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The Relationship between Metabolic Syndrome Components and the Incidence of Pancreatic Exocrine Insufficiency in Patients with Chronic Pancreatitis

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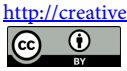

Abstract

Background and Objectives: Metabolic syndrome (MetS), characterized by central obesity, hyperglycemia, dyslipidemia, and hypertension, is highly prevalent in populations with chronic pancreatitis (CP). However, the role of MetS components in the development of pancreatic exocrine insufficiency (PEI) in patients with CP remains unclear. This review systematically synthesizes evidence to elucidate the relationship between MetS components and PEI pathogenesis. **Methods:** A structured methodology was employed to evaluate existing literature. Studies were identified through systematic searches of PubMed, Embase, and Scopus using predefined keywords such as "metabolic syndrome," "pancreatic exocrine insufficiency," and "chronic pancreatitis." Inclusion criteria focused on original observational, cohort, and case-control studies reporting associations between individual MetS components and PEI in CP. Data were critically appraised for quality and relevance, and findings were synthesized to highlight trends, inconsistencies, and gaps in the evidence. **Results:** The review identified hyperglycemia, dyslipidemia, and abdominal obesity as significant contributors to pancreatic damage, mediated by mechanisms such as chronic inflammation, oxidative stress, lipotoxicity, and impaired insulin signaling. However, the role of hypertension in PEI pathogenesis re-

mains less defined. Variability in reported associations was observed, influenced by differences in diagnostic criteria, study populations, and methodologies. **Conclusions:** Early recognition and management of MetS components are crucial to preventing or mitigating PEI in CP patients. Lifestyle interventions, pharmacological therapies, and pancreatic enzyme replacement therapy (PERT) are key elements of a multidisciplinary care approach. Future research should focus on large-scale prospective studies, mechanistic investigations, and randomized controlled trials to establish causal relationships and develop targeted interventions. These efforts are critical to enhancing diagnostic, preventive, and therapeutic outcomes for CP patients with coexisting metabolic syndrome (MetS).

Keywords

Metabolic Syndrome, Pancreatic Exocrine Insufficiency, Chronic Pancreatitis, Hyperglycemia, Dyslipidemia, Abdominal Obesity, Hypertension, Pancreatic Damage

1. Introduction

1.1. Overview of the Topic

Chronic pancreatitis (CP) is a chronic inflammatory condition characterized by irreversible damage to the pancreas, resulting in fibrosis and loss of both exocrine and endocrine function. CP affects approximately 4 - 8 per 100,000 individuals annually, with a rising trend observed in various regions, including the United States and Europe. The primary etiologies include alcohol abuse, smoking, genetic mutations, and idiopathic causes. The progression of CP often results in pancreatic exocrine insufficiency (PEI), a condition in which the pancreas fails to produce sufficient digestive enzymes. This results in severe complications such as malabsorption, steatorrhea, and deficiencies in fat-soluble vitamins, all of which severely impair quality of life and increase healthcare costs [1] [2]. By understanding these complications, researchers and clinicians can better develop targeted interventions to alleviate the disease burden and improve patient prognosis.

Metabolic syndrome (MetS) is a cluster of interrelated conditions that significantly heighten the risk of cardiovascular disease and type 2 diabetes. The components of MetS include obesity, particularly central adiposity; diabetes or impaired glucose tolerance; dyslipidemia, characterized by elevated triglycerides and low HDL cholesterol; and hypertension. These conditions are clinically significant because their synergistic effects exponentially increase the risk of atherosclerotic cardiovascular disease and other metabolic complications [3] [4]. The high prevalence of MetS, affecting 20% - 25% of adults worldwide, underscores the urgent need for a comprehensive, preventive approach to mitigate its global health burden. Integrating early detection with holistic management strategies is crucial for reducing the significant morbidity and mortality associated with MetS.

Furthermore, international organizations such as the American Pancreatic Association and the European Pancreatic Club advocate for robust efforts to manage these conditions, which are pivotal to improving long-term public health outcomes [5] [6]. Addressing CP and MetS through multidisciplinary strategies highlights the need for early diagnosis, personalized treatment plans, and patient education, aligning with global efforts to improve public health outcomes and reduce morbidity and mortality worldwide. Early identification and intervention in individuals at risk can not only enhance the quality of life but also alleviate the economic burden associated with these conditions.

1.2. Relevance of the Topic

Pancreatic exocrine insufficiency (PEI), a common complication of chronic pancreatitis (CP), affects more than half of CP patients, with its prevalence increasing alongside disease severity and duration. PEI results in maldigestion, malnutrition, and deficiencies in fat-soluble vitamins, significantly diminishing quality of life and contributing to higher healthcare costs [7] [8]. Metabolic syndrome (MetS), particularly its components such as obesity and type 2 diabetes mellitus (T2DM), further exacerbates the progression of CP and the development of PEI. Obesity and type 2 diabetes mellitus (T2DM) are notable contributors to pancreatic dysfunction, with studies showing that fecal elastase-1 levels inversely correlate with diabetes duration and glycated hemoglobin (HbA1c) levels [9] [10]. This highlights a bidirectional relationship where metabolic dysregulation worsens pancreatic exocrine impairment, complicating disease management. Pancreatic steatosis, a hallmark of Metabolic Syndrome (MetS), promotes chronic, low-grade inflammation, which accelerates exocrine dysfunction and highlights the need for targeted interventions [11]. This connection underscores the importance of identifying and addressing shared pathological mechanisms between MetS and CP to develop comprehensive management strategies.

