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Review Article

Hepato-pancreatic fat-fetuin A based axis in context of diabetes and its reversal

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ABSTRACT

Recent research has focused on reversing type 2 diabetes mellitus (T2DM) via lifestyle-related approaches, including low-calorie diets. Metabolic parameters such as fat accumulation in the liver and pancreas have garnered much attention in this context. Pancreatic fat has been linked with adverse metabolic consequences including T2DM and metabolic syndrome. Obesity is the primary factor leading to ectopic fat in organs such as the liver and pancreas. This review examines the potential role of pancreatic fat in the pathogenesis of T2DM and whether it can be a potential target in reversing this chronic condition.

Keywords: T2DM, Pancreatic fat, Obesity, Diabetes reversal

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by progressive β-cell exhaustion that is accentuated by insulin resistance. The resistance is primarily triggered by central obesity and is accompanied by fat accumulation in non-adipose tissues including the liver, skeletal muscle and the heart.[1] Both visceral fat and ectopic fat deposition are linked to metabolic consequences including diabetes.[2] Fatty storage in the pancreas or the term non-alcoholic fatty pancreas disease was introduced in 2007 and an evolving body of research has since linked it to chronic pancreatitis and pancreatic cancer.[2-4] The identified mechanisms for both these conditions are lipotoxicity and local inflammation. Further, the fatty pancreas has also been linked to β-cell dysfunction leading to impaired insulin secretion due to β-cell apoptosis.[5]

The growing body of evidence linking hepatic as well as pancreatic fat to the pathogenesis of T2DM prompted the authors to review the evidence and clinical implications in the potential reversal of this condition.

PANCREATIC FAT AND CLINICAL IMPLICATIONS

The pancreas lies in the retroperitoneal space of the upper abdomen and is 12-15 cm in length and 5 cm in width with a thickness of 3 cm (Figure 1).

The term fatty pancreas was first described by Ogilvie, who reported that obese cadavers had a 17% higher pancreatic weight compared to lean cadavers.[6] The primary mechanisms of fat storage in the pancreas is due to infiltration by adipocytes and ectopic intracellular accumulation as lipid droplets. Nonalcoholic fatty pancreas disease (NAFPD) is defined as pancreatic fat accumulation associated with obesity and absence of significant alcohol consumption.[7] Table 1 describes the classification of pancreatic fat and the common

nomenclature used to describe conditions associated with it.[6]

Table 1: Nomenclature of the fat in the pancreas.[6]

Name	Definition
Pancreatic steatosis; pancreatic lipomatosis; fatty pancreas	General terms for pancreatic fat accumulation
Fatty replacement	Death of acinar cells-replacement with adipocytes
Fatty infiltration	Infiltration with adipocytes due to obesity
NAFPD	Pancreatic fat accumulation + obesity and metabolic syndrome
NASP	Pancreatitis due to pancreatic fat accumulation

NAFPD: Nonalcoholic fatty pancreas disease; NASP: non-alcoholic steatopancreatitis

The prevalence of NAFPD ranges from 16% to 35% in Asian population although accurate data is lacking. NAFPD has been linked with several metabolic risk factors primarily obesity, age, and non-alcoholic fatty liver disease (NAFLD).[8] Since NAFLD has a strong association with T2DM, it stands to reason that NAFPD would show a similar association.[8] Besides obesity, age, and NAFLD, the etiopathogenesis of NAFPD includes alcohol consumption, malnutrition, low birth weight, drugs such as rosiglitazone, steroids, octreotide, and gemcitabine; and rare disorders such as cystic fibrosis, b-thalassemia, Diamond-Blackfan anemia, and hereditary hemochromatosis. The clinical consequences of pancreatic fat include impaired insulin secretion, chronic pancreatitis, possible link to pancreatic cancer, and exocrine dysfunction.[6]

DIAGNOSIS OF NAFPD

Since pancreatic fat accumulation is the cardinal feature of NAFPD, a histological biopsy is considered the most accurate method of diagnosis, however, practical difficulties mean that this method cannot be used routinely. Hence, non-invasive methods include transabdominal ultrasonography (TUS), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance elastography (MRE) and magnetic resonance spectroscopy.[8]

METABOLIC CONSEQUENCES OF LIVER AND PANCREATIC FAT

Pancreatic fat increases with age, while volume and parenchyma decrease with age. However, the metabolic implications of hepato-pancreatic fat are devastating. Macauley et al found that the mean pancreatic volume was found to be 33% less in type 2 diabetes than in normal individuals.

