

Impact of non-alcoholic fatty pancreas disease on glucose metabolism

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Keywords

Diabetes mellitus, Metabolic syndrome, Non-alcoholic fatty pancreas disease

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J Diabetes Investig 2017; 8: 735–747

doi: 10.1111/jdi.12665

ABSTRACT

With the increasing global epidemic of obesity, the clinical importance of non-alcoholic fatty pancreas disease (NAFPD) has grown. Even though the pancreas might be more susceptible to ectopic fat deposition compared with the liver, NAFPD is rarely discussed because of the limitation of detection techniques. In the past, NAFPD was considered as an innocent condition or just part of clinical manifestations during the course of obesity. Recently, a growing body of research suggests that NAFPD might be associated with β -cell dysfunction, insulin resistance and inflammation, which possibly lead to the development of diabetes and metabolic syndrome. The present review summarized the current literature on the epidemiology, potential pathophysiology, diagnostic techniques, impact of NAFPD on β -cell function and insulin resistance, and the clinical relevance of the interplay between NAFPD and glucometabolic disorders.

INTRODUCTION

Obesity has emerged as a major health problem worldwide, as it is linked to several metabolic complications, including type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease. In the past two decades, there has been a growing awareness that obesity is not a homogeneous condition, and the regional distribution of adipose tissue plays a pivotal role in obesity-associated disturbances of glucose and lipid metabolism^{1–3}. When the circulating levels of triglycerides and free fatty acids (FFAs) exceed the metabolic capacity of adipose tissue needs, they are accumulated as ectopic fat in non-adipose tissues, such as skeletal muscle, the liver, heart and pancreas^{4–6}. Fat infiltration of the liver in the absence of significant alcohol consumption and other chronic conditions of the liver is termed as NAFLD. It can progress to local liver injury, cirrhosis and hepatocellular carcinoma⁷. In addition, NAFLD has been shown to be associated with insulin resistance, type 2 diabetes, metabolic syndrome and atherosclerosis^{8–10}.

Lipid deposition in the pancreas has recently gained more attention. Nowadays, a growing body of evidence has shown that non-alcoholic fatty pancreas disease (NAFPD) might be associated with lipotoxicity, insulin resistance and inflammation, which possibly leads to the development of glucometabolic

disorders. In 1933, Ogilvie first used the term ‘pancreatic lipomatosis’ to represent the pathological process of excessive fat storage in the pancreas¹¹. Owing to the lack of distinction between the accumulation of triglycerides in acinar cells, β -cells or intrapancreatic adipocyte infiltration, so far many synonymous (such as pancreatic steatosis, pancreatic lipomatosis or fatty pancreas) have been used for all forms of pancreatic fat accumulation. According to a current article by Smits *et al.*, NAFPD is specifically defined as pancreatic fat accumulation in association with obesity in the absence of significant alcohol consumption¹². However, the precise definition of ‘significant alcohol consumption’ in this context is uncertain. In general, most published literature regarding NAFPD has stated that ‘significant alcohol consumption’ is defined as >2 drinks (~10 g of alcohol per one drink unit) per day, and some studies have used sex-specific definitions: >3 drinks on average per day in men and >2 drinks on average per day in women. Unlike NAFLD, the pathophysiology and clinical implications of NAFPD have not been well established.

Therefore, the aim of the present literature review was to summarize the impact of NAFPD on glucose metabolism. In particular, we will focus on the current knowledge regarding the possible pathophysiology and diagnostic techniques, effects on β -cell function and insulin resistance, and the clinical relevance of the interplay between NAFPD and glucometabolic disorders (Table 1).

Received 7 February 2017; revised 15 March 2017; accepted 26 March 2017

Table 1 | Summary of human studies investigating the association between pancreatic steatosis and glucometabolic disorders

First author (reference)	Study design and population	Assessment of pancreatic steatosis	No. patients	Prevalence of fatty pancreas	Assessment of β -cell function	Results
Tushuizen <i>et al.</i> (2007) ⁴³	Case-control study; Caucasian men; aged 35–65 years; alcohol intake <20 units/week	¹ H-MRS	Total: 36 Subgroup: 12/24 (type 2 diabetes/non-type 2 diabetes)	–	OGTT-derived insulinogenic index	Patients with type 2 diabetes have higher pancreatic fat content than those with non-type 2 diabetes. Pancreatic fat content negatively correlates with β -cell function only in non-type 2 diabetes group. Pancreatic fat content is not associated with BMI, WC, TG, FFAs, VAT, hepatic fat content. Hyperechoic pancreas is associated with BMI, hepatic steatosis, alcohol use
Al-Haddad <i>et al.</i> (2009) ⁵³	Case-control study in USA; patients who underwent EUS; median age 65 years	EUS	Total: 120 Subgroup: 60/60 (hyperechoic pancreas/healthy control)	–	–	–
Lee <i>et al.</i> (2009) ¹⁵	Cross-sectional study in South Korea; adults visiting an obesity clinic; mean age 44.9 \pm 9.5 years; alcohol intake <20 g/day in women and <40 g/day in men	Abdominal US	Total: 293 Subgroup: 180/113 (NAFPD/non-NAFPD)	61.4%	–	HOMA-IR, TG and VAT tend to increase with the degree of NAFPD. The incidence of metabolic syndrome and the number of metabolic syndrome parameters are higher in NAFPD group compared with in the control group
Lingvay <i>et al.</i> (2009) ³⁰	Cross-sectional study in USA; volunteer with normal or abnormal glucose tolerance; alcohol intake <2 units/day	MRS	Total: 79 Subgroup: 15/30/23/11 (NGT plus BMI <25/NGT plus BMI \geq 25/IGT or IFG/type 2 diabetes)	–	–	In normoglycemic population, overweight or obese subjects have higher pancreatic fat content compared with lean subjects. Subjects with similar BMI, but with abnormal glucose tolerance (IGT or IFG, or type 2 diabetes) have even higher pancreatic fat content. Post-challenge blood glucose level has the strongest relationship to pancreatic fat content. Pancreatic and hepatic fat contents are only weakly correlated

