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The Role of Nanomaterials in the Diagnosis and Treatment of Acute Pancreatitis

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Aim: to show the clinical significance of nanomaterials in the diagnosis and treatment of acute pancreatitis.
Key points. It was possible to develop nanomaterials that improved the sensitivity of laboratory tests and the resolution of magnetic resonance imaging in the diagnosis of acute pancreatitis. The use of nanomaterials in the treatment of acute pancreatitis helps to relieve inflammation and reduce the degree of damage to the acinar cells of the pancreas. The use of nanoparticles can solve the problem of stable resistance of bacteria to antibacterial drugs.
Conclusion. Nanomaterials have shown high efficacy and safety in numerous *in vitro* and *in vivo* (animal) experiments in the diagnosis and treatment of acute pancreatitis.
Keywords: nanoscience, nanoparticles, nanomaterials, nanosystem, acute pancreatitis, inflammation of the pancreas
Conflict of interest: the authors declare that there is no conflict of interest.

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Роль наноматериалов в диагностике и лечении острого панкреатита

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Цель обзора: показать клиническое значение наноматериалов в диагностике и лечении острого панкреатита.
Основные положения. Удалось разработать наноматериалы, которые улучшили чувствительность лабораторных тестов и разрешающую способность магнитно-резонансной томографии в диагностике острого панкреатита. Применение наноматериалов в лечении острого панкреатита способствует купированию воспаления и уменьшению степени повреждения ацинарных клеток поджелудочной железы. Использование наночастиц может решить вопрос устойчивой резистентности бактерий к антибактериальным препаратам.
Заключение. Наноматериалы показали высокую эффективность и безопасность в многочисленных экспериментах *in vitro* и *in vivo* (на животных) в диагностике и лечении острого панкреатита.
Ключевые слова: нанонаука, наночастицы, наноматериалы, наносистема, острый панкреатит, воспаление поджелудочной железы
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Introduction

In recent years, there has been a significant increase in the incidence of acute pancreatitis (AP). According to a recent system review and meta-analysis, the overall global incidence of AP has increased by 3.07 % per year over the past 56 years, which has led to an increase in financial costs and burden on health systems in various countries [1]. The overall incidence of AP is 33–74 cases per 100,000 people per year, and the mortality rate is 1–16 cases per 100,000 people per year [2, 3]. Despite the fact that AP in most cases (80 %) occurs in a mild form, 20 % of patients develop a moderate or severe course of the disease, and mortality in this group of patients reaches 30–40 % [4].

It is known that the pathogenesis of AP is based on the following pathophysiological processes: excessive accumulation Ca^{2+} in the cell cytoplasm [5], premature intraacinar trypsinogen activation [6], mitochondrial damage [7],

endoplasmic reticulum stress [8, 9], and impaired autophagy [10]. These pathologic disorders are potential therapeutic targets for developing new drugs and studying the effects of nanomaterials.

Nanoscience studies phenomena and objects at the atomic, molecular, and macromolecular levels whose characteristics differ significantly from those of their macroanalogues. Currently, nanoparticles are widely used in medical biology. They are successfully used both in the diagnosis and treatment of various diseases. Nanoparticles used in diagnostics increase the sensitivity of imaging methods in detecting pathological changes in human organs and tissues [11]. It should be noted that nanomaterials can be used as a carrier (delivery system) for drugs in diseases of various profiles. The main advantage of a nanomaterial loaded with a drug over the usual use of a drug is that the "nanoparticle + drug" complex acts more effectively on specific target cells (for example, on tumor cells or macrophages), achieving the maximum therapeutic effect, and at the same time minimizing the side effects of the drug [12, 13]. Some nanomaterials have photodynamic or photothermal therapeutic effects and can be used in the treatment of various oncological diseases [14, 15].

The aim of this literature review is to demonstrate the clinical significance of nanomaterials used in the diagnosis and treatment of AP.

In preparing this review, we analyzed the literature sources in publications included in the scientometric databases PubMed and Scopus. Preference was given to sources published over the past ten years. Review articles and original experimental works where nanomaterials were used in the diagnosis and treatment of AP were selected for viewing.

Laboratory diagnosis of acute pancreatitis

Currently, the activity of α-amylase in both blood serum and urine is evaluated as an important biomarker for the diagnosis of AP: α-amylase is a calcium metalloenzyme present in normal human blood serum, urine, and saliva [16]. It should be noted that in 19–32 % of cases in patients with a clinical picture of AP, the level of α-amylase at the time of admission is not changed, which may be due to late testing from the onset of the disease, exocrine insufficiency — such as a manifestation of pancreatic atrophy, or hypertriglyceridemia, which can give falsely low results [17].

