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A mini review on role of macro- and micronutrients in managing intrapancreatic fat deposition

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Abstract

The increasing prevalence of obesity has drawn attention to intra-pancreatic fat deposition (IPFD), a condition associated with metabolic disorders such as type 2 diabetes, chronic pancreatitis, and pancreatic cancer. Although initially linked to general obesity, IPFD is now recognized in non-obese individuals, with its prevalence often underestimated due to the absence in International Classification of Diseases. Chemical shift-encoded magnetic resonance imaging (MRI) has become the preferred method for non-invasive quantification of IPFD, providing insights into its role in metabolic dysfunctions, including insulin resistance and lipotoxicity. This rapid review explored the pathophysiology of IPFD, focusing on fatty infiltration and replacement mechanisms, and discussed how dietary factors can influence their progression and management. Recent studies on macronutrient and micronutrient intake in relation to IPFD, particularly those using chemical shift-encoded MRI, were reviewed to identify dietary contributors and their metabolic impacts. Among macronutrients, excessive monosaccharide intake linked to worse outcomes, while resistant starch and monounsaturated fats showed protective effects. Micronutrients like manganese, selenium, iodine, and vitamins B3, B6, B12, and folate demonstrated significant metabolic benefits. Further research is needed to identify other dietary contributors and develop effective targeted nutritional interventions to reduce the burden of IPFD.

Keywords: intra-pancreatic fat deposition (IPFD); metabolic diseases, dietary intake, magnetic resonance imaging

1. INTRODUCTION

The increasing prevalence of obesity has brought attention to organ dysfunction linked to ectopic fat accumulation, such as intra-pancreatic fat deposition (IPFD), also known as fatty pancreas disease [1]. While a small amount of intra-pancreatic fat is normal and tends to increase with age, its excessive accumulation is more prevalent among individuals of Asian descent and has been strongly correlated to metabolic disorders, such as type 2 diabetes mellitus, chronic pancreatitis, and pancreatic ductal adenocarcinoma [1]. Although IPFD was initially thought to be exclusive to those with general obesity when first described by Robertson Ogilvie in the 1930s, it has since been recognized in non-obese individuals

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as well [2–4]. The absence of an International Classification of Diseases (ICD) code for fatty pancreas disease complicates its prevalence estimation in large-scale studies [5].

Chemical shift-encoded magnetic resonance imaging (MRI) has become the gold standard for quantifying IPFD [6]. Unlike computed tomography, which relies on attenuation values, MRI provides superior resolution for parenchymal organs such as the pancreas, enabling precise, non-invasive assessment of fat accumulation [6–8]. For example, an observational study from Hong Kong involving over 8000 individuals used MRI to estimate the prevalence of IPFD, which was 16.1% [9]. However, this finding represented a specific population, and its generalizability was deemed uncertain, highlighting the need for additional studies across diverse cohorts.

Several studies found the significant role of diet in the pathogenesis and treatment management of IPFD. For example, a randomized controlled trial from Israel demonstrated that a Mediterranean diet (characterized by low in carbohydrates and rich in unsaturated fats [(MUFA)]) significantly reduced IPFD (quantified by MRI) compared to a low-fat diet over an 18-month period [10]. This suggests that dietary modifications may play an important role in managing this condition.

In this rapid review, the primary objective was to introduce the pathophysiology of IPFD and the secondary objective was to review how dietary components, both macronutrients (carbohydrates and fats) and micronutrients (minerals and vitamins), can influence the development and progression of MRI-derived IPFD measurements and its associated metabolic sequalae.

2. PATHOPHYSIOLOGY & MECHANISM OF INTRA-PANCREATIC FAT DEPOSITION (IPFD)

IPFD has a significant impact on both endocrine and exocrine pancreatic diseases, including diabetes mellitus, cardiovascular conditions, acute and chronic pancreatitis, and pancreatic cancer.

IPFD has been associated with a spectrum of pancreatic diseases. A comprehensive review published in Nature Reviews Gastroenterology and Hepatology consolidated evidence from several large general-population-based cohort studies and systematic literature reviews linking IPFD with diabetes mellitus, acute and chronic pancreatitis, and pancreatic cancer [11]. The pathogenesis of these diseases often progresses along a continuum influenced by both the extent and distribution of fat within the pancreas.

IPFD develops through two primary mechanisms: fatty infiltration and fatty replacement. Fatty infiltration refers to the accumulation of excess adipocytes in pancreatic tissue, primarily in individuals without pre-existing pancreatic diseases, and is often driven by obesity [12–14]. By contrast, fatty replacement involves the substitution of pancreatic acinar cells with adipocytes following cell death. This process is commonly seen in cases of recurrent pancreatitis and is linked to genetic predisposition, viral infections, iron overload, corticosteroid use, or pancreatic duct obstruction [13]. Morphologically, IPFD is evidenced by inter-lobular or intra-lobular fat deposits, indicating both the degree and location of fat accumulation within pancreatic tissue. Understanding these mechanisms is essential for comprehending the development and progression of pancreatic diseases associated with IPFD.

