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Acute Pancreatitis and Diabetes Mellitus—A Relation

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Abstract: Diabetes following acute pancreatitis (AP) is becoming increasingly recognized. It is unclear what subtype of diabetes mellitus (DM) occurs; however, type 3c diabetes mellitus (T3cDM) is gaining increasing recognition. Type 3c diabetes (also known as pancreatogenesis diabetes) is diabetes that comes secondary to pancreatic diseases, involving the exocrine and digestive functions of the pancreas. It also occurs following surgical removal of the pancreas. Around 5–10% of cases of diabetes in the Western world are related to pancreatic diseases. Chronic pancreatitis is most often the cause. Diabetes can also develop as a direct consequence of other diseases, including diseases of the exocrine pancreas. Historically, diabetes due to diseases of the exocrine pancreas was described as pancreatogenic or pancreatogenous diabetes mellitus, but recent literature refers to it as type 3c diabetes. It is important to note that type 3c diabetes is not a single entity; it occurs because of a variety of exocrine pancreatic diseases with varying mechanisms of hyperglycaemia. It has been observed that some patients have transient hyperglycaemia following AP episode with a subset developing persistent impaired glucose metabolism; however, the exact timeline is not well defined. The data on risk factors for developing DM after AP is limited and mixed; however, it is likely that severity of AP may impact the propensity to develop DM. The endocrine and exocrine pancreas are closely linked, and studies have found significant overlap in dysfunction of both after AP. Finally, there are some data to suggest that diabetes predisposes patients to structural changes in the pancreas and increased risk of developing AP.

Keywords: Pancreatitis, Diabetes mellitus.

Review Paper

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INTRODUCTION

Incidence of Acute pancreatitis (AP) is common, and over the past decade there has been a trend towards increased number of admissions, but lowered mortality [1, 2]. Specifically, in the United States, AP is responsible for 250,000 admissions each year and has shown an increase in 20% of admissions over the past 10 years [3]. The vast majority (80%) of admissions are mild, self-limited disease; however, long term consequences are still present [4]. One of those complications is endocrine dysfunction, and specifically impaired glucose metabolism or diabetes. Diabetes is prevalent and its burden is felt worldwide. According to the World Health Organization, it affects around 422 million adults worldwide [5]. Type 2 diabetes mellitus (T2DM) is the most common sub-type; however, more and more recognition has been given towards other sub-types, namely diabetes related to disorders of the exocrine pancreas. Diabetes of the exocrine pancreas or type 3c diabetes mellitus (T3cDM) is increasingly common and also under-recognized by providers [6]. One study found it to be more prevalent than type 1 diabetes mellitus (T1DM) [7], and T3cDM accounts for 5% to 10% of diabetes in the western population [8]. Furthermore, there is a well-established relationship between diabetes and chronic pancreatitis [9], as well as pancreatic cancer [9, 10] but there is more and more emerging evidence for the association of diabetes with AP [11].

The Goal of This Review Is To:

Summarize the existing literature on prevalence, natural history, risk factors of impaired glucose metabolism after AP; to explore the relationship with exocrine insufficiency; to discuss the potential bi-directional relationship between diabetes and AP; as well as to discuss the role of screening, diagnosis and treatment of diabetes in this cohort.

DM OF EXOCRINE PANCREAS

Classification of T3cDM is important, as the proposed pathophysiology for T3cDM differs from T1DM and T2DM. The proposed mechanism involves inflammation, fibrosis, and sclerosis of pancreatic

endocrine tissue (including cells that secrete glucagon, somatostatin, and pancreatic polypeptide), which leads to a reduction in total number of insulins producing islet cells and alteration of their function [1]. T3cDM affects all cells in the islets of Langerhans and therefore has features of both insulin resistance and insulin deficiency. Furthermore, several additional hormones are affected including glucagon, pancreatic polypeptide, incretin, adipokines (in the AP episode) leading to a unique clinical entity. This is characterized by a patient who has risk for hyperglycemic and hypoglycaemic events with increased insulin requirements early in the disease course, but decreased risk of diabetic ketoacidosis [11].

The long-term management also differs in T3cDM. One study followed patients for up to 13 years and differentiated impaired glucose metabolism into T2DM and T3cDM. They found that all of the patients who had T3cDM eventually required insulin, where as those diagnosed with T2DM were predominantly controlled by oral medications [2]. This observation supports the proposed mechanism that T3cDM is due to inflammation, scarring and islet loss, leading to less insulin secretion, rather than predominant insulin resistance found in T2DM.