A deeper understanding of these processes is essential for creating interventions that target pancreatic health and the metabolic imbalances driving disease progression. Diabetes mellitus, present in up to 72% of CP patients with severe PEI, further complicates management and increases the risk of metabolic and nutritional complications [12]. Early diagnosis and management of PEI, as emphasized by the American Gastroenterological Association, are essential for mitigating these challenges, as timely interventions can prevent long-term nutritional deficiencies and improve patient outcomes. Screening at-risk populations, particularly those with longstanding diabetes, is critical to addressing the overlapping challenges of MetS and CP. Integrating metabolic and nutritional management into CP care can help develop holistic and effective therapeutic strategies, ultimately reducing healthcare costs and improving patient quality of life.

1.3. Objectives of the Review

Despite advances in understanding the relationship between metabolic syndrome

(MetS) and pancreatic exocrine insufficiency (PEI), significant gaps remain in clarifying the precise mechanisms involved and the specific contributions of individual MetS components. This review aims to synthesize current evidence on how hyperglycemia, dyslipidemia, abdominal obesity, and hypertension influence the development and progression of PEI in patients with chronic pancreatitis (CP). We hypothesize that hyperglycemia, dyslipidemia, and abdominal obesity act as independent risk factors for PEI through shared mechanisms of chronic inflammation, oxidative stress, and pancreatic fibrosis, while the role of hypertension remains less well-defined. By systematically evaluating the literature, we aim to highlight critical areas for future research, identify potential therapeutic targets, and propose strategies for earlier diagnosis and management of PEI in high-risk chronic pain (CP) populations.

2. Chronic Pancreatitis and Pancreatic Exocrine Insufficiency

2.1. Pathophysiology of Chronic Pancreatitis and Development of Pancreatic Exocrine Insufficiency

Chronic pancreatitis (CP) and pancreatic exocrine insufficiency (PEI) are tightly linked through overlapping inflammatory and structural mechanisms. In CP, persistent inflammation triggers progressive fibrosis, leading to the destruction of acinar and ductal cells, which are critical for enzyme production and transport [13]. As healthy tissue is replaced by fibrotic scar tissue, the pancreas loses its ability to synthesize and secrete digestive enzymes, a hallmark of PEI [14] [15]. Impaired lipase secretion, in particular, leads to fat malabsorption, resulting in steatorrhea and nutrient deficiencies. Ductal obstruction, caused by strictures or intraductal stones, compounds dysfunction by blocking or reducing enzyme flow to the duodenum [16]. Reduced bicarbonate secretion decreases the stability of digestive enzymes, particularly lipase, in the acidic duodenal environment, which intensifies malabsorption [16]. Together, these processes create a self-perpetuating cycle where inflammation, fibrosis, and enzymatic insufficiency reinforce and strengthen each other, driving progression from CP to clinically significant PEI.

2.2. Clinical Manifestations of Pancreatic Exocrine Insufficiency

PEI presents with symptoms of malnutrition, weight loss, and fat-soluble vitamin deficiencies (A, D, E, and K), reflecting impaired digestion and absorption [14]. Although steatorrhea is considered a hallmark, it may be absent in patients who reduce dietary fat intake, leading to diagnostic delays and underdiagnosis [17]. Complications like osteoporosis and sarcopenia often develop over time, highlighting the systemic impact of sustained nutrient deficiencies [14]. These symptoms overlap with those of CP, complicating diagnosis, but worsening nutritional deficits in PEI are a distinguishing feature.

Given the overlap between CP and PEI symptoms, objective testing is essential. The fecal elastase-1 (FE-1) test is a widely used first-line diagnostic tool due to its non-invasiveness and high sensitivity for moderate to severe pancreatic enzyme

insufficiency (PEI) [17] [18]. While functional tests, such as the 13C-labeled mixed triglyceride (C-MTG) breath test, can assess lipase activity [16] [18], their limited availability restricts their clinical use. Imaging techniques such as secretin-enhanced MRCP offer insight into ductal morphology and pancreatic exocrine function, but remain experimental and limited in availability [18]. In high-risk settings, such as after severe necrotizing pancreatitis or pancreatic head cancer, empirical pancreatic enzyme replacement therapy may be initiated without formal testing, as the high pretest probability of PEI can exceed 80% [17]. Although direct tests, such as the cholecystokinin (CCK) stimulation test, provide highly sensitive data, their invasiveness and lack of standardization limit their widespread clinical adoption [18]. These challenges highlight the need for improved diagnostic accessibility and consistency to ensure timely and accurate management of PEI.

In addition to diagnostic challenges, understanding the underlying pathophysiological mechanisms that drive PEI is critical for improving early detection and management. Although chronic pancreatitis (CP) and metabolic syndrome (MetS) have distinct primary etiologies, they converge on several key pathophysiological mechanisms—namely, chronic inflammation, oxidative stress, lipotoxicity, and fibrosis—that critically impair pancreatic exocrine function [19]. Persistent inflammatory signaling in CP drives acinar cell loss and ductal dysfunction, while metabolic syndrome (MetS) exacerbates this injury through systemic metabolic disturbances [20]. Obesity-related visceral fat deposition, dysregulated adipokine secretion, and hyperglycemia further promote pancreatic steatosis and fibrosis, accelerating the onset and severity of pancreatic exocrine insufficiency (PEI) [19]. Recognizing the overlapping inflammatory and metabolic pathways that connect CP and MetS is essential to understanding the progression to PEI and identifying targets for early intervention.

