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REVIEW

Epidemiological studies on the prevention and treatment of nonalcoholic fatty pancreatic disease

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Abstract:
Nonalcoholic fatty pancreatic disease (NAFPD) has an incidence of 11.05%–69.7%. Owing to the lack of standardized screening tools, the prevalence of NAFPD widely varies among studies depending on the ethnic groups analyzed and the different diagnostic methods adopted. Obesity is a chronic disease attributable to multiple psychosocial factors, and its prevalence has reached epidemic proportions worldwide, showing doubling in the last 3 decades. Obesity is closely associated with conditions such as hyperlipidemia, type 2 diabetes mellitus (T2DM), cardiovascular disease, metabolic syndrome, and cancer. Diet and exercise are the central components of NAFPD prevention and treatment, whereas the progress in pharmacologic treatment has been lagging. Studies have demonstrated that glucagon-like peptide-1 (GLP-1) can lower blood glucose, and also has effects of reducing body weight and the risk of cardiovascular disease. Thus, the role of GLP-1 in T2DM and NAFPD warrants further investigations.
Key Words: nonalcoholic fatty pancreatic disease, epidemiology, prevention, treatment.

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***Abbreviations*:** NAFPD, Nonalcoholic fatty pancreatic disease; T2DM, type 2 diabetes mellitus; GLP-1, glucagon-like peptide-1; CI, confidence interval; OR, odds ratio; GLP-1, glucagon-like peptide-1; PSC, pancreatic stellate cell; BMSCs, bone marrow stromal cells.

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Large-sample analyses on the prevalence of nonalcoholic fatty pancreatic disease (NAFPD) are lacking. A study in China investigated a total of 4418 subjects, of whom 488 were diagnosed with NAFPD and 3930 were found not to have NAFPD (detection rate, 11.05%). Overall, there were 2287 male subjects and 2131 female subjects, with a male-to-female ratio of 1.07:1. Specifically, 1433 subjects were aged < 45 years and 1492 subjects were aged 45–54 years. The number of male subjects was higher than that of female subjects in these 2 age groups ($P < 0.05$). In addition, 1493 subjects were aged > 54 years, and the proportions of male and female subjects were not significantly different in this age group ($P > 0.05$). Of the 488 patients with NAFPD, 277 were men and 211 were women. The prevalence of NAFPD was higher among men than among women ($P < 0.05$). Comparisons between the age groups revealed that in the < 55 years age group, the prevalence of NAFPD in men was higher than that in women. However, the NAFPD prevalence increased among women aged > 55 years, indicating no significant difference in the prevalence of NAFPD between men and women aged > 55 years [1].

Definitive data on NAFPD prevalence among the general population are limited because of the lack of standardized screening tools. Therefore, the prevalence of NAFPD widely varies depending on the ethnic groups analyzed and the different diagnostic methods adopted. In a study among 230 patients who underwent endoscopy in the United States, 27.8% were found to have a fatty pancreas. Wang et al. [2] reported that the prevalence of fatty pancreas in a population in China was about 2.7%. Older age, central obesity, and fatty liver disease were independent risk factors for fatty pancreatic disease. Another study in South Korea showed that the prevalence of NAFPD was up to 61.4% among 293 patients who visited an obesity clinic. By comparison, a large cohort study in Taiwan reported that the prevalence of NAFPD was 16% among 8097 subjects who underwent abdominal ultrasound as part of health checkups. The prevalence in Taiwan was similar to that reported in a Hong Kong study that employed magnetic resonance imaging (MRI) to quantify pancreatic fat content [3]. NAFPD can also occur in children. A retrospective single-center study in the United States showed that about 10% of the 232 pediatric patients aged 2–18 years who underwent abdominal computed tomography had pancreatic steatosis [4].

As with nonalcoholic fatty liver disease, the risk of NAFPD increases with age and is higher in men than in women. Saisho et al. found that pancreatic fat content linearly increased with age and reached a plateau at around age 50 years. Wang et al. [2] showed that the NAFPD prevalence was the highest among men aged 40–49 years, whereas the prevalence in women was very low among the younger age groups but rapidly increased in those after menopause. Taken together, these studies suggest that there may be sex differences in the propensity for ectopic fat deposition in the pancreas. Aging and hormonal changes seem to be involved in NAFPD development, although additional studies are needed to verify this presumption.

Singh et al. [5] collected data on the percentage of pancreatic fat content from 9 studies (in a total of 1209 healthy subjects who underwent MRI), and found that the weighted average and weighted standard deviation were 4.48% and 0.87%, respectively. Data from 11 studies (12,675 subjects) showed that the overall prevalence of NAFPD was 33% (95% confidence interval [CI], 24%–41%).