Diagnostic Criteria

Some have proposed targeting the characteristics specific to T3cDM which included: impaired beta cell function, lack of insulin resistance, deficiency of lipid-soluble vitamins A, D, E, and K, and impaired release of glucagon-like peptide-1 and pancreatic polypeptide [1]. Specifically, Ewald and Bretzel [3] proposed the following diagnostic criteria: (all of the following must be met)

A Diagnosis of Diabetes Mellitus

Evidence of exocrine pancreatic insufficiency (fecal elastase 1 [FE1] < 200 μg/g or abnormal direct function testing)

- Abnormal pancreatic imaging (endoscopic ultrasound, magnetic resonance imaging, and computed tomography)
- Absence of T1DM associated autoimmune markers (antibodies against glutamine acid decarboxylase, islet cell antigen, or insulin).
- These criteria have undergone criticism for being particularly difficult to implement clinically [5], however, they provide a potentially more specific approach to diagnosing T3cDM.

Diagnostic Criteria

Finally, another study measured baseline and post-stimulation insulin and C peptide levels as a distinguishing marker for insulin resistance versus beta cell destruction. Amongst the small number of patients in the study, they found a trend towards lower C peptide and insulin levels in those who had severe AP (compared to mild disease); however, they also found an increase in C peptide and insulin levels in those who developed DM in general [6]. In general, the wide range of diseases that lead to T3cDM and the variable timeline of disease development makes it difficult to have clear cut diagnostic criteria. Currently, it is favored to first establish a diagnosis of DM, and then to pay particular attention to a patient's pre-disposing conditions, namely, disease of the pancreas, to determine if their pathology more closely aligns with T3cDM versus other subtypes (T1DM or T2DM). Careful delineation of T3cDM from other subtypes is important to ensure optimal follow-up and treatment [7].

This, and other data, suggests that the theory of greater islet cell loss, leads to greater risk of developing T3cDM and impaired glucose metabolism. This has been supported by several studies [11-13]. Of note, some of these studies have predominantly severe cases, while others have a majority of mild cases, and often direct cohort comparison was difficult. The meta-analysis, however, was able to compare larger cohorts of severe AP and mild AP and found an incidence of DM of 39% compared to 14%, respectively [18].

Other studies, however, have shown no relationship between severity of AP and development of T3cDM. These studies conclude that a mechanism, other than pure necrosis and cell loss, is at play. There are certainly limitations to these studies. In particular the meta-analysis [17], again included many studies with only severe cases of AP and was not able to do a sub-analysis based on severity of disease.

It is important to mention there has been an evolution in the classification of severity of AP: from Ranson's criteria, to APACHE II, to Balthazar score, to the Atlanta classification of AP and BISAP score, to more recently revised Atlanta criteria [4]. Many of the studies reviewed used the Atlanta criteria to classify severity; however, others used the APACHE score, and others incorporated computed tomography data (Balthazar score) to assess pancreatic necrosis. This may have led to an inability to directly compare these studies and draw broad conclusions.

Given the evidence and data collected so far, it is very likely that severity of AP and total islet cell destruction and loss plays a part in the pathophysiology of T3cDM; however, it is also likely that this is not the sole risk factor or mechanism at play.

ETIOLOGY

Several studies examined etiology of pancreatitis and risk of developing T3cDM. It is well established that the three most common causes of AP are: gallstone, alcohol, and hypertriglyceridemia [4]. Several studies found that alcohol was associated with greater risk of developing T3cDM [18, 19]. These studies postulate that alcohol's effect on the pancreas directly

and via its metabolites leads to multiple pathways of damage ultimately leading to atrophy, fibrosis, and premature activation of digestive enzymes. Furthermore, the specific activation of pancreatic stellate cells (by metabolites) leads to ongoing inflammatory response, fibrosis, and damage after the initial insult occurs [7]. Others, however, have found no significant association with etiology and development of T3cDM [9-11] suggesting confounding variables exist with alcoholic pancreatitis and development of T3cDM.