3. Metabolic Syndrome and Its Components

3.1. Definition and Diagnostic Criteria of MetS

Metabolic syndrome (MetS) refers to a group of medical conditions that predispose individuals to cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Diagnosis requires at least three of the following five criteria: increased waist circumference, elevated triglycerides (≥150 mg/dL), elevated fasting blood glucose levels (≥100 mg/dL), elevated blood pressure (≥130/85 mmHg), and decreased high-density lipoprotein cholesterol (HDL-C) [21]. These criteria provide a standardized framework for identifying at-risk individuals, but they must also account for variations across sex and ethnic groups. For example, waist circumference and HDL-C cutoffs differ based on sex and ethnicity, acknowledging genetic and metabolic diversity in the global population.

Compared to other ethnic groups, individuals of South Asian descent are more predisposed to insulin resistance and central obesity. To reflect these risks, the waist circumference threshold for South Asian men is 90 cm, lower than the 102 cm threshold for men of European descent [21]. This adjustment underscores the

importance of tailoring diagnostic criteria to address population-specific vulnerabilities. While fasting blood glucose is the most commonly used marker of insulin resistance, other measures may be more effective in identifying high-risk individuals who are at risk for future cardiovascular disease in specific populations. For instance, the homeostatic model assessment of insulin resistance (HOMA-IR) and hyperinsulinemia has been shown to diagnose more African American women with MetS than fasting glucose levels alone [22]. This suggests that relying on a single measure could underdiagnose patients in certain groups, highlighting the need for more comprehensive diagnostic tools. This reveals gaps in attempts to standardize criteria and may leave some patients undiagnosed, preventing early intervention and thereby increasing their risks for complications of cardiovascular disease and type 2 diabetes mellitus. This underscores the critical need for flexible diagnostic strategies that adapt to the unique characteristics of diverse populations, ensuring equitable healthcare outcomes. While global health organizations largely agree on MetS criteria, incorporating population-specific considerations remains essential to providing comprehensive care.

3.2. Pathophysiology of MetS

Insulin resistance, together with systemic inflammation and oxidative stress, plays a central role in both the diagnostic criteria and the pathophysiology of metabolic syndrome (MetS), forming a feedback loop that exacerbates the condition. Several mechanisms have been proposed as the underlying cause of this resistance, including impaired protein activation and upregulation of p85α [23]. The downstream effects of these mechanisms ultimately lead to insufficient insulin signaling in tissues such as the liver, adipose tissue, and skeletal muscle, preventing proper glucose uptake and resulting in elevated blood glucose levels. Adipose tissue secretes adiponectin, a protein that is responsive to insulin and has anti-inflammatory properties. Adiponectin is consistently decreased in insulin-resistant obese patients, and pharmacologic treatments that increase adiponectin levels have been shown to lower blood glucose levels [24]. This establishes adiponectin as a reliable marker of metabolic dysfunction, as it also suppresses free fatty acid synthesis in the postprandial state. Additionally, adiponectin inhibits proinflammatory cytokines such as TNFα, IL-6, and IL-1β, as evidenced by its low levels in inflammatory conditions like coronary artery disease and COPD [25]. Given its ability to act on various tissues throughout the body, adiponectin's influence extends beyond insulin resistance, potentially contributing to other mechanisms of metabolic syndrome.

3.3. Complications Associated with MetS

The long-term effects of metabolic syndrome (MetS) may manifest as cardiovascular disease, type 2 diabetes mellitus (T2DM), and nonalcoholic fatty liver disease (NAFLD). The pathophysiologies of these conditions correspond to each MetS criterion, including insulin resistance, the release of proinflammatory cytokines,

and increased lipolysis, resulting in elevated fatty acid levels. NAFLD, characterized by the storage of fat in hepatocytes, often arises due to cardiovascular risk determinants such as insulin resistance and hypertension. These manifestations directly align with the criteria and mechanisms of MetS, suggesting that the progression or prevention of MetS influences the development and severity of these complications. Patients with MetS have also been found to exhibit pancreatic insults on ultrasound, despite no prior episodes of acute pancreatitis [26]. As hypertriglyceridemia is a well-known cause of acute pancreatitis, this finding highlights another link between MetS criteria and its long-term complications. Additionally, the lipolytic effects of adiponectin contribute to elevated serum triglyceride levels, further connecting the development of pancreatitis and MetS. These relationships underscore the natural consequences of the individual criteria that define metabolic syndrome and highlight the critical need for early intervention to mitigate these outcomes.

4. Potential Mechanisms Linking MetS and PEI

4.1. Role of Chronic Inflammation

Alcohol consumption and smoking are the predominant risk factors for chronic pancreatitis (CP), while metabolic syndrome (MetS), genetic predisposition, and autoimmune disorders account for approximately 20% of cases [19]. A growing body of evidence suggests that endocrine dysregulation in MetS is a key driver of chronic inflammation and pancreatic injury. Persistent inflammatory signaling leads to recurrent cellular damage, ultimately resulting in necrosis and fibrosis of the pancreatic parenchyma. The MetS-associated chronic inflammatory state generates an oxidative burden, initiating cellular changes at the transcriptional level, such as the activation of nuclear factor kappa B (NF-κB) [19]. The toxic cytokines produced through these changes are key mediators of pancreatic injury.

