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Editorial Board Member of *World Journal of Meta-Analysis*, Zheng Li, PhD, Assistant Professor, Lecturer, College of Health Sciences, Jiangsu Normal University, Xuzhou 221000, Jiangsu Province, China. lizhengcpu@163.com

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Pancreatic fat in type 2 diabetes: Causal or coincidental?

Soham Mukherjee, Deep Maheshwari, Rimesh Pal, Naresh Sachdeva

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Soham Mukherjee, Deep Maheshwari, Rimesh Pal, Naresh Sachdeva, Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Naresh Sachdeva, MSc, PhD, Professor, Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Endocrinology Lab, Research Block-B Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India. naresh_pgi@hotmail.com

Abstract

Type 2 diabetes (T2D) is a multifactorial metabolic disorder affecting more than 450 million people across the globe. With the increasing prevalence of T2D and obesity, the role of fat accumulation at sites other than subcutaneous adipose tissue has received significant attention in the pathophysiology of T2D. Over the past decade and a half, a pressing concern has emerged on investigating the association of pancreatic fat accumulation or pancreatic steatosis with the development of disease. While a few reports have suggested a possible association between pancreatic fat and T2D and/or impaired glucose metabolism, a few reports suggest a lack of such association. Pancreatic fat has also been linked with genetic risk of developing T2D, prediabetes, reduced insulin secretion, and beta cell dysfunction albeit some confounding factors such as age and ethnicity may affect the outcome. With the technological advancements in clinical imaging and progress in assessment of pancreatic beta cell function, our understanding of the role of pancreatic fat in causing insulin resistance and development of various etiologies of T2D has significantly improved. This review summarizes various findings on the possible association of pancreatic fat accumulation with the pathophysiology of T2D.

Key Words: Type 2 diabetes; Pancreatic fat; Steatosis; Glucose metabolism; Beta cell function; Non-alcoholic fatty pancreas disease; Obesity; Insulin resistance

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Core Tip: The concomitant rise in the incidences of obesity and type-2 diabetes (T2D) has increased interest in understanding the role of pancreatic fat accumulation or pancreatic steatosis in causing T2D. In the past few years, various researchers have attempted to decipher whether pancreatic fat has any causative role in the pathogenesis of T2D. While a few cross-sectional and retrospective studies have shown a positive association between pancreatic fat and T2D, there is a lack of well-controlled, prospective, and long-term follow-up studies that could clearly establish the role of pancreatic fat in causing T2D. Therefore, in light of the presently available evidence, the role of pancreatic fat as an independent predictor of T2D must be interpreted with caution.

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INTRODUCTION

The global increase in the incidence and prevalence of type 2 diabetes mellitus (T2D) has been linked to a parallel epidemic of obesity observed during the last few decades. This association of T2D and obesity has brought research interest in adipose tissue biology with gradual conceptual changes, and adipose tissue is no longer considered an inert lipid store but rather a metabolically active endocrine organ with an enormous capacity to secrete numerous metabolically active compounds and hormones[1-3].

In obese individuals, when storage capacity in adipose tissue is overwhelmed by the circulating lipids, progressive and abnormal accumulation in non-adipose tissue results in steatosis, which may involve the liver, skeletal tissue, heart, and pancreas[4,5]. Accumulating lipid droplets within cells may result in cellular dysfunction and cell death, also known as lipotoxicity[6]. Further, human studies suggest that lipid content in hepatocytes and skeletal tissue is a more important determinant for insulin resistance than circulating free fatty acids[7]. Although obesity-related ectopic fat deposition in the liver, primarily caused by non-alcoholic fatty liver disease (NAFLD), and its relationship with metabolic syndrome and T2D have been studied extensively, ectopic fat accumulation in other organs, especially the pancreas, and their clinical significance have received little attention from the researchers until recently.