The report by Lesmana et al. [6] included 1054 subjects, of whom 720 (68.3%) were men. The imaging results showed that shadows in the pancreas were not detected in 153 subjects (14.5%). Of the remaining 901 subjects, 315 (35%) showed a fatty pancreas. It has been reported that the development of fatty pancreas in men is significantly associated with age > 35 years; high systolic and diastolic blood pressure; fasting blood glucose > 100 mg/dL; and triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels. In Indonesia, studies have shown that NAFPD has a high prevalence and is closely linked to other metabolic conditions. Pham et al. [4] reported that the prevalence of pancreatic steatosis among obese children (19%) was more than double of that among nonobese children (8%). A report in Hong Kong showed that 16.1% of the community cohort of adult Hong Kong Chinese volunteers had a fatty pancreas. Fatty pancreas is associated with central obesity, hypertriglyceridemia, and hyperferritinemia. Patients with a fatty pancreas show increased insulin resistance.

Epidemiological studies on obesity and NAFPD

The prevalence of obesity has reached epidemic proportions worldwide, showing doubling in the last 3 decades. Obesity, especially abdominal obesity, is associated with insulin resistance, which, in turn, can lead to pancreatic steatosis and NAFPD [7].

Obesity is a chronic disease that is attributable to multiple psychosocial factors. Its prevalence is increasing among adults, adolescents, and children. Given the alarming increase in the number of overweight and obese individuals worldwide, the term “global epidemic” in relation to obesity was introduced by the World Health Organization (WHO). According to the WHO statistics, an estimated 200 million adults

worldwide were obese and 18 million children under the age of 5 years were considered overweight in 1995. In 2000, the number of obese adults has increased to > 300 million, with 115 million obese adults in developing countries. In 2014, > 1.9 billion adults aged ≥ 18 years were overweight, among whom 600 million individuals were obese. Overall, approximately 13% of the global adult population (11% of men and 15% of women) were obese in 2014. The global prevalence of obesity has doubled between 1980 and 2014. In 2013, 42 million children under the age of 5 years were overweight or obese [8]. According to the data from the National Health and Nutrition Examination Survey, the prevalence of obesity in the United States is 34.9% [9]. The average body mass index (BMI) is increasing globally. It is estimated that 36.9% of men and 38% of women have a BMI of ≥ 25 kg/m^2 [10,11].

The prevalence of obesity, defined as a BMI of ≥ 30 kg/m^2, has dramatically increased in many countries in the last few decades. Thus, obesity is a huge health concern. The latest data in the United States show that more than two-third of adults were overweight or obese (BMI ≥ 25 kg/m^2) and 6.4% of individuals were morbidly obese (BMI ≥ 40 kg/m^2, class 3 obesity) in 2011–2012 [2]. Obesity is associated with certain chronic diseases, such as hypertension, hyperlipidemia, T2DM, cardiovascular disease, metabolic syndrome, and cancer. In 2010, an estimated 3.4 million deaths due to obesity were recorded worldwide. According to the data from the National Health and Nutrition Examination Survey, the prevalence of obesity in the United States is 34.9%. The average BMI is increasing globally [10].

Obesity, especially abdominal obesity, is associated with insulin resistance, which leads to T2DM. Hyperinsulinemia and hyperglycemia can lead to vascular endothelial dysfunction, dyslipidemia, and the development of atherosclerotic cardiovascular disease. These conditions also lead to fat deposition in many organs, such as the heart, kidney, liver, and pancreas [13].

Importantly, obesity is also considered a major risk factor for many solid tumors. Epidemiological studies have shown that obesity is associated with an increased incidence of endometrial cancer, postmenopausal breast cancer, esophageal adenocarcinoma, colon cancer, hepatocellular carcinoma, renal cell carcinoma, and prostate cancer [14]. Notably, obesity is associated with an increased incidence of pancreatic cancer, which is a type of cancer that affects the global population.

Large-scale epidemiological studies have shown a link between obesity and pancreatic cancer. A large population-based case–control study of pancreatic cancer showed that obesity was statistically significantly associated with a 50%–60% increased risk of pancreatic cancer. Several mechanisms have been proposed to explain the increased cancer risk related to obesity, including inflammation, insulin resistance, circulating lipids, cytokines, and changes in microbiota. Chronic inflammation is a known major risk factor for many cancers, including esophageal adenocarcinoma, gastric cancer, colorectal cancer, and hepatocellular carcinoma. Adipose tissue inflammation is a hallmark of obesity. It can lead to pancreatic cancer by increasing the secretion of proinflammatory cytokines that promote cancer growth. Adipose tissue comprises (pre)adipocytes, immune cells, fibroblasts, endothelial cells, and stem/progenitor cells. Many of these cells are able to release a myriad of proinflammatory cytokines, such as tumor necrosis factor-α, transforming growth factor-β, interleukin-6, and leptin, which, in turn, stimulate cancer cell proliferation. This implies that obesity-induced adipose tissue inflammation plays an important role in pancreatic cancer development. Furthermore, obesity is frequently associated with insulin resistance and T2DM, in which levels of insulin and insulin-like growth factor 1 are elevated. Diabetes has been shown to be associated with an increased risk of cancer [15].

