Section A -Research paper

Relation between diabetes mellitus, pancreatic steatosis and pancreatic cancer: Review Article

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Abstract:

Numerous reasons have stymied advancement in the fight against pancreatic cancer. One of them is the overwhelming majority of patients' inability to identify the condition early. The current study proposes a fresh strategy for quickening development. This includes a focus on post-acute and chronic pancreatitis, diabetes mellitus, and excess intra-pancreatic fat deposition, all of which have the same goal of impacting the tumor's macroenvironment and microenvironment in the pancreas, and not in other organs. The two entities have the potential to be used in future screening plans in an effort to find pancreatic cancer earlier.

Keywords: Diabetes mellitus, pancreatic steatosis and pancreatic cancer.

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Introduction:

Since the 1990s, pancreatic cancer incidence has increased (**1**). Early detection of pancreatic cancer is essential because 90% of pancreatic cancer patients are terminal at the time of diagnosis, it is necessary to reduce the burden of this illness (**2**).

A meta-analysis of 35 cohort studies found that people with prevalent diabetes had a 1.9-times higher incidence of pancreatic cancer than those without diabetes (**3**).

Later, a Mayo Clinic study showed that incident diabetes—not all types of diabetes may be an indicator of pancreatic cancer. Patients with pancreatic cancer and matched controls had their temporal fasting plasma glucose profiles created over a period of 60 months. According to the study, hyperglycemia started to develop 30–36 months before pancreatic cancer was discovered, and it reached the diabetic threshold 6–12 months before cancer was discovered. Additionally, fasting plasma glucose levels increase with tumor volume, with 1.1–2.0 mL (considerably less than the average tumor volume) being the smallest tumor volume associated with hyperglycemia at pancreatic cancer diagnosis of 11.5 mL) (**4**).

Relation between pancreatitis and pancreatic steatosis:

The loss of function that results from -cell lipotoxicity and lipoapoptosis may be a result of pancreatic lipomatosis. Pancreatic steatosis differs from liver steatosis in that it is histologically distinct from the liver, where triglyceride accumulation is largely intracellular, and marked by an increase in adipocytes. However, intracellular fat buildup in acinar and islet cells can be observed by

electronic microscopy or immunohistochemistry and may take place prior to adipocyte infiltration. Adipocytes may influence the function of acinar and islet cells via a paracrine action, but intracellular lipids may produce lipotoxicity and subsequently injury to islet or acinar cells, despite the clinical importance of intracellular vs extracellular triglycerides being uncertain (**5**).

Relation between diabetes mellitus and pancreatic steatosis

Chronic hyperglycemia and issues with the metabolism of proteins, fats, and carbohydrates are hallmarks of the metabolic condition diabetes mellitus, which has several underlying causes. Diabetes, which accounts for more than one-third of all kidney disease patients who are on dialysis, is the main factor that leads to renal failure. Type 1 or type 2 insulin secretion issues, or a combination of these issues, are the root cause. (**6**).

Egypt according to the International Diabetes Federation (IDF), is one of the top 10 countries in the world for the number of diabetes patients. The Middle East and North Africa (MENA) region is expected to see a 96% increase in the number of diabetic patients between the years 2013 and 2035, or from 34.6 million to 67.9 million (**7**).

In Egypt, persons between the ages of 20 and 79 have a diabetes prevalence of approximately 15.56%, and the disease accounts for 86,478 deaths each year. In Egypt, the IDF calculated that 2.2 million people had pre-diabetes and 7.5 million persons with diabetes in 2013 (**8**).

Furthermore, according to **Jain and Saraf (9)** 43% of Egyptians with diabetes and the majority of those with pre-diabetes are probably undiagnosed. The dramatic rise in diabetes prevalence in Egypt from around 4.4 million in 2007 to 7.5 million in 2013 over a very short period of time is concerning. By 2035, it is anticipated that this figure would increase to 13.1 million.

Etiology and varieties

Type 1, type 2, gestational diabetes, and "other specific types" are the four major Types of Diabetes Mellitus Classifications (**10**).

