Literature review

**Hegyi P et al (2009),** In this study, they have studied the pathophysiology of acute necrotizing pancreatitis and by the review they tried to illuminate new aspects of cell physiology and pathology of acute necrotizing pancreatitis. Firstly, they explored the effects of high doses of arginine on different tissues. Then, they concentrated on the pancreas and proved that the arginine could cause a necrotizing acute pancreatitis. Finally they characterized the early and late phases of this model of acute experimental pancreatitis.

**Dawra R et al (2007),** In this study, by using Male C57BL/6 (25–30 g) and Balb/c (18–22 g) mice, they concluded that, high doses of L-arginine induced acute pancreatitis in mice was associated with injury to the lungs and injury to the pancreas developed gradually. The succession of events was associated with the development of pancreatitis appears to be spread over a longer time span in this model, which might be highly advantageous in dissecting out the events related to the pathophysiology of pancreatitis. This model holds the potential of generating information to afford a complete understanding of the molecular mechanisms responsible for the development and progression of acute pancreatitis.

**Gloor B et al (2001),** in this study the author has concluded that the antibiotic can be used as prophylaxis and was effective in preventing infection in necrotizing pancreatitis, but optimal choice and duration of administration of the antibiotic agent(s) need to be carefully determined to avoid the sequelae of multiresistant organisms.

**Shi C et al (2007),** In this study the author has concluded that aprotinin induces major protection in the pancreas without affecting the production of IL-10. Sequestration of neutrophils to the pancreas and lungs may be regulated by PKC and proteases. The inhibition of proteases and the PKC signaling pathway could ameliorate the increase in the pancreatic protease activity after induction of acute pancreatitis. Pretreatment with PKC inhibitors and protease inhibitors may provide a potential therapeutic effect in acute pancreatitis, though further studies have to investigate this. The inhibitory effect on both proteases and inflammation, however, lasts longer than single protease inhibition and could provide a part in multimodal treatment in acute pancreatitis.
Mareninova OA et al (2006), In their study, they demonstrate key roles for caspases, XIAP, and RIP in the regulation of cell-death responses of pancreatitis. They show how manipulating death-signaling mechanisms changes the necrosis/apoptosis pattern in experimental pancreatitis. These signals represent potential therapeutic targets in the treatment of pancreatitis, especially to prevent or attenuate necrosing pancreatitis.

Kono H et al (2001), In this study, they had described the cause of pancreatic injury by the high dose of ethanol was prevented by medium chain triglycerides. Importantly, in this study, increase in fibrosis was observed only after 8 week, leading to the conclusion that chronic alcohol-induced pancreatic injury is dependent on the total amount of alcohol consumed and the type of dietary fat. Furthermore, this was the first demonstration of reproducible chronic alcohol-induced pancreatitis in a relatively short experimental period. Thus this animal model may be useful for the study of mechanisms of chronic alcohol-induced pancreatitis and for developing useful therapeutic strategies.

Westerloo DJV. et al (2005), In this study they conceived that fibrosis is an a dynamic process that can be stopped and possibly even reversed. PSCs and HSCs share many functional characteristics and this was the reason to believe that in pancreatic fibrosis similar mechanisms exist. In line with these data, they postulate that the treatment with troglitazone after initial fibrosis has been established results in inhibition of PSCs which stops fibrosis progression but might also in part enhance the resolution of pancreatic fibrosis indicating that glitazones may be a valuable therapy for chronic pancreatitis. Because this was the first time that any anti-inflammatory/anti-fibrotic strategy has been shown to be effective in a therapeutic setting during experimental chronic pancreatitis.

Koehler JA et al (2009), In this study, they concluded that their finding does not support the hypothesis that GLP-1R activation sensitizes the murine pancreas to the development of pancreatic inflammation. Similarly, they did not detect any difference in the extent of pancreatic inflammation in Glp1r mice. Taken together, the available data demonstrate that GLP-1R activation leads to increases in mass and changes in expression of pancreatitis-associated genes but does not modify pancreatitis susceptibility or severity in the murine pancreas.
Mayer et al (2000), This study had suggested that local mediator release, with a probable IL-1β-IL-1RA imbalance in severe cases, and was followed by the systemic appearance of pro- and anti-inflammatory mediators. The pattern of local and systemic mediators in complicated acute pancreatitis suggests a role for systemic lymphocyte activation (triggered by local release of mediators) in distant organ complications in severe acute pancreatitis.

