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Pancreatitis, Diabetes and Alcohol Intake: The Interrelationship and Effects on the Human Body

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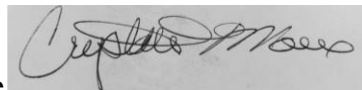
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Abstract

Pancreatitis and diabetes are both physiological problems with the pancreas. Pancreatitis is an inflammation of the pancreas. Pancreatic enzymes increase within the pancreas and destroy the organ (Columbia University, 2019). The Islet of Langerhans cells are an element of the pancreas that allows for release of hormones. Specifically, these hormones are insulin and glucagon, which maintain blood sugar. When these hormones are not regulated appropriately by the pancreas, the patient will develop diabetes, specifically type II diabetes (Columbia University, 2019). Pancreatitis and diabetes have both been linked to increased risk of pancreatic cancer. These disease processes will be introduced using a case report of a 47-year-old female who presents with abdominal pain, diabetes and daily alcohol use. Literature was reviewed using CINAHL and PubMed to answer clinical questions. The aim of this paper is to provide information on the relationship between diseases of the pancreas, and how they correlate with pancreatic cancer. The case study is discussed in relation to symptomology and risk factors. Additionally, information will be provided on environmental causes, diagnostic testing and treatment options. This will include new research using stem cell therapy in the treatment of pancreatitis, as well as future investigational needs.

Background

Pancreatitis, Diabetes and Alcohol Intake: The Interrelationship and Effects on the Human Body

Pancreatitis is the fourth leading cause of cancer death in men and the fifth leading cause of cancer death in women, worldwide (Lai et al., 2013). The incidence of pancreatitis in the United States is 4.4-11.9 cases per 100,000 people per year, with a prevalence of 36.9-41.8 cases per 100,000 (Stram, Lui & Singhi, 2016). Pancreatitis and diabetes are both diseases of the pancreas. The International Diabetes Foundation reports that 415 million people are diagnosed with diabetes worldwide (Zimmet, 2017). Alcohol use/abuse can decrease the functional capacity of the pancreas, and has been found to correlate with pancreatitis and an increased risk of pancreatic cancer. Alcohol alters the ability of the pancreas to release hormones, as the tissue becomes further damaged.   Overtime, this can affect the body's ability to regulate blood sugar, thus leading to poor diabetic control.

Multiple incidences of pancreatitis increase the risk of pancreatic cancer. Lai et al. (2013) found numerous risk factors connected with the diagnosis of pancreatic cancer. These include but are not limited to: cigarette smoking, male gender with gastric stomach ulcers, a diet high in fat, chronic pancreatitis, type II diabetes and the use of diabetic pharmacological treatment, specifically insulin. Additional risk factors include: obesity, life-style choices, alcohol intake, increasing age, family history of pancreatic cancer, certain genetic factors and other dietary influences. Cigarette smoking, obesity, alcohol intake and dietary choices can be changed or altered by the person to correct and minimize the actual risk of pancreatic cancer (Pourhoseingholi, Ashtari, Hajizadeh, Fazeli, & Zali 2017). Having chronic recurrent bouts of pancreatitis as well as being diabetic increases a patient's risk of pancreatic cancer by almost 23-fold when compared to non-diabetic patients with pancreatitis (Lai et al., 2013).

Pancreatitis, diabetes and alcoholism all have their own significant risk factors and increased risk of comorbidities, the deadliest being pancreatic cancer. Pancreatic cancer has a 97% mortality rate, with North America having the highest incidence rate worldwide. The 5-year survival rate after diagnosis is as low as 6% (Pourhoseingholi et al., 2017).

The presented case will evaluate a patient with a differential diagnosis that includes pancreatitis. A discussion will follow: considering the science of the disease, the associated risk factors, diagnostic testing, and treatment options including the new alternative of mesenchymal stem cell therapy.