Ogilvie first described the term "pancreatic lipomatosis" to denote excessive fat accumulation in pancreatic tissue. After that, various terminologies were used to describe the same, which include pancreatic steatosis, fatty infiltration or replacement, fatty pancreas, and non-alcoholic fatty pancreas disease (NAFPD)[8]. However, pancreatic fat accumulation or steatosis may also be seen in nonobese individuals due to various other etiologies, including chronic alcohol use, viral infections, chemotherapy, and cystic fibrosis[8,9]. Therefore, some authors suggested restricted use of the term NAFPD for those cases of pancreatic steatosis which are associated with metabolic syndrome and obesity, as this condition may be reversed by weight loss or the use of certain medications[9-11]. Whereas, in the other situations where irreversible fatty replacement occurs following acinar cell death, the preferred terminology used is 'fatty replacement'[9]. Table 1 depicts the nomenclature used to describe accumulation of fat in the pancreas[9,12]. The pancreas can be roughly sub-divided into endocrine pancreas containing islets and exocrine pancreas that is responsible for secretion of digestive enzymes, and is comprised of lobes, segregated by connective tissues. Pancreatic fat accumulation involves intralobular or interlobular adipocyte infiltration or presence of intracellular lipid droplets[13,14].

The association between T2D and NAFPD is controversial. Some studies reported more pancreatic fat accumulation in T2D subjects than in those without diabetes, while others reported no difference[15-17]. In this review, we will discuss the epidemiology of NAFPD, the pathophysiology of pancreatic fat accumulation in T2D, its relationship with T2D, and the effect of anti-diabetic medications on pancreatic steatosis.

EPIDEMIOLOGY

The studies documenting the true global prevalence of pancreatic steatosis are limited[18]. Besides, the available data is highly variable, affected largely by the ethnicity and age of the population being studied and the modality used for the detection of pancreatic fat[19]. Accordingly, the prevalence of pancreatic steatosis in the general population is estimated to be roughly between 16% to 35%[3-6,20-23]. In a recently conducted cross-sectional study in Japan, the prevalence of pancreatic fat accumulation, as determined using transabdominal ultrasonography, was 46.8%. Amongst the subjects with pancreatic steatosis, there was preponderance of males and subjects with higher prevalence of lifestyle-related

Table 1 Nomenclature of pancreatic fat accumulation

Name	Definition
Pancreatic steatosis or fatty pancreas or pancreatic lipomatosis	General terminology for accumulation of pancreatic fat
Lipomatous pseudohypertrophy	An extreme form of pancreatic fat accumulation with uniform or focal enlargement of the pancreas and replacement of exocrine system by adipose tissue which is unrelated to obesity
Fatty replacement	Replacement with adipocytes following death of pancreatic acinar cells
Fatty infiltration	Obesity-related infiltration of the pancreas with adipocytes
NAFPD	Pancreatic fat accumulation along with obesity and metabolic syndrome
Non-alcoholic fatty steatopancreatitis	Pancreatitis resulting from accumulation of pancreatic fat

NAFPD: Non-alcoholic fatty pancreas disease.

diseases, including fatty liver disease[7,24].

A systemic review and meta-analysis involving over 12000 individuals showed a prevalence rate of 33% [95% confidence interval (CI): 24%-41%]. The results of meta-regression showed that the prevalence of pancreatic steatosis was associated with hypertension, T2D, and metabolic syndrome. Of note, 9 of 11 studies included in this study were conducted in Asian populations, thereby raising questions regarding the generalizability of the data[8,25]. More studies in different ethnic populations, especially those with high rates of obesity and metabolic syndrome, would be valuable in delineating the true global prevalence of pancreatic steatosis.

DIAGNOSIS OF NAFPD

Pancreatic enzymes are rarely raised in NAFPD, therefore, serological investigations are not useful in diagnosing NAFPD. There are various imaging modalities available, however, there are certain challenges associated with the use of these technologies in diagnosing NAFPD, as listed below.

Transabdominal ultrasonography: It is a widely available and non-invasive method of pancreatic fat assessment. It detects pancreatic steatosis as an increase in echogenicity within the pancreatic parenchyma, as compared to renal and hepatic echogenicity. This is an operator dependent procedure and presence of overlying bowel gas shadow and obesity may interfere with the visualization and interpretation of pancreatic steatosis[26].

Endoscopic ultrasound (EUS): It is an invasive endoscopic procedure, which allows good visualization of the pancreas. Various studies have revealed the relationship between increased pancreatic echogenicity and the presence of obesity and fatty liver[22,27]. This modality is also limited by operator dependency. Further, apart from NAFPD, the presence of pancreatic fibrosis may also result in increased echogenicity of pancreatic parenchyma, thus resulting in false positive interpretation[28].

Computed tomography (CT): Fat infiltration in the pancreas is detected as hypodensity (in Hounsfield units) as compared to the adjacent spleen[29]. However, this method is also operator dependent. Saisho *et al*[16] demonstrated that CT evaluation using fat/parenchyma ratio is a useful method to detect NAFPD.

