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A Review on the Characterization, Causes, and Treatment of the Pancreatitis Disease

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ABSTRACT

Pancreatitis is a disease which is caused by inflammation of the pancreas. Pancreas is a large gland that is damaged when digestive enzymes are become activated before releasing into small intestine and these digestive enzymes attack the pancreas. There are two main types of pancreatitis, one is acute pancreatitis and the other is chronic pancreatitis. The pain sometimes goes into the back. Fever may occur in acute pancreatitis and symptoms may appear in a few days. And weight loss, fatty stool, and diarrhea may occur in chronic pancreatitis. In severe cases of this disease, infection, bleeding, and permanent tissue damage may occur. A few infections like fungal, bacterial, parasitical, and viral can be major causes of pancreatitis. To diagnose the pancreatitis medical imaging like ultrasound and CT scan will be very useful. And acute pancreatitis diagnosis was generally based on the threefold increase in the blood of lipase and amylase. Antibiotics, intravenous fluids, pain medication are those treatments that are used to treat the acute pancreatitis. Generally, no eating and drinking will be allowed during treatment and tube is injected in the stomach. This method is known as endoscope cholangiopancreatography (ERCP). This procedure is used to open the pancreatic tube. In some cases, there is a need to remove the gallbladder to treat the pancreatitis. In chronic pancreatitis treatment, a nasogastric tube will be very useful to supply enough nutrition. Lon-term dietary changes and pancreatic enzyme replacement will also be required. And sometimes surgery will be done to eliminate the defective parts of the pancreas.

Keywords: ERCP, Sphincterotomy, Exocrine intolerance, Pseudocyst, Pancreatitis

I. INTRODUCTION

Pancreatitis is a disease which is caused by the inflammation of the pancreas. Pancreatitis is basically an inflammation of the pancreas (Zheng *et al*., 2013). Pancreas is a large gland that is damaged when digestive enzymes are become activated before releasing into small intestine and these digestive enzymes attack the pancreas (Shah *et al*., 2009). And the pancreas is such a large gland that is situated behind the stomach and is close to the duodenum that is an important first part of the small intestine. Pancreas is a gland that is covered with the help of stomach and duodenum and its length is 12-20 cm that contains a lobe-like structure. In some people the head of the gland is present in the right side of the spinal column and extended to the spleen. The two main functions of pancreas are that it secretes powerful digestive enzymes and secretes hormones (Kanno *et al*., 2015). The digestive enzymes are released into the duodenum by the pancreas with the help of the tube that is known as pancreatic duct. The bile is such a liquid that is produced by liver and pancreatic juice in combination with the bile is stored in gallbladder where they help in digestion of fats and proteins in food.

And insulin and glucagon are those hormones that are secreted into the bloodstream by the pancreas and these hormones help in the regulation of blood glucose level. The digestive enzymes do not activate until they reach the small intestine but when enzymes are become activated before releasing into small intestine then these attack pancreases and damage those tissues that produce them (Zheng *et al*., 2013). There are two main types of pancreatitis, one is acute pancreatitis and the other is chronic pancreatitis. Pain in the upper abdomen, vomiting, and nausea are the symptoms of pancreatitis. The pain sometimes goes into the back. Fever may occur in acute pancreatitis and symptoms may appear in a few days. And weight loss, fatty stool, and diarrhea may occur in chronic pancreatitis. In severe cases of this

disease, infection, bleeding, and permanent tissue damage may occur. A few infections like fungal, bacterial, parasitical, and viral can be major causes of pancreatitis.

To diagnose the pancreatitis medical imaging like ultrasound and CT scan will be very useful. And acute pancreatitis diagnosis was generally based on the threefold increase in the blood of lipase and amylase. Antibiotics, intravenous fluids, pain medication are those treatments that are used to treat the acute pancreatitis. Generally, no eating and drinking will be allowed during treatment and tube is injected in the stomach. This method is known as endoscope cholangiopancreatography (ERCP) (Masamune *et al*., 2009). This procedure is used to open the pancreatic tube. In some cases, there is a need to remove the gallbladder to treat the pancreatitis. In chronic pancreatitis treatment, a nasogastric tube will be very useful to supply enough nutrition. Lon-term dietary changes and pancreatic enzyme replacement will also be required. And sometimes surgery will be done to eliminate the defective parts of the pancreas. Morphine is such a medicine which is used to control the pain in abdominal.