Case Report

A 47-year old patient presents to the clinic with abdominal pain that has been present for the past 12 hours and started fairly soon after dinner the previous night. The pain is located in the middle abdominal area and extends into the right upper quadrant. Radiation of the pain is noted into the patient's back and also the right shoulder. The pain is an 8-9/10 on the pain scale, and has a dull quality. Since the pain started, it has not receded and has actually worsened with time. She has never had pain like this before, however she has noted abdominal pain after meals occasionally, which typically resolved within a few hours. The patient attempted to use a warm water bottle to help with the pain, but this was not successful. Her only pain relief comes when she sits hunched over or is side-lying. Any activity or lying supine increases her pain significantly. Correlated symptoms include, nausea with emesis x 3 last night after the evening meal. The initial emesis consisted of food particles and subsequent emesis was a "yellow liquid." Possibly had a low-grade fever, but does not have a thermometer at home. Patient denies change in stool appearance or color, as well as blood in the stool. Prior to this episode, appetite had been unchanged, weight remains stable and she denies recent infection.

Past medical history significant for diabetes, hypertension and obesity. She does not report any allergies. Current medications include: Lisinopril 20mg and Metformin 1000mg per day. Her only hospitalizations were to have children, x 2. She has no past surgical history. Family history significant for father deceased from a stroke at the age of 65 and mother having a history of gallstones. The patient is married and lives with her male spouse. She works as a financial consultant. She consumes 1-2 glasses of wine nightly with dinner, but recently has increased this related to dining with guests. She denies recreational drug use and tobacco use. The patient does not exercise because she cannot find the time to add this to her current lifestyle. She admits to a diet of "comfort foods" as this is the foods her "children like to eat" such as, macaroni and cheese or spaghetti and meatballs.

Vital signs are Temp: 99.5°F, BP: 116/70, HR: 102, Resp: 20 and BMI: 30 kg/m^2 Review of systems as noted above. Physical exam as follows: general appearance: appears stated age, no acute distress; mobility: ambulates without assistance; build: obese. Skin: warm, dry and intact, without rashes or lesions. Eyes: conjunctiva; clear. Neck: range of motion normal. Cardiovascular: rate: regular; rhythm: regular; heart sounds: normal S1, S2. Resp/Thorax: auscultation: clear bilaterally, without wheezing, rhonchi or rales; effort: no respiratory distress; rate: no tachypnea. Abdomen: exam shows: soft, non-distended, tender especially in RUQ, no masses noted; bowel sounds: diminished all four quadrants. Musc/Skel: edema: none; mobility: gait normal without assistive device. Neuro: mental status: alert; orientation: person, place, time. Psych: affect: appropriate; grooming: appropriate; mood: appropriate to situation.

Differential diagnoses include: cholecystitis, pancreatitis, choledocholithiasis, hepatitis and gastroenteritis. Choosing diagnostic testing should be based on the differential diagnoses. An ultrasound of the abdomen is the gold standard test to determine pancreatitis versus

gallbladder disease. It is non-invasive and relatively inexpensive. Serum lab testing should include: alkaline phosphatase, liver function tests (AST and ALT), amylase, lipase, CBC, electrolytes and calcium. Testing should be selected based on the information it can provide the practitioner, but also how that information will affect the treatment plan. Based on the results of the diagnostic testing the patient would be referred to a surgeon for a cholecystectomy and follow-up would be determined based on the surgical plan.

Literature Review

Diseases of the pancreas can increase the risk of pancreatic cancer, including both pancreatitis and diabetes. If pancreatitis and diabetes can be prevented or controlled the risk of pancreatic cancer decreases. The literature review will provide information related to disease processes within the pancreas, environmental causes, symptoms of disease, risk factors, diagnostic testing and treatment options for such diseases, including new research on the use of stem cell therapy in the treatment of pancreatitis. Information was compiled from CINAHL and PubMed using the following terms in varying combinations: pancreatitis, diabetes, alcohol, pancreatitis treatment and pancreatic cancer. An article search was also conducted specifically in *The Lancet* and *The Journal of Clinical Diabetes and Endocrinology* using the terms pancreatitis, alcohol and diabetes.