Magnetic resonance imaging (MRI): MRI is the most preferred method for detecting pancreatic steatosis at present. It is non-invasive, safe, and highly sensitive for detecting pancreatic fat. Its accuracy in identifying pancreatic steatosis is comparable with that of histopathological examination[30,31].

MRI proton density fat fraction: This modality allows quantification of pancreatic fat with high accuracy[32].

PATHOPHYSIOLOGY OF PANCREATIC FAT ACCUMULATION

Obesity has been implicated as the most important risk factor for NAFPD[33]. Increased BMI in human studies was found to be associated with pancreatic fat accumulation[21]. Moreover, animal studies in mice models revealed that obesogenic diets for mothers during pregnancy and lactation might result in NAFPD through alterations in circadian metabolic patterns and endoplasmic reticulum stress[34,35]. In obesity, both mechanisms of pancreatic steatosis, *i.e.*, fat replacement (adipocytes replacing dead acinar cells) and fat infiltration (*i.e.*, fat accumulation), go hand in hand[9].

Age and male sex are other risk factors for NAFPD[36]. Evidence from epidemiological studies indicates a positive association of NAFPD with age[36,37]. NAFLD is another important risk factor for

pancreatic steatosis. Lee *et al*[38] found a concurrence rate of 67.9% between NAFLD and NAFLD, with a high negative predictive value for NAFLD (96.4%) in patients with a normal pancreas. Uygun and colleagues reported a strong association between non-alcoholic steatohepatitis (NASH) and NAFLD. About half of these patients with NASH had concurrent NAFLD[39]. In contrast to the above finding, another study reported that NAFLD was significantly associated with advanced stage of hepatic fibrosis but lacked any correlation with NASH[40].

Besides, sedentary lifestyle, smoking, consumption of excessive meat, hypertension, hyperferritinemia, and low lipase activity in serum are other potential risk factors for pancreatic steatosis[20-22,41-43]. The various risk factors for NAFLD are summarised in Figure 1.

While the association between obesity and NAFLD has been conclusively demonstrated, the underlying mechanism remains unclear. Contemporary research on NAFLD mainly focuses on the prevalence and clinical implications, but the literature is scarce regarding genetics and underlying molecular mechanisms. However, some evidence points towards the role of adipocyte-derived cytokines and inflammatory factors in the pathogenesis of NAFLD, particularly those induced by free fatty acids (FFAs). Animal studies in rats revealed that FFA-induced hyperlipidemia was associated with increased expression of tumor necrosis factor (TNF- α), interleukin (IL-6), and monocyte chemoattractant protein-1 (MCP-1) with a significant simultaneous increase in body fat[44,45]. An *in vitro* study has shown that palmitic acid (a saturated FFA) could induce increased expression as well as secretion of IL-6 and IL-8, which was associated with a significant increase in intracellular fat content[46]. However, there is some contradictory evidence as well. In a recent *ex vivo* study on blood mononuclear cells, palmitic acid, γ -linolenic acid, and arachidonic acid were found to have minor effects on the gene expression of pro-inflammatory factors, including TNF- α , IL-6, and cyclooxygenase-2, whereas, oleic acid, α -linolenic acid, and docosahexaenoic acid reduced the expression of these genes[47]. Further research in this area is warranted to draw some meaningful conclusions.

Further, progressive accumulation of pancreatic fat may have a role in the pathogenesis of pancreatic cancer. This hypothesis was endorsed by a study which showed relation between high-fat diets and pancreatic cancer risk[48]. There is also evidence in the literature which revealed a direct association between pancreatic steatosis and the incidence of pancreatic cancer[49,50].

Influence of adipocyte-derived factors on beta cell function

Adipocytes and preadipocytes secrete adiponectin and leptin, respectively[51]. The direct effect of adiponectin and leptin on beta-cell survival and function has been studied widely using *in vitro* models and are detailed in several reviews[52-55]. Adiponectin secreted from the adjacent adipocytes acts on beta cells *via* the adiponectin receptor 1 and thereby promotes beta cell survival and insulin secretion. Leptin secreted from preadipocytes acts on the leptin receptor in a paracrine fashion, resulting in inhibition of insulin release.