About 2-9% is the mortality rate with severe acute pancreatitis and it can be higher than 2-9% when necrosis of pancreas will occur. Many scoring systems will be used to find out the severity of an attack of pancreatitis. And demographic and laboratory data is combined to find out the severity or possibilities of death. Pancreatitis can not only occur in humans but it can happen in other animals like dogs. Due to fatty food pancreatitis, will happen in dogs and symptoms can be same. About 17 million cases of pancreatic were occurred in 2013. Acute pancreatitis occurred in 30 per 100,000 people a year. It is commonly occurring in men rather than in women. And chronic pancreatitis began between the ages of 30 and 40 and it is mostly rare in children (Lohr *et al*., 2007). Acute pancreatitis was first described in 1882 and chronic pancreatitis was first described in 1946.

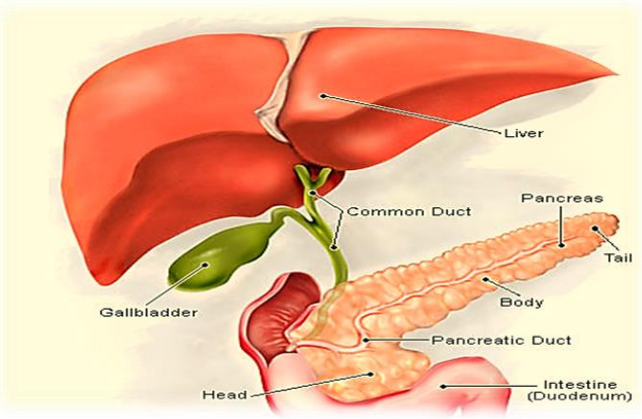

Figure 1: Illustration of pancreas, and the dependence of its functions with the secretion of liver and gall bladder

II. HISTORICAL BACKGROUND

There was no intension towards the pancreas that it can be an organ and it is related to disease. Then Herophilus, a Greek anatomist and surgeon was the first-person wo discovered pancreas and he was born in Chalcedon. He was the first founder of the ancient school of Medicine in Alexandria, Egypt. He was also the first one who performed the dissection of human bodies. Ruphos was the first person who gave the name “pancreas” (Longnecker., 2014). The meaning of this word is “all flesh”. Galen was the most famous physician who describes the role of pancreas that act as cushion to save the large blood vessels. And he was the first person who gave the word “law”. Johann Georg Wirsting discovered the pancreatic duct on March 2, 1642 and during this period the study of the pancreas started**.** Reignier de Graaf, a 22-year-old student who used the hollow quill of goose feather to cannulate the dog’s pancreatic duct. (Howard)Claud Bernard had discovered the role of pancreas in digestion of food. Reginald Fitz described pancreatitis as a disease in 1889. And the first disease that was reported due to the tumor in the islets of pancreas was hyperinsulinemia in 1927. After this Zollinger and Ellison reported peptic ulcer disease that was also caused by tumor in islets.

Moyse. A student in Paris was the first person who described the histology of pancreas (Longnecker., 2014). He described the structure of exocrine acini, that is an important part of pancreas. Paul Langerhans, a student of Berlin Institute of Pathology describes the islets of pancreas and due to description by Langerhans now it is

known as “islets of Langerhans”, and it is an endocrine system present within pancreas and this was an important step. After the discovery of x-rays by Wilhelm Conrad Roentgen, it was used to diagnose the pancreatic disease. And the use of radiologic images to detect the pancreatitis was also an important step. Human blood types were discovered by Karl Landsteiner and this was an important step in the advancement of pancreatic surgery. For this discovery, a Nobel prize was awarded to Karl Landsteiner. Dr. O. Whipple described the one-stage pancreaticoduodenectomy that was recorded for the first time.