Additionally, MetS-induced oxidative stress facilitates the fusion of lysosomal and zymogen granules, triggering premature intrapancreatic protease activation and contributing to the progressive tissue destruction that is a hallmark feature of pancreatitis pathogenesis [20]. This highlights how MetS-driven oxidative stress not only exacerbates pancreatic inflammation but also actively contributes to its pathophysiology. Notably, pancreatic stellate cells (PSCs) play a pivotal role in fibrotic remodeling in CP [19]. Their activation under sustained inflammatory and oxidative stress conditions leads to excessive extracellular matrix deposition and replacement of functional pancreatic parenchyma with fibrotic tissue [19]. This process is central to the irreversible progression of CP. It underscores the intricate interplay between metabolic dysregulation, oxidative stress, and pancreatic fibrosis, further reinforcing metabolic syndrome (MetS) as a significant contributor to CP pathogenesis.

4.2. Obesity and Increased Intrapancreatic Fat

With the prevalence of modern diets, obesity has become an increasingly signifi-

cant contributor to pancreatitis. Several mechanisms have been proposed to explain the link between obesity and pancreatic inflammation. Obesity correlates with a higher incidence of biliary diseases, such as biliary sludge and cholelithiasis, both well-established risk factors for pancreatitis [27]. Gallstone-related biliary obstruction can cause backflow of pancreatic juice, leading to the entrapment of digestive enzymes within the pancreatic parenchyma and subsequent enzyme-mediated tissue damage. Beyond its impact on biliary pathology, obesity induces structural changes in the pancreas through the redistribution of visceral fat, particularly along the basolateral membrane of exocrine pancreatic acinar cells [27]. Visceral fat deposition is associated with a poorer prognosis for pancreatitis compared to subcutaneous fat. Unlike subcutaneous adipose tissue, visceral fat undergoes rapid lipolysis, releasing unsaturated fatty acids (UFAs) that exacerbate pancreatic injury [20]. UFAs readily bind calcium, facilitating saponification—a key process contributing to liquefactive necrosis in pancreatitis. UFAs also drive pancreatic damage through the release of inflammatory cytokines, which will be discussed later. These findings collectively illustrate how obesity's metabolic effects extend beyond general inflammation, playing a direct role in the pathophysiology of pancreatitis. Based on this theory, waist circumference (WC) has been proposed as a predictor of CP prognosis. Clinicians can estimate the degree of dyslipidemia and fatty infiltration in various organs by measuring the waist circumference (WC) [28]. Consequently, the hypertriglyceridemic waist (HTGW) phenotype has been proposed as a reliable and cost-effective tool for assessing the risk of pancreatitis.

4.3. Dyslipidemia and Pancreatic Microcirculation

Closely related to obesity, hypertriglyceridemia also increases the risk of acute pancreatitis (AP). Dyslipidemia-induced lipolysis releases excessive cytotoxic UFAs, initiating a cascade of cellular damage mediated by inflammatory cells and cytokines, including TNF-α, IL-1, IL-6, and platelet-activating factor (PAF) [20]. Similar to the general pathophysiology of MetS progressing to CP, hypertriglyceridemia induces pancreatic injury through inflammatory mechanisms. Additionally, the hyperviscosity state associated with hypertriglyceridemia may impair pancreatic perfusion, leading to ischemia and necrosis, though the pancreas-specific nature of this effect remains unclear [29]. Given the strong link between dyslipidemia and pancreatitis, treatment strategies for dyslipidemia-induced CP should focus on reducing lipid levels to prevent irreversible pancreatic damage. Traditional therapy includes insulin and heparin for rapid triglyceride (TG) reduction, followed by long-term maintenance with fibrates, niacin, and omega-3 fatty acids to control TG levels [30]. These treatments aim to mitigate the impact of dyslipidemia on pancreatic health and reduce the risk of further pancreatic injury. Plasmapheresis (PEX) has been proposed as an alternative for acute management, offering potential benefits by removing not only TGs but also pro-inflammatory mediators implicated in disease progression [29]. This approach suggests that directly elim-

inating inflammatory contributors may provide additional therapeutic advantages beyond lipid control. However, further research is needed to evaluate PEX's mortality benefits and risk profile before it can be incorporated into standard treatment protocols [30]. These proposed mechanisms underscore key mediators linking dyslipidemia to pancreatic injury, highlighting potential targets for future therapeutic strategies.

4.4. Impact of Insulin Resistance and Hyperglycemia

Beyond obesity and dyslipidemia, diabetes and chronic hyperglycemia can also contribute to pancreatic acinar injury. Diabetic patients exhibit hallmark features of insulin dysfunction, including reduced insulin secretion, insulin resistance, and diminished responsiveness to insulin-stimulating compounds such as glucagon-like peptides (GLP-1) and arginine. Solomon *et al.* (2012) demonstrated that after 24 hours of experimental hyperglycemia, healthy subjects exhibited a decrease in disposition index (DI), indicating early signs of β-cell dysfunction. The study also found that hyperglycemia reduced the responses of healthy subjects to GLP-1 and arginine, revealing its negative impact on β-cell reserve and secretory capacity. Interestingly, the same experiment showed that in type 2 diabetic subjects, hyperglycemia did not impair the glucagon-suppression response to GLP-1, suggesting that pancreatic α cells remain relatively spared [31]. These findings indicate that even short-term hyperglycemia can significantly impact pancreatic function, further linking chronic metabolic disturbances with pancreatic dysfunction. These findings highlight insulin's critical role in metabolism, as it regulates hormonal balance and exerts a protective effect on pancreatic acinar cells during pancreatitis. Furthermore, Bruce *et al.* (2021) demonstrated that, in murine models of pancreatitis, insulin protected pancreatic acinar cells from cytotoxic [Ca^{2+}] overload, preserved ATP production, and maintained glycolytic flux, regardless of whether the diabetes was type I or type II. This suggests that insulin plays a protective role in pancreatic function during metabolic crises [32]. These findings further illuminate the connection between MetS and CP, emphasizing the importance of insulin regulation in pancreatic health. Accordingly, **Table 1** summarizes the proposed mechanisms by which individual components of metabolic syndrome contribute to the development and progression of pancreatic exocrine insufficiency.