Sympathetic stimulation and fasting state result in adrenaline and glucagon secretion, which in turn leads to activation of β -adrenergic receptors and glucagon receptor on adipocytes, respectively, with a consequent increase in lipolysis and release and local elevation of fatty acids[56]. In acute conditions, fatty acids act on fatty acid receptor 1 (FFAR1/GPR40) and stimulate insulin release from the beta cells [57]. However, when chronically elevated, fatty acids at high concentrations may lead to endoplasmic reticulum stress and beta cell apoptosis[58,59]. Fatty acids can also act on the Toll-like receptor 4 (TLR4) and mediate beta cell death and islet inflammation[55,60]. TLR4-dependent activation of IL-8 and MCP-1 results in monocyte chemotaxis. Besides, activation of TLR4 on tissue macrophages induces the cytotoxic cytokine IL-1 β release resulting in beta cell death[60].

ASSOCIATION OF PANCREATIC FAT AND T2D

Studies showing association of pancreatic fat with T2D

With respect to pancreatic fat accumulation, several studies have reported its positive association with the development of T2D[39] (Table 2). In 2007, Tushuizen *et al*[15], reported the association between beta cell dysfunction and pancreatic fat content, leading to T2D development for the first time. The authors observed higher median pancreatic fat content in T2D subjects as compared to age and BMI matched controls (20.4% *vs* 9.7%, $P = 0.032$). However, they noted a significant association of pancreatic fat content with beta cell dysfunction in non-diabetic controls, rather than in patients with T2D. These findings suggest that pancreatic fat accumulation may contribute to beta cell dysfunction and T2D development in susceptible individuals and once overt diabetes sets in, additional factors may account for further decline in beta cell function. Nevertheless, all subjects demonstrated that pancreatic fat content had an inverse correlation with insulinogenic index and beta-cell glucose sensitivity. The findings suggest that pancreatic fat accumulation might contribute to the development of T2D, although the results need to be validated in larger cohorts[15]. A cross-sectional study in 2013 by Ou *et al*[37], found that NAFLD participants were more likely to acquire prediabetes [odds ratio (OR) = 1.798, 95%CI: 1.544-2.094] or diabetes (OR = 2.578, 95%CI: 2.024-3.284). Amongst all subjects, those with fatty pancreas were associated with diabetes (OR = 1.379; 95%CI: 1.047-1.816) as well as prediabetes (OR = 1.222;

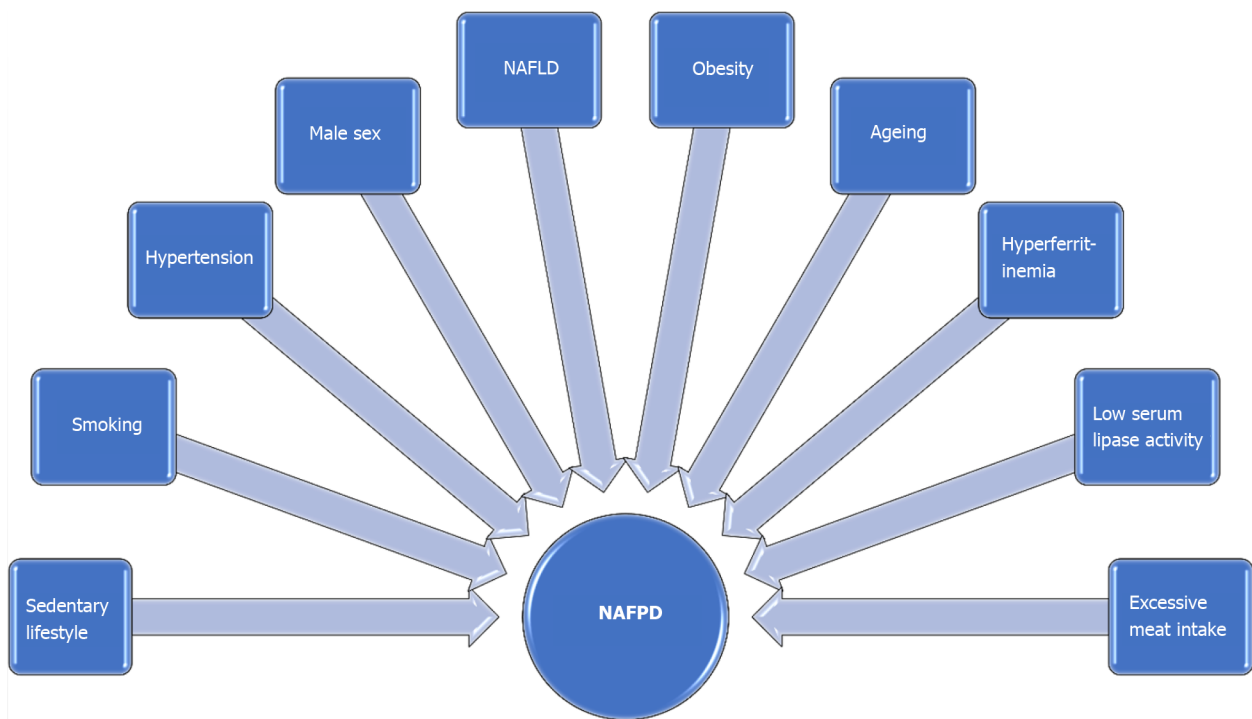
Table 2 Studies showing association or lack of association between pancreatic fat and type 2 diabetes