Type 1:

Insulin insufficiency in type 1 diabetes mellitus is brought on by the loss of the insulin-producing beta cells in the pancreatic islets of Langerhans. Subtypes of this class include idiopathic and immune-mediated subtypes. The majority of type 1 diabetes cases are immune-mediated, in which beta cells and subsequently insulin are killed by an autoimmune attack mediated by T cells. It causes about 10% of cases of diabetes mellitus in North America and Europe. Most affected people are often healthy and at a healthy weight when symptoms first arise. Especially early on, insulin sensitivity and response are frequently normal. Even though type 1 diabetes can affect both adults and children, it was historically known as "juvenile diabetes" since most cases of diabetes affect youngsters (**11**).

Type 2:

Type 2 diabetes has two characteristics, including insulin resistance and perhaps decreased insulin production. The reduced sensitivity of physiological tissues to insulin is thought to be caused in part by the insulin receptor. However, the specific problems are not known. The most common form of diabetic mellitus is type 2 DM. Reduced insulin sensitivity is the main characteristic in the early stages of type 2. Various techniques and drugs that increase insulin sensitivity or lessen the liver's synthesis of glucose can be used to treat high blood sugar at this stage (**10**).

Genetics and Type 2 diabetes is primarily brought on by lifestyle decisions.

Numerous lifestyle factors, including obesity (defined as a body mass index of greater than 30), are known to have an impact on type 2 diabetes 30), inactivity, poor food, stress, and urbanization (**12**).

Dietary elements affect the likelihood of getting type 2 DM as well. The kind of lipids consumed matters as well because polyunsaturated and monounsaturated fats reduce risk while trans fatty acids and saturated fats increase it. 7% of instances are thought to be caused by inactivity (**13**).

Gestational diabetes:

Pregnancy-related diabetes mellitus (GDM) shares characteristics with type 2 diabetes mellitus (DM), including a combination of relatively insufficient insulin secretion and responsiveness. It happens in 2-10% of pregnancies and may become better or go away after birth. But after giving birth, type 2 diabetes is typically discovered in 5–10% of women who had gestational diabetes. Although completely manageable, gestational diabetes needs close medical monitoring the entire time. According to the National Diabetes Clearinghouse (**14**), management options involve dietary modifications, glucose testing, and in rare cases circumstances, the use of insulin.

Other types:

Congenital diabetes, which results from genetic problems in insulin production, cystic fibrosis-related diabetes, steroid diabetes brought on by large doses of glucocorticoids, and various types of monogenic diabetes are further types of diabetes mellitus. As the underlying processes of Alzheimer's disease may involve insulin resistance by the brain, "type 3 diabetes" has been proposed as a label for the condition (**15**).

Pathophysiology:

The main hormone, insulin, controls how much glucose enters most of the body's cells, including the liver, muscles, and adipose tissue. Therefore, all types of diabetes mellitus are primarily caused by a lack of insulin or by the insensitivity of its receptors **(10)**.

The three primary sources of glucose for the body are gluconeogenesis, which is the body's process for generating glucose from non-carbohydrate substrates, intestinal absorption of food, and the breakdown of glycogen, the liver's stored form of glucose. Insulin is necessary to keep appropriate blood glucose levels. Insulin can hasten the process of gluconeogenesis, the uptake of glucose into fat and muscle cells, and the storage of glucose as glycogen (**10**).

The pancreatic islets of Langerhans contain beta cells, sometimes referred to as -cells, which release insulin into the blood in response to elevated blood glucose levels, typically following meals. Insulin is used by almost two-thirds of all body cells to remove glucose from the circulation for use as fuel, as a building block for other molecules that are required, or for storage. As a result of lower blood glucose levels, the beta cells produce less insulin and glycogen breaks down into glucose. Glucagon, a hormone that competes with insulin for blood sugar control, is primarily responsible for controlling this process (**16**).

Glucose won't be adequately absorbed by the body's cells that require it, and it won't be properly stored in the liver and muscles if there isn't enough insulin available, the cells don't respond well to insulin's effects (insulin resistance or insulin insensitivity), or the insulin is defective. Inadequate protein synthesis, persistently increased blood glucose levels, and other metabolic abnormalities such acidosis are the end results (**10**).

When the blood glucose level stays high for an extended period of time, the

kidneys approach a reabsorption threshold and glucose is expelled in the urine (glycosuria). As a result, there is a rise in the osmotic pressure of the urine, increased polyuria, and greater fluid loss because the kidneys are unable to reabsorb water. Dehydration and increased thirst (polydipsia) are brought on by the body's osmotic replacement of lost blood volume with water stored in body cells and other compartments (**17**).