An important diagnostic limitation of serum α-amylase is its lack of specificity. In addition to AP, there are a number of diseases, such as acute mesenteric ischemia, acute intestinal obstruction, peritonitis, hepatitis, renal and hepatic insufficiency, diabetic ketoacidosis, and pneumonia, which can also be accompanied by an increase in serum α-amylase. The sensitivity and specificity of α-amylase as a diagnostic test for AP depends on the selected threshold value. If the threshold level is raised to 1000 IU/L (more than three times higher than the upper limit of normal), the specificity of α-amylase is close to 95 %, but the sensitivity in some studies is reduced to 61 % [17].

In this regard, the idea of developing nano-materials that would improve the performance of the α-amylase test appeared. A group of scientists from Saudi Arabia and Egypt created a special nanooptical dual-core sensor complex Pd-(2-aminothiazole) (urea) to assess the activity of α-amylase in blood serum and urine samples of patients with AP. Alpha-amylase activity measured by quenching the luminescence intensity of the nanooptical sensor binuclear complex Pd-(2-aminothiazole) (urea) at 457 nm with 2-chloro-4-nitrophenol, which is formed as a result of the reaction of the enzyme (α-amylase) with 2-chloro-4-nitrophenyl-α-d-a maltotriziod substrate (CNPG3). The study of this complex revealed that the sensitivity to detect α-amylase was 96.88 %, and the specificity was 94.41 % [18].

With the help of nanotechnology, researchers from China for the first time created a nanoprobe based on tetraphenylethylene with aggregation-induced radiation to detect α-amylase in human body fluids. A low-molecular α-amylase sensor system based on luminogens with aggregation-induced radiation (AIEgen) was used in the development of the probe. Luminogens are specific components of a luminescent substance that cause the phenomenon of luminescence. The mechanism for determining the enzyme is based on the properties of a nanoprobe, which does not emit a signal in an aqueous medium due to its good solubility, but insoluble luminogen residues are released after hydrolysis with α-amylase, significantly increasing fluorescence. Having a high selectivity to α-amylase compared to other proteins, this nanoprobe showed a rather high sensitivity and a fast detection rate (up to 3 minutes) of α-amylase, which is important in the early diagnosis of AP [19].

Lipase is also used as a biomarker for the diagnosis of AP. The level of lipase in the blood serum of an AP patient increases within 4–8 hours after the onset of symptoms, reaches a maximum

after 24 hours, and returns to normal after 8–14 days [20]. The main advantage of lipase is its high sensitivity to alcoholic AP and late clinical manifestations of the disease, which is associated with its longer presence in the blood of patients than amylase. It should be noted that an increase in serum lipase levels is not specific for AP. Inflammatory bowel diseases, diabetic ketoacidosis, mumps, hyperlipoproteinemia of types 1 and 4, acute renal failure, bone fractures, and intestinal infarction can also be accompanied by lipazemia [21, 22]. The sensitivity of lipase in the diagnosis of AP ranges from 85 to 100 % [3, 19].

A team of scientists from India has developed a selectively sensitive supramolecular self-organizing nanostructure for lipase detection using the aggregation-inducing property of naphthalene diimine (NDI). The radiation of naphthalene diimine is manifested by blue-green luminescence. This nanostructure determines the lipase content by hydrolysis of the benzyl ester bond with a detection limit of 10.0 ± 0.8 ug/L^{-1} [23]. Based on the aggregation-induced mechanism of tetraphenylethylene glutamate radiation, the latter was successfully applied to real samples of human blood serum in order to determine the level of lipase. This method is more suitable for linear determination of lipase levels in the range from 0 to 80 U/L, which corresponds to the range of lipase concentrations in human blood serum, taking into account the dilution coefficient, if necessary. The experimental results showed a high sensitivity of the method and rapid determination of lipase in blood serum [24].

Currently, trypsin is often used as a marker of AP in clinical practice [25]. Nanotechnology has enabled the development of an electrochemical nanosensor, which is a highly sensitive system for determining the level of trypsin in blood serum. The system is based on a hybrid membrane for ion permeability assessment based on anodic alumina oxide (AAO), modified with trypsin. Due to the peptide hydrolysis reaction triggered by trypsin, the electrical characteristics of the surface of the hybrid ion membrane change. The advantages of this method are simple operation, low cost, and no pre-preparation of the sample used for analysis. The lowest trypsin detection concentration can be achieved at 0.1 pM (picomol/L). In addition, the electrochemical sensor can also be used in other enzyme evaluation systems by replacing the corresponding substrates [26].

