Introduction

Acute pancreatitis (AP) is a life- threatening inflammatory disorder with a significant impact on patient health ***(Melo et al., 2010).***

It is defined as inflammatory process of the pancreas with possible peripancreatic tissue and multiple-organ involvement inducing multi-organ dysfunction syndrome (MODS) with an increased mortality rate ***(Bradley, 1993).***

AP is a multi-system disease with alterations not only in the pancreas, but also in liver, lungs and kidneys, which may lead to distant organ dysfunction and death. The liver is critical organ for metabolic homeostasis and toxic substance clearance and plays an important role in the systemic response to critical illness ***(Ueda et al., 1999).***

Although its exact nature is still unknown, acute panreatitis progresses with a local production of inflammatory mediators, eventually leading to systemic inflammatory response syndrome. Knowing that almost all pancreatic mediators released from the pancreas to the blood stream may pass through the liver before their dilution in the systemic circulation, it would be reasonable to assume a determinant role of this organ in development of the inflammatory response associated with acute pancreatitis. Thus, recent studies have shown the involvement of the liver in the complex network of events triggering the multi-organ dysfunction associated with the disease ***(Folch-Puy, 2007).***

The majority of patients of AP present with a mild disease, however approximately 20% run a severe course and require appropriate management in an intensive care unit ***(Al Mofleh, 2008).***

The current ideal drug for the treatment of severe acute pancreatitis (SAP) is still in need and standardized treatment of consensus is only confined to fluid therapy, nutritional support, treatment of necrosis and infection, endoscopic procedure of biliary stones ***(Yin et al., 2015).***

In the past years, a number of researches about the initiation and propagation of AP have been done, but to date no fully effective drugs or treatment is available ***(Zhijian et al., 2015).***

The effects of glucocorticoids on acute pancreatitis (AP) have remained contradictory.

Aim of the Study

The aim of the study was to investigate the time courses of the effects of the exogenous glucocorticoids agonist dexamethasone on microscopical changes occurring in the pancreas and livers of rats used as model of AP induced by L-Arginine.

THE PANCREAS

Pancreas is a mixed gland which produces both digestive enzymes and hormones. It is a retroperitoneal organ that has three parts: the head, body and tail. The head of pancreas lies in C shaped curve of duodenum, the central body crosses the midline of human body, and the tail extends to the helium of the spleen. A thin layer of loose connective tissue forms the capsule, and the septa which extend into gland dividing it into ill-defined lobules. Between the lobules there are large amounts of connective tissue surrounding large ducts, blood vessels and nerves. The exocrine part synthesizes and secrets enzymes into duodenum which are essential for digestion in intestine. The endocrine part (islets of Langerhans) synthesizes and secrets hormones that regulate glucose, lipid, and protein metabolism in the body ***(Ross and Pawlina, 2011).***

The exocrine part of pancreas closely resembles the parotid gland. The secretary units are acini, which are formed by simple epithelial pyramidal serous cells. The periacinar connective tissue is minimal without Myoepithelial cell. The acinar cells are characterized by distinct basophilia in basal cytoplasm and by acidophilic zymogene granules in apical cytoplasm, basal nucleus. Each acinus is drained by a short intercalated duct of simple sequanous epithelium. This duct is divided into

internal part present inside the acinus called centro-acinar cells, and intercalated duct secrets (HCO_3^-) bicarbonate ions which alkalinizes the transported hydrolytic enzymes produced in acini. The digestive enzymes include several proteases, α- amylase, lipases and nucleases. The proteases are secreted as inactive zymogenes and then activation occurs in the duodenum. The pancreatic tissue is protected against autodigestion by restricting this activation in the duodenum ***(Mescher, 2013).***

The endocrine part (islets of Langerhans) are ovoid masses of endocrine cells embedded in acinar exocrine tissue more numerous at tail arranged in cords separated by fenestrated blood capillaries. Five cell types are present in these islets of Langerhans: cells producing glucagon, cells secreting insulin, cells secreting somatostatin, PP cells secreting pancreatic polypeptide and G cells producing gastrin ***(Gartner and Hiatt, 2014).***