Table 1 (Continued)

First author (reference)	Study design and population	Assessment of pancreatic steatosis	No. patients	Prevalence of fatty pancreas	Assessment of β -cell function	Results
van Greenen <i>et al.</i> (2010) ¹⁴	Retrospective study in the Netherlands; deceased adults who underwent autopsy; mean age of death 68 \pm 14 years; alcohol intake <14 units/week in women and <21 units/week in men	Pathology	Total: 80	–	–	Intralobular pancreatic fat is associated with non-alcoholic steatohepatitis. Total pancreatic fat is a significant predictor for NAFLD
Choi, <i>et al.</i> (2010) ¹⁸	Cross-sectional study in South Korea; subjects who underwent EUS; mean age 52.1 \pm 12.2 years	EUS	Total: 284 Subgroup: 110/174 (hyperechogenic pancreas/non-hyperechogenic pancreas)	38.7%	–	Hyperechogenic pancreas is associated with fatty liver, male, aged >60 years, hypertension, and VAT
Heni <i>et al.</i> (2010) ¹⁹	Cross-sectional study in Germany; healthy Caucasian subjects with increased risk of type 2 diabetes	MRI	Total: 51 Subgroup: 23/28 (IFG and/or IGT/NGT)	–	OGTT-derived insulinogenic index	Pancreatic fat content negatively correlates with insulin secretion only in subjects with IGT and/or IFG. Pancreatic fat content positively correlates with BMI, VAT, and WC. No association of pancreatic fat contents with age, sex and hepatic fat content
Rossi <i>et al.</i> (2011) ²⁰	Cross-sectional study in Italy; obese subjects without diabetes; mean age 49.1 \pm 13.0 years; alcohol intake <20 g/day in women and <30 g/day in men	MRI	Total: 38 Subgroup: 18/20 (men/women)	–	–	Obese subjects had higher pancreatic fat content than lean subjects. Obese men had higher pancreatic fat content than obese women despite same BMI. Pancreatic fat content is positively related with WC, VAT, TG and fat intake, and negatively related to adiponectin. No association between pancreatic fat content and insulin resistance

Table 1 (Continued)

First author (reference)	Study design and population	Assessment of pancreatic steatosis	No. patients	Prevalence of fatty pancreas	Assessment of β -cell function	Results
Lê <i>et al.</i> (2011) ⁴⁴	Cross-sectional study; young obese African Americans or Hispanics; aged 13–25 years	MRI	Total: 138 Subgroup: 74/64 (Hispanic/African American)	–	IVGTT-derived disposition index	Hispanics had higher pancreatic fat content than African Americans, and the ethnic difference becomes greater with increasing age. Pancreatic fat content is positively associated with VAT, hepatic fat content and FFAs. No association between pancreatic fat content and insulin sensitivity or β -cell function. The presence of fatty pancreas is associated with BMI, fatty liver, hyperlipidemia and metabolic syndrome. Subjects with increasing number of metabolic syndrome parameters have a higher risk of fatty pancreas. No association between fatty pancreas and chronic pancreatitis or pancreatic adenocarcinoma. Pancreatic fat content gradually increases between NGT, IFG and IFG/IGT. Pancreatic fat content is positively associated with age, BMI and 2-h plasma glucose, and negatively related to insulin sensitivity and e-cholesterol. No association between pancreatic fat and β -cell function. The prevalence of NAFPD gradually increases between NGT, prediabetes and diabetes. NAFPD is associated with an increased risk for diabetes. NAFPD is related to prediabetes only in men, but not in women.
Sepe <i>et al.</i> (2011) ²⁶	Cross-sectional study in USA; patients who are referred for EUS; mean age 62.9 \pm 13.9 years	EUS	Total: 230 Subgroup: 64/166 (fatty pancreas/non-fatty pancreas)	27.8%	–	
van der Zijl <i>et al.</i> (2011) ⁴⁵	Case-control study; overweight Caucasian subjects with a family history of type 2 diabetes; alcohol intake <20 units/week	¹ H-MRS	Total: 64 Subgroup: 16/29/19 (NGT/IFG/IG and/or IGT)	–	Hyperglycemic hyperinsulinemic clamp-derived disposition index	
Ou <i>et al.</i> (2013) ²³	Cross-sectional study in Taiwan; adults who underwent health check-up; alcohol intake <20 g/day	Abdominal US	Total: 7,464 Subgroup: 5,756/1,225/483 (NGT/prediabetes/diabetes)	–	–	