III. TYPES OF PANCREATITIS

There are two main types of pancreatitis: acute pancreatitis and chronic pancreatitis.

A. Acute pancreatitis

Acute pancreatitis is such type of inflammation that can last only for a short time and it can resolve within a few days with the help of treatment. And pain during this disease can range from mild condition to severe. Many people that are suffering from acute pancreatitis recovered completely after taking right treatment. Under severe conditions of pancreatitis bleeding in the gland, infection, serious tissue damage, infection, cyst formation can happen. And this condition is also harmful for vital organs like kidneys, heart, and lungs. During severe complications, acute pancreatitis is also a life-threatening disease (Roberts *et al*., 2013). Approximately 210,000 people living in United State admit in hospitals that are suffering from acute pancreatitis. Fever may occur in acute pancreatitis and symptoms may appear in a few days. Acute pancreatitis occurred in 30 per 100,000 people a year. It is commonly occurring in men rather than in women (Peery *et al*., 2012).

Acute pancreatitis commonly caused by gallstones that are small, pebble-like substances that are made up of hardened bile which will cause inflammation of the pancreas when it will pass through the bile duct (Fig. 2). Acute pancreatitis is also caused by consuming alcoholic drinks, and by consuming alcoholic drinks acute pancreatitis can be caused within a few days (Peery *et al*., 2012). And it is also caused by infections, tumors, medications, and genetic abnormalities of the pancreas. Because of physiological findings, laboratory values, and radiological imaging acute pancreatitis is classified as mild, moderate, or sever. In mild conditions of disease, it will not associate with damage of organs and its treatment is possible and patient will be fully recovered after proper treatment. While moderate, or severe conditions of disease are associated with tissue damage and it can lead to life threatening illness. And acute pancreatitis can be categorized as acute interstitial and acute hemorrhagic disease.

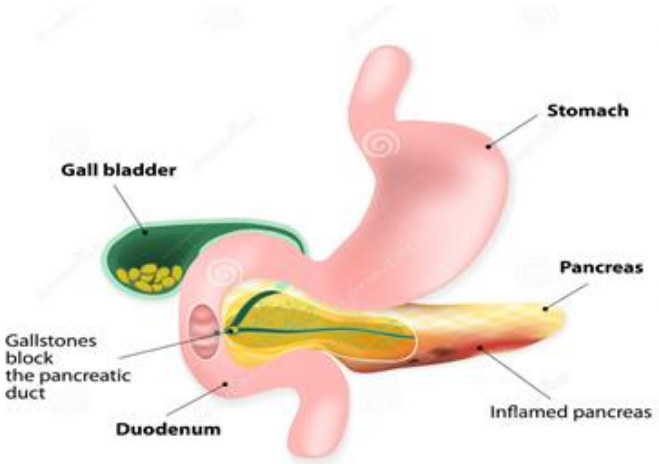

Figure 2: Formation of stones in gall bladder and inflammation of the pancreas result in acute pancreatitis

B. Chronic pancreatitis

Chronic pancreatitis is such a type of disease in which inflammation of the pancreas will be long lasting and it will not be healed or improved. Its condition will worse with time and it will lead to permanent damage. Chronic pancreatitis will happen after an episode of acute pancreatitis. It is also caused by consuming heavy alcohol. If chronic pancreatitis is caused by heavy alcohol, then it is possible that symptoms of the disease may not appear for many years and the patient will develop severe pancreatitis symptoms (Lohr et al., 2007). This disease will happen during the age of 30 and 40. Like acute pancreatitis, it is also caused by the attack of digestive enzymes to the pancreas and then it will cause pain in this tissue. It is also caused by high levels of blood fats, autoimmune conditions, high levels of calcium in blood, some medicines, and cystic fibrosis. Smoking can increase the chances of both acute and chronic pancreatitis (Braganza et al., 2010).