The liver:

Liver is largest gland in the body. It is located in the right upper quadrant of abdominal cavity just inferior to the diaphragm. The liver is subdivided into four lobes right, left, quadrate and caudate. The first two of which constitute its bulk. Most of the liver is covered by a thin capsule and peritoneum, which are loosely attached over the entire circumference of the liver except at helium (porta hepatis),

where blood and lymph vessels and bile ducts enter and exit. Liver has both exocrine and endocrine functions. The main is the digestion function by production of bile which is important for digestion and absorption of fat ***(Mescher, 2010).***

The bulk of liver is composed of uniform pranchymal cells hepatocytes. Hepatocytes are 5 to 12 sides poly-gonal cells closely packed together to form anastmosing plates, one cell in thickness and are separated by sinusoidal capillaries that perfuse the cells with mixed portal and arterial blood. At the center of each lobule there is a relatively large venule (central vein) into which the sinusoids drain. The plates of cells radiate from the central vein to the periphery of the lobules as do the sinusoids. At the angles of the hexagon are portal areas, characterized by the presence of the portal triads.

Hepatocyte nuclei are large, spherical and centrally located. Many cells in liver are binucleated. Most cells in adult liver are tetraploid. Hepatocytes cytoplasm is generally acidophilic and contains basophilic regions (that represent rough endoplasmic reticulum), free ribosomes, numerous mitochondria (800 to 1000 mitochondria per cell), multiple small Golgi complexes, large numbers of peroxisomes, glycogen granules, lipid droplets, lipofuscion pigment within lysosomes and smooth endoplasmic

reticulum can be extensive in hepatocytes. As noted previously, the hepatocyte is polyhedral, and described as having six surfaces, two surfaces face the perisinasoidal space, two surfaces faces a neighboring hepatocyte and bile canaliculus. The surfaces that face the perisinusoidal space correspond to the basal surface of other epithelial cells; the surfaces that face neighboring cells and bile canaliculi correspond to lateral and apical surfaces ***(Ross and Pawlina, 2011).***

PANCREATITIS

Pancreatitis means inflammation of pancreas, necro-inflammatory disease of pancreas that can manifest as either an acute or chronic disease ***(Vonlaufen et al., 2007).***

Chronic pancreatitis is progressive and potential fatal disease caused by persistent unresolved inflammation and pancreatic fibrosis typically accompanied by intractable abdominal pain, particularly during the early phase ***(Coté et al., 2011, Nøjgaard et al., 2011).***

Acute pancreatitis

Acute pancreatitis (AP) is sudden acute inflammatory processes of pancreas ***(Larusah et al., 2012).***

It is triggered by intra-acinar activation of protelytic pancreatic enzymes leading to digestive injury of pancreas. Inflammatory mediators play an important role in acute pancreatitis, especially in resultant multiple organ dysfunction syndrome, the primary cause of death in acute pancreatitis ***(Bhatia et al., 2000).***

It's potentially lethal and incidence of acute pancreatitis has been increasing over recent years. Approximately 20-25% of patients suffer a severe attack, 30-50% of these will die ***(Bhatia et al., 2005).***

Many causes and factors are responsible for acute pancreatitis, like alcohol, gallstones, hereditary pancreatitis,

hypercalcemia, hyper-lipidemia, malnutrition, abdominal trauma, penetrating ulcers, malignancy, drugs like steroids, sulfonamides, furosemide, thiazides, infectious like mumps, coxsackie virus, mycoplasma pneumonia, ascaris, clonorchis, and structural abnormalities like choledochocele and pancreas divisum ***(Robbinsk 1997; Robbinsk, 2002).***

Alcohol and gall stones are the etiology of acute pancreatitis in many adults and although some differences exist based on sex and ethnicity ***(Banks 2002; Yadav-Lowenfels, 2006)***.