The authors also found gross abnormalities of the pancreas in early type 2 diabetes, documenting a lower volume, irregular morphology, and higher fat content in these individuals.[9] The morphologic findings included irregular and serrated border in T2DM patients as compared to normal individuals.[9]

A meta-analysis by Singh et al found that NAFPD is highly prevalent and is associated with increased risk of metabolic syndrome and its components including hypertension and diabetes. The authors suggested using 6.2% as the normal pancreatic fat cut-off point.[10]

NAFPD AND LONG-TERM REMISSION OF T2DM

The twin cycle hypothesis postulates that excess fat might lead to dysfunction of both liver and pancreas resulting in the etiopathogenesis of T2DM (Figure 2).[11]

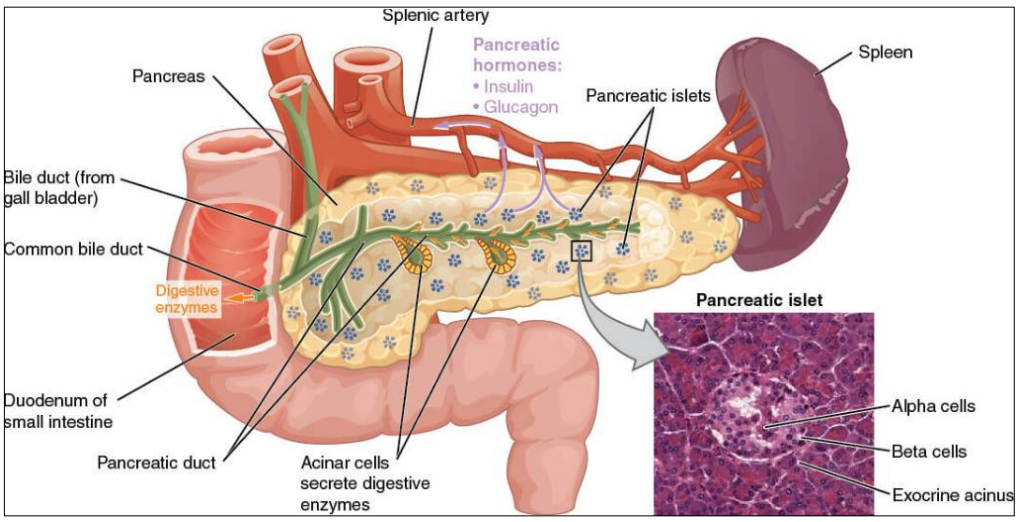

Figure 1: Gross anatomy of the pancreas.

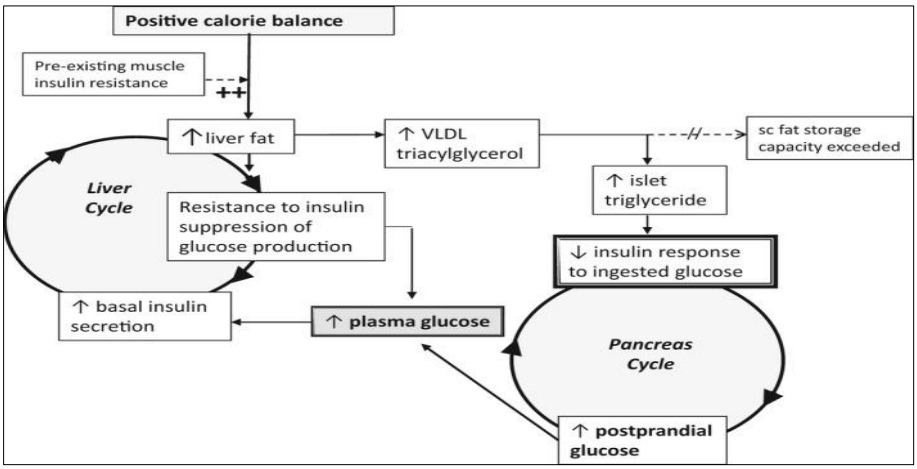

Figure 2: Twin cycle hypothesis.[11]

The infiltration of adipocytes causes inflammation leading to activation of Fetuin A, which is a hepatokine that impairs beta-cell function and accentuates inflammation. Research has indicated that elevated circulating Fetuin-A is associated with obesity and related complications, including TDM and metabolic syndrome.[12]

CONCLUSION

An evolving body of research has demonstrated that elevated pancreatic fat is linked to impaired glucose metabolism leading to T2DM. Pancreatic volume decreases with age and in T2DM, while the fat content increases with age as well as in T2DM. Research has also zeroed in on the key role played by Fetuin A, with elevated levels being implicated in insulin resistance as well as hyperglycemia. Approaches to reduce pancreatic fat may have clinical implications in the reversal of T2DM and warrant further research.

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