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Investigating the Mechanistic Relationship Between Hyperinsulinemia and Pancreatic Cancer

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers globally with a five-year survival rate around 10%. This review investigates a lesser-known risk factor of PDAC, hyperinsulinemia, and explores recent scientific literature to establish a sequence of events and mechanisms connecting both conditions. The objective of this paper is not only to establish the observed connection between hyperinsulinemia and pancreatic cancer but to also assert the clearly defined mechanisms underlying the pathogenesis of pancreatic cancer from hyperinsulinemia and explore them on a cellular level. The results of this review are presented in *Figure 1* and found that hyperinsulinemia can promote the overproduction and early activation of pancreatic digestive enzymes, prompting acute pancreatitis which can become chronic. Chronic pancreatitis holds the pancreas in a perpetually inflamed state, promoting an environment that facilitates the development of PDAC. From these results, it can be concluded that the progression of hyperinsulinemia into PDAC can be defined by a mechanistic progression of degradation. Some terms used to research for this review include pancreatic inflammation, hyperinsulinemia, pancreatic digestive enzymes, pancreatitis, and pancreatic ductal adenocarcinoma. The intent of this review is to inform of the risks associated with hyperinsulinemia in relation to PDAC and to advise clinicians to screen patients with hyperinsulinemia for pancreatic degeneration.

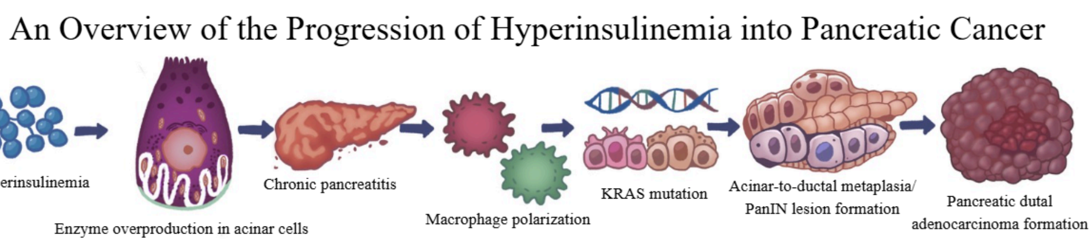

Figure 1. This diagram presents an overview of the progression of hyperinsulinemia into pancreatic cancer, summarizing the entire mechanism discussed in this review.

INTRODUCTION

As life expectancy in the United States continues to increase, so does the incidence of pancreatic cancer. As a result, pancreatic ductal adenocarcinoma (PDAC), the most common subtype accounting for approximately 90% of cases, has a poor prognosis with a five-year survival rate of roughly 10% [1]. The poor prognosis of PDAC combined with the projected 31.45% increase in incidences of the condition from 1990 to 2040 convey the threat PDAC poses [2]. Conditions such as hyperinsulinemia, which is defined as the presence of elevated insulin levels in the body as a result of insulin resistance, place patients at a higher risk of developing PDAC [3]. Furthermore, pancreatic cancer along with cancers of the lung, liver, and breast are all projected to become the leading causes of cancer death by 2030 [4]. Pancreatic cancer, in particular, is notoriously difficult to diagnose and, consequently, to treat. This can be partly attributed to the disease often being diagnosed at advanced stages with relatively few presenting symptoms. One of the only notable symptoms in the early stages of PDAC is jaundice due to the tumor at the head of the pancreas obstructing movement in and out of the bile duct [5]. Pancreatic intraepithelial neoplasias, or microscopic sized growths, (PanINs) are also a known precursor to pancreatic cancer, and their severity ranges from PanIN-1A to PanIN-3. While PanINs do provide a good indication of patients at a higher risk for pancreatic cancer, with patients possessing PanIN-3 lesions having the greatest chance of developing pancreatic cancer, they are extremely small <5 mm and deep within the pancreas which makes them difficult to detect [6]. With the diagnosis and treatment for this cancer being so difficult, as a result of the disease's rapid progression and malignance, it is important to focus on methods of prevention.