However, the etiology in children is often drugs, infectious, trauma, and anatomic anomalies such as choledochal cyst and abnormal union of pancreatobiliary junction ***(DeBanto et al., 2002; Benifla and Weizman, 2003; Werlin et al., 2003; Nydegger et al., 2006).***

Obesity is likely to contribute to acute pancreatitis ***(Papachristou et al., 2006).***

In one case report, a 16 years-old male patient hospitalized due to severe pain in upper abdomen nausea and vomiting, L-arginine-induced acute pancreatitis was diagnosed ***(Saka et al., 2004; Dawra and Saluja, 2012).***

Only 10% of all cases of pancreatitis are idiopathic ***(Guda et al., 2011).***

Factors causing and mechanism of pathogenesis of acute pancreatitis:

The pathogenesis of severe acute pancreatitis (SAP), as a common clinical acute abdomens with a relatively high mortality rate has been the focus of researchers for sometime. Intracellular trypsinogen activation has consistently be observed early during the course of pancreatitis in experimental models ***(Willemer et al, 1989; Hofbauer et al, 1998; Saluja et al, 1999; Halangk and Lerch, 2005; and Saluja et al, 2007).***

On the other hand, activation of NF-Kappa B, (an early event paralleling trypsinogen activation in time course), has also been shown to result in acute pancreatitis (AP) ***(Chen et al, 2002; and Aleksic et al, 2007).***

Several factors are involved in the intracellular zymogen activation, these are summarized by **Sah and Saluja (2012)** as follows:-

a) A sustained global rise in Ca^{++} in acinar cell. The endoplasmic reticulum membrane Raynodine Receptors and plasma membrane store operated calcium channels are the sources of this calcium.

b) Co-localization of lysosome and zymogens. Premature trypsinogen activation takes place in membrane-bound compartments of autophagic nature where zymogen and lysosomal contents co-localize. However, it appears that this process requires additional conditions, most likely, low pH.

c) Sensitizing effects of low extracellular pH. Acidemia has been known to be a precipitant of AP. Also inhibited bicarbonate secretion by duct cells appears to be another mechanism leading to low pH.

d) Impaired autophagy, zymophagy and lysosomal cathepsins. Genetic inhibition of autophagy, while up regulating of zymophagy led to reduced trypsinogen activation. Under physiological conditions, cathepsin L degrades prematurely activated trypsinogen, but during pancreatitis, this autophagic degradation is retarded due to imbalance between cathepsin B (which activates trypsinogen) and cathepsin L.

In appropriate intracellular activation of proteolytic enzymes induces pancreatic tissue damage in presence of intracellular lysosomal enzymes and activation of trypsinogen to trypsin. Trypsin in turn activates a cascade of phospholipase, elastases and other mediators with increased neutrophil migration to pancreas. Consequently, a variety of inflammatory cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), platelets activating factors and tumor necrosis factor (TNF) are released ***(Pooran et al., 2003).***

The serum levels of pro-inflammatory cytokines such as IL1, IL6,, IL8, IL18 and tumor necrosis factor (TNF) have been reported to be significantly higher in AP, which recruit neutrophils, monocytes and lymphocytes into the pancreas, resulting in systemic inflammatory respons ***(Zhang et al, 2009; and Nieminen et al, 2014).***

Anti-inflammatory cytokines, however do not match the increase of pro-inflammatory cytokines, if the active inflammatory response is not sufficiently strong. An excessive inflammatory response can lead to early organ dysfunction and SAP ***(Li et al., 2014).***

Therefore, the outcome of this disease depends on the balance between the pro-inflammatory and anti-inflammatory responses. IL-35, is a recently characterized potent anti-inflammatory cytokine that is predominantly produced by Fox $P3^+$ regulatory T cells (Tregs) ***(Collison et al., 2007).***

In SAP, the inflammatory process is amplified by the release of cytokines and reactive oxygen species (ROS). The intensity of oxidative stress correlates well with the severity of AP ***(Braganza et al, 1995; and Rau et al, 2000).***

Reactive oxidative species (ROS) are inevitable epiphenomenon or the cause of vital processes, particularly aerobic metabolism. When production of ROS exceeds their catabolism, in any physiologic and pathologic conditions, oxidant-derived celluler injury can occur which is known as oxidative stress. Interestingly, there is an ample evidence suggesting that oxidative stress is a common pivotal factor in the pathogenesis of pancreatitis ***(Gooshe et al., 2015).***

Oxygen – and nitrogen – derived free radicals (FRs) and lipid peroxidetion play an important role in

development of local inflammation and systemic complications during acute pancreatitis.