2.1. Inter-lobular fat

Excess fat accumulation in the pancreas leads to the formation of inter-lobular adipocytes, which are resistant to lipolysis under normal conditions [15]. However, during lipolysis, these adipocytes release unsaturated fatty acids that inhibit mitochondrial complexes I and IV [16–18]. This mitochondrial dysfunction results in parenchymal necrosis and can lead to multisystem organ failure, exacerbating the severity of acute pancreatitis [19–22]. Elevated levels of fatty acids also stimulate the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, and worsen disease severity [17,23,24]. Moreover, mitochondrial dysregulation caused by these fatty acids raises intracellular calcium levels and oxidative stress, promoting apoptosis of β-cells and acinar cells [16,17,25,26]. This apoptosis impairs insulin secretion, increases insulin resistance, and contributes

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to the progression of metabolic syndrome [26,27].

2.2. Intra-lobular fat

Intracellular fat accumulation in acinar cells leads to the formation of lipid droplets, which disrupts the release of adipokines by increasing lipocalin-2 [28,29] and decreasing adiponectin and fetuin levels [30–32]. This disruption creates a pro-inflammatory environment that exacerbates systemic inflammation and metabolic disturbances, including lipotoxicity and endocrine dysfunction [33–36]. In addition to these metabolic effects, excess IPFD has been associated with pancreatic tumorigenesis. Elevated cytokine levels, such as C-C motif ligand 2, attract monocytes to the pancreas, where they become inflammatory macrophages [37,38]. High levels of inflammatory markers like leptin are associated with tumor necrosis factor-α, suggesting a role of IPFD in early pancreatic cancer development [39].

IPFD is also associated with the acinar-to-adipocyte transdifferentiation, a process where pancreatic acinar cells are transformed into adipocyte-like cells. This transformation is primarily driven by chronic inflammation and recurrent episodes of pancreatitis (such as c-Myc, Gata6, HNF6, STK11, and EWSR1/FLI1) drive this process [40–43], leading to the fatty replacement of pancreatic tissue [44]. Furthermore, intra-cellular fat in β-cells can lead to their dedifferentiation and functional impairment. Elevated free fatty acids reduce the expression of essential transcription factors (i.e., GATA6 and PAX4) and lead to β-cell dysfunction. This reduction further accelerates the development of diabetes mellitus and chronic pancreatitis [45–47].

The abovementioned mechanisms, including inter-lobular fat deposition, intra-lobular lipid accumulation and the acinar-to-adipocyte transdifferentiation, collectively illustrate the complex pathogenesis of IPFD and its contribution to pancreatic dysfunction. Given that these pathophysiological processes might lead to metabolic disturbances, it is essential to consider the role of moderating factors such as dietary intake.

3. DIET

Dietary intake emerges as an important modifiable factor influencing metabolic disturbances. Research showed that IPFD and elevated levels of fatty acids disrupt metabolism, impairing both insulin secretion and β-cell function [33,48,49]. Dietary intake is crucial in the pathogenesis and treatment management of IPFD, with both macronutrients and micronutrients influencing the progression of metabolic syndrome associated with IPFD [10,50,51]. Understanding how dietary components affect IPFD is essential for developing targeted prevention and treatment strategy.

3.1. Macronutrients

3.1.1. Association with carbohydrate intake

Carbohydrates, a primary energy source, play a central role in metabolic processes [52]. However, excessive consumption of refined carbohydrates and simple sugars is strongly associated with the development of IPFD and an increased risk of metabolic syndrome [53]. The impact of dietary carbohydrates on metabolic pathways and their association with IPFD are varied and depend on whether it consists of simple sugars or polysaccharides.

Simple sugars, such as monosaccharides (e.g., glucose, fructose), are rapidly digested and absorbed in the small intestine to provide energy [54,55]. High fructose intake, particularly from processed foods, has been shown to enhance triglyceride synthesis, disrupt normal metabolic pathways, and contribute to the development of insulin resistance [56,57]. For example, excessive intake of monosaccharides is associated with impaired insulin regulation, with fructose consumption specifically associated with elevated fasting insulin levels and increased insulin resistance in individuals both with and without pre-existing metabolic conditions [58]. In individuals with high IPFD, monosaccharide intake is positively associated with insulin traits, suggesting the consumption of food high in free glucose and fructose may exacerbate the risk of metabolic syndrome following acute pancreatitis [58].

By contrast, polysaccharides (starch and non-starch polysaccharides) which consist of long chains of monosaccharide units connected by glycosidic bonds, have demonstrated a protective effect [58].