S.No.	Title	Inference/key observation	Ref.
Studies showing association of pancreatic fat with T2D			
1	Pancreatic fat infiltration, β -cell function and insulin resistance: A study of the young patients with obesity	Elevated blood glucose levels and reduced beta cell function (HOMA- β and IGI) were reduced in subjects with HPF	Wen <i>et al</i> [65], 2022
2	Association of pancreatic fat content with type II diabetes mellitus	Elevated fat content in the pancreatic tail region may identify patients at risk for T2D	Nadarajah <i>et al</i> [64], 2020
3	Pancreatic steatosis associates with impaired insulin secretion in genetically predisposed individuals	Pancreatic fat leads to impairment of beta-cell function in subjects at genetic risk for diabetes	Wagner <i>et al</i> [66], 2020
4	Longitudinal association of fatty pancreas with the incidence of type-2 diabetes in lean individuals: a 6-year computed tomography-based cohort study	Lean subjects with fatty pancreas can lead to development of T2D	Yamazaki <i>et al</i> [67], 2020
5	Association of pancreatic steatosis with chronic pancreatitis, obesity, and type 2 diabetes mellitus	T2D is associated with higher pancreatic fat along with visceral and subcutaneous adiposity	Tirkes <i>et al</i> [62], 2019
6	Pancreatic fat content is associated with β -cell function and insulin resistance in Chinese type 2 diabetes subjects	Male subjects with T2D, demonstrated positive association between pancreatic fat content and insulin resistance	Lu <i>et al</i> [63], 2019
7	The effect of fatty pancreas on serum glucose parameters in patients with non-alcoholic steatohepatitis	NASH patients with high pancreatic fat had impairment in glucose metabolism	Uygun <i>et al</i> [39], 2015
8	Pancreatic fat and β -cell function in overweight/obese children with non-alcoholic fatty liver disease	Association of higher pancreatic fat content in subjects with prediabetes as compared to non-diabetic NAFLD obese children	Pacifico <i>et al</i> [61], 2015
9	The association between non-alcoholic fatty pancreas disease and diabetes	NAFLD and fatty pancreas were linked to diabetes, irrespective of age, gender, obesity, or other cardiometabolic risk factors	Ou <i>et al</i> [37], 2013
10	Pancreatic fat content and β -cell function in men with and without type 2 diabetes	Inverse correlation of pancreatic fat content with insulinogenic index and beta-cell glucose sensitivity in all the study subjects	Tushuizen <i>et al</i> [15], 2007
Studies showing lack of association of pancreatic fat with T2D			
1	Lack of independent association between fatty pancreas and incidence of type 2 diabetes: 5-year Japanese cohort study	No independent association between T2D and pancreatic fat was observed upon correction for possible confounders such as BMI and hepatic attenuation	Yamazaki <i>et al</i> [68], 2016
2	Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans	Pancreatic fat was related to age, but not to blood glucose levels. No association between pancreatic fat and insulin secretion or beta cell activity in T2D subjects was observed	Begovatz <i>et al</i> [71], 2015
3	Ethnic differences in pancreatic fat accumulation and its relationship with other fat depots and inflammatory markers	No correlation between pancreatic fat and beta cell function was observed, during intravenous glucose tolerance tests in obese normoglycemic adolescents	Lê <i>et al</i> [69], 2011
4	Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on β -cell function in individuals with impaired glucose metabolism	Pancreatic fat was increased in individuals with impaired glucose tolerance, without any direct relation with β -cell function	van der Zijl <i>et al</i> [70], 2011
5	Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome	Association between pancreatic fat and insulin resistance was mediated by visceral adiposity	Lee <i>et al</i> [38], 2009
6	Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes	Pancreatic fat levels increases with aging and obesity; however, it remained unchanged in subjects with T2D	Saisho <i>et al</i> [16], 2007

HPF: High pancreatic fat; HOMA- β : Homeostasis model assessment of β -cell function; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; T2D: Type 2 diabetes; IGI: insulinogenic index.