They damage the lipid membranes, structural and enzymatic proteins and DNA of the cells. The major target of FRs is the polyunsaturated fatty acids of the lipid-rich membranes. Lipid peroxidation results in loss of the membrane fluidity and integrity, leading to cell death.

NF-Kappa B activation has been observed in experimental models paralleling trypsinogen activation in time course. Presence of pathological Ca^{++}, cytokines, ROS as well as activation of novel isoforms of protein kinase C are responsible for NF-Kappa B activation. It links the inflammatory responses and regulates several forms of pro-inflammatory gene expressions including TNFα, IL1, IL8, chemokines, selectin-E and intracellular adhesion molecule-1 (ICAM-1) ***(Gukovsky et al, 1998; Tando et al, 1999; Logsdon, 2000; Schmid and Adler, 2000; Tando et al, 2002; and Sah and Saluja, 2012).***

Studies have found the local pancreatic rennin-angiotensin system (RAS) was significantly upregulated in drug induced severe acute pancreatitis (SAP) this might be due to causing microcirculation disturbance and inflammation. They also postulated that the angiotensin 1 receptor antagonist and other RAS inhibitors may be beneficial in the clinical treatment of AP ***(Zhijian et al., 2015).***

Symptoms of acute pancreatitis and complications:

Acute pancreatitis present as patient with an acute abdominal pain, sudden and severe, continuous poorly localized and radiating to back, vomiting may be early feature. In mild attack, the acute abdominal pains are minimal with rapidly resolving abdominal signs like abdominal distension, some abdominal tenderness, and guarding, absent bowel sounds, minimal systemic illness, moderate tachycardia. The severe attack is characterized by severe acute abdominal pain, severe toxaemia and shock, generalised peritonitis, diffuse abdominal tenderness, guarding, rigidify, absent bowel sounds, acute respiratory distress syndrome ***(Raftery, 2007).***

Clinical presentation exhibits to a broad spectrum of severity ranging from mild self limited disease to severe progression disease with organ dysfunction and often death. The Atlanta classification defines three grades of severity based on clinical criteria namely mild-moderate-and severe pancreatitis. Mild pancreatitis shows no evidence of organ dysfunction and no local or systemic complication, moderately severe acute pancreatitis exhibits to local complications or systemic complications with either no or transient

organ dysfunction, severe pancreatitis is characterized by persistence of single or multiorgan dysfunction ***(Banks et al., 2012).***

Local complications include acute peripancreatic fluid collections acute, necrosis collection, pancreatic pseudocyt and walled off necrosis ***(Banks et al., 2012; Sarr, 2012; Thoeni et al., 2012; Windsor-Petrov, 2013).***

Other local complications include perturbance of gastric emptying, splenic or portal vein thrombosis and necrosis of colone ***(Sarr 2012; Strambu et al., 2012).***

Multiple organ failure is defined as shock, pulmonary insufficiency, renal failure ***(Tabeta, 2004),*** and gastrointestinal bleeding ***(Dellinger et al., 2012).*** Among one of the effected organs is the liver ***(Grasso et al., 2011).***

Other complications include chronic pancreatitis characterized by fibrosis and loss of acinar cell function and tumor of pancreas ***(Robbins, 1997; Robbins, 2002).***

Diagnosis of acute pancreatitis:

The diagnosis of acute pancreatitis requires at least two of the three features: 1) abdominal pain (epigastric pain often radiating to left flank and the