Pancreatic cancer is possibly the deadliest cancer diagnosis and it has a very poor short-term survival rate. Only 24% of patients with pancreatic cancer will survive beyond one year and only 6% will survive beyond 5 years. The occurrence of cases and the rate of death from pancreatic cancer are close to analogous because pancreatic cancer is rarely diagnosed at a stage that is treatable (Pourhoseingholi et al., 2017). Type I and type II diabetes have both been shown to increase the risk of pancreatic cancer by 1.8 times when compared to the non-diabetic

population (Pourhoseingholi et al., 2017). Additionally, diabetic patients with a history of

gallstones, gallbladder disease or cholecystectomy are at even higher risk of disease

development. The patients that also had a comorbidity of chronic pancreatitis were at a

significantly increased probability of pancreatic cancer (Lai et al., 2013). Chronic pancreatitis is

one of the disease processes that heightens the risk of pancreatic cancer. Once a patient has

pancreatic cancer they are at higher risk of developing diabetes, if they do not already have the

disease, and this risk is further increased in patients with chronic pancreatitis (Lai et al., 2013).

Many risk factors are associated with pancreatic cancer, pancreatitis and diabetes.

Alcohol use, especially abuse and long-term use, is a major risk factor for pancreatic cancer and

pancreatitis. It is also "an independent risk factor for the development of type II diabetes"

(Alcohol Research, 2017). The probability of disease is increased when the patient continues to

ingest alcohol after an initial diagnosis of pancreatitis. Patients who smoke tobacco, consume a

high-fat diet, are obese, have a genetic risk or have been exposed to certain infections have an

increased likelihood of cancer, especially in a patient who also heavily consumes alcohol (Stram,

Liu & Singhi, 2016).   Excessive alcohol intake weakens the body's ability to regulate glucose

and negatively affects pancreatic beta-cell function. This also occurs in peripheral tissues,

adipose tissue and the liver where it causes an insulin resistance (Alcohol Research, 2017).

Alcohol abuse in addition to smoking tobacco, another independent risk factor, has a cumulative

effect in both the diagnosis and progression of pancreatic disease. Smoking alone, increases the

risk of pancreatitis by three times and doubles the risk of pancreatic cancer, when compared to

non-smokers (Lugea, 2017).   Obese patients are at higher risk for poor outcomes and can have a

deteriorating condition. The adipose tissue, or fat, becomes increasingly inflamed which can

lead to a systemic inflammation (İnce & Baysal, 2014).

Insulin resistance is a noted risk in type II diabetic patients who have pancreatic disease. The diabetic patient's body compensates for this resistance by over producing insulin and insulin-like growth factors (IGF1). This plethora increases the activity of IGF1 and leads to cell proliferation, inhibition of cell apoptosis and increases cancer causing abnormalities of the tissue (Lai et al, 2016). The change in cell activity within the diabetic pancreas has been shown to increase the incidence of pancreatitis, when compared to non-diabetic cohorts. This may be accredited to an increased incidence of gallbladder disease, gallstones and obesity which are more common in the diabetic patient (Davis, Drinkwater & Davis, 2014). Overall, a diabetic patient is at approximately 73% higher risk of being hospitalized with acute pancreatitis versus a non-diabetic patient (Davis et al., 2014).

Physiologically, the pancreas changes in many ways related to disease processes and environmental risk factors. Many pathophysiological aspects of pancreatitis are still undetermined and are being researched. One hypothesis, which has been postulated for more than one hundred years, is pancreatic autodigestion. İnce & Baysal (2014) explain this theory as: "premature activation of pancreatic proenzymes (zymogens) induces autolysis, which triggers inflammatory events followed by continued damage to the pancreas and/or non-pancreatic tissues in some way" (p. 352). In the initial phases of an acute pancreas attack, the body produces a systemic inflammatory response syndrome (SIRS) that occurs in relation to the inflammatory action. Next, a compensatory anti-inflammatory action occurs that results in an infectious process related to the immunosuppression. The diagnosis of SIRS requires two or more of the following criteria: fever $\geq 38°$ C, heart rate >90 beats per minute, respirations > 20 per minute and/or white blood count (WBC) >12,000 and neutrophil bands > 10% (İnce & Baysal, 2014).