Table 1 (Continued)

First author (reference)	Study design and population	Assessment of pancreatic steatosis	No. patients	Prevalence of fatty pancreas	Assessment of β -cell function	Results
Wu <i>et al.</i> (2013) ²⁴	Cross-sectional study in Taiwan; adults who underwent health check-up; mean age 50.8 \pm 12.4 years	Abdominal US	Total: 557 Subgroup: 72/485 (fatty pancreas/non-fatty pancreas)	12.9%	–	Subjects with fatty pancreas have a greater proportion of obesity, hypertension, dyslipidemia (e.g., high TG, low HDL-cholesterol) and hyperglycemia than those without fatty pancreas. The incidence of metabolic syndrome and the numbers of metabolic syndrome parameters are higher in subjects with fatty pancreas compared with in the control group
Wong <i>et al.</i> (2014) ³²	Cross-sectional study in Hong Kong; healthy adults; mean age 48 \pm 10 years; alcohol intake <10 g/day (<70 g/week) in women and <20 g/day (<140 g/week) in men	MRI	Total: 685 Subgroup: 110/575 (NAFPD/non-NAFPD)	16.1%	HOMA- β	NAFPD is more common in men and in postmenopausal women. Subjects with both NAFPD and NAFLD had higher HOMA-IR than did those with either condition alone
Wang <i>et al.</i> (2014) ¹⁶	Cross-sectional study in Taiwan; adults who underwent health check-up; alcohol intake <20 g/day	Abdominal US	Total: 8,097 Subgroup: 1,297/6,800 (NAFPD/non-NAFPD)	16.0%	–	NAFPD is associated with central obesity, hypertriglyceridemia, hyperferritinemia and insulin resistance. No association between NAFPD and β -cell function
Lesmana <i>et al.</i> (2015) ²⁵	Cross-sectional study in Indonesia; adults who underwent routine medical check-up; mean age 43.1 \pm 12.19 years; alcohol intake <20 g/day	Abdominal US	Total: 901 Subgroup: 315/586 (NAFPD/non-NAFPD)	35%	–	Subjects with NAFPD have a greater proportion of diabetes and NAFLD than those without NAFPD. NAFPD is associated with age, obesity, diabetes and NAFLD

Table 1 (Continued)

First author (reference)	Study design and population	Assessment of pancreatic steatosis	No. patients	Prevalence of fatty pancreas	Assessment of β -cell function	Results
Della Corte <i>et al.</i> (2015) ¹⁷	Cross-sectional study in Italy; consecutive children and adolescents with NAFLD; mean age 13.16 \pm 2.69 years	Abdominal US	Total: 121 Subgroup: 58/63 (NAFPD/non-NAFPD)	48%	–	Subjects with NAFPD have a higher BMI, inflammatory cytokine (eg, TNF- α , IL-1 β), fasting insulin, insulin resistance, and lower insulin sensitivity index compared with those without NAFPD. NAFPD is positively associated with hepatic fibrosis, steatosis and NAFLD activity score. No association between NAFPD and IL-6
Begovatz <i>et al.</i> (2015) ²⁹	Cross-sectional study in Germany; Caucasian subjects; alcohol intake <10 g/day in women and <20 g/day in men	MRI and ¹ H-MRS	Total: 56 Subgroup: 28/14/14 (NGT/IFG and/or IGT/type 2 diabetes)	–	OGTT-derived insulinogenic index	Pancreatic fat consists of an inhomogenous distribution of adipose tissue infiltration instead of uniform pancreatic steatosis. Pancreatic fat infiltration increased with age and decreasing glucose tolerance. No association of pancreatic fat infiltration with β -cell function regardless of glucose tolerance status
Yamazaki <i>et al.</i> (2016) ²⁸	5-year retrospective cohort study in Japan; volunteer who underwent a health check; mean age 51.8 \pm 9.8 years	CT scan	Total: 813 New-onset type 2 diabetes during follow-up: 62 (7.6%)	–	–	Pancreatic steatosis at baseline is positively associated with incident type 2 diabetes in a univariate analysis; however, the association disappears after adjustment for potential confounders (ie, age, sex, BMI, liver attenuation and alcohol intake). Pancreatic steatosis is not independently associated with future type 2 diabetes

BMI, body mass index; CT, computed tomography; EUS, endoscopic ultrasonography; FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; HOMA- β , the homeostasis model assessment of β -cell function; HOMA-IR, the homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IVGTT, intravenous glucose tolerance test; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NAFPD, non-alcoholic fatty pancreas disease; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; TG, triglycerides; TNF- α , tumor necrosis factor- α ; US, ultrasonography; VAT, visceral adipose tissue; WC, waist circumference.

PATHOPHYSIOLOGY

To date, the pathophysiology of NAFLD remains unclear. Obesity leads to adipocyte infiltration in the pancreas. In addition, there are two potential mechanisms for pancreatic fat accumulation: (i) death of acinar cells, followed by the replacement of adipose tissue; and (ii) intracellular triglyceride accumulation associated with excessive energy balance¹².