5. Epidemiological Evidence

5.1. Prevalence Studies

Hyperglycemia, dyslipidemia, and abdominal obesity contribute to pancreatic damage through mechanisms such as chronic inflammation, oxidative stress, lipotoxicity, and impaired insulin signaling. Given that exocrine pancreatic insufficiency (PEI) increases morbidity and mortality among chronic pancreatitis (CP) patients [33], understanding the relationship between metabolic syndrome (MetS) and PEI is of significant clinical importance. Studies have shown a strong correlation between hyperglycemia, diabetes mellitus (DM), and PEI in CP patients,

Table 1. Summary of metabolic syndrome components and their proposed roles in the development of pancreatic exocrine insufficiency.

MetS Component	Mechanism Contributing to PEI	Supporting Evidence	Key Reference
Hyperglycemia	Chronic inflammation, oxidative stress. β-cell dysfunction, pancreatic fibrosis	Strong association in CP patients; experimental models show early impairment	[25] [31] [32] [34]
Dyslipidemia	Lipotoxicity, inflammatory cytokine release, microvascular ischemia	Associated with acute and chronic pancreatic injury	[26] [29] [30]
Abdominal Obesity	Increased visceral fat, proinflammatory adipokines, fatty infiltration of pancreas	Predictive of worse CP outcomes and PEI development	[27] [28] [35]
Hypertension	Microvascular damage, possible indirect effects on pancreas	Conflicting evidence; limited direct association	[29] [30]

with diabetes being associated with reduced pancreatic volume and function [34]. This bidirectional relationship is evident in the increased prevalence of PEI among CP patients with preexisting diabetes, as well as the onset of diabetes, either type 2 or type 3C, following CP development. Additionally, diabetes, dyslipidemia, and abdominal obesity contribute to pancreatic fat accumulation, further exacerbating exocrine insufficiency [35]. While these metabolic factors are well established in CP progression, the role of hypertension in PEI remains unclear and warrants further investigation.

The prevalence of MetS among CP and PEI patients is notably high, particularly regarding hyperglycemia and diabetes. Epidemiological data suggest that diabetes affects up to 80% of CP patients over their lifetime, with its incidence increasing with CP duration [36]. Among CP patients with PEI, the prevalence of diabetes is approximately 60% [12]. Although PEI is primarily attributed to pancreatic parenchymal loss and ductal obstruction, the exact mechanisms linking diabetes mellitus (DM) and PEI remain an ongoing area of research. Obesity, a significant risk factor for diabetes, nearly triples the likelihood of developing diabetes in CP patients [37]. This association is particularly concerning given the global rise in obesity. Moreover, obesity increases intrapancreatic fat deposition, known as fatty pancreas, which impairs both endocrine and exocrine pancreatic functions [38]. The simultaneous dysfunction of these two major pancreatic components compounds the metabolic burden in CP patients, further contributing to disease progression.

Research indicates that more than half of CP patients will develop PEI, though the risk is multifactorial [12]. The prevalence varies based on the etiology and duration of CP. Still, several studies have identified diabetes as a significant risk factor, with odds ratios demonstrating more than a twofold increase in PEI risk [33]. Additionally, Bellin *et al.* found that PEI itself increases the risk of developing di-

abetes in CP patients, independent of BMI. Racial disparities have also been observed, with Black CP patients being more likely to develop diabetes than other racial groups [37]. These findings suggest that while MetS components contribute to PEI and CP progression, demographic and genetic factors may also influence disease susceptibility.

5.2. Longitudinal and Retrospective Cohort Studies

Observational studies have employed various methods to control for confounding variables and better understand the causal links between MetS components and PEI. Multivariate logistic regression analyses help isolate the effects of individual MetS factors, adjusting for variables such as age, BMI, and lipid profiles. Longitudinal studies provide additional insights by tracking changes over time, revealing significant associations between hyperglycemia, dyslipidemia, and PEI severity [33]. For instance, longitudinal cohort studies have shown that diabetes significantly increases PEI risk, likely through mechanisms involving chronic inflammation and impaired insulin signaling. Dyslipidemia and abdominal obesity further contribute to PEI progression, reinforcing the need for targeted metabolic interventions. Given that PEI is an independent risk factor for mortality in CP patients [15], optimizing metabolic management could play a crucial role in improving patient outcomes.