Pancreatic steatosis and diabetes mellitus are related:

A subtype of pancreatic steatosis known NAFPD, short for non-alcoholic fatty pancreas disease has received more attention as the prevalence of obesity and the metabolic syndrome has increased. NAFPD raises the risk of diabetes, b-cell malfunction, and insulin resistance (IR).3,4 However, it is still unclear how common NAFPD and T2DM are and how they develop in people. In all ethnic groupings, Diabetes is a pathophysiological component that is caused by IR.

However, a prior study revealed shows even at lower BMI levels, South Asians have a higher predisposition for IR. The fact that South Asians may be a contributing factor to this finding have more visceral fat deposited in their bodies than Caucasians. Furthermore, in a given BMI, Asian diabetes Patients from countries like China are more likely than Westerners to develop ectopic fat deposition. Research on the lipid profile of NAFPD and T2DM in Chinese populations may be helpful to better comprehend interethnic discrepancies (**18**).

In order to keep obese patients' normal glucose homeostasis, insulin secretion rises concurrently with insulin resistance; however, patients who are predisposed to diabetes are unable to sufficiently offset the higher insulin needs (**19**).

Insulin resistant individuals may not be able to type 2 diabetes mellitus as a result of fat accumulation in the pancreatic islets, which causes a decrease in insulin secretion, in order to satisfy the rising demands of insulin. Additionally, higher pancreatic fat proportions were associated with higher insulin levels in obese non-diabetic subjects. According to estimates, pancreatic cell damage is visible for more than ten years before diabetes is identified (**20**), suggesting that diminished -cell function may take time to show the harmful effects of pancreatic fat buildup.

An important group of organic compounds known as lipids can be divided up even further into several classes and subclasses. These molecules are essential for storing energy and the primary building blocks of biological membranes. Lipids are also important messenger molecules. Lipids may act as IR mediators, according to prior research (21).

Lipid profile modification can be a biomarker for specific diseases and a disease predictor development in the future because it can occur before the beginning of diseases as well as as a result of them. As of now, Through research on ectopic fat deposition and T2DM, the potential disease biomarkers PC, PE, Cer, PI, and TAG have been found lipidomics study of human plasma (**22**). By utilizing the analytical strength of MDMS-DL19, which successfully separates different types enables the quantitative and qualitative study of lipids individually, Net and Han (**23**) combined lipidomics with clinical research.

According to reports, plasmalogens negatively correlated with obesity, prediabetes, likewise type 2 diabetes. The two most typical kinds of plasmalogen are pPC and pPE. Although the precise roles of plasmalogens are still unknown, it has been shown that they can shield

mammalian cells from reactive oxygen species' (ROS) harmful effects (**24**).

As peroxisomes are crucial for lipid metabolism and ROS control, their malfunction can exacerbate dyslipidemia. Similar results emerged from the examination of plasma pPC classes. It is generally known that plasmalogens are natural defenses against ROS. Alterations in plasmalogen homeostasis may worsen mitochondrial dysfunction and free fatty acid accumulation, which may increase the level of ROS. Through a variety of intracellular mechanisms that are sensitive to stress, oxidative stress would lead to IR. When ROS attack and cleave the vinyl lipid peroxidation products, such as 4-hydroxyalkenals, are formed when plasmalogens' sn-1 positional ether bond is broken. A sensitive indicator of lipid peroxidation called 4-hydroxyalkenals may show how much oxidative stress is present in the body (25). More proof shows the relationship between decreased levels of lysoPE and lysoPC and metabolic illnesses was found by **Tonks et al. (22**) who also found a decrease in lysoPE and lysoPC levels in these individuals' plasma.

According to **Wang et al.** (**26**) Type 2 diabetic mellitus (DM2) newly diagnosed patients had considerably more pancreatic fat than those without fatty pancreas, who also have a higher chance of developing diabetes. Reduced insulin production and a rise in the formation of DM2 are the results of pancreatic islets cell fat infiltration. Type 2 diabetes mellitus and widespread atherosclerosis are substantially more likely to occur when there is >25% pancreatic fatty infiltration.