Human and animal studies have shown that NAFLD frequently coexists with NAFLD^{13–15}. Individuals with NAFLD have a higher prevalence of NAFLD compared with those without NAFLD^{14,16,17}. Both NAFLD and NAFLD are strongly associated with obesity and visceral adipose tissue (VAT)^{15,18–20}. Of note, the pancreas seems to be more susceptible to fat deposition compared with the liver. In mice, during the period of 3–15 weeks on a high-fat diet, there was an increase in pancreatic fat but not hepatic fat²¹. Based on the viewpoint of ectopic fat deposition, it is conceivable that some possible common mechanisms might exist between NAFLD and NAFLD.

Fat accumulation in the liver or pancreas associated with obesity might result from a mismatch between energy supply, formation, consumption, β -oxidation or disposal of triglycerides¹⁰. The potential sources of lipids in the liver or pancreas might come from circulating FFAs, *de novo* lipogenesis and dietary fat intakes. There is a relationship between overfeeding, an increase in VAT and subsequent ectopic fat deposition. Mice fed with a high-fat diet to induce obesity have an increase in VAT, adipocyte hypertrophy, hepatopancreatic steatosis and glucose intolerance¹³. VAT appears to be a pathogenic factor in the development of hepatic and pancreatic steatosis. It can release greater amounts of adipokines and pro-inflammatory cytokines, promoting insulin resistance, enhancing triglyceride lipolysis and thus releasing FFAs into the circulation. Increasing the availability of FFAs to all tissues leads to self-reinforcing cycles that interact to bring excess adipocytes and ectopic fat deposition in the liver and pancreas.

TECHNOLOGY OF ASSESSING PANCREATIC STEATOSIS

Histology and biochemical measurements are the most direct and straightforward way to assess pancreatic steatosis. In contrast with the liver, where triglycerides accumulate in hepatocytes, pancreatic steatosis is histologically characterized by adipocyte infiltration and intracellular fat deposition in both acinar and islet cells²². However, because of the difficulties of obtaining adequate pancreatic specimens and rapid autolysis encountered in autopsy, no dichotomous histopathological cut-off is used to define 'fatty pancreas.' Recently, several imaging techniques, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have been used to detect pancreatic steatosis. Nevertheless, there is no consensus over the 'gold standard' for *in vivo* quantification of pancreatic fat content.

Abdominal US is a non-invasive and less-costly method in the diagnosis of NAFLD. In most studies, the diagnostic criteria for NAFLD using abdominal US are an increase in echogenicity of the pancreatic body over that of the kidney^{15–17,23–25}, which is metabolically more stable than the liver. As the pancreas cannot be compared directly with the kidney in the same acoustic window, the examiner needs to compare the echogenicity differences between the liver and the kidney, and between the liver and the pancreas, to obtain an objective pancreas–kidney echogenicity contrast. However, as the pancreas is located in the retroperitoneal space, overlying bowel gas or obesity can obscure the pancreas. The evaluation of the pancreas by abdominal US is highly dependent on the skill of the operators as well as the quality of the machine.

Endoscopic ultrasonography (EUS) can provide detailed images of the entire pancreas and simultaneously compare the echogenicity of the pancreas with adjacent organs in real time. Some grading systems using EUS to classify the intensity of NAFLD have been reported based on the echogenicity of pancreatic parenchyma and pancreatic duct margins²⁶. Although abdominal US and EUS are cost-effective modalities to screen NAFLD, they cannot accurately quantify the degree of pancreatic steatosis.

CT scan is an operator independent and simple procedure that can be carried out with a short acquisition time. The amount of pancreatic steatosis on CT scans can be assessed using Hounsfield Units. CT scans show the fatty pancreas as a decrease in attenuation compared with the spleen. However, the clinical value of CT scan in the diagnosis of NAFLD remains controversial. Some studies have proposed that CT scan is a less valuable technique for judgment of pancreatic steatosis compared with other imaging¹⁵, whereas others have not^{27,28}. To compare the echogenicity on abdominal US with objective Hounsfield Units on CT scan, Lee *et al.*¹⁵ have found there was no statistically significant difference in clinical and biochemical parameters between individuals with and without NAFLD, defined by CT scan. This discrepant finding in abdominal US and CT scan might be due to an inhomogenous distribution of pancreatic adipose tissue infiltration²⁹, resulting in heterogeneous patterns with a large difference in Hounsfield Units on CT scan. In contrast, Kim *et al.*²⁷ have reported that pancreatic attenuation on CT scan had a good negative correlation with the histological pancreatic fat fraction, considering CT scan as a reliable modality for quantifying pancreatic fat content.

Currently, there is strong evidence emerging for the use of MRI and MRS in detection and quantification of pancreatic steatosis. Like CT scan, MRI and MRS are non-invasive and reproducible techniques to measure the fat content of the whole pancreas. MRI is based on the signal differences between fat and water, whereas MRS is based on the differences in resonance frequencies of protons. Pancreatic fat content measured by MRS correlated well with biochemical determination of

intra-islet triglyceride concentrations, considering MRS-measured fat content in the whole pancreas as a useful surrogate marker for islet fat content^{30,31}. However, MRI and MRS still have some limitations, such as high cost, long scanning duration and susceptibility to MR chemical shift artifact as a result of the surrounding visceral fat.