Farghaly EFB (2008), In this study it was proved that N-acetylcysteine in protection of the pancreas from the experimentally induced pancreatitis by L-arginine especially if administered before induction. Supplemental antioxidant therapy seems promising in the regulation of the progress of acute pancreatitis and it is recommended to be given to patients at an earlier stage or those at risk for the development of acute pancreatitis.

Czako L. et al (1998), In this study it was conceived that allopurinol significantly ameliorated the pancreatic edema, necrosis and inflammation at 48 hr after arginine administration. Oxygen-derived free radicals are generated at an early stage of arginine -induced acute pancreatitis. Prophylactic allopurinol treatment prevents the generation of reactive oxygen metabolite's, reduces the serum amylase concentration, and exerts a beneficial effect on the development of histopathological changes.

Mooren FC. et al (2003), In this experiment it was suggested that pancreatic duct obstruction rapidly changes the physiological response of the exocrine pancreas to a Ca²⁺-signaling pattern that has been associated with premature digestive enzyme activation and the onset of pancreatitis, both of which can be prevented by administration of an intracellular calcium chelator.

Szabolcs A et al (2006), In this study the author has described about the pineal product, melatonin which plays an important role in L-arginine -induced acute pancreatitis. This is an antioxidant that is able to counteract some of the L-Arg-induced changes during acute pancreatitis and may therefore be helpful in the supportive therapy of patients with acute necrotizing pancreatitis.

Abdin AA et al (2010), In this study the author has described about the pentoxifylline and alpha lipoic acid respectively provided protection against L-arginine induced acute pancreatitis possibly by their antioxidant and anti-inflammatory effect. Treatment with alpha lipoic acid exhibited pronounced improvement in the course of pancreatitis when compared to treatment with
Moreover, the combination of pentoxifylline and alpha lipoic acid offered the most evident protection when compared to groups that received monotherapy; pointing to the effectiveness of such combination therapy.

**Abou-Assi S et al (2002)**, In this study it was concluded that despite concerns that metabolic expenditure is increased and that food-stimulated pancreatic secretion might exacerbate the disease process, hypocaloric enteral feeding seems to be safer and less expensive than parenteral feeding and bowel rest in patients with acute pancreatitis.

**Kakkar R et al (1998)**, In this it was concluded that, there is an increase in the lipid peroxidation product and activity of antioxidant enzymes in the liver and pancreas during initiation and progression of STZ-induced diabetes. The low activity of antioxidant enzymes in pancreas compared with liver suggests the increased susceptibility of pancreatic tissue to oxidative damage during development of diabetes. These results suggest that despite an increase in the activity of antioxidant enzymes there is an enhanced formation of lipid peroxidation product which could be due to a decrease in non-enzyme antioxidants. In conclusion, oxidative stress is associated with the development and progression of diabetes mellitus.

**Song AM et al (2002)**, In this study the severity of lung injury was evaluated by measuring lactate dehydrogenase levels in the bronchoalveolar lavage fluid and by quantitating neutrophil sequestration in the lung. In both the pharmacologically inhibited and genetically altered mice, the severity of pancreatitis and pancreatitis-associated lung injury was reduced compared with the noninhibited strains of COX-2-sufficient mice. This reduction in injury indicates that COX-2 plays an important proinflammatory role in pancreatitis and its associated lung injury. Their findings support the concept that COX-2 inhibitors may play a beneficial role in the prevention of acute pancreatitis or in the reduction of its severity.

**Hardman J et al (2005)**, In this study they described that the intravenous selenium given 24 hours after induction of experimental acute pancreatitis was associated with a reduction in the histological stigmata of pancreatic injury and a dramatic reduction in broncho-alveolar lavage protein content. Serum selenium fell during the course of experimental acute pancreatitis and this effect was not reversed by exogenous selenium supplementation.
**Holtz HG et al (1995),** In this study, it was proved that the isovolemic hemodilution with dextran 70-6% prevented the adverse effect of contrast medium on the pancreatic microcirculation in acute pancreatitis and resulted in a significant improvement of capillary perfusion during the observation period. The therapeutic action is most pronounced in areas at special risk to develop necrosis due to severely impaired capillary flow. Since there is already strong experimental evidence for the beneficial effect of isovolemic hemodilution with dextran in acute pancreatitis the prevention of contrast medium induced injury by isovolemic hemodilution shortly after hospital admission could favorably alter the prognosis of acute necrotizing pancreatitis in two ways.

