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Non-Alcoholic Fatty Pancreas Disease and Type 2 Diabetes Mellitus

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Article Info

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Abstract

Obesity results in fat deposition in multiple organs as liver, pancreas, heart and kidneys. Oxidative stress leads to local release of fat-derived cytokines and induction of inflammatory process and organ dysfunction. Available data about the effect of obesity on pancreatic fat and cytokines, and pathogenesis of nonalcoholic fatty pancreas disease (NAFPD) are limited. This study aims to clarify effect of obesity on pancreatic fat and the relation between NAFPD and type 2 diabetes mellitus (T2DM). The available data suggest that in T2DM, obesity leads to nonalcoholic fatty pancreatic disease and decrease pancreatic fat achieved by dietary energy restriction alone may reverse T2DM through stabilization of both β-cells function and improve of hepatic insulin sensitivity.

Keywords: Diabetes Mellitus; Nonalcoholic Fatty Pancreas; Obesity.

Introduction

More than one billion are overweight people with body mass index (BMI) ≥ 25 worldwide; nearly 350 million of them are obese (BMI ≥ 30.0) [1]. Obesity is associated with multiple diseases, like diabetes mellitus, hypertension, and dyslipidemia. Obesity may cause fatty infiltration of several organs e.g. liver, pancreas, heart and kidneys. Oxidative stress potentiates the releases fat-derived cytokines locally which leads to inflammatory process and organ dysfunction [2]. Adipose tissue meets expectations as a endocrine organ with creation of adipokines asleptin, adiponectin, and cytokines as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), andmonocyte chemotactic protein-1 (MCP-1) [3]. In obese persons it was discovered that there is an increase leptin and decrease adiponectin production by fat cells which will results in macrophage and monocyte infiltration in the fat tissues. Macrophages infiltration produces IL-1b and myeloperoxidase (MPO), which further intensify the inflammatory progression [4]. The pancreas consists of 99% digestive glandular tissue and only 1% hormone-secreting islet cells. Ogilvie, [5] founds 17% pancreatic fat in obese cadavers compared to 9% pancreatic fat in lean cadavers. Olsen (1978) [6] found that pancreatic fat (pancreatic lipomatosis) was correlated with age, obesity, and T2DM. Newly, magnetic resonance imaging (MRI) and computed tomography (CT) studies have correlated pancreatic fat with obesity [7]. Some authors suggest that obesity increases the severity of acute pancreatitis [8]. Fatty liver disease (FLD) is common; approximately one in five overweight individuals has fatty liver. People with an FLD are also likely to develop excess fatty deposits in the pancreas. Some authors suggested that, it is possible to reverse a fatty liver and fatty pancreas [9]. It has been suggested that in metabolic syndrome, fat accumulation in the pancreas might prompt a comparable process that is termed as non-alcoholic steatopancreat it is (NASP). Patient with fatty pancreas is at risk of developing pancreatic cancer. Some studies suggest that diabetics are at higher risk of this cancer [10].

Nine percent of the global population has T2DM [11]. It is widely accepted that T2DM produced through a mixture over insulin resistance and poor insulin secretion. It was accepted that, insulin resistance alone cannot cause hyperglycemia [12], and T2DM arises only when the acute insulin response regarding the pancreatic β-cells is compromised [13]. However, the actual mechanisms underlying this process is still unclear. Excess pancreatic intracellular fatty acids metabolites may be a potential mechanism for T2DM [14]. A study done in obese rodents suggests that pancreatic triacylglycerol has an importance of in the pathogenesis of T2DM [15]. Mild concentrations of fatty acid exposure results in marked *in vitro* accumulation of triacylglycerol in human pancreatic islets [16].

Discussion

It was found that increased age, obesity, Cushing's syndrome, cystic fibrosis, and lipomatouspseudo hypertrophy have been associated with increased pancreatic fat infiltration. Lee et al. [15] assumed that pancreatic fat infiltration was a reversible process. It was discovered that, pancreatic islet cells are resistant to fatty infiltration [15]. Some studies found that obese mice with leptin-deficiency have increased percent of pancreatic cytokines and fat. Mathur et al. [17], found pancreas of the obese mice were heavier 'compared to those of their lean counterparts with significant increased intralobular and total pancreatic fat in the obese mice. Lipid analysis of obese mice pancreas showed marked increased triglycerides, total fat, and free fatty acids (FFAs) as well as significant increased cholesterol [17]. Matsumoto et al. [18] suggested a classification of fatty infiltration of the pancreas depends on the sparing of fat in the posterior aspect of the head of the pancreas, the uncinate and the area around the common bile duct due to differences in the embryologic development of the ventral and dorsal pancreatic buds [18]. Kovanlikaya et al. [19] confirmed the correlation between pancreatic fat and BMI using the 3-point Dixon technique.