EPIDEMIOLOGY OF NAFLD

There are limited data on the prevalence of NAFLD in the general population because of the lack of standard screening tools. The prevalence of NAFLD varies widely depending on the ethnicity of the population and diagnostic methodology applied. Among 230 individuals referred for EUS examination in the USA, 27.8% were found to have fatty pancreas²⁶. A study in Indonesia reported that 35% of 901 adults who underwent a routine medical check-up had NAFLD detected by abdominal US²⁵, whereas the other study in South Korea showed the prevalence of NAFLD increased to 61.4% among 293 individuals visiting an obesity clinic¹⁵. By contrast, a large cohort study in Taiwan involving 8,097 individuals who underwent a health check-up reported 16% prevalence of NAFLD detected by abdominal US¹⁶. The population prevalence in Taiwan was similar to that reported in a Hong Kong study, which used MRI to quantify pancreatic fat content³². In addition, NAFLD can even occur in children. A retrospective single-center study in the USA showed pancreatic steatosis was identified in ~10% of 232 pediatric patients aged 2–18 years who underwent abdominal CT scan³³.

Like NAFLD, the risk of NAFLD increases with age, and it occurs more often in men than in women^{16,18–20}. Men have a higher pancreatic fat content compared with women of comparable body mass index (BMI)²⁰. Saisho *et al.*³⁴ have found that pancreatic fat content increased linearly with age throughout childhood and reached a plateau until the age of ~50 years. Wong *et al.*³² have shown that men had the highest prevalence of NAFLD at the age of 40–49 years, whereas the prevalence of NAFLD in women was very low in early life, but rapidly increased after menopause. These studies imply that sex might reflect the difference in propensity for ectopic fat deposition in the pancreas. Aging and hormonal changes appear to have relevance to the development of NAFLD, but more studies are required to examine this speculation.

NAFLD AND β -CELL DYSFUNCTION

Several studies have suggested a potential interplay between dysglycemia, NAFLD and β -cell dysfunction (Figure 1). The explanation most commonly offered for the relationship of NAFLD to β -cell dysfunction is based on glucolipotoxicity. In β -cells, hyperglycemia inhibits carnitine-palmitoyl transferase-1 through increasing malonyl coenzyme A, decreasing mitochondria β -oxidation, and thereby promoting intracellular triglyceride accumulation. In addition, insulin resistance decreases the inhibitory action of insulin on peripheral lipolysis, thus increasing circulating FFAs. Chronic exposure of β -cells to

elevated FFAs results in increased triacylglycerol content, decreased insulin gene expression, blunted glucose-stimulated insulin secretion and increased risk of apoptosis^{35,36}. The adverse effect of glucolipotoxicity contributes to β -cell dysfunction and causes a vicious cycle of continuous deterioration of the glucometabolic state.

Several *in vitro* and animal studies have shown a link between pancreatic steatosis and β -cell dysfunction. A reduced insulinogenic signaling on pancreatic acinar cells, as occurs in diabetes, might have an influence on viability and growth of cells, apoptosis, and subsequent fat replacement^{37,38}. In rats, chronic high-fat diet can induce an increase in pancreatic FFAs, acute inflammatory response, resulting in the damage of acinar cells and islets, as well as fatty infiltration in the pancreas³⁹. However, the relationship between pancreatic steatosis and β -cell dysfunction in humans remains inconsistent. Previous studies have found pancreatic volume reduction and steatosis in diabetes patients^{40,41}. In non-diabetic non-obese children with a mutation in carboxyl-ester lipase, pancreatic steatosis reflects early events in the pathogenesis of diabetes⁴². Otherwise, several studies have shown that pancreatic fat content is inversely correlated with insulin secretion in individuals with impaired fasting glucose or impaired glucose tolerance, but not in individuals with normoglycemia or type 2 diabetes^{19,43}. Similarly, in young obese normoglycemic individuals, there is no significant association between pancreatic fat content and β -cell function⁴⁴. These results show the concept of pancreatic steatosis being crucial in the deterioration of glucose homeostasis. Once diabetes develops, other factors superimposing the effect of pancreatic steatosis might contribute to a progressive decline in β -cell function.

In contrast, some studies have found no association of NAFLD with β -cell function. A community cohort study in Hong Kong showed no significant correlation between NAFLD and the homeostasis model assessment of β -cell function after adjusting for hepatic fat content and BMI³². Using hyperglycemic clamp as the gold standard measurement of β -cell function, van der Zijl *et al.*⁴⁵ could not establish an association between pancreatic fat content and β -cell function despite the fact that the impairments in β -cell function in individuals with impaired glucose metabolism were accompanied by pancreatic fat deposition. Similar findings were also obtained in a study by Begovatz *et al.*²⁹, who found no association between pancreatic adipose tissue infiltration and the first-phase insulin response to oral glucose challenge, regardless of glucose tolerance status. These contradictory findings about the relationship between NAFLD and β -cell dysfunction might possibly arise from methodology differences (including techniques to measure pancreatic fat content and methods to assess β -cell function) or from differences in age and ethnicity of the population.

