Nanotechnology Role in Acute Pancreatitis

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Abstract

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas with a wide clinical spectrum ranging from mild, self-limiting symptoms to severe necrotizing disease with multi-organ failure. It remains a significant health burden globally, commonly triggered by gallstones and excessive alcohol intake. Pathophysiologically, AP arises from premature activation of pancreatic enzymes, particularly trypsin, leading to autodigestion, inflammation, and tissue damage. Despite advancements in understanding its etiology and pathogenesis, specific treatments for AP remain limited, with current management focused on supportive care. In recent years, nanotechnology has emerged as a promising approach for improving diagnostics and therapeutics in numerous biomedical applications, including AP. Nanoparticles possess unique physicochemical properties that enhance drug solubility, bioavailability, and targeted delivery, minimizing systemic toxicity. Furthermore, nano-antioxidants such as selenium nanoparticles have demonstrated potential in mitigating oxidative stress, a key contributor to pancreatic injury. Nanotechnology enables innovative strategies for early detection, controlled drug delivery, and modulation of inflammatory responses in AP. This review highlights the pathophysiology and clinical implications of AP and explores the expanding role of nanotechnology in enhancing diagnostic accuracy and therapeutic efficacy. Emphasis is placed on the mechanisms through which nanoparticles exert protective effects on pancreatic tissue and their potential integration into standard clinical practice. Continued research into nano-based interventions offers promising prospects for the development of targeted, efficient, and less invasive treatment modalities for acute pancreatitis.

Keywords: Pancreatitis, Nanotechnology, review.

Review of literature

Etiology of acute pancreatitis: Gallstone impaction in the common bile duct, which stops pancreatic enzymes from moving through the ampulla of Vater, is the most prevalent cause of acute pancreatitis (gallstone pancreatitis). Pancreatitis from excessive alcohol usage is the second most frequent cause. Gallstones and drunkenness are often responsible for 60–75% of cases of acute pancreatitis [(1)].

The following are some potential causes of acute pancreatitis [(2)]: Obstruction of the pancreatic duct that is not connected to gallstones (for example, because of biliary sludge, pancreatic divisum, parasites, especially Fasciola and Ascaris lumbricoides, or pancreatic cancer or other periampullary neoplasms). Drugs including sulfonamides, steroids, hormone replacement therapy, metronidazole,

azathioprine, mercaptopurine, salicylates, anti-convulsants, diuretics, and amino acids like cerulein and L-arginine.

Viral infections brought on by the coxsackievirus, CMV, or mumps virus. Metabolic conditions, such as hyperparathyroidism, hypertriglyceridemia, and other hypercalcemic conditions. Ischemia brought on by shock, vasculitis, embolism, or vascular thrombosis.
• In patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), both blunt force and iatrogenic trauma occurred during surgery or endoscopy [Post-ERCP pancreatitis] [(2)].

Germline mutations in the genes encoding pancreatic enzymes or their inhibitors may cause acute pancreatitis. Recurrent bouts of acute pancreatitis, usually beginning in infancy, are a hallmark of hereditary pancreatitis, a rare autosomal dominant illness with an 80% penetrance rate [(3)].

Changes in the PRSS1 gene, which codes for trypsinogen, the precursor to the pancreatic enzyme trypsin, are among these germline mutations. The method by which trypsin cleaves and inactivates itself is disrupted by pathogenic mutations, removing a crucial negative feedback loop. In addition to causing excessive trypsin activation, this deficiency causes other digestive enzymes that depend on trypsin for activation to become hyperactive. The pancreas becomes susceptible to injury and autodigestion as a consequence of the unchecked protease activity that results. Hereditary pancreatitis is less often linked to loss-of-function mutations in genes that encode protease inhibitors, such as SPINK1 [(4)].

Idiopathic pancreatitis, in which no apparent etiology can be found, accounts for 10% to 20% of cases. With symptoms mostly limited to the pancreas, there is growing evidence that many of these instances may have a genetic basis, such as germline mutations in the CFTR gene [(5)].
Pathogenesis: Abnormally activated pancreatic enzymes cause the pancreas to self-digest, which results in acute pancreatitis. Trypsin has the ability to change other pancreatic enzyme zymogen forms into their active forms after it has been activated. Tissue damage and inflammation may result from the premature activation of trypsin in the pancreatic material, which can release proenzymes such phospholipases and elastases. Additionally, trypsin transforms prekallikrein into its active form, which initiates the kinin system. Additionally, it activates the coagulation and complement systems by activating factor XII (Hageman factor)[(6)].

•Routes Through Which Enzymes Activate in Acute Pancreatitis: Three mechanisms might cause the first activation of enzymes that may lead to acute pancreatitis, according to Kumar et al. [(1)]:
1. Obstruction of the pancreatic duct: Extrinsic compression of the ductal system by a mass, such as gallstone or biliary sludge impaction, prevents ductal flow, raises intraductal pressure, and permits the buildup of an interstitial fluid rich in enzymes. Local fat necrosis might occur because lipase is secreted in an active state. Then, via a leaky microvasculature, injured tissues, periacinar myofibroblasts, and leukocytes produce proinflammatory cytokines that increase local inflammation and interstitial edema, which further impairs local blood flow, leading to ischemic damage to acinar cells and vascular insufficiency.

