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TOPIC HIGHLIGHT

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Pancreatic endocrine and exocrine changes in celiac disease

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Abstract

Although there is a great deal of information on celiac disease and associated involvement of other non-intestinal sites, data on concomitant changes in the structure and function of the pancreas is limited. The present review critically examines pancreatic endocrine changes that have been well documented in the literature, including insulin-dependent diabetes mellitus. Pancreatic exocrine alterations may also occur, and if severe, marked malnutrition with pancreatic failure and ductal calcification have been observed. Finally, other pancreatic disorders have been recorded with celiac disease.

Key words: Celiac disease; Gluten-sensitive enteropathy; Diabetes mellitus; Chronic pancreatitis; Pancreatic function

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INTRODUCTION

Considerable information has already been published on both the intestinal and the extra-intestinal manifestations of celiac disease. Pancreatic changes may be caused by celiac disease or co-exist with celiac disease. Both endocrine and exocrine function of the pancreas may be substantially changed in celiac disease. As a result, superimposed or more severe clinical changes may appear and marked nutritional disturbances may result. Although data is very limited, there is increasing evidence that impaired endocrine and exocrine pancreatic function in celiac disease may be favorably influenced by gluten-free diet treatment.

PANCREATIC ENDOCRINE CHANGES

Over the past decade or so, a number of studies from Europe[1,2] and North America[3,4] have demonstrated that the prevalence of celiac disease in patients with type 1 diabetes is increased. This association is due, at least in part, to sharing of the human leukocyte antigen allele, DR3, and, by linkage disequilibrium, DQ2[5]. In addition to a common "autoimmune" basis, it is conceivable that some celiacs have developed diabetic changes secondary to severe pancreatic insufficiency with exocrine dysfunction. Earlier serological studies employed IgA antibody studies for celiac screening, particularly using IgA endomysial antibody (EMA) testing. This eventually became the "gold standard" for serological studies, until subsequent identification of tissue transglutaminase (TTG) as the tissue antigen for endomysial antibodies[6]. As a result, IgA TTG antibodies (using ELISA methodology) became a very attractive alternative for first line screening and also permitted development of a quantitative assay.

A recent TTG prospective study[7] in children and adolescents with type 1 diabetes evaluated TTG antibody titres in 125 males and 108 females followed in a pediatric diabetes center. Altogether, 26 patients, including 15 males and 11 females, had positive TTG titres and, of these, 19 were also positive for EMA. In those positive for both TTG and EMA, small intestinal biopsies were done. Histopathological abnormalities described in celiac disease were detected ranging from increased numbers of intraepithelial lymphocytes to severe crypt hyperplastic villous atrophy (Marsh 3 lesion)[7]. These studies also suggested that serial TTG serological measurements in insulin-dependent diabetics might play a role in monitoring their serological responses as well as the compliance to the gluten-free diet. In children and adolescents, close monitoring is critical as compliance in these age groups may be especially difficult to assess. While over 40% of the diabetics in this study were asymptomatic[7], prospective serological screening appeared to facilitate selection for biopsy evaluation.

Earlier detection of celiac disease has been urged in type 1 diabetes, even in children, because of the long-term risks of undiagnosed celiac disease. It has been suggested that the longer the duration of untreated celiac disease (also in dermatitis herpetiformis), the higher the risk of

enteropathy-associated T cell lymphoma[8]. Moreover, adherence to a gluten-free diet appears to reduce the risk of enteropathy-associated T cell lymphomas in celiac disease. Finally, the association of lymphoma, celiac disease and type 1 diabetes has also been documented in 4 cases[9].

Other long-term complications may occur including iron deficiency anemia, osteoporosis, infertility and growth retardation. These appear to be most significant when patients are poorly compliant with a gluten-free diet, or if diagnosis is delayed until later in life[10]. Finally, improved glucose control with a gluten-free diet has also been shown in type 1 diabetes with concomitant celiac disease[11]. In these studies with type 1 diabetes in celiac disease, pancreatic exocrine function was not evaluated.