Although many studies have pointed to an upward trend in pancreatic steatosis on the progression of the diabetic state, there is no clear evidence of a causal link between pancreatic steatosis and β -cell dysfunction in humans. The inconsistent

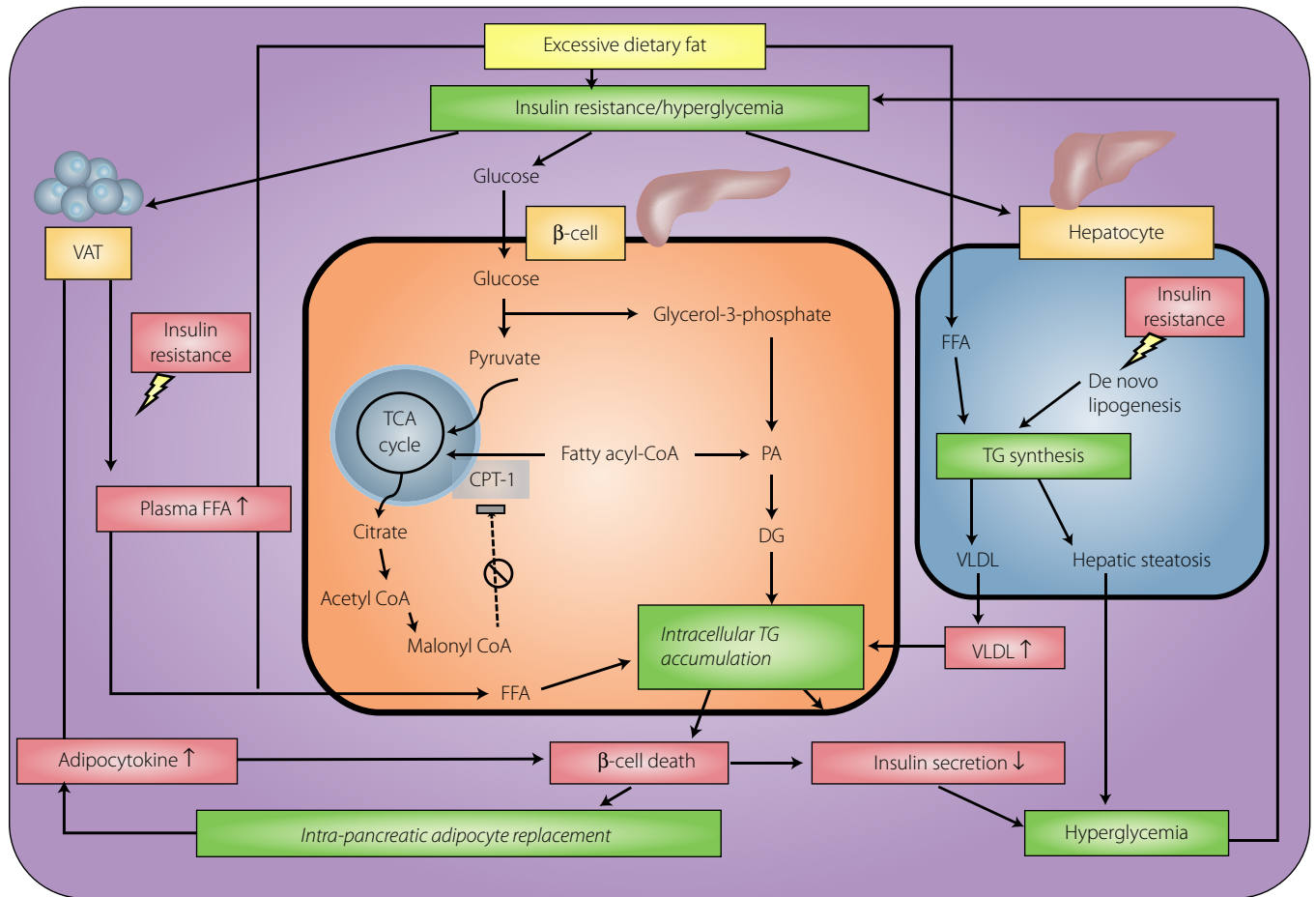


Figure 1 | A potential interplay between dysglycemia, non-alcoholic fatty pancreas disease (NAFPD) and β -cell dysfunction. During long-term intake of excessive calories, dietary fatty acids and hyperinsulinemia stimulate hepatic steatosis, leading to increased export of very-low-density lipoprotein (VLDL), which will increase fat delivery to the islets. In β -cells, hyperglycemia inhibits carnitine-palmitoyl transferase-1 (CPT-1) through increasing malonyl coenzyme A (malonyl CoA), decreasing mitochondria β -oxidation and further promoting intracellular triglyceride (TG) accumulation. In contrast, insulin resistance enhances triglyceride lipolysis and free fatty acid (FFA) release from visceral adipose tissue (VAT), thus increasing circulating FFAs. Chronic exposure of β -cell to elevated FFAs results in increased intracellular triacylglycerol content, decreased insulin gene expression and blunted glucose-stimulated insulin secretion. In addition, adipocyte-derived cytokines and FFAs also contribute to β -cell destruction, which further blunts insulin secretion as well as promotes intrapancreatic replacement by adipocytes. When fat deposition in the pancreas exceeds the tolerance threshold, hyperglycemia will supervene and causes a vicious cycle of continuous deterioration of glucometabolic state. DG, diglycerides; PA, phosphatidic acid; TCA, tricarboxylic acid.

results cast doubt on whether pancreatic steatosis might cause lipotoxicity to β -cells, or whether its presence is merely a marker of β -cell dysfunction⁴⁶. Additional large-scale longitudinal studies are warranted to investigate the contributing role of pancreatic steatosis during the progressive β -cell failure.