C. Autoimmune Pancreatitis: a subtype of chronic pancreatitis

Yoshida was the first person who described the autoimmune pancreatitis and this disease is also known as lymphoplasmacytic scleroding pancreatitis, idiopathic duct destructive chronic pancreatitis. Autoimmune pancreatitis (AIP) is a special subtype of chronic pancreatitis that is related to autoimmune mediated (Kamisawa et al., 2012). It is unique and it shared some characteristics with AIDS according to the clinical manifestations, pathophysiology, and treatment. The rate of AIP occurrence is 1.4 per 100,000 individuals annually (Kanno et al., 2015). The symptoms of AIP include jaundice, abdominal pain, general fatigue, weight loss, and even not any symptom. It is very difficult to diagnose the AIP simply by seeing the symptoms due to specificity. Glucocorticoids was used as drug on daily basis for treatment.

IV. SIGNS AND SYMPTOMS

Pancreatitis disease includes the symptoms of upper abdominal pain that can be mild and severe. The abdominal pain can be suddenly and it can be gradually. Usually, pain started after eating and this pain occurred with ulcer pain and gallbladder pain. Abdominal pain is an important symptom of acute pancreatitis. People that are suffering from acute pancreatitis usually feel very ill. The patient of acute pancreatitis required medical attention because abdominal pain may last for several days (Frey *et al*., 2006).Signs and symptoms of acute pancreatitis includes, abdominal pain that may radiate to the back, nausea and vomiting, worsening pain after eating, tenderness to touch of the abdomen, fever and chills, a rapid pulse, a swollen and tender abdomen, lethargy and weakness (Fig. 3). Dehydration and low blood pressure are caused by severe acute pancreatitis. In acute pancreatitis heart, kidneys, lungs can be failed. And bleeding in pancreas can also occur acute pancreatitis, shock, and even death can also happen (Szentesi *et al*., 2016).

People that are suffering from chronic pancreatitis feel pain in upper abdominal. And some people feel no pain. In this condition pancreas, do not make digestive enzymes. Patient often lose their weight even during the normal diet and appetite. As pancreas is not making digestive enzymes and there is no digestion of proteins and fats of food and there will be no absorption of nutrients (Braganza *et al*., 2010). And this condition may cause malnutrition due to release of fat in stool. And the signs and symptoms of chronic disease may include, nausea, vomiting, weight loss, diarrhea, oily stools, foul smelling, abdominal pain.

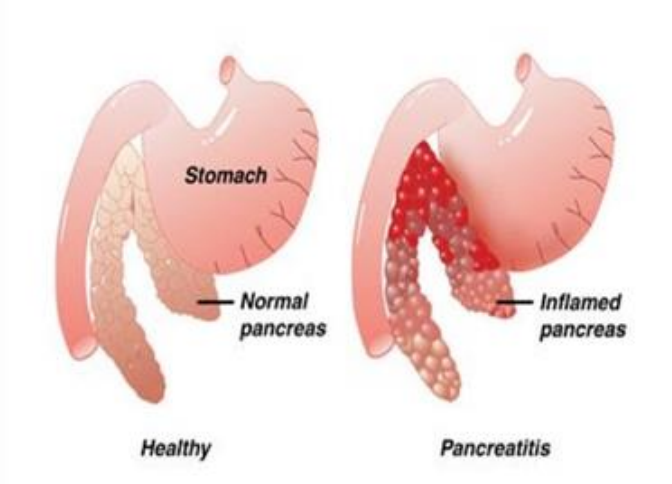

Figure 3: Structure of pancreas in healthy and inflamed situation

V. CAUSES AND PREVALENCE

Different types of pancreatitis have different causatives; it can be any mechanical issue or metabolic disturbance or related to the transport of different enzymes that are carrying the cascade of enzymes involved in the digestion (Frey *et al*., 2006). Few of the reason for the spread of disease are given below:

1. **Hereditary pancreatitis**

This is a recurrent damage to pancreas due to abrupt regulation of trypsin which is called as the chief regulating agent responsible for pancreatic digestive enzymes activation. The patient suffers from inflammation that is initiated due to injury of pancreas (Brenner *et al*., 2012). Trypsin is also disturbed due to pathogenic variant genes in germ line that affect its regulation.