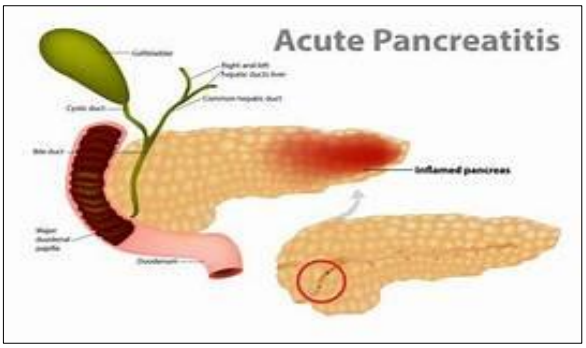
Other Risk Factors

There has been limited exploration of other risk factors associated with increased endocrine dysfunction after AP. One study explored a predictive model for developing diabetes post-AP and created a nomogram [3]. The investigators found that body mass index, age, glucose, triglycerides and low-density lipoprotein at time of admission were associated with increased risk of DM over a 3-month follow-up period. This study highlights other comorbid conditions that may contribute to worsened impaired glucose metabolism after an AP episode. Another smaller study monitored patients up to 3.5 years after AP and found that obesity and hyperlipidemia were risk factors. For these risk factors it is difficult to distinguish between traditional risk factors for DM and their novel impact on T3cDM after AP. The studies conducted so far did not have control groups to distinguish natural progression to DM compared to development of DM after AP. Though the examination of risk factors for developing T3cDM is limited, it may begin to highlight particular patient populations who warrant closer follow-up after an AP episode.

Concomitant Endocrine and Exocrine Insufficiency

Many studies explored both endocrine and exocrine impairment after AP, and some found significant overlap [12]. Some studies cite as high as 40% overlap [6] where as others have as low as 3% overlap [8]. Many of these studies used FE1 to measure pancreatic exocrine insufficiency; however, others used need for pancreatic enzyme replacement therapy and a meta-analysis used a variety of measures (secretin-caerulein infusion testing, serum pancreolauryl testing, fecal elastase and fecal fat testing, self-reported need for enzyme replacement) [13].

For chronic pancreatitis, FE1 is a commonly used indirect measure of pancreatic exocrine function. For the diagnosis of chronic pancreatitis, it has increased sensitivity with increased severity of disease (63% mild, 100% moderate, 100% severe) and specificity of 93% [15]. FE1 has been subject to criticism as a test for exocrine function. Specifically, it is thought it is a useful tool in ruling out pancreatic exocrine insufficiency when you have a low pre-test probability, however, often leads to many false positives [5]. Furthermore, some definitions of T3cDM have even included the need for evidence of exocrine dysfunction [14]. It is therefore important to characterize the relationship between endocrine and exocrine dysfunction in patients after AP and to determine the best marker for disease overlap.



Diabetes as an Etiology for Acute Pancreatitis

One study examined this, using population level data derived from the Taiwan National Health Insurance claims database. The investigators first looked at the risk of developing AP in those with DM and compared those to controls. They found an increased HR of 1.72 of developing AP in those who were diabetic, and this was even higher if they had a history of 'hyperglycemic crisis" (HR, 6.32). This study also found a similar relationship between developing DM after AP that many other studies have found (HR, 2.15) [4]. This study proposed that given the higher HR in those with a history of hyperglycemic crisis, there might be a "severity-response" relationship. Another study approached this question by examining the structural changes that occur in the pancreas as a result of DM [2]. They found pancreatic weight and volume were decreased in those with T1DM (no significant decrease in T2DM), and at autopsy, the investigators found fibrosis with minimal inflammatory changes and no duct abnormalities in these patients. Additionally, these patients were largely asymptomatic, despite having reduced FE1 levels. This study highlights a disease entity separate from chronic pancreatitis. This suggests pancreatic fibrosis and exocrine dysfunction exists separately (or on a continuum) from chronic pancreatitis and occurs most predominantly in those with T1DM. Though this cohort did not develop AP episodes, this study does highlight the presence of structural changes within the pancreas that may increase a patient's risk for developing AP, further showing the complex interplay between the endocrine and exocrine pancreas.

CONCLUSIONS

In conclusion, DM (including T3cDM) and impaired glucose metabolism is common and increasingly recognized following AP. Among the types of DM, T3cDM is an increasingly recognized entity and has been found following AP. Though the diagnostic criteria have varied over time and it is largely underrecognized, its unique disease profile warrants further attention. These patients typically require insulin earlier than those with T2DM and often have difficult to manage hypo- and hyperglycemic episodes. Several

large studies estimate prevalence of about 15% at 1 year and even greater proportion of cases at 5 years. Severity appears to affect propensity of developing diabetes, and several studies have found that alcohol may also be correlated. Physicians should be aware and aim to screen patients yearly following AP episode, and pay particular attention to those with severe episodes, alcoholic pancreatitis, and diabetes risk factors. Finally, there are data suggesting diabetes leads to structural changes in the pancreas potentially predisposing to AP, further highlighting the complex interplay between AP and the endocrine pancreas. This review highlights that diabetes following AP is an increasingly recognized clinical entity; however, currently the data are limited and heterogeneous and future studies are needed to clarify the existing gaps in knowledge.

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