6. Clinical Implications and Management Strategies

6.1. Screening and Early Detection

Screening for pancreatic exocrine insufficiency (PEI) in patients with chronic pancreatitis (CP) and metabolic syndrome (MetS) features is crucial for early intervention and optimizing patient outcomes. PEI often develops insidiously in CP, and its association with MetS risk factors, such as obesity, dyslipidemia, and impaired glycemic control underscores the need for proactive and tailored screening strategies [39]. A multifaceted approach combining clinical evaluation, biochemical tests, imaging, and endoscopic assessments provides the most comprehensive plan for screening high-risk individuals. Clinically, assessing for signs and symptoms of steatorrhea, malabsorption, and weight loss is essential. However, initial presentation may be limited as PEI develops gradually [5]. Furthermore, symptoms alone may not reliably indicate PEI severity, so the integration of objective diagnostic tools is necessary. Among these, the fecal elastase-1 (FE-1) test is a practical first-line screening tool due to its noninvasiveness. FE-1 provides a quantifiable measure of pancreatic enzyme production, with levels of less than 200 μg/g indicating PEI and less than 100 μg/g strongly suggestive of severe insufficiency [40]. Despite being widely used, FE-1 has limitations in detecting mild PEI and may yield false-positive results in cases of watery stools, emphasizing the need for support from other diagnostic modalities.

Imaging studies, such as magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT), serve as adjuncts by visualizing structural changes

in the pancreas. Significant correlations have been observed between low FE-1 levels and imaging findings, such as ductal dilation, parenchymal atrophy, and intraductal stones, which collectively reflect disease severity [41]. This highlights the complementary role of imaging in relating structural context to biochemical abnormalities to achieve a better understanding of disease progression. Additionally, endoscopic ultrasound (EUS), enhanced by elastography, offers significant promise as a screening tool. Dominguez-Muñoz *et al.* (2015) [42] demonstrated the utility of EUEUS elastography, which quantifies pancreatic parenchymal stiffness and provides an indirect but reliable marker for exocrine dysfunction. Based on the findings, integrating EUS-elastography into the screening protocol, especially in patients with uncertain biochemical or imaging findings, can help improve diagnostic precision and early detection of PEI. By employing a comprehensive screening approach that combines clinical evaluation, biochemical testing, imaging, and advanced endoscopic techniques, healthcare providers can enhance early detection and intervention for pancreatic exocrine insufficiency, ultimately preventing further complications associated with chronic pancreatitis and metabolic syndrome.

Clinicians can identify metabolic syndrome (MetS)-related risk in patients with chronic pancreatitis (CP) by focusing on diagnostic criteria and comprehensive risk assessments. MetS is characterized by elevated waist circumference, high blood pressure, elevated fasting glucose, high triglycerides, and low high-density lipoprotein (HDL) cholesterol, all of which are related to an increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [43]. Beyond these criteria, factors such as family history, smoking, age, and gender should also be considered to provide a more comprehensive risk evaluation. Continuous risk scores, such as MetS-Z scores, can further enhance risk stratification by associating changes in waist circumference, glucose levels, and systolic blood pressure with the likelihood of developing CVD and T2DM [44]. Elevated MetS-Z scores are strongly associated with an increased risk of future disease, underscoring their significance in the early identification and management of patients with CP. Moreover, the use of this scoring system establishes a baseline metric and facilitates continuous monitoring of disease progression, enabling clinicians to make timely and evidence-based adjustments to therapeutic interventions.

6.2. Lifestyle Modifications and Medical Management

The etiology of pancreatic exocrine insufficiency (PEI) is most related to chronic pancreatitis (CP). PEI can be effectively mitigated through targeted lifestyle interventions that focus on reducing risk factors of the underlying causes. Smoking cessation plays a critical role, as smoking has been strongly linked to pancreatic damage and progression of chronic pancreatitis, a primary risk factor for PEI [45]. Eliminating tobacco exposure can, therefore, significantly reduce pancreatic inflammation with downstream benefits in preventing PEI development. Moreover, alcohol consumption is a significant contributor to pancreatic pa-

thology, as it is a leading cause of both acute pancreatitis and chronic pancreatitis. Moderating or abstaining from alcohol intake can slow down the progression of acute to chronic pancreatitis or worsening chronic injury and inflammation, reducing the overall risk of PEI [46]. Conditions like diabetes mellitus with poor glycemic control have been associated with exocrine impairment due to microvascular damage and pancreatic atrophy. Rates of moderate to severe PEI are reported at 30% - 50% in Type I Diabetes and up to 35% in Type II Diabetes [18]. Therefore, managing blood glucose levels through nutritional optimization and regular physical activity is essential in reducing the risk of diabetes, preserving pancreatic function, and preventing progression of PEI. Overall, adopting these lifestyle modifications can play a crucial role in preventing the development of pancreatic exocrine insufficiency.

Metabolic syndrome (MetS) treatments have a significant impact on pancreatic outcomes, primarily by addressing key metabolic risk factors such as insulin resistance, dyslipidemia, and obesity, which are closely associated with pancreatic dysfunction. Lifestyle modifications, including a healthy diet, increased physical activity, and avoidance of tobacco and alcohol use, are foundational in managing MetS. These interventions improve pancreatic health by reducing sustained inflammation, oxidative stress, and adiposity, thereby slowing the progression of chronic pancreatitis (CP) and its complications, such as pancreatic exocrine insufficiency (PEI) [47]. Pharmacological treatments also play a role when lifestyle changes are insufficient, addressing hypertension, diabetes mellitus (DM) or insulin resistance, and dyslipidemia. Metformin, a widely used medication for type 2 diabetes mellitus (DM), has demonstrated efficacy in preserving pancreatic β-cell function by reducing oxidative stress and inflammation, thereby lowering the risk of DM progression [48]. Similarly, glucagon-like peptide-1 (GLP-1) receptor agonists improve glycemic control and promote weight loss, which helps mitigate obesity-related pancreatic stress. Notably, recent evidence suggests these agents provide protective effects on the pancreas without significantly increasing the risk of acute pancreatitis, contrary to earlier conflicting findings [49].