Adipocytes enlargement leads to release of FFAs from omental and peripheral fat [3]. FFAs potentiate their own release by convincing insulin resistance which will leads to increased lipolysis [20]. Animal studies revealed that elevated serum FFAs have several effects including i) increase accumulation of triglyceride, ii) pro-inflammatory NF-κB pathway activation, and iii) rise of tissue cytokines and reactive oxygen species (ROS) [21]. The change in the individual fats may result in increased TNF-and IL-1b, which have been linked to increased pancreatic triglycerides in the obese [22]. The raise of tissue cytokines will lead to fat oxidation, lipolysis, increase insulin resistance, and angiogenesis [23]. Mathur et al. [17] found a fourfold increase FFAs levels in the pancreatic tissue. Many research studies have interrelated serum FFAs with elevated level of serum cytokines [24]. Suganami et al. [25] observed that saturated fats induce cytokine production from adipose tissue macrophages. It was discovered that, pancreas of obese mice have significant increased IL-1b and TNF-a [17].

In humans, it was discovered that saturated fats palmitate and myristic acid are the only fatty acids that correlate with serum cytokine levels [26]. Palmitate is a vital fat for the production of ceramide, which is identified to facilitate inflammation [27]. Mathur A et al. [17] found more than fourfold increase in both palmitic and myristic acid levels in the obese murine pancreas compared to their lean counterparts. Raised insulin levels are identified to produce oxidative stress and fibrogenesis. Lipid peroxidation is another significant mediator of the second hit; with FFAs are the major sources [2]. Mitochondrion is considered the primary site of lipid peroxidation. Mitochondrial dysfunction has been documented in the pancreas of patients with type T2DM and leads to increased oxidation and generation of ROS [28]. Yan et al. [29] found that, diet with high fat content will results in increased lipid peroxidation and ROS and decreased pancreatic microcirculation in rats. These changes would produce an inflammatory state that was named nonalcoholic steatopancreatitis (NASP).

Patel NS et al. [30] used an advanced chemical shift-based gradient-echo MRI technique that measures the proton-density-fat-fraction (PDFF), a standardized and reproducible quantitative marker of fat content in the tissue. Older MRI techniques assessing steatosis are limited by T1 bias, T2 decay and multi-frequency signal-interference effects of protons in fat. This technique corrects the above restrictive factors and provides a more accurate evaluation of steatosis content using the PDFF measurement.

It was previously demonstrated that weight loss over 8 weeks in people with T2DM can normalize the intrapancreatic triacylglycerol concentration and the acute insulin response with normalization of blood glucose level [31]. This normoglycemic state will continue, as long as weight regain is avoided [32]. In patients with T2DM, weight loss allows retrieval of first-phase insulin secretion and declines increased pancreatic triacylglycerol content [33]. Local lipolysis will lead to increase interstitial and intracellular concentrations of fatty acids which will inhibit pancreatic β-cell function. Fatty acid receptors are expressed in the pancreatic β-cells and allow recovery of insulin secretion when knocked out. Weight loss after Bariatric surgery is associated with decreased intrapancreatic triacylglycerol exclusively in T2DM individuals, with restoration of first-phase insulin secretion. In the normal glucose tolerance (NGT) group, no change occurred in the intrapancreatic triacylglycerol [34]. T2DM is associated with substandard glucagon-like peptide 1 (GLP-1) response to food ingestion [35] after Roux-en-Y gastric bypass (RYGB) is 2.6 fold increase of insulin secretion assessed by the intravenous glucose tolerance test disposition index has been reported [36].

It was detected that, calorie restriction alone has a similar restoration of normoglycemia [37]. Heni et al. [38] found that a negative correlation between pancreatic fat and insulin secretion in persons with impaired glucose tolerance/ impaired fasting glucose (IGT/IFG) and therefore, might represent an additional pathogenic factor of β-cell dysfunction.

Some studies found that fat, loss of the pancreas can reverse effects of T2DM, the pancreas can become able to make insulin normally, and blood glucose returns to normal. If fat in the pancreas really is the key factor that triggers T2DM, it offers a potential target for reversing the disease through drugs. However, at present the only way of lowering fat levels in the pancreas is to go on a strict diet [39]. Lim et al. [31] found that dietary energy restriction alone resulted in normalization of both β-cells function and hepatic insulin sensitivity in T2DM. This was associated with decreased liver and pancreatic triacylglycerol stores. The abnormalities underlying T2DM are reversible by decreasing dietary energy intake. Steven et al. [40] found that weight loss is associated with decrease intrapancreatic triacylglycerol in T2DM due to rather than decreased total body fat.

Conflict of Interest: I declare that there is no conflict of interest

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