Hypertriglyceridemia is one of the possible causes of AP. It is known that the level of triglycerides in the patient's blood serum affects the severity of the disease, and its early control can improve the prognosis of AP [27]. Nanotechnology has been used to develop a sensitive electrochemical biosensor for detecting triglycerides in blood serum samples. The biosensor's operation is based on electrochemical oxidation of glycerol on glass-carbon electrodes modified with magnetic nanoparticles that are bound to the enzyme lipase and copper oxide nanoparticles that were deposited on multi-walled carbon nanotubes obtained due to pectin dispersion. Glycerol is formed by an enzymatic reaction between triglycerides present in blood samples and immobilized lipase. The proposed electrochemical biosensor improves the performance of other methods developed for the quantitative determination of triglycerides. Determination of triglycerides requires pretreatment of serum samples. The PLS-1 algorithm was used for quantitative determination of triglycerides. The sensitivity of the method was 1.64 × 10.6 aL/g^{-1}. It should be noted that the electrochemical biosensor showed good performance, reproducibility, and stability for 20 days. It can be a good alternative for determining triglycerides in clinical human serum samples [28].

Instrumental diagnosis of acute pancreatitis

The diagnosis of AP is verified by instrumental confirmation of the characteristic signs of pancreatic inflammation using such imaging methods as ultrasound (US), contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) [29]. Early diagnosis of severe AP is important not only for the choice of treatment tactics, but also for the prognosis of the disease itself. Improvement of instrumental visualization methods and increasing their sensitivity in identifying early signs of destructive AP can be achieved with the help of nanotechnologies.

To date, a special contrast agent for MRI based on gadolinium using nanoparticles (diethylenetriamine pentaacetic acid gadolinium, Gd-DTPA-FA) has been developed. Upon enzymatic hydrolysis by lipase, the fat-soluble Gd-DTPA-FA is converted to the water-soluble Gd-DTPA complex and leads to changes in the signal intensity observed in MRI *in vitro*. This nanocontrast substance has demonstrated low cytotoxicity and excellent biocompatibility in both *in vitro* and *in vivo* studies. In addition, the results of the study also showed that it is highly effective and specific for early detection of AP [30].

It should be noted that macrophages play a special role in the pathogenesis of AP. A group of scientists from China developed special mannosylated liposomes loaded with

gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), later called M-Gd-NL, which were specifically targeted at macrophages in AP. It is important to note that in a rat study using M-Gd-NL, it was possible to distinguish mild AP from severe AP by changing the MRI signal. This nanomaterial has the effect of amplifying the T1-weighted MRI signal in a lipase medium. In severe AP, the T1-weighted MRI signal was higher than in mild AP. No toxic side effects were observed in the animals. It should be noted that this study has its limitations: 1) mannose receptors are expressed not only on macrophages, but also on other cells; 2) distinguishing the severity of AP *in vivo* was performed only with M-Gd-NL, and not with Gd-NL or Gd-DTPA, due to the huge workload on AP models in rats and MRI; 3) macrophages are overexpressed in every type of inflammation, not just in AP. Consequently, mannose-coated liposomes recognize not only macrophages associated with AP, but also all other macrophages [31].

Unfortunately, unlike the widespread use of nanomaterials in the laboratory diagnostics of AP, their use in improving the visualization of instrumental methods is limited only to MRI. There are no data on improving the performance of ultrasound or computed tomography.

Treatment of acute pancreatitis

Despite numerous previous studies, it should be noted that there are still no effective and safe drugs for the treatment of AP in medicine. Thanks to advances in molecular biology, it is now known that damage to pancreatic acinar cells occurs at an early stage of AP development due to activation of the proteolytic enzyme trypsin [25]. At the same time, other damage mechanisms are also activated in parallel, such as cytokine storm, autophagy, apoptosis, and endoplasmic reticulum stress [25]. Macrophages and neutrophils recruited in the pancreatic destruction zones secrete cytokines such as IL-1β, IL-6, IL-17, and TNF-α, which disrupt oxidative homeostasis [32]. The appearance of reactive oxygen and nitrogen species further aggravates damage to pancreatic cells [33].

Cerium dioxide nanoparticles (nanocerium) are considered as the most promising inorganic antioxidants for biomedical applications. Nanocerium is a unique nanomaterial that has the properties of catalase and superoxide dismutase and is able to remove the active forms of oxygen free radicals. In experimental work on mice, nanocerium demonstrated the ability to reduce the production of reactive oxygen species and the level of pancreatic enzymes-amylase and lipase in blood serum, as well as restore the membrane potential of mitochondria and reduce the secretion of inflammatory cytokines, thus reducing the degree of damage to pancreatic cells, which was confirmed by histological examination [34, 35].

A strong endogenous antioxidant compound is bilirubin. If the level of its concentration in tissues is low, it can sufficiently reduce intracellular oxidative stress. In addition, bilirubin can have anti-inflammatory, immunomodulatory, and protective effects, as has been shown in a number of experimental studies [36–38]. Taking into account the properties of bilirubin, a group of researchers from China, using nanotechnology, developed nanoparticles that were combined with bilirubin (BRSNPs). In experimental work on mice, scientists showed that nanobilirubin (BRSNPs) showed a pronounced anti-inflammatory effect, due to a decrease in the degree of oxidative stress and a decrease in the expression of pro-inflammatory cytokines. In addition, bilirubin also showed a protective effect on the pancreatic acinar cells themselves [38].