The islet cells, are produced and dispelled within the pancreas, control endocrine activity by producing insulin and glucagon hormones that are used to normalize blood glucose levels. Islet cells are either alpha or beta-cells. Alpha cells are responsible for the production of glucagon. Subsequently, glucagon increases blood glucose and encourages the liver to digest glycogen into glucose and then releases this into the blood stream. Glucagon prompts adipose tissue to change triglycerides into glucose releasing them into the blood stream as well. The beta-cells generate insulin to lower the increased glucose level produced by the alpha cells. This stimulates the liver, muscles and adipose tissue to absorb and store glucose in the form of glycogen. The action of the alpha cells, beta-cells and the pancreas are all controlled by the sympathetic and parasympathetic segments of the autonomic nervous system (Alcohol Research, 2017). When these cells are damaged, as in pancreatitis, alcohol abuse or diabetes, it affects the functional ability of the entire organ as well as multiple other body processes.

Pathological changes can also be induced by specific genetic alterations. These mutations increase the risk for pancreatic cancer. A genetic risk is noted in approximately 10% of patients diagnosed with pancreatic cancer. Genes that have been associated with pancreatic cancer are BRCA1, BRCA2, PALB2, ATM, CDKN2A, APC, MLH1, MSH2, MSH6, PMS2, PRSS1 and STK11 (Pourhoseingholi et al., 2017). All of these genetic mutations can be generally classified into three categories: autosomal dominant, autosomal recessive and modifier gene mutations (Stram, Lui, & Singhi, 2016). Of the mutations, the most frequently connected with chronic pancreatitis are PRSS1, CFTR, and SPINK1 (Stram et al, 2016).

The risk factors change the physical make-up of the pancreas, especially alcohol abuse. The arrangement of the perilobular and interlobular parenchymal fibers of the pancreas become irregular and unbalanced. With the distribution change, the pancreas becomes hardened and

consolidated in appearance, with the individual lobes becoming more diverse. The ducts change

as well, because they are typically buried within the fibrosed tissue causing dilation and

potentially malformation. These changes can result in the creation of pseudocysts within the

organ, typically inside the body or tail of the pancreas. A pseudocyst is present in 25-50% of

patients with chronic pancreatitis (Stram et al, 2016). These cysts are composed of "turbid,

necrotic debris which is rich in exocrine enzymes" (Stram et al, 2016, p. 644). As the pancreas

becomes more damaged from repeated insults it "appears opaque, shrunken, and reduced in size

due to parenchymal atrophy and continuing fibrosis" (Stram et al, 2016).   It is also possible for

the patient to develop calculi, most commonly found in the ducts and the branches of the ducts.

Calculi is comprised of calcium carbonate. As pancreatic disease progresses, there is large-scale

loss of acinar, ductal and islet cells (Stram et al, 2016, p. 644). As previously discussed, the

noted cells allow the pancreas to perform and prevent dysfunction in glucose metabolism.

     An accurate diagnosis is the first step in identifying or ruling out a disease process such

as: pancreatitis, cholecystitis, liver disease or hepatitis, pancreatic cancer, gastritis, etc. The

United States Preventative Services Task Force does not recommend routine screening for

pancreatic cancer. This pertains to patients that are asymptomatic and are at low to average risk,

because the benefit of screening does not decrease mortality (Cruz, Young & Ruffin, 2014).

Symptoms that may prompt further investigation for pancreatic disease include: unexplained or

unplanned weight loss, abdominal pain, nausea, vomiting, generalized weakness, anorexia,

constipation, intolerance to specific foods, jaundice, dark urine, and acholic stool (Cruz et al.,

2014). During the early stages of pancreatic disease, especially that caused by alcohol abuse, the

occurrence of abdominal pain is frequent and severe. As the disease progresses, the pain actually

improves because of the extensive damage to the organ and nerves (Stram et al., 2016). The

abdominal pain is a result of exocrine and endocrine malfunction. This malfunction tends to be

progressive in nature with increasing fibro-inflammation, resulting in damage to the pancreas

that is permanent and irreversible (Stram et al., 2016).