This can be done by analyzing the risk factors often associated with pancreatic cancer. Some commonly associated risk factors include excessive alcohol consumption and smoking, but there are more. A relatively newly realized independent risk factor of pancreatic cancer is hyperinsulinemia. One of the key functions of the pancreas is to produce insulin. The cells within the pancreas that produce insulin are known as beta cells (β-cells). Because hyperinsulinemia occurs when the body has built up an insulin resistance, the β-cells are forced to rapidly increase insulin output to maintain blood glucose homeostasis [3]. This puts immense strain on the pancreas and contributes to problems which influence pancreatic cancer development. The goal of this review is to culminate recent research surrounding the lesser publicly known risk factor of hyperinsulinemia to formulate a logical progression of events leading to pancreatic cancer.

METHODS

This paper is based on a structured literature review of peer-reviewed research sources exploring the link between hyperinsulinemia and pancreatic cancer. The academic search engine this review utilized was Google Scholar. Google scholar was employed to ensure academic credibility in regard to the studies referenced, many of which come from the National Library of Medicine, ScienceDirect, and PubMed. Some search terms imputed into Google Scholar include: "insulin releasing digestive enzymes”, "insulin’s role in digestive enzyme production", "early digestive enzyme activity", "pancreatic cancer prognosis", "pancreatic cancer incidences by 2030", and "hyperinsulinemia and pancreatic cancer". In order to ensure up-to-date findings, the majority of studies published prior to 2020 were excluded due to the understanding of this topic rapidly evolving with more recent contributions. However, studies that were included and published prior to 2020 are mentioned in this review to define well-established concepts. For instance, the study regarding the islet-acinar axis was not published after 2020, yet it defines a key mechanism that is still accepted by the scientific community at this present time; this makes its findings useful to this review. Moreover, statistics asserting percentages of the population afflicted with a condition were taken after 2020 in order to present data that most accurately represents the current global population.

BACKGROUND

In relation to the hyperinsulinemia-pancreatic cancer connection this paper will discuss the early activation of pancreatic digestive enzymes and pancreatitis, so it's important to understand details about all four of these conditions for context. As aforementioned, hyperinsulinemia most frequently occurs as the result of a built up insulin resistance in the body which forces the pancreas to maintain elevated levels of insulin [3].

The most notable precursors to hyperinsulinemia include hypertension, a large concentration of visceral fat, and obesity [7]. Hypertension is defined by the World Health Organization as any blood pressure higher than 140/90 mmHg and is estimated to be present in 1.28 billion adults between the ages of 30 and 79 [8]. Visceral fat is found inside the body’s abdominal walls and envelops organs. The typical function of visceral fat is to serve as protection, but when there is too much present in the body it becomes harmful; visceral fat is known to contribute to diabetes, stroke, and heart disease [9]. Lastly, obesity is defined as the surplus of fat in the body that could potentially lead to harm and is present in 16% of adults globally as of 2022 [10].

For some background on two of the other conditions relevant to this review, premature activation of pancreatic digestive enzymes frequently accompanies pancreatitis since enzyme activation induces the inflammation defining pancreatitis. The main digestive enzymes produced by pancreatic acinar cells are lipases, proteases, and amylases. Lipases hydrolyze fats, proteases degrade proteins, and amylases convert starches into sugars for usable energy. The protease enzymes, after being produced in the pancreas, typically remain dormant until they reach their destination in the duodenum of the small intestine [11]. However, in an atypical environment the dormant enzymes, also referred to as zymogens, become active in the pancreas which leads to damage and inflammation, especially due to the strength of particular proteases presented in *Table 1*.

Table 1. A chart presenting inactive and active protease variants [12, 13].

Inactive form of the protease enzyme (zymogen)	Active form of the protease enzyme (in a typical environment this would occur in the small intestine)
trypsinogen	trypsin (one of the strongest active protease enzymes)
chymotrypsinogen	chymotrypsin
procarboxypeptidase	carboxypeptidase

This premature activation of digestive enzymes, influenced by various factors such as hyperinsulinemia, contributes to pancreatic inflammation. This result directly mirrors the conditions present in pancreatitis, which is defined as inflammation of the pancreas. One occurrence of premature enzyme activation would lead to a condition known as acute pancreatitis, whereas constant or frequent occurrences could cause the condition to become chronic. Pancreatitis becomes a risk factor for pancreatic cancer when it is chronic or longstanding [14]. Unfortunately, pancreatitis has become more prevalent in the last few decades with there being a 59% global increase in incidences of the condition from 1990 to 2021 [15].