NAFPD AND INSULIN RESISTANCE

The association between NAFPD and insulin resistance is still controversial. In healthy monozygotic twins, pancreatic fat content was associated with insulin sensitivity index and plasma adiponectin, which plays a unique role in maintaining insulin sensitivity⁴⁷. In addition, Della Corte *et al.*¹⁷ found obese children with NAFLD complicated with NAFPD had a higher

insulin resistance and circulating levels of tumor necrosis factor- α and interleukin-1 β than those without NAFPD. Similarly, a community cohort study also proved that adults with both NAFPD and NAFLD had a higher homeostasis model assessment of insulin resistance (HOMA-IR) than those with either condition alone. Pancreatic fat content was associated with HOMA-IR, even after adjusting for hepatic fat content and BMI³². A study involving patients with impaired fasting glucose and/or impaired glucose tolerance that used hyperglycemic clamp to assess insulin sensitivity showed an inverse correlation between pancreatic fat content and insulin sensitivity⁴⁵. Furthermore, Lee *et al.*¹⁵ found HOMA-IR tended to increase with the severity of NAFPD. In multivariate logistic regression analysis,

HOMA-IR was correlated with NAFLD after adjustment for age, BMI and lipid profiles. However, the significant association between NAFLD and HOMA-IR disappeared after further adjustment for VAT, suggesting that VAT might be a much stronger relational factor or mediate the association between NAFLD and insulin resistance.

In contrast, Lê *et al.*⁴⁴ did not find any relationship between pancreatic fat content and markers of insulin resistance in obese young individuals. Similar findings were also obtained in a study by Rossi *et al.*²⁰, who found that insulin resistance was related with hepatic fat instead of pancreatic fat in obese adults. Because of the inconsistent results of the available studies, whether NAFLD is a causal factor of insulin resistance or is just part of a cluster of abnormalities during the course of obesity remains a matter for speculation.

CLINICAL IMPLICATIONS OF NAFLD

NAFLD and metabolic syndrome

NAFLD has been shown to be associated with obesity and the features of metabolic syndrome. Ogilvie¹¹ found that the degree of adiposity in the pancreas was higher in obese cadavers than in lean ones (17 vs 9%, respectively). In C57BL/6 mice, diet-induced obesity developed common features of metabolic syndrome, elevated insulin resistance and NAFLD¹³. Most human studies have shown pancreatic fat content increased with BMI and waist circumference^{16,17,19,20,25,26,30,32,45}. The association between NAFLD and VAT is found in some studies^{15,19,20,44}, but not others⁴³. Ethnicity has an influence on the association between pancreatic steatosis and VAT, resulting in a stronger relationship between pancreatic fat content and VAT in Hispanics than African Americans⁴⁴.

In contrast, several studies have shown that individuals with fatty pancreas have an increased prevalence of metabolic syndrome compared with those without fatty pancreas. The number of metabolic syndrome components in fatty pancreas groups was significantly higher than in normal groups^{15,24,26}. Triglycerides and VAT gradually increased with the severity of pancreatic steatosis¹⁵. Sepe *et al.*²⁶ found a higher prevalence of fatty pancreas in patients with metabolic syndrome than those without metabolic syndrome. The presence of any metabolic syndrome components increased the prevalence of fatty pancreas by 37%. Hyperlipidemia was related with fatty pancreas in univariate analysis, but not in multivariate analysis. Hypertension showed a trend toward an association with fatty pancreas despite no statistical significance²⁶. Wu *et al.*²⁴ reported that compared with healthy controls, those with fatty pancreas had higher levels of several metabolic risk factors (including BMI, waist circumference, triglycerides, fasting plasma glucose, hemoglobin A1c and systolic blood pressure), as well as lower levels of high-density lipoprotein cholesterol. These aforementioned studies show that NAFLD might be the pancreatic manifestation of metabolic syndrome. Insulin resistance probably represents as a link between NAFLD and metabolic syndrome. However, all previous studies are cross-sectional in design,

which cannot clearly clarify cause and effect relationships. Future longitudinal studies are warranted to investigate the association between NAFLD and the development of metabolic syndrome.