95%CI: 1.002-1.491), particularly in males. Similarly, an observational study in obese children with NAFLD by Pacifico *et al*[61] reported a significantly higher pancreatic fat content in subjects with prediabetes (3.60%) as compared to non-diabetic subjects (1.90%).

Over the last 5 years, the number of studies demonstrating the association between pancreatic fat content and T2D development has been on the rise. A retrospective study by Tirkes *et al*[62] in 2019, reported a direct association between pancreatic fat accumulation and fat within the visceral compartment. Subjects with T2D had higher pancreatic steatosis and elevated subcutaneous fat content. A retrospective study by Lu *et al*[63] in 2019, reported that T2D subjects ($n = 78$) had more pancreatic fat in comparison to non-diabetic subjects ($n = 35$) (pancreatic fat content 7.06% *vs* 5.36%). The pancreatic fat content had a positive association with insulin resistance and abnormal glucose metabolism as assessed by oral glucose tolerance test (OGTT) in male T2D subjects. The authors also reported that subjects with shorter diabetes duration were associated with insulin resistance and beta cell dysfunction. Another retrospective study by Nadarajah *et al*[64] in 2020, was performed to determine



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Figure 1 Implicated risk factors for non-alcoholic fatty pancreas disease. NAFP: Non-alcoholic fatty pancreas disease.

the association between regional pancreatic fat content and the risk of developing T2D. A significant difference was observed in the fat content in the pancreatic head, pancreatic body, and pancreatic tail in subjects with T2D and healthy controls, respectively. Upon regression analysis between the healthy control and prediabetes group, a significant difference was observed between fat content in the pancreatic tail region (OR = 1.1, 95%CI: 1.026–1.178; $P = 0.007$). ROC curve analysis showed an 81.3% specificity and 45.5% sensitivity in predicting the development of T2D within 4 years in subjects with fat content > 10% in the pancreatic tail region. Recently, a retrospective study in obese young subjects was performed, where pancreatic fat content was analysed by IDEAL-IQ MRI, on the basis of which the subjects were subgrouped as having high pancreatic fat (HPF) (> 6.2%) and normal pancreatic fat (NPF) (< 6.2%). The early and total insulin secretion during OGTT, *i.e.*, $AUC_{INS_{0-120}}/AUC_{GLU_{0-120}}$, was reported to be significantly reduced in the HPF group when compared with the NPF group (6.41 *vs* 16.01). Further, the subjects with HPF had significantly higher glucose levels during OGTT and the beta cell function in terms of homeostasis model assessment of β -cell function (HOMA- β) and insulinogenic index was also significantly reduced[65].

The genetic background has also been implicated in influencing pancreatic fat accumulation and insulin secretion. Subjects with a high genetic risk of T2D reported an increase in pancreatic fat content associated with lower insulin secretion by Wagner *et al*[66] in 2020. Upon multivariate regression analysis, insulin secretion was observed to be negatively correlated with pancreatic fat and genetic risk score for T2D. Therefore, based on the intensity of the genetic risk score of T2D, pancreatic fat may have a different association with insulin secretion. Recently, a retrospective cohort study by Yamazaki *et al* [67] in 2020, demonstrated a strong link between high levels of pancreatic fat and T2D in lean individuals. Subjects with low pancreas attenuation (< 46.9 HU) on CT were reported to have fatty pancreas and the incidence of T2D (4.13%) was higher at lower pancreas attenuation levels in lean individuals. Upon regression analysis, a strong association between pancreas attenuation and T2D incidence was observed (OR = 2.62, in subjects with fatty pancreas and OR = 1.20, in subjects with normal pancreas). A similar association was observed when P/S (ratio of pancreas attenuation to spleen attenuation) & P-S (difference between pancreas attenuation and spleen attenuation) were calculated.