Resistant starch is not absorbed in the small intestine; instead, it is fermented in the large intestine, which improves metabolic health by reducing the levels of insulin, glucagon-like peptide-1 (GLP-1), and gastric inhibitory polypeptide [59,60]. Increasing the intake of resistant starch through functional foods can reduce the risk of metabolic syndrome, especially for individuals with high IPFD.

IPFD also acts as an important modifier in the relationship between dietary carbohydrate intake and metabolic outcomes. Specifically, individuals with high IPFD demonstrated a notable difference in the impact of carbohydrate consumption on insulin-related traits, compared to those with lower levels of IPFD [58]. Therefore, IPFD is a part of the pathogenesis of metabolic syndrome in post-pancreatitis settings, where a habitual dietary intake of carbohydrates (low intake of resistant starch and high intake of monosaccharides) and high IPFD may synergistically increase the risk of developing insulin resistance.

3.1.2. Association with fat intake

Fat, a macronutrient found in most food groups, plays a vital role in energy production, supporting physiological functions, and maintaining structural integrity within the body. Dietary fat intake also influences metabolic pathways and leads to metabolic adaptations that affect insulin sensitivity and fat storage [61,62]. Previous research has highlighted the impact of dietary fat intake on ectopic fat accumulation and the metabolic sequelae associated with IPFD. A randomized controlled trial demonstrated that a Mediterranean diet, rich in unsaturated fats and low in carbohydrates, significantly reduced IPFD [10]. Another randomized controlled trial of nutritional intervention found that high-fat diets, including ketone supplementation, significantly lowered plasma glucose levels in individuals with new-onset diabetes after pancreatitis (NODAP).

The relationship between dietary fat intake and insulin resistance is significantly influenced by the extent of ectopic fat deposition. In individuals with high IPFD, there is a significant inverse association between total dietary fat intake and insulin resistance, where higher fat intake is related with reduced insulin resistance [51]. However, this relationship is not observed in individuals with low IPFD [51]. This context-dependent effect suggests that high IPFD modifies the metabolic response to dietary fat and contributes to insulin resistance, particularly following acute pancreatitis [63].

The composition and quality of dietary fat further influence insulin resistance. For instance, a study comparing three isocaloric diets, one high in monounsaturated fats (MUFA), one high in saturated fats, and one high in carbohydrates, showed that the MUFA-rich diet significantly improved insulin sensitivity and reduced plasma glucose levels [64]. In addition, MUFA intake was associated with improved markers of insulin resistance in individuals with high IPFD [51]. These findings indicate that the type of dietary fat consumed plays an important role in the metabolic pathways. In particular, dietary intake of MUFA instead of saturated fats could benefit individuals with high IPFD and a history of pancreatitis by reducing the risk of metabolic syndrome associated with IPFD.

3.2. Micronutrients

3.2.1. Association with mineral intake

Minerals are essential inorganic elements vital for human health, playing key roles in biochemical processes for both functional and structural purposes. They activate insulin receptors and help regulate insulin sensitivity [65]. Several minerals, such as iron, phosphorus, and zinc, were associated with metabolic changes following acute pancreatitis [66]. In particular, manganese and iodine were deemed important in glucose metabolism as it showed significant association with fasting plasma glucose and glycated hemoglobin [66].

In individuals with acute pancreatitis who are at higher risk of developing IPFD, manganese-related antioxidant activity is often altered. Plasma levels of manganese superoxide dismutase (MnSOD) decrease, while MnSOD levels in erythrocytes increase [67]. This imbalance was due to oxidative stress. MnSOD catalyzes the conversion of the disproportionate superoxide anion radicals into hydrogen peroxide and molecular oxygen, thereby helping to reduce reactive oxidant species and oxidative stress [68,69]. This reduction ultimately improves islet β-cell function, impacting glucose

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metabolism and insulin secretion [68]. Given that MnSOD relies on manganese as a critical component for its enzymatic activity [66,67], adequate manganese intake may help improve glucose metabolism and reduce acute inflammation associated with IPFD.

Selenium and iodine intake also influence the severity and progression of IPFD, including its association with NODAP. Selenium, a key antioxidant, and iodine, essential for thyroid hormone production, work together to regulate glucose metabolism [70,71]. For instance, a 1-μg increase in selenium and iodine intake was significantly associated with a 1.71% decrease in insulin sensitivity (homeostatic model assessment of insulin sensitivity [HOMA-S]) and 0.17 mmol/mol increase in glycated hemoglobin [66]. These findings highlighted their role in enhancing insulin sensitivity [66]. This dual mineral effect not only impacts the metabolic syndrome associated with IPFD, but also influences the severity of IPFD by decreasing thyroid stimulating hormone level.