**Andriulli A et al (1998),** In this study the author suspected that antisecretory agents, such as somatostatin and octreotide, are able to reduce mortality without affecting complications, whereas antiproteases, such as gabexate mesilate, have no effect on mortality but do reduce complications. This trial exploring the efficacy of combining antisecretory agents with antiproteases would be of great benefit in patients with severe acute pancreatitis.

**Kaiser AM (1995),** In this study they found the severity of acute pancreatitis is inversely related to the degree of apoptosis suggests that apoptosis may be a teleologically beneficial response to acinar cell injury in general and especially in acute pancreatitis.

**Holst JJ et al (1992),** In this study the author has investigated that a major target for the NO system in the pancreas could be fluid secretion. In fact, neither bicarbonate nor protein concentrations in the juice were changed by nitro arginine, so that it’s entire inhibitory effect could be explained by inhibition of the fluid secretion. They therefore suggest that in the porcine pancreas the NO system participates in the regulation of not only vascular resistance but also fluid secretion.

**Patel AG et al (1995),** In this study the author has concluded that nitric oxide has a selective role in mediating changes in pancreatic perfusion and secretion. It seems to be important in stimulus-secretion coupling with both secretin and cholecystokinin but is only responsible for the accompanying increase in pancreatic blood flow with cholecystokinin.

**Sawa H et al (2007),** In this study it was evaluated that the toll-like receptor 4 was implicated in the mechanism of organ dysfunction and bacterial translocation in severe acute pancreatitis, and
toll-like receptor 4 may trigger the inflammatory response and function defensively against infection.

**Lin YY et al (2008)**, In this study the siRNA mediated gene knockdown of pancreatitis-associated protein appeared to worsen pancreatitis severity but they demonstrated some different effects when compared to antisense gene knockdown in certain instances. They observed difference may be due to the inhibition profile discrepancy between two knockdown methods and/or different mechanisms of action for siRNA compared with antisense technology.

**Norman J (1998)**, In this study the author has described inflammatory mediators are believed to be primarily responsible for the systemic manifestations of acute pancreatitis and its associated distant organ dysfunction. The predictable nature in which they are produced may allow for novel approaches to treating this disease.

**Poch B et al (1999)**, In this study the data suggested that oxygen free radicals and infiltrating polymorphonuclear leukocytes aggravate acute pancreatitis and that both are important mediators of local destruction and systemic activation of polymorphonuclear leukocytes.

**Zhang XP et al (2008)**, The author concluded that the acute renal injury caused by severe acute pancreatitis is not only able to aggravate the state of pancreatitis, but it also develops into renal failure and elevates patients’ mortality. Studies have found that the injury due to massive inflammatory mediators, microcirculation changes and apoptosis, among others, may play important roles in the pathogenic mechanism of acute renal injury.

**Namkung W et al (2004)**, In this study these findings suggested that protease-activated receptor 2 may have a dual role in acute pancreatitis: protecting acinar and duct cells against pancreatitis-induced cell damage while mediating or aggravating the systemic complications of acute pancreatitis, which are the major cause of mortality in the early phase of necrotizing pancreatitis.

**Sidhu S et al (2010)**, In this study it was concluded that the melatonin treatment was found to be beneficial in acute pancreatitis. Severity of acute pancreatitis was significantly reduced in melatonin group. Nucleic acid content, rate of DNA synthesis, pancreatic proteins and pancreatic amylase content were significantly improved. Histopathological examination showed significantly lower total scores in melatonin group. Results of melatonin group were comparable to that of
positive control, CCK-8 group. Thus melatonin treatment was found to promote the spontaneous regeneration process of pancreatic tissue.

**Hackert t et al (2010),** In this study it was proved that the pantoprazole possesses an anti-inflammatory in vivo effect based on hydroxyl radical scavenging properties and attenuates the course of experimental acute pancreatitis. This is mediated via a reduced expression of inflammatory mediators and adhesive proteins. Consequently, platelet and leukocyte activations as key steps in the pathogenesis of AP are reduced after Pantoprazole administration. Therefore, this widely used agent may have a beneficial effect not only in the prevention of gastric ulcer prophylaxis and treatment of gastro duodenal reflux disease, but also on the clinical course of acute pancreatitis itself.