Studies have shown that healthy weight loss can reduce the cancer incidence in women. Retrospective clinical studies have demonstrated that bariatric surgery reduces the incidence of a variety of cancers.

Ectopic visceral fat is a major risk factor for obesity complications, including insulin resistance and metabolic syndrome.

Studies have shown that 58% of obese children have a fatty pancreas. Compared with obese children without a fatty pancreas, those with a fatty pancreas show a higher incidence of metabolic syndrome (P = 0.013) and insulin resistance (P = 0.012). Regression analysis has shown that fatty pancreas is an independent predictor of metabolic syndrome and insulin resistance. Fatty pancreas has been reported to be associated with an increased risk of metabolic syndrome (odds ratio [OR], 11.40; 95% CI, 2.69–48.22) and insulin resistance (OR, 7.85; 95% CI, 2.20–28.05) in obese children [16].

Pancreatic fat deposition may cause dysregulation of insulin secretion in pancreatic cells. The increase in lipolysis in obese individuals leads to increased levels of free fatty acids in the pancreas and other body organs. In addition, adipose-related proinflammatory conditions, reactive long-chain fatty acyl coenzymes, toxic metabolites, protein kinase C activation, and increased oxidative stress all contribute to insulin resistance and metabolic syndrome [17].

Evidence from studies examining animal tissue indicates that the development of pancreatic adipogenesis is associated with increased proinflammatory cytokines and decreased B-cell numbers. Studies in adults and adolescents have demonstrated a crucial link between fatty pancreas and cardiometabolic events, including insulin resistance.

Unlike studies in adults, studies in children have

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shown that fatty pancreas is significantly associated with central obesity but not with BMI. This is similar to the finding of a previous study in adolescents, [18] which reported that fat deposition in the pancreas is associated with central obesity and not systemic adiposity. Central obesity is related to ectopic fat deposition in certain organs, including the pancreas.

In addition, studies have shown a strong correlation between hyperlipidemia and fatty pancreas, which is consistent with reports in the literature (i.e., there is a significant positive correlation between hyperlipidemia and fatty pancreas in obese children). A systematic review and meta-analysis has shown that circulating triglyceride, high-density lipoprotein cholesterol, glycated hemoglobin, insulin, and homeostasis model assessment-insulin resistance are highly correlated with pancreatic fat deposition [19]. A high-fat diet induces fatty pancreas in animals [8], whereas hypercholesterolemia may induce pancreatic fat deposition in humans [20]. In addition, obesity-related insulin resistance leads to increased lipolysis, which plays a role in fatty infiltration of the pancreas, leading to further impairment of B-cell function. Thus, obese individuals are susceptible to T2DM.

Studies have found a strong correlation between fatty pancreas and metabolic syndrome. The presence of fatty pancreas increases the risk of metabolic syndrome in obese children, which indicates early fat accumulation in the pancreas during metabolic decompensation. This implies that fatty pancreas is associated with metabolic syndrome as well as certain metabolic syndrome parameters in obese children. Maggio et al. observed that obese adolescents with a pancreatic fat content of > 5% detected on MRI exhibited a higher risk of metabolic syndrome.

Studies have indicated a strong correlation among metabolic syndrome, insulin resistance, and fatty pancreas. However, owing to the lack of follow-up data in children with these conditions, the causal relationship between fatty pancreas and other obesity complications remains to be investigated. Nonetheless, previous histopathologic studies have confirmed the impact of pancreatic fat accumulation and inflammation on β-cell dysfunction. Singh et al. [5] reported that weight loss could significantly reduce pancreatic fat, thereby reducing insulin resistance and hyperlipidemia.

Collectively, obese children exhibit higher levels of fat accumulation in the pancreas than lean children. Fatty pancreas is closely associated with central obesity. Obese children with a fatty pancreas are more susceptible to insulin resistance and metabolic syndrome.

NAFPD was first described by Oligvie in 1933. NAFPD is associated with uncommon susceptibility factors such as age and obesity. Owing to differences in terminologies and the lack of standardized diagnostic criteria, the reported prevalence of NAFPD varies across different studies [21]. It has been reported that the prevalence of NAFPD in the Asian adult population is 16%–35% [22].