In addition to earlier research, Lin et al. (27) identified additional T2DM-related lipid biomarkers and offer the justification for clarifying the connection between NAFPD and T2DM in terms of lipids. In this study, multi-dimensional mass spectrometry-based shotgun lipidomics (MDMS-SL) was used to assess the potential discriminating lipid profile of the fasting plasma of 105 Chinese people (39 NAFPD patients, 38 T2DM patients, and 30 healthy controls). The findings indicated elevated oxidative stress and peroxisomal dysfunction in the patients as evidenced by a significant rise in 4-hydroxynonenal and a striking decrease in plasmalogen in the two diagnostic groups. The lipidomics data were subjected to a multivariate statistical analysis, and 60 distinct metabolites were discovered. A metabolic network developed using IPA predictions and Ingenuity pathway analysis (IPA) results also revealed a relationship between disease progression and lipid metabolism, molecular transport, carbohydrate metabolism, and small molecule biochemistry. Our findings showed that NAFPD is a pathogenetic predictor of T2DM, not a bystander, and lipid biomarkers can predict the sneaky development of T2DM.

Relation between pancreatic cancer and pancreatic steatosis

Everyone working in the field of pancreatic cancer, including clinicians, researchers, and patients most significantly, must overcome significant obstacles. Patients typically present with vague symptoms in a clinical environment, such as abdominal pain, nausea, or weight loss. The symptoms of other pancreatic illnesses, such as diabetes mellitus and pancreatitis, which can either mimic or occur before the diagnosis of pancreatic cancer, make it more difficult to make an accurate diagnosis of pancreatic cancer. Consequently, a third of individuals had locally invasive progressed illness at the time of diagnosis, and nearly 50% have metastatic disease. 90% of people who receive a diagnosis of pancreatic ductal

adenocarcinoma (PDAC) die from the condition (**28**).

Guidelines still prescribe upfront surgery for the small percentage of patients (10–20%) who present with conditions that can be treated locally (29). However, the National Comprehensive Cancer Network's (NCCN) Clinical Practice Guidelines in Oncology (30) recommended NAT for patients who had borderline resectability and took into account NAT in resectable patients.

The removal of pancreatic cancer through surgery is thought to need the highest level of surgical skill and perioperative intensive care experience. Because of Perioperative mortality in pancreatic surgery is now only approximately 3-4% in advanced patients, which is still in line with surgical perioperative mortality as a whole. Although, hospitals that perform fewer than five pancreatic resections annually have reported fatality rates as high as 16.5%. Patients get chemotherapy treatment in both the curative adjuvant and palliative settings (**31**).

Although Tuveson and **Clevers** (**32**) have fought pancreatic cancer for many years and have improved our understanding of its pathology, no effective treatment, particularly for advanced stages, has been discovered. In order to develop more effective, tailored treatments, contemporary modeling More and more aspects of cancer, such as tissue environment crosstalk, are being addressed by systems.

Epidemiology:

Pancreatic cancer is becoming more common and is killing more people worldwide. A 2.3-fold rise since 1990, 448,000 cases (232000 in males) were reported in 2017. Likewise, from 196 000 to 44 1000, pancreatic cancer fatalities climbed 2.3-fold. A expanding and aging population as well as an increase in the incidence of risk factors for pancreatic cancer are the most likely causes of this trend. It's interesting to see that rich nations have a higher occurrence. Ages 65–69 for men and 75–79 for women are the peak ages for disease incidence (**33**).

In the US, pancreatic cancer only ranks ninth for women and tenth for men overall, but it is the fourth leading cause of cancer-related fatalities for both sexes. Furthermore, according to projections, pancreatic cancer would rank second in terms of cancer-related fatalities by 2030, surpassing colorectal, prostate, and breast cancer (**34**).

Risk factors for pancreatic cancer include smoking, high fasting glucose/Diabetes mellitus, obesity, and familial predisposition (lifetime relative risk up to 50 compared to normal population). Another connection between pancreatic cancer risk and to environmental toxin exposure. The majority of them are insecticides, namely pendimethalin and EPTC (**35**).

Furthermore, there is evidence that exposure to heavy metals like nickel increases the risk of pancreatic cancer, even if the observed effect is not consistently present across all trace elements. Lead, chromium, and nickel exposure were found to cause KRAS mutations in pancreatic cancer to occur more frequently (**36**).

Pancreatic steatosis and pancreatic cancer are related:

As a result of research showing that pancreatic steatosis is highly linked in resection specimens with precancerous pancreatic intraepithelial neoplasia (PanIN) lesions, it has recently attracted significant new interest in the pathophysiology of PDAC stands for pancreatic ductal adenocarcinoma. Pancreatic steatosis is a word used to

describe the buildup of fat in the pancreas caused by a variety of etiologies, much like PDAC. Additionally, it has a favorable correlation with diabetes mellitus (DM), age, and obesity (**37**).