NAFLD and diabetes

Insulin resistance is a common pathway for the development of NAFLD, NAFLD and diabetes. The consequence of pancreatic fat infiltration might provoke a decrease in β -cell number and function, leading to more rapid progression to diabetes. To date, some studies have shown that NAFLD is associated with diabetes independently of NAFLD, suggesting that possible mechanisms (e.g., β -cell failure) other than insulin resistance link NAFLD to diabetes²³. In contrast, Della Corte *et al.*¹⁷ found that approximately 50% of pediatric patients with NAFLD and 80% of biopsy-proven non-alcoholic steatohepatitis concurrently had NAFLD. Compared with those without NAFLD, children with NAFLD complicated by NAFLD had a higher insulin resistance and a more advanced form of liver disease¹⁷. This result is in agreement with a study carried out in adults, showing that individuals with non-alcoholic steatohepatitis and NAFLD had higher glucose parameters as well as prevalence of prediabetes and diabetes than those with non-alcoholic steatohepatitis alone⁴⁸. In addition, Lee *et al.*¹⁵ showed that most individuals with NAFLD (96.6%) concurrently had NAFLD. The positive predictive value of NAFLD in NAFLD was 69.4%, whereas the negative predictive value of NAFLD in normal pancreas was 96.4%. Taken together, these studies imply that NAFLD might be used as an initial indicator of ectopic fat deposition and as an additional factor, other than NAFLD, able to deteriorate gluco-insulinemic disarray.

So far, whether NAFLD contributes to the development of type 2 diabetes remains inconclusive. In obese Zucker diabetic fatty rats, a rapid increase in pancreatic fat preceded the onset of hyperglycemia⁴⁹. Wang *et al.*¹⁶ reported that the NAFLD group had a higher proportion of type 2 diabetes than the non-NAFLD group. Some human studies have shown that individuals with type 2 diabetes had an increased MRS- or MRI-measured pancreatic fat content compared with their non-diabetes group^{30,43,50}, whereas the other study observed no difference in pancreatic fat content measured by CT scans or histology at autopsy³⁴. This discrepancy might be attributed to different methods for assessing pancreatic fat content.

Although a growing body of evidence has linked NAFLD to diabetes through insulin resistance and β -cell dysfunction, most studies were cross-sectional in design. To our best knowledge, there is so far only one 5-year retrospective cohort study by Yamazaki *et al.*²⁸ that investigated longitudinal effects of pancreatic steatosis on incident diabetes. In that study, pancreatic steatosis at baseline was associated with an increased incidence of type 2 diabetes in univariate analysis. The association disappeared after adjustment for potential confounders (e.g., age, sex, BMI, liver attenuation and alcohol intake), suggesting that pancreatic steatosis seems not to be an independent risk factor for

future type 2 diabetes²⁸. However, that study still had some limitations. First, it remains to be elucidated whether the findings could be observed in populations other than the Japanese population, because the pathogenesis of type 2 diabetes and adipose tissue distribution can vary in different ethnicities. Second, the study participants were mainly middle-aged adults (mean age 51 ± 9.8 years), and the follow-up period of 5 years is relatively short. Thus, statistical power might not be sufficient to detect an association in this relatively low-risk subgroup. Therefore, additional studies with longer follow up in other ethnic groups are warranted to verify the clinical relevance of NAFLD in type 2 diabetes.

DRAIN FAT OUT OF THE PANCREAS: NORMALIZATION OF β -CELL FUNCTION AND REVERSAL OF TYPE 2 DIABETES

Type 2 diabetes has been considered as an inevitably progressive process, but it is now understood as a potentially reversible metabolic state precipitated by chronic excess ectopic fat deposition⁵¹. A current study used MRI to compare pancreatic fat change before and after bariatric surgery between participants with type 2 diabetes and the normoglycemic group. Participants with type 2 diabetes were found to have an attenuated first-phase insulin response and increased pancreatic fat content compared with the BMI-matched normoglycemic group. Of note, 8 weeks after bariatric surgery, first-phase insulin response and pancreatic fat content both returned to normal uniquely in the type 2 diabetes group, but not in the normoglycemic group⁵⁰. These findings are consistent with a previous study, which showed that acute restriction of dietary energy intake can normalize β -cell function in step with decreasing pancreatic fat content⁵². Even though a cause-and-effect relationship between pancreatic steatosis and type 2 diabetes has not been clearly clarified, the time-course data suggest that pancreatic steatosis might play a pivotal role in glucose metabolism. The various thresholds of susceptibility to the adverse metabolic effects of excess fat deposition in the pancreas could be a crucial point to determine whether or not β -cell failure occurs. In addition, the varying degree of liposusceptibility in relation to ethnic difference could explain the discrepancy of results on the relationship between NAFLD and β -cell function in previous studies.

CONCLUSION

With the rise in epidemic of obesity, NAFLD has become a growing health problem that deserves greater attention. Emerging studies suggest that NAFLD should not only be considered as an inert accumulation of fat, but also as an early marker of glucometabolic disturbance. *In vitro* and animal studies have shown that NAFLD might contribute to glucometabolic disorders through effects on insulin resistance and β -cell dysfunction. However, the data in humans remain inconclusive. To date, evidence to support the long-term effects of NAFLD on glucose homeostasis is insufficient, and much remains

unknown about NAFLD. Additional longitudinal research is required to explore the detailed mechanism and validate the clinical implications of NAFLD. In contrast, most past studies on NAFLD merely focus on pancreatic fat content at a single point in time and dismiss the influence of individual degree of liposusceptibility. Future studies must focus on tracing the time sequence of pathophysiological events in the dynamic change of pancreatic steatosis, and hence to unravel the role of NAFLD in the development of diabetes and related metabolic disorders.

DISCLOSURE

The authors declare no conflict of interest.

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