THE OBSERVED LINK BETWEEN HYPERINSULINEMIA AND PANCREATIC CANCER:

Multiple studies have documented the connection between hyperinsulinemia and pancreatic cancer. Wolpin et al. (2013) found that the peripheral insulin resistance commonly associated with hyperinsulinemia contributed to a higher risk of pancreatic cancer by observing data from different cohorts within the United States, while another cohort study examined 572,021 Korean adults, all of whom did not have cancer at the start of observation and found that patients with hyperinsulinemia and the associated insulin resistance had a higher risk of pancreatic cancer mortality [16, 17]. Cohorts of male smokers indicated further that higher insulin levels, or hyperinsulinemia, and insulin resistance are correlated with exocrine pancreatic cancer risk [18]. Lastly, another study solidifying these findings looked into different prospective causes of pancreatic cancer and found that higher baseline insulin levels contributed to an increased risk of pancreatic cancer [19]. These studies concluded that there is a connection between hyperinsulinemia and pancreatic cancer. While this link has been established, the mechanisms behind how hyperinsulinemia progresses into pancreatic cancer are unclear and remain an active area of study. This review will attempt to draw the most logical conclusions from the available scientific literature surrounding the potential internal chain of events between hyperinsulinemia and pancreatic cancer.

RESULTS

Hyperinsulinemia could cause a patient to develop pancreatic cancer by essentially setting in motion a chain of events. This begins with abnormally high insulin levels, hyperinsulinemia, which creates strain on the pancreas due to greater amounts of insulin being produced by pancreatic β-cells. The following stage is the overproduction and early activation of digestive enzymes, due to the insulin receptors on acinar cells which release digestive enzymes, resulting in pancreatitis or inflammation of the pancreas; inflammation is a natural bodily response to a harmful stimulant that involves the immune system. Chronic pancreatitis damages the pancreas and can hinder its ability to produce insulin; all this tissue injury subsequently leads to cancer. It's important to note that this order of events is not definitive, nor is it the only order these conditions can occur in. For instance, a study by Scherer et al. (2014) presents the idea that another form of pancreatitis, hypertriglyceridemic pancreatitis, can eventually contribute to the presence of hyperinsulinemia [20]. This study conveys how the order of these conditions is subject to change. The specific order discussed in this paper was created to present a possible progression of events in an organized manner and should not be taken as the only way through which hyperinsulinemia may lead to pancreatic cancer. This progression of events could be useful in assessing patients at a higher risk of PDAC and in monitoring degradation of the pancreas.

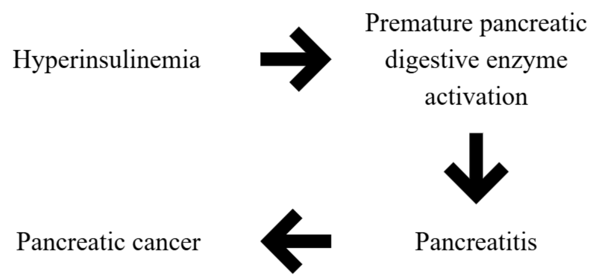

Figure 2. This diagram shows the sequence of events discussed in a simplistic manner.

THE HYPERINSULINEMIA MECHANISM:

In experimental studies, hyperinsulinemia has been observed to contribute to the overproduction and early activation of pancreatic digestive enzymes in an inductive relationship as shown in *Figure 2*. One study from Zhang et al. (2022) makes the association of insulin suppression resulting in fewer PanIN lesions [21]. A different study published by Zhang et al. (2023) in the journal entitled *Cell Metabolism* furthers this idea by exploring the mechanisms behind this conclusion. The *Cell Metabolism* study discussed the effects of hyperinsulinemia on acinar cells, which produce pancreatic digestive enzymes. The consensus of the study was that large amounts of insulin were bound with the insulin receptors (Insr) of acinar cells in mice and resulted in the overproduction of digestive enzymes as well as their early activation. Notably, the activation of the protease enzyme trypsin, one of the strongest pancreatic digestive enzymes, led to increased inflammation of the pancreas and PDAC incidences [22]. This study provides an explanation as to the mechanisms occurring in acinar cells rather than simply associating insulin suppression with a lower risk of PDAC. It is necessary to acknowledge that these studies are relatively recent and further investigation must be done to definitively characterize specific mechanisms.