2. Primary acinar cell injury: Acute pancreatitis caused by drugs, viral infections, ischemia, and direct damage to the pancreas all include this pathogenic route.

3. Inadequate proenzyme intracellular transport in acinar cells: After being synthesized in the endoplasmic reticulum, hydrolytic enzymes bound for lysosomes and digesting enzymes meant for zymogen granules

(and eventual extracellular release) are transported via different routes in healthy acinar cells. However, lysosomal hydrolases and pancreatic proenzymes are bundled together in several animal models of metabolic damage. This results in the localized release of active enzymes, phospholipase-induced lysosomal rupture, and proenzyme activation.

There are many ways that drinking alcohol might cause pancreatitis. It causes the sphincter of Oddi to constrict and briefly increases pancreatic exocrine secretion. Alcohol also causes oxidative stress, which weakens cell membranes, and other direct harmful effects on acinar cells. Additionally, long-term alcohol use encourages the production of pancreatic fluid that is high in protein, which leads to the development of thick protein plugs that block tiny pancreatic ducts [(7)].

Pathological changes: According to Kumar et al.[(1)], the main alterations seen in acute pancreatitis are:
•Microvascular leakage that causes edema.

•Lipases-induced fat necrosis.

• An immediate inflammatory reaction.

• Damage to the pancreatic parenchyma caused by proteolysis.

• Blood vessel damage that results in interstitial hemorrhage.

Mild types include localized areas of pancreatic and peripancreatic fat necrosis and interstitial edema. Fatty acids are generated as enzymes break down fat cells, and when they combine with calcium, they produce insoluble salts that precipitate on the spot [(8)].

In more severe types, including acute necrotizing pancreatitis, blood vessels and acinar and ductal cells are impacted. Macroscopically, the pancreas exhibits reddish-black hemorrhagic areas interspersed with foci of yellow-white, chalky fat necrosis. Furthermore, fat necrosis may occur in fat beyond the abdominal cavity, such as subcutaneous fat, and extrapancreatic fat, such as the omentum and intestinal mesentery. Globules of fat from enzymatically broken-down adipose tissue are usually seen in the peritoneum as a serous, somewhat turbid, brown-tinged fluid [(9)].

Hemorrhagic pancreatitis, the most severe kind of pancreatitis, is characterized by extensive parenchymal damage and diffuse bleeding inside the gland's contents [(10)].

Clinical features: The primary sign of acute pancreatitis is abdominal discomfort. From moderate and unpleasant to severe and incapacitating, its intensity varies. According to Portelli and Jones [(11)], 20% of patients have severe acute pancreatitis that is accompanied by multi-organ failure, with a death incidence of up to 40%. The other 80% of cases are mild and self-limiting.
A severe case of acute pancreatitis is a serious medical emergency. An "acute abdomen" with discomfort, guarding, and the unsettling lack of bowel noises is often experienced by those who are affected. The discomfort is often severe, persistent, and localized to the upper back [(3)].

The systemic release of digestive enzymes and the rapid initiation of the inflammatory response are responsible for the symptoms of severe acute pancreatitis. Leukocytosis, disseminated intravascular coagulation, diffuse fat necrosis, and acute respiratory distress syndrome brought on by diffuse alveolar injury may all be seen during the first clinical assessment. Increased microvascular permeability and the ensuing hypovolemia may induce peripheral vascular collapse or shock to occur quickly. Endotoxemia,

which results from the collapse of the barriers between the circulation and the gut flora, and renal failure brought on by acute tubular necrosis exacerbate this [12].

Laboratory investigations: The main method of diagnosing acute pancreatitis is ruling out other possible reasons for stomach discomfort. blood lipase levels rising between 72 and 96 hours after markedly high blood amylase levels during the first 24 hours are diagnostic of acute pancreatitis. In regions of fat necrosis, calcium precipitation may result in hypocalcemia; if this condition continues, it suggests a bad prognosis. Magnetic resonance imaging (MRI) or computed tomography (CT) may be used to identify the enlarged, inflammatory pancreatic [13].

About 5% of individuals with acute pancreatitis die from shock during the first week of their illness, while the majority of patients recover over time. Serious side effects include acute respiratory distress syndrome and severe renal failure. Pancreatic pseudocysts or sterile or infected abscesses are among the sequelae that may occur in individuals who survive [1].

Chronic pancreatitis, which affects 20% of people with acute pancreatitis, may develop over time from recurrent episodes of acute pancreatitis, independent of the cause. This is characterized by chronic inflammation, fibrosis, and scarring that finally results in the loss of the islets of Langerhans and permanent exocrine pancreatic damage. Clinical manifestations include diabetic mellitus (caused by islet cell loss) and chronic malabsorption (caused by pancreatic exocrine insufficiency)[14].