Given that it is inflammation that plays an important role in the development of AP, suppressing the mechanisms responsible for the development of the inflammatory response may be the key to success. It is known that nuclear factor Kappa B (nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB), a universal transcription factor, plays an important role in coordinating the immune response and inflammation, and is crucial in the development of AP at an early stage [39]. Celastrol (a herbal remedy, unregistered in the Russian Federation) inhibits the activation of NF-κB, thus showing pronounced anti-inflammatory, antioxidant, and antitumor activity [40, 41].

Taking into account the properties of this compound, it was possible to develop nanoparticles containing celastrol (CLT)-loaded PEG-PLGA nanoparticles coated with neutrophilic cell membranes with a particle size of 150 nm. The main advantage of these nanoparticles is that they can easily penetrate the blood-pancreatic barrier and accumulate as much as possible in the pancreatic parenchyma. In an experimental model of AP in rats, it was proved that nanoparticles with celastrol reduce amylase, pancreatic myeloperoxidase in blood serum and the level of proinflammatory cytokines, locally and systemically. The main conclusion of the study indicates that this nanomaterial can be used in the treatment of AP [42].

Currently, nanoparticles (carbon-based nanomaterials such as fullerenes and graphene) and mesoporous materials (silicon dioxide or manganese dioxide) are widely used as carriers of drugs for the treatment of various diseases [43, 44]. A team of scientists from China has developed a special transport nanosystem — a system of carrier bubbles that contains a powdered mixture of an acid initiator (diethylenetriamine pentaacetic acid anhydride), a foaming agent (sodium bicarbonate), a surfactant (sodium dodecyl sulfate), and a poorly water-soluble drug curcumin. Thanks to this transport system, it was possible to increase the bioavailability of a poorly soluble drug in water — curcumin, when taken orally. In the intestinal lumen, this nanocarrier system with curcumin is converted into a nanoemulsion that penetrates the intestinal M-cells and is then transferred by lymph to the pancreas. The study revealed that delivery of curcumin using a nanomaterial resulted in faster relief of pancreatic inflammation in rats compared to animals treated with curcumin alone. This work has demonstrated that the use of nanocarriers in the treatment of AP can increase the bioavailability of poorly water-soluble drugs administered *per os* [45].

Progressive pancreatic inflammation can lead to necrotizing pancreatitis in 20 % of patients. It is known that 40–70 % of patients with necrotic pancreatitis are infected with necrosis zones, which causes a twofold increase in mortality [46]. Infection most often occurs with gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, or gram-positive bacteria such as *Staphylococcus aureus*, enterococci, and anaerobic bacteria [47]. It should be noted that the irrational and uncontrolled use of antibiotics in clinical practice has led to the development of stable bacterial resistance to many modern antibacterial agents worldwide [48].

Much attention is currently being paid to this issue. In order to overcome the resistance of bacteria to antibiotics, silver nanoparticles are often used, which can be obtained by physical, chemical and biological means. The biological method of synthesis using bacteria, fungi and plant extracts is simple, eco-friendly, economical and safer in comparison with physical and chemical methods that use high temperatures or toxic additives. In experimental work, it was shown that resistant bacterial resistance to silver nanoparticles rarely develops. This may be due to the simultaneous effect of several antibacterial mechanisms: 1) destruction of the bacterial cell membrane structure; 2) formation of reactive oxygen species and oxidative damage to microorganisms; 3) damage to the bacterial cell DNA [49].

It should be noted that, despite the fact that nanomaterials containing silver have a wide spectrum of action and high antimicrobial activity against *Escherichia coli, Klebsiella pneumoniae*, and *Staphylococcus aureus* [50], they have some potential for toxic damage to the eyes, skin, respiratory, nervous, hepatobiliary, and reproductive systems. The potential cytotoxicity of silver nanoparticles depends on their size, shape, and concentration, as well as on the route of administration [51]. In this regard, there is a need to conduct new research for a more in-depth assessment of the biocompatibility of nanomaterials and the production of safe silver nanoparticles for humans.

Conclusion

Acute pancreatitis is a common disease that can be life-threatening in severe cases. Early diagnosis and comprehensive treatment of patients with AP are of great importance for the prognosis of the disease. The development of various nanomaterials and their use in numerous experiments *in vitro* and *in vivo* (animals) have demonstrated high efficiency and safety in the diagnosis and treatment of AP.

However, it should be noted that the available nanomaterials are still quite far from being widely used in clinics and their potential threat to humans remains unknown. In this regard, there is a need to conduct new research to assess the compatibility and safety of these nanomaterials for humans.

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