PANCREATIC EXOCRINE CHANGES

Pancreatic exocrine function may also be substantially altered in celiac disease. Even though the precise prevalence of altered pancreatic function in celiac disease is not known, impaired pancreatic function may be a cause of impaired digestion and absorption resulting in malnutrition[12]. It has been estimated that over 20% of patients with celiac disease have defective exocrine pancreatic function[13]. This may be related to several factors. First, impaired secretion and/or release of pancreatic stimulating hormones from the diseased proximal small intestine may be important[14]. Immunohistochemical studies on small intestinal biopsies from untreated celiac disease have demonstrated significant alterations in enteric endocrine cells, including an absence of secretin cells[15].

Moreover, studies with test meals in celiacs have suggested impaired secretion of cholecystokinin-pancreozymin, resulting in reduced pancreatic exocrine cell stimulation[16]. Second, deficiencies of amino acids may result from impaired small intestinal amino acid uptake, leading to reduction in precursors of pancreatic enzyme synthesis[12,17]. Third, protein malnutrition may lead to structural changes in the pancreas, including atrophy of acinar cells and pancreatic fibrosis, resulting in impaired pancreatic exocrine function[12]. Pancreatic enzyme measurements were also found to be reduced with mucosal atrophy and could be inversely correlated with the degree of intestinal damage[18]. Earlier studies measuring xylose absorption were limited in ability to separate pancreatic and intestinal causes of steatorrhea, especially if the degree of impairment was mild[19]. Subsequent attempts to define altered intestinal permeability using large molecules (e.g., cellulobiose, mannitol)[20] or separate pancreatic insufficiency from intestinal dysfunction with noninvasive stable isotopes[21] have not become widely accepted.

Severe structural changes have also been documented. Pancreatic calcification, most often associated with chronic or persisting pancreatic inflammation, has been traditionally associated with excessive alcohol use.

Atrophy, fibrosis and altered pancreatic function have also been detected in experimental animals treated with diets deficient in protein, in adults with protein energy malnutrition, in children with kwashiorkor and in some early autopsy studies of patients with celiac disease[16,17,22-24]. In addition, pancreatic calcification has been reported with chronic protein malnutrition in the Indian subcontinent and in some African countries[25]. Finally, an adult patient with celiac disease and non-alcohol related pancreatitis with calcification has been described in North America[26]. Possible effects on pancreatic exocrine function in celiac disease poorly compliant to a gluten-free diet has not been evaluated.

MISCELLANEOUS DISORDERS

A number of other miscellaneous pancreatic disorders have been associated with celiac disease. Pancreatic mucinous adenomas have been associated with celiac disease in a patient with polycystic kidney disease[27]. In addition, pancreatic and ampullary carcinomas have been recorded in celiac disease[28,29], although the celiac disease has often only been recognized after pancreatoduodenectomy suggesting that subclinical celiac disease may be "unmasked" by major upper gastrointestinal surgery and should be considered in the differential diagnosis after pancreatoduodenectomy[22,29].

Celiac disease has been associated with chronic calcific pancreatitis in patients with pancreas divisum[30]. Diabetes-related autoantibodies may appear in children with celiac disease, including antibodies to insulin, immunoglobulin, islet cells and glucagon[31]. Early-onset vitamin B12 malabsorption in children with celiac disease has also been documented and related to impaired pancreatic exocrine secretion[32]. Finally, macroamylasemia has also been attributed to gluten-related amylase autoantibodies (particularly in childhood)[33].

Because of the possible deleterious effects of biliary tract lithiasis on pancreatic structure and function, gallbladder function in celiac disease may also be important and carefully examined in celiac disease. In some, slow emptying of the gallbladder has been documented, associated with impaired contraction response to fat[34,35]. Studies of enteric endocrine cells have demonstrated significant quantitative and qualitative changes in celiacs[15]. In addition, studies with test meals have suggested impaired secretion of cholecystokinin in patients with celiac disease, and, possibly, impaired gallbladder responsiveness to cholecystokinin[15,34]. In spite of these physiological alterations, there does not appear to be a significant predisposition to gallstones in celiac disease and consequently, secondary pancreatic damage. Only 9 of 350 celiac patients had a cholecystectomy for gallstone disease[14]; however, in a survey of elderly celiacs initially diagnosed after the age of 60 years, approximately 20% had developed gallstone disease[36,37].

CONCLUSION

In summary the endocrine and exocrine function of the pancreas may be impaired in celiac disease and their pathogenesis may be closely linked. Further studies are needed to explore the importance of detection of endocrine and exocrine pancreatic disorders in celiac disease, along with potential treatment options.

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