The acinar cells burden that is referred as hyper stimulation, intracellular hypercalcemia, the trypsinogen produced intracellularly converts into trypsin. Trypsin causes activation of the rest of digestive enzymes that are causing injury. Immune system becomes active because of the injury and it stimulates the release of molecules which have an inflammatory response, resulting in the action of macrophages ultimately

activating stellate cells of pancreas. This recurrent damage leads to fibrosis and chronic pancreatitis (Lohr *et al*., 2007).

2. ***Acute pancreatitis***

This type of pancreatitis arises because of increase in the lipase or serum amylase more than thrice the upper terminal point of normal, systematic inflammation, alcoholism, presence of gallstones, cigarette smoking, surgery of abdomen, cystic fibrosis and familial pancreatitis can also result in pancreatitis and epigastric origin abdominal pain. If injury continues then fibrosis improves its state and develops clinical manifestations from acute to chronic pancreatitis.

3. ***Chronic pancreatitis***

It results because of inflammatory collections of mass, parenchyma and ductal calcification and presence of pseudocyst. It advances due to endocrine intolerance progressing finally to mellitus type 3 and exocrine intolerance resulting in maldigesting. Both acute and chronic pancreatitis can root your pancreas to yield scarcer of the enzymes that are required to break and process nutrients from the food you eat. This can clue to malnutrition, diarrhea and weight loss, even though you may be eating the same foods or the same amount of food (Rockey *et al*., 2015).

4. ***Pancreatic cancer***

Excessive presence of inflammation in your pancreas resulted because of chronic pancreatitis is a major risk element for advancing pancreatic cancer. It mostly results when pancreatic cells undergo mutations and cells suffer uncontrollable growth. These accumulating pancreatic cells ensure the development of tumor. If these tumors go uncheck then it would spread violently to nearby cells damaging the entirety of body (Means., 2013). Any of the tumor that occurs on the walls of duct in pancreas it is then called as pancreatic exocrine cells or pancreatic adenocarcinoma. And if the cancer is prevailing in the cells responsible for producing hormones then it is called as islet cell tumors. Certain factors can terribly enhance the levels of severity of cancer, these may be development of lynch syndrome and FAMM or familial atypical mole malignant melanoma syndrome, prevalence of chronic stage of pancreatitis, old age as mostly people after age 65 suffers from the adversity of this cancer, excessive uptake of alcohol, Jaundice is another disease that arises if cancer goes unchecked. Growth of the tumor will press your nerves in the abdominal region and it can become severe (Yang *et al*., 2013).

VI. PATHOGENESIS OF PANCREATITIS

When acute pancreatitis has been caused then complete functional and structural restitution is possible if we remove initiating element while chronic pancreatitis is linked with irreversible alterations. It is expected that biliary stones can result in the complete obstruction of ducts in pancreas and any attack of pancreatitis can result in hypertension of pancreatic ducts, and intraacinar activation of enzymes that are involved in digestion by hydrolases of lysosomes. Most of the patients suffer from pathogenesis after years of ethanol abuse. Following are also considerable reason for the pathogenesis of the disease (Marrache *et al*., 2013). When the pancreas is not infected stellate cells perform important functions related to tissue morphology because they are chief controllers of synthesis and breakdown of extracellular fluids. Certain tissues undergo homeostasis resulting because of the secretion from metalloproteinase and their inhibitors present in the matrix.

Homeostasis also results from the phagocytosis by necrotic acinar cells. During injury in pancreas the stellate cells become activated and they produce elevated amount of extracellular proteins in matrix. There are countless susceptibility factors related to genetics that are involving enzymes like proteases which are stimulating pathogenesis of the disease. It can therefore be said that not a single instead a combination of various pathological stimuli especially immune mediated reactions would ultimately be essential to proceed chronic pancreatitis. The pathogenesis of the disease is so much severe that it couldn’t be reduced to one event (Kim *et al*., 2009).