The gold standard diagnostic test is an ultrasound of the abdomen. Abdominal ultrasound

will definitively diagnose gallbladder disease. If the ultrasound is negative for cholecystitis, but

does not adequately diagnose pancreatic disease, a CT scan should be ordered. According to

Cruz et al. (2014), "pancreas protocol CT involves triphasic (i.e., arterial, late, and venous

phases) cross-sectional imaging that allows for enhancement between the parenchyma and

adenocarcinoma." Another testing option is the fecal elastase-1 (FE) test. This is a non-invasive

test used to diagnose pancreatic exocrine insufficiency. The FE test is highly specific and

sensitive in diagnosing exocrine dysfunction and is considered a first line test (Vujasinovic et al.,

2014). Nutritional serum markers have been found to be abnormal in patients with pancreatic

disease. Poor digestion, poor nutrition and nutritional serum markers can indicate disease when

a patient is otherwise asymptomatic. Vitamin D, iron and folic acid insufficiencies were the

most commonly noted deficits in patients with pancreatitis, especially those with chronic

pancreatitis (Vujasinovic et al., 2014). Other serum lab tests that are indicated in patients with

pancreatitis include serum amylase and lipase. The patient with pancreatitis will have elevated

levels, that are at least three times the upper limit of normal (İnce & Baysal, 2014).

Different disease measurement scales have been developed to aid the clinician in

diagnosing pancreatic disease and determining its severity. One such scale is the Acute

Physiology and Chronic Health Examination (APACHE-II) scoring system. It is the scale

recommended by the American Gastroenterology Association (AGA). The APACHE-II has 12

physiologic markers in addition to risk factors such as, age and the existence of comorbidities.

However, this system has been found to be difficult to administer and is not a reliable predictor within the first 24 hours of a hospital admission (İnce & Baysal, 2014). Another available scale is the Imrie Scoring System, and it is appropriate for use within the first 48 hours of hospital admission. This scale has 9 items, with three or more positive indicators determining the severity of the disease. Other scales have been developed including: 2012 Atlanta Revision, 2013 Atlanta Revision and the SIRS score, which was discussed earlier. However, the American College of Gastroenterology (ACG) suggest looking at the whole patient: radiological testing, laboratory testing and symptomology, rather than diagnosing based on a scoring system (İnce & Baysal, 2014). İnce & Baysal (2014) recommend: considering the patient "age, BMI, elevated hematocrit and BUN levels, SIRS, comorbidity, pulmonary effusion and infiltrate, variable mental state and presence of other findings" (p. 353). This information is critical in the diagnosis and plan of care, as well as determining the risk for mortality.

When a patient has a diagnosis of any pancreatic disease, a treatment plan needs to be determined. Historically, treatment for pancreatitis has been supportive. It has been aimed at diminishing symptoms with no entirely successful treatments available (Jung, Yi, Son, Song & Hong, 2015). As a result, pancreatic diseases require multiple hospitalizations and frequent medical office visits. This creates a financial burden for the patient and stretches medical resources (Stram et al., 2014). Patients may be started on medication to discourage pancreatic enzyme production, antibiotics to prevent infection and nutritional supplementation to aid in healing (Jung et al, 2015).

Diabetes treatment must be initiated and implemented to prevent the progression of pancreatic disease. However, research has shown that patients treated with insulin, at any time, are at an increased risk of pancreatic cancer. Diabetics treated with metformin where not found

to have this increased risk (Lai et al, 2013). Diabetes can be caused by pancreatitis and is known

as pancreatogenic diabetes or type 3c. It should be treated with metformin and insulin should be

used with extreme caution as it increases the risk of pancreatic cancer.   In pancreatogenic

diabetes, metformin has actually been shown to be protective against pancreatic cancer

(Vujasinovic et al., 2014).

The treatment plan should include a support system to help the patient maintain maximal

functioning. Support systems should be considered a treatment and are encouraged for all

patients, to minimize complications and disease progression. Peer support has been researched

and found to be effective for pancreatic disease. "Peer support can encourage appropriate

regular care, can provide practical and emotional support for complex behaviors that are critical

to staying healthy, and can help individuals cope with the stressors chronic diseases and

conditions so often entail" while "sustaining preventative and disease management behaviors"

(Fisher et al., 2017, background section, para. 1). Patients require education regarding self-

management as well as self-management support. Teaching these behaviors allows the patient to

take control of the disease and manage the illness. Four functions have been determined in the

use of peer support: assistance in management of every day function, social and psychological

support that strengthens self-management and coping, education and assistance in utilizing

community resources and continuing support throughout the life of the patient (Fisher et al.,

2017). In random control trials, 83.7% of patients showed significantly positive results when

provided with peer support. This contributed to maintenance of "a variety of complex health

behaviors in prevention and disease management" (Fisher et al., 2017, conclusion section).