**Hackert T et al (2007),** In this study the results proved that 24 h after cerulein application, histology exhibited a mild acute pancreatitis, whereas GDOC induced severe necrotizing acute pancreatitis. Intravital microscopy showed significantly more platelet-endothelium interaction, reduced erythrocyte velocity, and increased leukocyte adherence in animals with acute pancreatitis compared to control animals. Thromboxane levels were significantly elevated in all acute pancreatitis animals and correlated with the extent of platelet activation and severity of acute pancreatitis. Further it was concluded that the platelet activation plays an important role in acute, especially necrotizing, pancreatitis. Mainly temporary platelet-endothelium interaction is observed during mild acute pancreatitis, whereas severe acute pancreatitis is characterized by firm adhesion with consecutive coagulatory activation and perfusion failure.

**Szende B et al (2001),** In this study the author has described that the hydroxy-methyl derivative of arginine was formed and these compounds may be the source of formaldehyde generation. Arginine may be considered a formaldehyde capturer, carrier and generator molecule. These functions may also play role in the biological activity of arginine and its methylated and hydroxy-methylated derivatives. An interesting therapeutic possibility worthy of further investigation may be the administration of methylated and hydroxy- methylated arginine in order to induce tumour cell death or to prevent tumour cell proliferation.

**Brien GO et al (2005),** In this study it was described about the up regulation of pancreatic COX-2 protein expression subsequent to acute pancreatic was markely reduced after administration of
an adjuvant pharmacological COX-2 inhibitor. This leads them to conclude that COX-2 inhibitor plays a key role in both the severity of acute pancreatitis and subsequent development of end organ injury.

**Takaori K et al (1992),** In this study it was concluded that Endothelin-1, Endothelin-2 and Endothelin-3 decrease pancreatic tissue blood flow at a minimal dose of 10 pmol/kg, whereas systemic arterial blood pressure was not affected significantly. Their results suggest that Endothelin possibly play some regulatory roles in the microcirculation of the pancreas.

**Kihara Y et al (2001),** In this study the results show that TGF-β1 mRNA expression peaked earlier than that of ECM mRNA. Furthermore, increased level of the MMP-2 transcript was followed by disappearance of fibronectin. Our findings suggest that TGF-β1 plays an important role in ECM production in the early phase of acute pancreatitis, and that MMP-2 is involved in the subsequent healing process.

**Sidhu S et al (2008),** In this study the Emblica officinalis was found to be beneficial in acute necrotizing pancreatitis. Treatment with Emblica officinalis significantly improved the rate of DNA synthesis and total protein content of the pancreas. Histopathological scores were also lower in Emblica officinalis+ L-arginine group as compared to L-arginine alone group.

**Reding T (2005),** In this it was concluded that the animal model of chronic pancreatitis that pancreatic inflammation, particularly macrophage invasion, was strongly reduced after administration of a COX-2 inhibitor. Concurrently, histological and molecular markers of fibrosis indicated significant inhibition. They also demonstrated that COX-2 inhibitors may directly affect the migratory behavior of macrophages which contribute significantly to the acute and chronic phases of this disease.

**Um SH et al (2003),** In this study the expression of isoform nitric oxide synthase in the pancreas was examined by western blot analysis. The plasma concentration of NO metabolites was measured. The severity of pancreatitis was assessed by measuring serum amylase, pancreas water content and histopathological examination. Compared with controls, the cerulein group displayed significantly increased expression of isoform nitric oxide synthase and raised plasma NO metabolites. Treatment with L-NAME significantly decreased hyperamylasemia, plasma NO level, and the extent of pancreatic injury. Treatment with L-arginine reversed the effects of L-
NAME. These findings suggest that an enhanced formation of NO by isoform nitric oxide synthase plays an important role in the development of acute pancreatitis, and inhibition of NO production has the beneficial effects in reducing pancreas injury.

Ostrowski SE et al (2004), In their study they proposed the hypothesis is that growth and differentiation signals coupled with the M2/Th2 milieu favor acinar cell proliferation, while diminished growth signals and the M1/Th1 milieu favor apoptosis of acinar cells and remodeling/proliferation of the extracellular matrix, resulting in fibrosis.