Acute pancreatitis currently has no known particular therapy. The primary strategy is supportive treatment, which includes controlling blood pressure and using both non-opioid and opioid drugs to reduce pain. It is crucial to fully limit meals and drinks in order to relax the pancreas. Gram-negative bacteria from the gastrointestinal tract infect the necrotic tissue in 40–60% of instances of acute necrotizing pancreatitis, making the illness even more complicated [15].

Numerous experimental investigations have demonstrated that important pro-inflammatory cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) as well as oxygen-derived free radicals are responsible for tissue damage in acute pancreatitis. Thus, via antioxidative processes, the use of antioxidant medicines in the treatment of acute pancreatitis may help lessen oxidative cell damage in the pancreas. Selenium nanoparticles are one popular antioxidant [16–18].

Nanotechnology: Emerging technologies known as "nanotechnology" work with matter at the nanoscale to produce materials and gadgets with special qualities. According to Nasrollahzadeh et al. [19], the word "nano" is derived from the Greek word meaning "very small," with one nanometer being equivalent to one billionth of a meter.

Richard Zsigmondy, the 1925 chemistry Nobel Prize Laureate, was the first to use a microscope to measure particle sizes and came up with the name "nanometer" for this purpose. However, because of his talk on atomic-level matter manipulation, physics Nobel laureate Richard Feynman is considered the founder of contemporary nanotechnology. Fifteen years after Feynman's talk, Japanese physicist Norio Taniguchi came up with the name "nanotechnology" itself [20].

When Japanese scientist Iijima created carbon nanotubes in the 1980s, it marked the beginning of the golden age of nanotechnology. However, interest in nanotechnology really took off in the early years of the twenty-first century. One of the most promising areas of science and technology now is nanotechnology, and nanomaterials are expected to be essential to improving human lives soon [21].

There are two methods for creating nanomaterials: top-down and bottom-up. Using physical, chemical, or thermal processes, materials are reduced from a larger, macroscopic size to the nanoscale scale in the top-down method. The bottom-up method, on the other hand, assembles structures at the nanoscale by building them atom by atom or molecule by molecule. Although nanomaterials may take many different forms, such as nanoparticles, nanocages, nanobelts, nanofibers, and nanocrystals, only nanoparticles are commercially significant [(22)].

Because of their high surface-to-volume ratio, which influences optical, electrical, chemical, and mechanical properties and increases reactivity, nanoparticles have special physico-chemical features that set them apart from bulk materials. According to Afolalu et al.[(23)], they are divided into metallic nanoparticles, metal oxide nanoparticles, organic polymers, quantum dots, and carbon-based nanostructures.

Several methods, such as transmission electron microscopy and scanning electron microscopy, which assess morphology, size, and surface composition using a focussed electron beam, are used to characterize nanoparticles based on their morphology, size, and surface charge. Other methods include X-ray diffraction, a crucial technique for examining the structure, physical characteristics, and chemical makeup of nanomaterials, especially in powder form, and dynamic light scattering, which establishes the size distribution of particles in a suspension [(24)].

Numerous sectors may benefit from the use of nanotechnology. It operates in the fields of electronics, space exploration, transportation, energy and the environment, and, finally, health and medicine [(25)].

Using constructed nanodevices to monitor, repair, and regulate biological systems at the molecular level is known as nanomedicine, or the use of nanotechnology in health. Early, precise diagnosis and therapy with little adverse effects are its objectives [(26)].

Protein detection, gene therapy, vaccines, stem cell therapy, nanodiagnostics, early cancer diagnosis and treatment, tissue engineering, drug delivery, protein detection, gene therapy, vaccines, and nano-antioxidants are some of the applications of nanomedicine [(27)].

One important use of nanomedicine is targeted medication delivery. Reduced degradation, increased solubility, decreased systemic toxicity, and increased clinical efficacy are just a few advantages of using nanomaterials into medication formulations. Because of their tiny size, huge surface area, and structural stability, nanoparticles have a number of benefits as a drug delivery mechanism. Their compact size guarantees accurate medication intracellular absorption into specific cells, increasing its efficacy. According to Ílem-Özdemir et al.[(28)], nanoparticles' enormous surface area enables them to transport significant quantities of the medicine, and their structural stability guarantees effective delivery without degradation before reaching the target location.

Despite the body's natural barriers, nanoparticles may readily pass through cell walls, blood vessels, stomach epithelium, and blood-brain barriers. Because of their robust interactions with biomolecules, Sandhir et al. [(29)] emphasized the potential of antioxidant-active nanoparticles as a novel class of antioxidant therapeutics (nano-antioxidants), able to both prevent and cure disorders associated with oxidative stress. Additionally, their formation as nanoparticles will increase their efficacy since they have the innate capacity to trigger free radical scavenging activity [(30)].

The antioxidant activity of many nanoparticles, such as copper oxide, starch-assisted silver, and gold nanoparticles, has been assessed in earlier research, demonstrating their capacity to scavenge free radicals. As for the thyroid gland, liver, and brain, further research revealed that selenium nanoparticles have clear antioxidant action [(31)].

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