Iron is an essential mineral for the structural and functional components of protein. Previous study showed that individuals with NODAP experience disrupted iron metabolism, marked by elevated hepcidin and reduced ferritin levels [72]. Increased hepcidin impairs iron absorption and release, while low ferritin levels result in depleted iron stores, contributing to an imbalance in iron regulation and exacerbating metabolic syndrome. Furthermore, dietary intake of iron influenced glucose metabolism, with each milligram increase in total iron intake significantly associated with decrease in a 3.2% of HOMA-S among individuals with NODAP [66]. Dietary iron exists in two forms, which are haem and non-haem, differing in chemical structure, bioavailability, and food sources [73]. Notably, only non-heme iron intake is significantly associated with hepcidin and pancreas pathological changes, as indicated by the transverse relaxation rate of tissue water measured through MRI [74]. It is probable that dietary iron from plant-based sources (legumes, grains, vegetables, and dried fruits) may influence pathological changes in the pancreas.

3.3. Association with vitamin intake

Vitamins play crucial roles in metabolic pathways, where their deficiency can lead to metabolic disturbances including oxidative stress, insulin resistance, endothelial dysfunction, and impaired glucose and lipid metabolism [75]. In the context of endocrine and exocrine pancreatic diseases, ectopic fat accumulation may damage pancreatic cells, resulting in dysfunction and insufficiency. This impairment hinders nutrient digestion and absorption, resulting in malabsorptive conditions and subsequent vitamin deficiencies [76,77].

Water-soluble vitamins are particularly prone to deficiency compared to fat-soluble vitamins, as they must be obtained through dietary intake due to the human body's inability to synthesize them [78,79]. In particular, vitamin B3 intake shows a significant association with pancreatic beta-cell function (Homeostatic Model Assessment of beta-cell function [HOMA-β]) in individuals with NODAP [80]. Previous research found that each percent decrease in vitamin B3 intake was associated with a 1.35% reduction in HOMA-β, which highlighted its impact on insulin secretion and pancreatic function [80]. Nicotinic acid, a form of vitamin B3, likely mediates this effect by activating the nicotinic acid G-protein-coupled receptor GPR109a [80–82]. Activation of this receptor reduces the flux of free fatty acids to the liver by inhibiting their release from adipocytes [80]. Thus, it is possible to improve metabolic perturbation, enhance lipid homeostasis, and attenuate progression to IPFD. Similarly, habitual intake of other water-soluble vitamins such as vitamin B6, vitamin B12, and folate showed their association with IPFD, likely due to their roles in the methionine metabolism and phosphatidylcholine synthesis [83]. Vitamin B6 acts as a coenzyme in the conversion of methionine to cysteine, a process crucial for maintaining homocysteine levels and overall methylation capacity [83]. Vitamin B12 and folate are essential for the regeneration of methionine from homocysteine, thereby supporting the continuous availability of S-adenosylmethionine for methylation reactions [83]. These reactions are critical for the synthesis of phosphatidylcholine, a major phospholipid involved in cell membrane integrity and lipid transport. Consequently, a deficiency in these vitamins can disrupt methionine metabolism and phosphatidylcholine synthesis, promoting lipid droplet formation and leading to ectopic fat accumulation in the pancreas.

Of several fat-soluble vitamins, only one study to date has

demonstrated a significant finding. Habitual intake of vitamin A (in the form of provitamin carotenoid) showed significant association with HOMA-β in individuals with NODAP [80]. A 1% decrease in α-carotene, β-carotene, and total carotene intake, was associated with decrease in HOMA-β by 0.42%, 0.60%, and 0.63%, respectively [80]. Further studies are needed to demonstrate the role of fat-soluble vitamins in improving metabolic syndrome in individuals after an attack of AP through their beneficial effects on insulin secretion.

4. CONCLUSION

The increasing prevalence of IPFD underscored its role in metabolic disorders such as type 2 diabetes and chronic pancreatitis. Despite challenges in prevalence estimation due to the absence of an ICD code, advancements in MRI improved the current knowledge of IPFD. This review highlighted the influence of dietary macronutrients (i.e., resistant starch and MUFAs) and micronutrients (i.e., including manganese, selenium, and vitamins B3, B6, and B12) in managing IPFD. While the evidence detailing the mechanisms of IPFD and relationship with macronutrients are growing, the literature basis on micronutrients remains comparatively limited. In particular, the specific interactions between dietary components and the pathophysiological processes of IPFD (e.g., how resistant starch may counteract interlobular fat accumulation or how certain micronutrients might influence acinar-to-adipocyte transdifferentiation) remain underexplored. This discrepancy highlights an important research gap that warrants further investigation to design personalized nutritional strategies and improve clinical applications in IPFD management.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Availability of data and material

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Ethics approval

Not applicable.

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