Obesity and some aspects of the metabolic syndrome are known variables that can cause pancreatic steatosis which is a condition that can lead to acute pancreatitis. Acute pancreatitis of any origin that affects the fatty pancreas is typically intensely painful and has a significant risk of progressing to subclinical chronic pancreatitis (**38**).

A higher risk of developing pancreatic cancer is independently linked to having a fatty pancreas. Pancreatic cancer is made more deadly and spreads more quickly to PS's change of the tumor's microenvironment. Patients who get cancer in a pancreas without steatosis fare worse than those with increased pancreatic fat. Cell damage and the development of pancreatic cancer may be caused by chronic inflammation and excessive fat accumulation (39).

However, **Fujii et al. (38)** found that neither pancreatic cancer nor chronic pancreatitis are associated with fatty pancreas. The outcomes of NAFLD patients with pancreatic cancer were worse than those of NAFLD-free patients, demonstrating a positive association between NAFLD and pancreatic cancer in these patients. Similar to NAFLD-related liver cancer, NAFPD-related pancreatic cancer develops through a similar mechanism development.

Research on the natural history, long-term effects, and relationship between pancreatic steatosis and the metabolic syndrome has emerged as a result of the increased incidence of obesity, with an estimated global prevalence of 39% at present (World Health Organization (40)).

Additionally, the attenuation of the pancreas is connected to these clinical alterations on computed tomography (CT), which **Fukuda et al**. (41) have shown to be a significant and independent driver of PDAC.

According to **Pinnick et al**. (**42**)'s research, a low pancreas-to-spleen ratio on a CT scan is a reliable indicator of PDAC and can be utilized as an imaging characteristic to find the disease. This investigation was carried out, nevertheless, after PDAC had already been identified as a disease. Pancreatic steatosis can be caused by fatty infiltration brought on by obesity and metabolic syndrome as well as by tumor ductal obstruction leading to acinar cell death with fatty replacement, but the predominant pattern and time course of changes in the pancreas' CT-attenuation during the development of PDAC are still unknown. In another study, steatosis of the pancreas on CT for various benign conditions was examined, and it was seen in 30-51% of persons (43).

Aging, obesity, and diabetes mellitus are all positively correlated with PDAC and pancreatic steatosis. There is a dearth of information on the precise role that steatosis plays in the emergence the PDAC. Pancreatic steatosis is believed to be a complication of PDAC or to play a distinct role in the oncogenesis of PDAC, as it is caused by acinar cell loss and fatty replacement brought on by ductal tumor obstruction (44).

Rebours et al. (37) screened 110 resected pancreas samples for minor benign neuroendocrine tumors. More than half of the specimens (65%) had PanIN, which was unrelated to age or DM and highly linked with pancreatic fatty infiltration, particularly intralobular. PanIN and pancreatic steatosis were discovered to be substantially linked with obesity, subcutaneous and visceral fat. It is

suggested that pancreatic steatosis developed prior to the development of PanIN since pancreatic infiltration of fat was discovered throughout the pancreatic specimen in addition to around the PanIN lesion. Additionally, it has been demonstrated that pancreatic steatosis increases the lethality of PDAC and may promote lymphatic tumor diffusion in addition to being a risk factor for PDAC. Increased adipocyte infiltration compared to controls, entering the pancreatic tissues of PDAC patients has been seen in a recent pathology-based case-control research, independent of factors like diabetes and obesity **(45)**.

Rebours et al. (37) demonstrated a correlation between the location of the malignant lesion and the extent and degree of fat infiltration, a correlation that our small sample size prevented us from confirming. **Amin et al. (46)** showed that the abnormal fat infiltration seen in the pancreas is closely related to P/S ratio and P - S attenuation difference.

Hoogenboom et al. (47) It was looked into if in patients with probable pancreatic cancer, pancreatic steatosis on a CT scan is an indication of the illness at an early stage. In conclusion, pancreatic steatosis seen on CT up to three years before the clinical diagnosis is independently related with PDAC in overweight patients. Recognizing the imaging features of pre-diagnostic PDAC is essential for enhancing early detection and survival. After PDAC screening, individuals with this unique imaging feature may be used to stratify their risk of developing PDAC because PDAC screening is only advised in high-risk patients.

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