Insulin is able to affect acinar cells and play a key role in their function within a system known as the islet–acinar axis, or the relationship between the endocrine and exocrine pancreas. This axis describes the interaction between the islets of Langerhans, which house the pancreatic β-cells that produce insulin, and the surrounding acinar cells. The relationship arises from their close anatomical proximity. The endocrine islets release hormones, insulin, directly into the bloodstream, while the exocrine acinar cells secrete digestive products into ducts, enabling the two cell types to influence and regulate each other. The direct mechanisms and effects acinar cells exhibit on islets are still being studied, but there is a clearer picture of the impact of hormones released by islets on acinar cell digestive enzyme secretion and production. Insulin has been found to play a key role in regulating the secretion and production of acinar digestive enzymes, notably pancreatic amylase (P-type amylase), by binding to the Insr of the acinar cells and signaling the activation of the cells' chemical processes [23, 24]. This axis plays an important role in maintaining glucose homeostasis and dysregulation can result in metabolic disorders. Due to the carefully curated balance of this process, the presence of hyperinsulinemia poses a problem. When an acinar cell's Insr is overrun by insulin, it will begin to overproduce digestive enzymes which creates inflammation in the pancreas. In this state, the acinar cells become resistant to insulin over time which forces the pancreas to elevate insulin levels in an attempt to compensate for the new tolerance. This relationship is summarized by *Figure 3*.

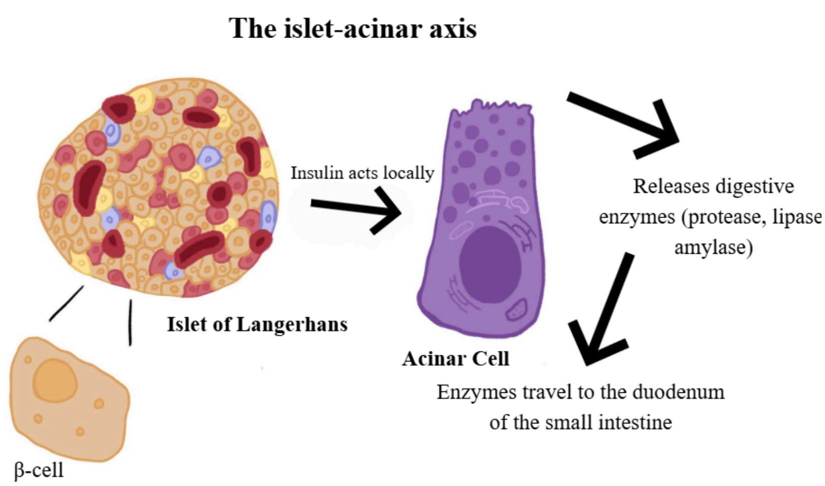

Figure 3. This diagram presents the islet-acinar interactions on a cellular level.

This digestive enzyme initiation and overproduction causes the pancreas to self-digest thus leading to the next logical step in the hyperinsulinemia to PDAC chain of events: pancreatitis. As previously mentioned, infrequent occurrences of digestive enzyme activation would cause acute pancreatitis, but constant occurrences causes the condition to become chronic. In the acute state, the M1 macrophage phenotype can further the already present inflammation in the pancreas by releasing "pro-inflammatory cytokines" [25]. These macrophages are the drivers of inflammation in the pancreas. For context, macrophages can shift phenotypes depending on the signals they receive, a process known as polarization [25]. The two possible phenotypes are M1 and M2 macrophages. The M1 macrophages are typically present in acute pancreatitis and secrete pro-inflammatory cytokines and reactive oxygen species (ROS) which exacerbates inflammation in the pancreas [26].