A proposed mechanism for pancreatic fat accumulation is lipomatosis, which is characterized by death of acinar cells and their replacement by adipocytes, fatty infiltration, and fatty accumulation. NAFPD can aggravate acute pancreatitis and may affect the endocrine and exocrine functions of the pancreas. Patients with NAFPD are prone to developing pancreatic cancer. NAFPD also increases morbidities during and after pancreatic surgery, as well as the mortality rate related to pancreatic cancer [23].

Pancreatic steatosis combined with acute pancreatitis has also been shown to exacerbate the inflammatory cascade. In the presence of obesity, these conditions result in more severe physical damage [24]. However, there is insufficient evidence to demonstrate the association between NAFPD and chronic inflammation or chronic pancreatitis.

NAFPD prevention and treatment

Few studies have investigated the treatment approaches for NAFPD. Nonetheless, the consensus is that diet and exercise are the central components of NAFPD prevention and treatment. Dietary regimens should be flexible and adapted to the lifestyle of people from different regions and ethnic backgrounds, with the attainment of total energy requirement as the final goal. The level of exercise should also be adjusted based on the ability of each individual. Practical exercise programs should be designed based on individual physical conditions. Regardless of the selected exercise types, the key is to perform aerobic exercises. Strenuous exercises and burnouts should be avoided.

Major progresses in pharmacologic treatment for NAFPD are lacking. Probiotics are the current focus of microbial-based therapies. Probiotics can significantly reduce oxidative stress and cytokine production, as well as improve the pancreatic function. A potential mechanism underlying the use of probiotics is that these agents alter the gut microbiota composition, which, in turn, alleviates dysbiosis, intestinal permeability, bacterial translocation, and endotoxemia, thereby improving NAFPD. However, large-scale controlled clinical trials are needed to confirm this hypothesis. The development of novel probiotic strains and relevant products is eagerly awaited.

Therapies targeting inflammation, including astaxanthin, linseed oil, pomegranate, quercetin, and hydroglycerin porphyrin also warrant further investigations and development.

Progress has been made in recent years with respect to the use of glucagon-like peptide-1 (GLP-1) receptor agonists for the treatment of diabetes and NAFPD. The potential of the incretin hormone GLP-1 as a

therapeutic target for T2DM has been demonstrated in a study showing that GLP-1 is responsible for 70% of insulin secretion in response to nutritional intake [25].

Studies have demonstrated that GLP-1 can lower the blood glucose levels. GLP-1 has also been shown to exhibit effects of reducing weight and the risk of cardiovascular disease. Seven GLP-1 agonists are currently licensed globally. According to the 2017 sales statistics, liraglutide and dulaglutid accounted for the largest market shares, with 56.4% and 20.3% of sales, respectively. GLP-1 agonists merit further research and development [26,27].

Pancreatic fibrosis is an important pathological outcome of NAFPD. Thus, the treatment of fibrosis has always been emphasized. Antioxidants were commonly used agents for treating fibrosis and may still be in use; however, their effectiveness remains uncertain. Novel drugs focus on inhibiting pancreatic stellate cell (PSC) activation and proliferation. Drugs that are currently available or under investigation include sorafenib, sarpogrelate, and human bone marrow stromal cells (BMSCs). BMSCs inhibit the toll-like receptor 4/nuclear factor-κB pathway through cell–cell interactions, thereby inhibiting PSC activation and proliferation.

The effectiveness of gene therapy is also uncertain. Viral vectors are the most commonly studied and utilized vectors, accounting for > 70% of vectors used in existing studies. However, big data on the efficacy of viral vectors from clinical controlled studies are lacking, and many questions remain to be addressed.

With the increased understanding of the mechanism of pancreatic fibrosis, an increasing number of regulatory genes involved in the initial and later stages of fibrosis will gradually be identified. Pancreatic fibrosis is a complex and dynamic process involving multiple genes. The modulation of target genes in different components has been shown to result in synergism. Therefore, research on gene therapy for pancreatic fibrosis should be intensified to attain the ultimate therapeutic goals of pancreatic fibrosis reversal, structural reconstruction, and functional restoration. It is believed that gene therapy will become a novel treatment strategy for the treatment of pancreatic fibrosis in the near future.

In summary, progress on NAFPD research has increased the understanding of this disease and laid the foundation for future comprehensive NAFPD investigations. According to current epidemiological data, NAFPD is a common disease. It was initially believed to be a component of metabolic syndrome; however, its impact on human health and disease is far from being understood. Therefore, extensive research on NAFPD is urgently needed for the benefits of human health. Comprehensive, multidisciplinary, and in-depth basic-to-clinical research should be conducted in the future. New breakthroughs in NAFPD prevention and treatment are eagerly awaited in the near future.

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