VII. NOSOLOGY AND DIAGNOSIS

Disease classification is done based on its severity either by local complications or organ failure and systemic complications. If the condition of the disease is mild, then the patient wouldn’t suffer from systemic complications and organ failure and rate of mortality

would also be rare. If the disease condition is moderately severe then patient's transient failure of organs would occur and he will suffer from local complications which is associated with less rates of mortality. If the disease is under severe condition, then organ failure would be persistent and rate of mortality would be approximately 20-30%. One of the renowned systems namely Atlanta Classification has classified the disease into two phases. Early phase lasts only up to 1 week followed usually by a late phase (Massague., 1998).

During early phase time of organ failure is critical which mainly determines the disease atrocity while the imaging would be bamboozling showing local complications for example necrosis and it is therefore not reliable mostly at the initiation of the disease. Late phase deals with some persistent symptoms involving both local and systemic difficulties which are most commonly seen in moderately severe diseased conditions. During these periods imaging method, may be crucial in determining the severity of disease, hard to manage. It could extend up to months or more enabling tough pancreatic collections to arise obtaining various attributes and terminologies. The evolution of acute collections of necrosis and peri pancreatic fluids results in walled off necrosis and pseudocyst respectively. Some types are based on severity and time duration of disease prevalence like Interstitial edematous pancreatitis, which is a diffuse process of inflammation including peripancreatic and pancreatic tissues resulting in enlargement and edema (Fig. 4). It is an acute form of acute pancreatitis visualized in 85% of patients. It usually is resolved within a week. And second type is Acute peripancreatic fluid collection which has changeable size and morphology and it may be numerous. They are mostly adjacent to that of pancreas without any considerable extension in parenchyma and it resides within anterior lesser sac. The fluid might collect in more distant locations uncommonly involving pelvis, splenic hilum, mediastinum, ligamentum venosum fissures etc (Braganza *et al*., 2010).

Figure 4: It shows calcified pancreatic duct stones with free intraabdominal fluid

VIII. DIAGNOSIS

Diagnostics for pancreatitis may involve several modern techniques and methods, some of the most common are, Transabdominal ultrasound include that sound waves are transmitted towards pancreas through a device held by hand that is glided by technician over abdomen. These waves bounce back of the pancreas, liver, gallbladder, and various other organs. The echoes generated by machine would produce impulses that creates image known as SONOGRAM – typically on amonito. The second one is Magnetic resonance cholangiopancreatography that utilizes magnetic resonance imaging technique which is noninvasive procedure that generates cross-section images of parts of body (Mahdavian *et al*., 2011). After sedating the patient, it lies in a tube which is cylinder like. Technician injects a dye in patient's vein which makes us see pancreas and rest of the related organs. The third one is Computerized tomography that is commonly referred as CT scan and it generates 3-D images of our body parts (Fig. 5). Patient is made to lie into donut-structured machine. This enables us to view gallstones and the damage extent in pancreas.

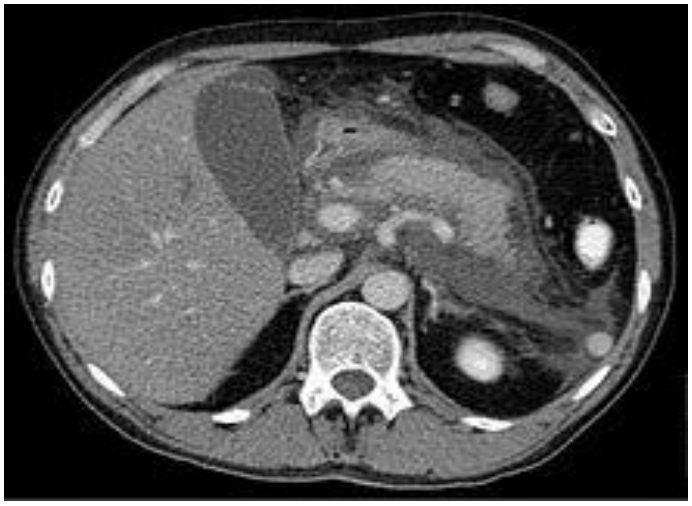

Figure 5: Axial CT in patients with acute pancreatitis showing fluid collection's surrounding pancreas