Conversely, the M2 macrophage, which is the phenotype commonly present in chronic pancreatitis, is associated with tissue repair and invokes an anti-inflammatory response. Interleukin-4 (IL-4) and interleukin-13 (IL-13) are two of the cytokines that promote the polarization of M2 macrophages to repair damage caused by M1 macrophages and other prior inflammatory damage in the pancreas [27]. The M2 macrophages then promote tumor growth through numerous steps. For instance, the M2 macrophages release Interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) which inhibit other immune cells, such as T cells, thus preventing a defensive response against tumor progression [28]. These cytokines act as a protective barrier for cancerous cells, allowing for unbridled growth. M2 macrophages then release the vascular endothelial growth factor (VEGF) which stimulates angiogenesis [29]. Angiogenesis is the process of new blood vessel formation necessary for typical tissue regeneration and repair in the body. This process also allows tumors to gain the necessary nutrients to sustain themselves during their development. The presence of M2 macrophages in the pancreas has been observed to contribute to a worsened prognosis in cases of pancreatic cancer [30]. Insulin can also directly influence macrophages, because they have insulin receptors. When these receptors are exposed to high levels of insulin over a long period of time, macrophages show a trend of shifting toward a more pro-inflammatory state, producing signals that worsen existing inflammation. This promotes further insulin resistance in adipose, fat, cells and liver cells. The presence of hyperinsulinemia creates a self-reinforcing cycle as high amounts of insulin signal inflammation, which causes more insulin resistance, and subsequently results in a greater need for increased insulin production in the pancreas [31]. Moreover, when a Kirsten ras oncogene homolog (KRAS) gene mutation is present, the combined forces of M1 and M2 macrophages contribute to acinar-to-ductal-metaplasia (ADM) [32]. ADM is defined as mature acinar cells transforming into the duct-like cells which line the pancreas in an effort to repair damage caused by inflammation. If ADM becomes chronic the pancreas begins to form PanIN lesions which are the precursors to PDAC [33].

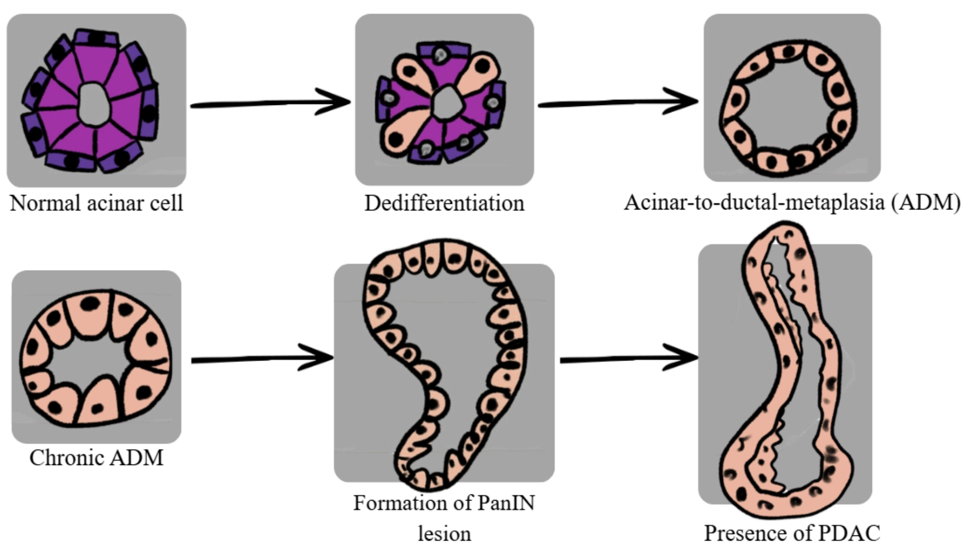

Figure 4. This diagram explains how ADM transitions into PDAC beginning with a normal acinar cell going through dedifferentiation and becoming a pancreatic duct-like cell.

The synergistic effects of M1 and M2 macrophages, with M1 macrophages promoting inflammation and M2 macrophages signaling repair and fibrosis, create an environment which directly facilitates the growth of PDAC as seen with the progression of ADM in *Figure 4*. The M1 and M2 macrophages are essentially vital stepping stones, prompting the progression of pancreatitis into PDAC. It is important to note that the presence of macrophages alone is not enough to trigger the development of pancreatic cancer. While macrophages create a suitable environment for tumor growth, as discussed, an oncogenic alteration is necessary for a malignant tumor to form. The most common example of an oncogenic alteration in pancreatic cells is the aforementioned KRAS mutation. When malignancy occurs, the M1 and M2 macrophages facilitate tumor growth, while not being the factor that initially formed the tumor.