Studies showing lack of association of pancreatic fat with T2D

While some of the cross-sectional observational studies have noted the association of NAFP with T2D, controversies exist in this regard (Table 2). There is some evidence that also suggests that NAFP may be a marker of beta cell dysfunction rather than a causative factor for the same.

Saisho *et al*[16] in 2007 reported that pancreatic fat, as measured by CT scans and at autopsy, increased with aging and obesity; however, it did not increase in T2D. Although most of the previously reported studies showing the association of pancreatic steatosis with T2D are cross-sectional in nature, the literature is sparse in regards to longitudinal studies. Yamazaki and colleagues, in a retrospective

cohort study, did not find an independent association between T2D and pancreatic steatosis as the association disappeared after the results were adjusted for potential confounders, including BMI and hepatic attenuation[68].

Many authors also did not find any independent association of pancreatic steatosis with marker of insulin resistance, the pathophysiologic hallmark of T2D. Lê *et al*[69] in 2011 did not observe any significant association between pancreatic fat fraction and markers of insulin sensitivity in obese individuals. They also noted that visceral adipose tissue and circulating free fatty acids were the most important determinant for pancreatic steatosis. In another study, pancreatic steatosis was found to be associated with visceral fat and HOMA-IR. However, after adjustment for the visceral fat area, the correlation with insulin resistance disappeared. It suggests that the association between pancreatic fat and insulin resistance was mediated by visceral adiposity. This observation revealed that a fatty pancreas might be a merely associated finding with generalized visceral adiposity[38].

Beta cell failure is required for transition from prediabetes to overt T2D stage. As far as beta cell function is concerned, most human and animal studies have shown an inverse relationship with pancreatic fat accumulation; however, contradictory evidence also exists.

van der Zijl *et al*[70] in 2011 demonstrated that the impairments in beta cell function as assessed by the hyperglycaemic clamp in patients with prediabetes were accompanied by pancreatic fat accumulation; however, they failed to show any relation between pancreatic steatosis and beta cell function. Lê *et al*[69] also did not find any correlations between pancreatic fat fraction and markers of beta cell function as assessed during intravenous glucose tolerance tests in obese normoglycemic adolescents. Further, no relations were observed between pancreatic fat infiltration and beta cell function across the spectrum of glucose tolerance in another study[71].

CONCLUSION

With the first report on pancreatic fat accumulation or pancreatic steatosis emerging as early as in 1933 [9], it took over 60 years to suggest a possible link between pancreatic steatosis and T2D, when van Geenen *et al*[72] in 1984 hypothesized that obesity and the associated insulin resistance are implicated in the infiltration of adipocytes in the pancreas. The studies conducted thereafter, established the fact that pancreatic fat accumulation is a major manifestation of metabolic syndrome, a common denominator in pathogenesis of T2D as well. The concept is still evolving and it is only after the studies in the past decade and a half that the picture is getting clearer. Several cross-sectional studies and a very few longitudinal studies have shown a positive association of pancreatic steatosis with T2D, however, BMI and NAFLD remain as potential confounders. Although the advancements in imaging technologies have now improved assessment of pancreatic fat content, there is a dearth of well-controlled prospective studies indicating functional consequences of pancreatic steatosis, especially in terms of insulin resistance and/or beta cell function.

Next, the age and population specific variations add to the complexities in correlating pancreatic fat with pathophysiology of T2D. Nevertheless, the emerging data suggests that pancreatic fat is an important contributing factor in the pathogenesis of T2D. Data from studies in lean subjects- and use of dynamic tests like OGTT and advanced methods of assessment of beta cell function indicate that pancreatic fat accumulation can predict development of T2D to some extent. Whether or not obesity, especially visceral obesity, is the initiating factor in causing pancreatic steatosis leading to T2D again remains to be seen. However, T2D being a multifactorial entity with varying genetic predispositions, the role of pancreatic fat must be interpreted with caution after taking into considerations various other factors associated with pathogenesis of T2D.

Finally, the concomitant increase in the incidence and prevalence of obesity and T2D worldwide necessitates the need for well controlled longitudinal cohort studies to stratify the role of pancreatic fat as an independent predictor of T2D.

FOOTNOTES

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ORCID number: Soham Mukherjee 0000-0003-1648-7610; Deep Maheshwari 0000-0003-4512-7948; Rimesh Pal 0000-0003-4859-9393; Naresh Sachdeva 0000-0001-6289-4749.

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