Additionally, pharmacological management of dyslipidemia, particularly with statins, may reduce pancreatic inflammation by lowering serum cholesterol levels and decreasing the formation of gallstones, a common risk factor for pancreatitis. While initial reports suggested that statins might elevate the risk of pancreatitis, more recent analyses indicate a reduction in pancreatitis incidence among statin users [50]. Overall, treatments for metabolic syndrome play a pivotal role in improving pancreatic health by mitigating metabolic derangements, underscoring the importance of individualized approaches and vigilant monitoring to achieve optimal outcomes.

6.3. Pancreatic Enzyme Replacement Therapy (PERT)

Pancreatic enzyme replacement therapy (PERT) is a fundamental treatment for addressing pancreatic exocrine insufficiency (PEI) in individuals with chronic

pancreatitis, especially when metabolic syndrome (MetS) is also present. Indications for PERT are primarily guided by clinical symptoms such as steatorrhea, malabsorption, weight loss, and fat-soluble vitamin deficiencies, which often arise due to progressive pancreatic atrophy, fibrosis, or ductal obstruction impairing enzyme secretion [51]. Metabolic disturbances such as obesity, diabetes mellitus, and dyslipidemia exacerbate exocrine dysfunction through mechanisms of lipotoxicity, oxidative stress, and microvascular damage. PERT is essential for restoring effective digestion and absorption, improving nutritional status, and mitigating PEI-related complications in this high-risk population [52]. PERT is designed to treat the meal, ensuring proper mixing with chyme and effective digestion of nutrients, thereby not treating the pancreas itself. Dosing must be carefully tailored to address the unique challenges associated with metabolic syndrome (MetS). For patients with obesity, increased dietary intake necessitates higher enzyme doses, whereas individuals with diabetes mellitus require precise titration to avoid malabsorption-induced calorie deficits that could destabilize glycemic control [53]. Regular monitoring of stool consistency, body weight, and nutritional markers, such as vitamins, is crucial for optimizing PERT therapy and maintaining a balance between pancreatic function and metabolic health. **Figure 1** illustrates the conceptual framework linking metabolic syndrome components to chronic pancreatic inflammation, fibrosis, and the subsequent development of pancreatic exocrine insufficiency.

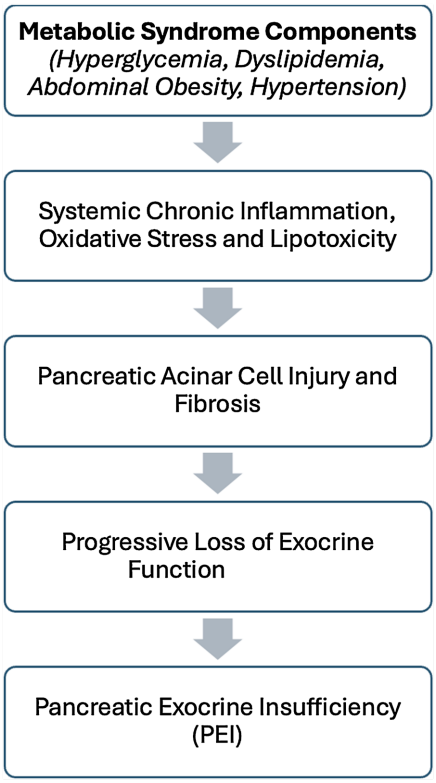

Figure 1. Proposed mechanisms linking metabolic syndrome components to the development of pancreatic exocrine insufficiency in chronic pancreatitis.

7. Gaps in Literature and Future Directions

7.1. Research Gaps

Despite significant advances in elucidating the role of metabolic syndrome (MetS) in chronic pancreatitis (CP), critical gaps remain regarding the mechanistic underpinnings of pancreatic exocrine insufficiency (PEI) and the differential impact of MetS components on disease progression, significant major limitation of existing studies is the lack of standardized criteria for defining both MetS and PEI, contributing to variability in study designs, diagnostic approaches, and reported outcomes [51] [54]. A critical evaluation of the current evidence reveals significant heterogeneity in methodological rigor. Many studies rely on retrospective analyses, small sample sizes, and inconsistent diagnostic thresholds, which undermine the generalizability and reproducibility of findings [51] [52]. For example, variations in defining central obesity, hyperglycemia, and dyslipidemia across studies introduce potential selection bias, while differences in fecal elastase-1 cutoff values or imaging modalities for diagnosing PEI contribute to misclassification [51] [53].

Furthermore, key confounding factors—such as smoking status, alcohol use, and genetic predisposition—are often inadequately controlled [19], and the potential for publication bias favoring studies with positive findings remains a concern. Collectively, these methodological disparities hinder the ability to draw definitive conclusions about the contribution of individual MetS components to the development of PEI. Establishing uniform definitions, standardized diagnostic criteria, and rigorous adjustment for confounders is essential to improve the reliability and clinical applicability of future research.