CONSEQUENCES OF PDAC:

PDAC, a condition with a poor prognosis, can also pose problems even after a patient overcomes the cancer; PDAC can lead to the development of type 3c diabetes mellitus (T3cDM). T3cDM is a lesser known diabetes variant and, consequently, it is oftentimes misdiagnosed as type 2 diabetes mellitus. T3cDM is defined as a form of diabetes resulting from pancreatic damage due to conditions such as chronic pancreatitis or pancreatic cancer [34]. T3cDM is a condition that can harm systems all around a patient's body. For instance, T3cDM can lead to organ damage due to blood vessel impairment, notably in the heart, eyes, and kidneys [35]. The issues T3cDM can pose and the lack of cohort studies surrounding the topic continues to prompt more research into this newly realized variant. A study found that out of 1868 subjects with a preexisting diabetes mellitus variant, 172, or 9.2%, of the participants fit the parameters for T3cDM. Furthermore, only 51.2% of the patients with T3cDM were initially diagnosed correctly, with the most common misdiagnosis being that of type 2 diabetes mellitus [36]. T3cDM having such inconsistent diagnosis rates should pose a concern in the medical community. With this condition posing a threat to systems all over the body, the high misdiagnosis rates, and the lack of research in comparison to type 2 diabetes mellitus it is imperative to enact methods of prevention. Chronic pancreatitis and pancreatic cancer are the two most common causes of T3cDM with chronic pancreatitis encompassing 78.5% of cases and pancreatic cancer contributing to 8% [34]. The conclusion can therefore be drawn that by avoiding these conditions, a person is at a significantly lower risk of T3cDM and puts into perspective the long term negative effects of chronic pancreatitis and pancreatic cancer.

DISCUSSION

Multiple cohort studies reached the conclusion that the presence of hyperinsulinemia is associated with an increased PDAC risk, but the exact molecular processes behind this association are still under investigation. Mechanistic studies formulate a plausible sequence of events between hyperinsulinemia, early pancreatic digestive enzyme activation, pancreatitis, and PDAC. In particular, evidence supports early enzyme activation triggering pancreatitis and pancreatitis resulting in pancreatic cancer. A major limitation in scientific literature is the lack of human data connecting hyperinsulinemia to the early activation of pancreatic digestive enzymes and the reliance on animal models. A notable study from 2023 previously mentioned observed hyperinsulinemia overwhelming the insulin receptors of acinar cells in mice, leading to the subsequent premature activation of pancreatic digestive enzymes [20]. Although these findings were derived from animal models, they provide a tangible mechanistic explanation for the progression of hyperinsulinemia into pancreatic cancer that aligns with epidemiological trends in humans. Further research is needed within human populations to definitively characterize these mechanisms and guide early intervention approaches.

CONCLUSION

Hyperinsulinemia has been linked to higher rates of pancreatic cancer. This review aimed to present a possible chain of events by delving into the mechanisms of how hyperinsulinemia progresses into pancreatic cancer. The consequent conditions proceed as follows: hyperinsulinemia, the early and overactivation of pancreatic digestive enzymes, chronic pancreatitis, and pancreatic cancer. The presented list contributes more insight into how hyperinsulinemia could progress into the observed higher incidences of pancreatic cancer associated with elevated insulin levels and insulin resistance. By attempting to structure the hyperinsulinemia-induced degradation of the pancreas into solid conceptualized conditions, clinicians can better understand which patients may be at a higher risk for pancreatic cancer. Although epidemiological studies have concluded that there is an association between hyperinsulinemia and pancreatic cancer, the molecular mechanisms defining this connection still remain undefined. This review contributes by organizing current mechanistic findings into a model of progression and highlights the need for further research in order to definitively characterize these steps of degradation. This would allow for the potential development of better solutions and treatment plans in the future.

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