch B., Gansauge F., Rau B. & Beger HG. (1999) The role of polymorphonuclear leukocytes and oxygen-derived free radicals in experimental acute pancreatitis: mediators of local destruction and activators of inflammation. *FEBS Lett* , 461 ,268-272.

Sakai Y., Masamune A., Satoh A. & Shimosegawa T. (2003) Macrophage migration inhibitory factor is a critical mediator of severe acute pancreatitis. *Gastroenterology* , 124 , 725-736.

Guzman E.A. & Rudnicki M. (2006) Intricacies of host response in acute pancreatitis. *J Am Coll Surg* , 202 , 509-519.

Deitch E.A., Xu D.Z., Qi L. & Beger R.D. (1991). Bacterial translocation form the gut impairs systemic immunity. *Surgery* , 109, 269-276.

Bonham M.J., Abu-Zidan F.M., Simovic M.O. & Windsor J.A. (1997) Gastric intramucosal pH predicts death in severe acute pancreatitis. *Br J Surg* , 84 , 1670-1674.

Kylanpaa-Back M.L., Takala A., Kemppainen E. & Repo H. (2001) Cellular markers of systemic inflammation and immune suppression in patients with organ failure due to severe acute pancreatitis. *Scand J Gastroenterol* , 36, 1100-1107.

Bhatnagar A., Wig D.J. & Majundar S. (2003) Immunological findings in acute and chronic pancreatitis. *ANZ J Surg* , 73, 59-64.

Andersson R., Andersson B., Andersson E. & Tingstedt B. (2007). Acute pancreatitis—from cellular signaling to complicated clinical course. *HPB* , 9(6), 414-420.

Johnson C.D. & Abu-Hilal M. (2004).Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* , 53 , 1340-1344.

Vege S.S., Gardner T.B., Chari S.T. & Sarr M.G. (2009) Low mortality and high morbidity in severe acute pancreatitis without organ failure : a case of revising the Atlanta classification to include “moderately severe acute pancreatitis” *Am J Gastroenterol* ; 104 : 710-715

Abou-Assi S., Craig K. & O’Keefe S.J. (2002) Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol,* 97, 2255-2262.

Olah A., Pardavi G., Belagyi T. & Mohamed G.E. (2002). Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition* , 18 , 259-262.

Owens N.A., Dukes L.G. & Goldsmith L.J. (1997) Comparison of the safety of early enteral vs parenteral nutrition in severe acute pancreatitis. *JPEN J Parenter Enteral Nutr* , 21, 14-20.

Kalfarentzos F., Kehagias J., Mead N. & Gogos C.A. (1997) Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg* , 84, 1665-1669.

Gupta R., Patel K., Calder P.C. & Johnson C.D. (2003) A randomized clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis. *Pancreatology*, 3, 406-413.

Pelletier G. (1997) Diagnosis of cystic lesions of the liver. *Ann Chir.* , 51(3), 267–271.

Mortele K.J. & Ros P.R. (2001) Cystic focal liver lesions in the adult: differential CT and MR imaging features. *Radiographics.* , 21(4), 895–910.

Aguilera V, Mora J, Sala T, & Berenguer J. (2003) Endoscopic treatment of pancreatitis and its complications. *Gastroenterol Hepatol.* 26(1), 13–18.

Shibasaki M., Bandai Y. & Ukai T. (2002) Pancreatic pseudocyst extending into the liver via hepatoduodenal ligament: a case report. *Hepatogastroenetrology* ,49(48), 1719–1721.

Scappaticci F. & Markowitz S.K. (1995) Intrahepatic pseudocyst complicating acute pancreatitis: imaging findings. *AJR Am J Roentgenol*.;165, 873–874.

Mehler C.I., Soyer P., Kardache M. & Rymer R. (1998) Computed tomography of intrahepatic pancreatic pseudocysts. *J Radiol*. , 79, 751–755.