7.2. Conflicting Findings and Controversies

While multiple studies report strong associations between hyperglycemia, dyslipidemia, and PEI progression [34], conflicting findings persist regarding the roles of other MetS components, particularly hypertension. Some cohort studies have demonstrated no significant link between hypertension and PEI development, whereas others propose indirect contributions mediated through pancreatic microvascular injury [29]. Similarly, the impact of dyslipidemia remains debated. At the same time, hypertriglyceridemia is a recognized risk factor for acute pancreatitis [29]; however, its independent association with PEI after adjusting for obesity and diabetes is less clear [30]. Therapeutic interventions further contribute to the controversy. Earlier reports raised concerns regarding an increased risk of pancreatitis with statins and GLP-1 receptor agonists [49], whereas more recent large-scale analyses suggest neutral or even protective effects [51]. These discrepancies likely reflect differences in study populations, confounder control, and the way outcomes are ascertained. Recognizing and addressing these conflicting findings is crucial. Future research must focus on refining phenotypic definitions, enhancing statistical adjustment for confounders, and designing prospective studies that can better establish causality rather than mere associations [51].

7.3. Proposed Research Areas

Addressing the current gaps and controversies requires future studies to adopt standardized diagnostic frameworks for both MetS and PEI, enabling greater comparability across investigations [51]. Particular emphasis should be placed on mechanistic research exploring the molecular pathways linking metabolic dysfunction to pancreatic injury, including the roles of chronic inflammation, oxidative stress, lipotoxicity, and dysregulated adipokine signaling [25]. Emerging evidence suggests that adiponectin deficiency, leptin resistance, and other adipokine abnormalities may be critical mediators of pancreatic fibrosis and exocrine dysfunction [22]. Investigating these pathways could identify novel therapeutic targets aimed at halting or reversing PEI progression. Furthermore, genetic studies should be prioritized to identify individuals at heightened risk for MetS-associated PEI [55]. Emerging evidence also suggests that autonomic neuropathy may contribute to pancreatic exocrine dysfunction, particularly among patients with longstanding diabetes, representing an important but understudied area for future investigation [13]. Genetic variants affecting lipid metabolism, insulin signaling, or fibrotic pathways may serve as biomarkers for early identification and risk stratification. Integrating genetic insights with clinical and metabolic profiling could enable a more personalized approach to CP management [55]. In summary, future research efforts should prioritize methodological standardization, mechanistic elucidation, and reconciliation of conflicting evidence, thereby advancing precision-targeted strategies to improve outcomes for patients with chronic pancreatitis, metabolic syndrome, and pancreatic exocrine insufficiency.

8. Conclusions

This review underscores the intricate interplay between chronic pancreatitis (CP), metabolic syndrome (MetS), and pancreatic exocrine insufficiency (PEI), highlighting how metabolic and inflammatory processes exacerbate pancreatic dysfunction. CP progresses to PEI through chronic inflammation, fibrosis, and destruction of acinar cells, leading to hallmark symptoms such as steatorrhea, malnutrition, and fat-soluble vitamin deficiencies. MetS emerges as a significant, modifiable risk factor for PEI, with hyperglycemia, dyslipidemia, and obesity driving systemic inflammation, oxidative stress, and lipotoxicity. These mechanisms contribute to pancreatic fibrosis, impaired enzyme secretion, and nutrient malabsorption, ultimately leading to worse patient outcomes.

In clinical practice, early detection and management of PEI are crucial, especially in CP patients with features of MetS. Diagnostic tools such as fecal elastase-1 (FE-1) testing, advanced imaging techniques, and endoscopic ultrasound (EUS) elastography enhance screening accuracy and facilitate timely intervention. Treatment strategies should focus on tailored pancreatic enzyme replacement therapy (PERT) and comprehensive management of Metabolic Syndrome (MetS) components. Addressing systemic inflammation and metabolic dysregulation can improve nutritional status, reduce morbidity, and enhance quality of life in this high-

risk population. Additionally, recognizing MetS as a modifiable risk factor for PEI reinforces the importance of targeted interventions. Effective management of hyperglycemia, dyslipidemia, and obesity could mitigate inflammatory and metabolic damage to the pancreas, potentially slowing CP progression and reducing PEI-related complications.

To translate evidence into practice, standardized diagnostic criteria for MetS and PEI must be established and widely adopted. Consistent definitions will enhance comparability across studies and improve diagnostic accuracy. Screening programs should be implemented for high-risk populations, particularly CP patients with MetS features. A multifaceted approach combining clinical assessment, FE-1 testing, imaging, and EUS can provide comprehensive evaluations and facilitate early detection. Moreover, lifestyle and medical interventions must be prioritized to manage the components of MetS effectively. Smoking cessation, weight management, and glycemic control play crucial roles in mitigating systemic inflammation and metabolic stress. Pharmacological treatments such as metformin, GLP-1 receptor agonists, and lipid-lowering agents may further address MetS components while preserving pancreatic function. Individualized treatment approaches, particularly in patients requiring PERT, should optimize enzyme dosing based on dietary intake, glycemic control, and metabolic demands to prevent malabsorption-related complications.

Future research should focus on addressing existing knowledge gaps. Longitudinal studies are needed to clarify causal relationships between MetS components and PEI progression, while genetic studies may identify high-risk individuals and enable personalized treatment strategies. Additionally, investigating novel therapeutic targets, such as anti-inflammatory pathways and adipokine modulation, could provide new avenues for intervention. By bridging the gap between research and clinical practice, healthcare providers can improve outcomes for patients with CP, MetS, and PEI, ultimately reducing disease burden and enhancing patient care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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