As presented, historically treatment has been symptomatic. However, current research is

investigating the use of mesenchymal stem cell (MSC) therapy for the treatment of both acute

and chronic pancreatitis. Subsequently, this would decrease the incidence of pancreatic cancer.

MSC's are found in bone marrow, the umbilical cord, adipose tissue and fetal membranes or

placenta. These cells are being researched because of their "immunomodulatory effects on the

secretion of a variety of anti-inflammatory molecules" (Kawakubo, Ohnishi, Kuwatani, &

Sakamoto, 2018, p.1). MSC's are regulators of immunity. Thus, allowing them to decrease

organ damage and injury that results from inflammation (Jung et al., 2015). In addition to

overriding inflammation, they also prevent apoptosis and fibrosis of pancreatic cells (Kawakubo

et al., 2018). The most effective MSCs are harvested from the bone marrow (Jung et al., 2015).

Mesenchymal stem cells have the potential to mend tissue that has been damaged by

acute and chronic diseases.   Stem cells have the ability to regenerate and can differentiate into

the cells or tissue that needs to be repaired (Jung et al., 2015). In other words, they can change to

fit the need of the damaged tissue. The ability to regenerate allows the MSCs to change into

mesoderm cells, chondrocytes, osteocytes, adipocytes, ectodermic and endodermic cells. A

major advantage of MSCs is that rejection is not a concern after implantation. MSCs do not

contain major histocompatibility complex class II antigens, thus preventing allogenic or

autogenic reactions to occur (Kawakubo et al, 2018).

The MSCs prevent apoptosis of the acinar cells, which aids in the functional repair

process within the pancreas. Apoptosis occurs in response to inflammation. In research

conducted on rats with severe acute pancreatitis, multiple apoptotic cells were present. With the

addition of MSCs, the total number of acinar apoptotic cells was significantly decreased and the

pancreatitis resolved. This specific research found that "MSCs improved pancreatic injury,

inhibited oxidative stress and inflammatory responses in an animal with severe acute

pancreatitis" (Jung et al., 2015, p. 747). Tu et al., as reported by Kawakubo (2018), found that

MSCs increased levels of aquaporin in acute severe pancreatitis. This resulted in the

penetrability of the mucosal layer within the intestine, further stimulating the healing of the

intestinal epithelial cells and conserving the stability that the intestinal mucosal barrier provides.

The MSCs travel to the areas of inflammation. The actual mechanics of MSCs are not

completely known, but they appear to aid in the pancreas's ability to self-repair and improve its

exocrine function (Jung et al., 2015). This science could improve outcomes for patients

diagnosed with pancreatitis.

Further research is recommended in the area of MSCs, and should be conducted on

human subjects to evaluate the long-term benefits and side-effects of this newest treatment

option. Until this time, practitioners must focus on prevention. Ideally, decreasing the incidence

of pancreatitis, diabetes and pancreatic cancer as it is currently the only definitive treatment.

Learning Points

- Prevention should be the first step in treatment of pancreatic diseases as the majority of
  risk factors are avoidable: obesity, excessive alcohol intake, tobacco use/abuse and poor
  control of diabetes.

- Damage to the pancreas is related to an inflammatory response that causes irreversible
  cell damage of the acinar, ductal and islet cells. Risk factors induce these pathological
  and physical changes to the pancreas.

- Further investigation and diagnostic testing is required when a patient presents with
  unexplained or unplanned weight loss, abdominal pain (possibly severe), nausea,
  vomiting, generalized weakness, anorexia, constipation, intolerance to specific foods,
  jaundice, dark urine and acholic stool.

- Initial diagnostic testing is done with an abdominal ultrasound. If this is inconclusive a pancreatic CT should be done in addition to basic lab work including a serum amylase.

- Treatment has historically been symptomatic. New research with mesenchymal stem cells has shown promise, and may improve patient outcomes, decrease mortality and decrease the incidence of pancreatic cancer.

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