Fourth one is Endoscopic ultrasound which shows that when we spray a patient with a solution to numb his throat the doctor inserts some endoscope- which is a thin, flexible and lighted tube placed right down the throat through stomach and inside of small intestine. Endoscope is attached with ultrasound which generates waves to produce visual images of pancreas and bile ducts (Riopel *et al*., 2013).

IX. COMPLICATIONS OF THE DISEASE

Patients with biliary obstruction are usually referred by doctors to undergo surgical operation, because it is a severe state in which ductal hypertension occurs blocking all pathways, restricting supply of all essential nutrients and blood which can ultimately result to death of organism (Longnecker., 2014). Open treatment is done only in those unfortunate patients having failed ES. Multi-organ failure (MOF), failure to improve, and deterioration is also a complicated situation due to sterile necrosis, predominately occurring in the third week. Surgeon has no clinical guidelines for this. Surgery would be the final option (Ding *et al*., 2009).

Hemorrhage and peritonitis is also can be related to pancreatitis mostly caused by infection (Fig. 6). In very rare cases these can occur in peritoneum, mostly the source of infection is another individual. Gut may rupture and it can burst, a hole may be generated because of ulcer, or stomach cancer (Jura *et al*., 2005). Other causes may include inflammation of pancreas or diverticulitis- that is inflammation in bowel boundary. Treatment may include angiography, embolization that appears indisputable in those individuals who fortunately bleed.

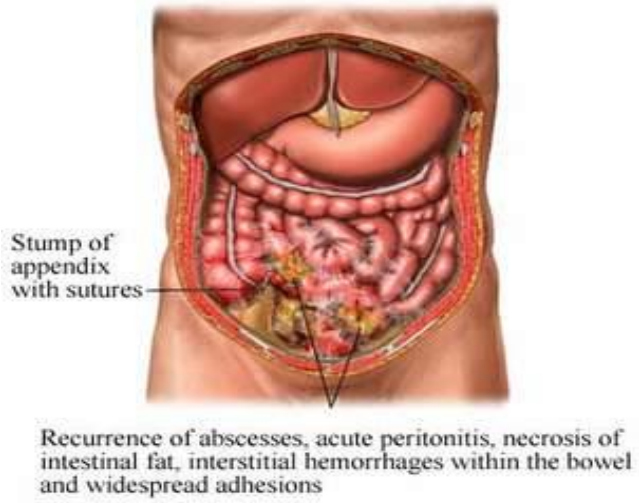

Figure 6: Peritonitis and hemorrhage causing severe complications in the pancreas leading to failure of its normal function

The most public source for obstruction is presence of gallstones in the common bile duct, a state called choledocholithiasis. Obstruction could also be owed to duodenal inflammation in Crohn's disease. In this state the duct may be seen for any procedure that may involve any procedure in which drainage will expose patient to the buildup of any external fistula (Jura *et al*., 2005).

X. EPIDEMIOLOGY

Pancreatitis has been affecting individuals on a mass scale due to uptake of improper food. The incidence of disease annually is quite disturbing acute pancreatitis about ~20-40 over 100,000 population (Yadav and Lowenfels., 2013). And these statistics had been increased from past 2-3 decades, mostly from increasing chances of gallstones and by increasing tests for disease. The fatalness of disease has been decreased (Szentesi et al., 2016).

Local complications, organ failure and demographic factors like age and obesity are related with the severity of acute pancreatitis. The incidence of chronic pancreatitis is ~4-9 over 100,000. It is less than AP but its rate is enhancing with the passage of time. Alcohol is

the single reason and smoking is also established now to be a risking factor. Several genetic signs are also reason for this. History of the disease depends on the age at present with etiology. Quality of life in patients with CP has been significantly lessened, mortality rates 3-4 times more than general (Hirota *et al*., 2012).

XI. TREATMENT

Preliminary treatments that can be provided within hospitals are fasting, pain medications, intravenous fluids. Fasting can be entailed by stop eating for some days to provide your pancreas a chance to recover itself. If the pancreas restores itself then you might begin taking liquids and eating foods. And with the course of time you could go back to normal diet. And if you are not feeling rescued from the situation then doctors might prescribe you a feeding tube in order to aid you get your nutrition (Means., 2013). In pain medications, the disease may cause severe pain. Doctors would give you proper medications to control pain. In Intravenous fluids body, might become dehydrated when it continuously devotes energy and fluids to repair pancreas therefore doctors give you extra fluids through intravenous system. Procedures for severe disease condition are removal of bile duct obstruction, gallbladder surgery, pancreas surgery, treatment for dependence on alcohol (Iino., 2014).

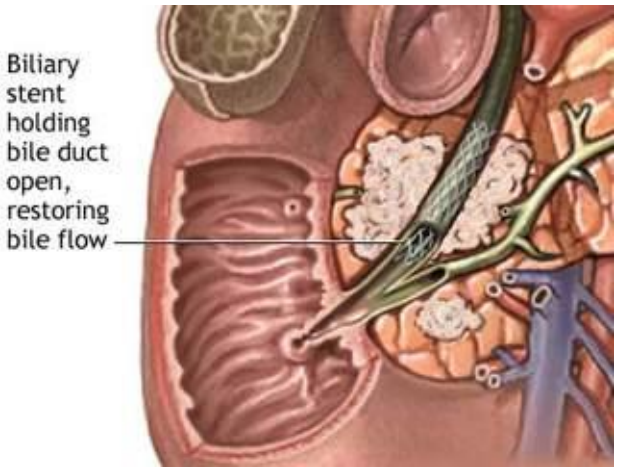

Figure 7: Biliary duct has been widened to restore flow of bile

In removal of bile duct obstruction pancreatitis that is because of the blocked ducts or narrowed bile tubes might require methods to widen the ducts. This is done by using ERCP method for first diagnosing the place and then putting instruments to cure the place. In gallbladder surgery, if gallbladder is causing the disease to become severe then it should be removed by surgery a method also called cholecystectomy pancreas (Fig. 7). Surgery is necessary to remove fluids collection in pancreas or to remove diseased tissues (Omary *et al*., 2007). Taking large amounts of drinks for years could be a reason for pancreatitis. If this is the cause, then health team would make you a part of program for alcohol addiction minimization. But if a person continuously drinks alcohol after the identification of disease then it may worsen the situation. *Enzymes are required to improve digestion because if you supplement your body with additional enzymes of pancreatic origin then it can help your body to breakdown and further process nutrients in the meals you take. These enzymes are taken with every meal.* The second important treatment is to change your diet because doctors might recommend you to take meals in low fats but high in nutrients (Mahdavian *et al*., 2011).

XII. CONCLUSION

We have seen how pancreatitis prevail, its symptoms and how the severity of disease can be lessened. A procedure known as an endoscopy (ERCP) may be done to open the pancreatic duct if blocked. In those with gallstones the gallbladder is often also removed. In conclusion, we can say that a spectrum of pancreatic sphincter, ductal, and malignancies of the pancreas can be effectively managed with ERCP and/or EUS-FNA. Sphincterotomy is effective in a large percentage of patients with recurrent pancreatitis as a result of SOD or pancreas divisum. Pancreatic ductal stones are readily detected and removed with ERCP. EUS is a very sensitive test for the changes of chronic pancreatitis in the ducts or the parenchyma. IPMN is the most common malignancy of the pancreas, and EUS and ERCP can readily detect ductal changes and the presence of a side-branch cystic lesion. In the future, EUS and ERCP could be used to deliver therapy to pancreatic malignancies.

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