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Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy:

Conclusions From a Review of Literature

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Abstract

Objective—Abnormalities in exocrine pancreatic function have been reported in diabetes mellitus (DM). We reviewed published literature to determine the nature of structural and functional alterations in the exocrine pancreas in DM.

Methods—We identified and abstracted data from original studies (n = 50) describing morphological, structural, and functional changes in the exocrine pancreas in types 1 and 2 DM.

Results—Pancreatic weight and volume are markedly lower in type 1 DM ($P < 0.005$) with insignificant decrease in type 2 DM compared with age-, sex-, and body mass index–matched controls. Pancreatic histopathological changes seen in most subjects with DM at autopsy (n = 7 studies, 1272 autopsies) include mild-to-marked interacinar fibrosis, scant inflammatory infiltrate, no pancreatic ductal changes, and hyalinization of arteries. In subjects with DM, pooled prevalence of decreased fecal elastase 1 (<200 μg/g) is higher, coefficient of fat absorption is near normal (mean, 91%–94%), and pancreatic exocrine dysfunction is nonprogressive over time. Diabetes mellitus is asymptomatic in regard to the exocrine pancreas.

Conclusions—In types 1 and 2 DM, moderate-to-severe subclinical pancreatic fibrosis and modest exocrine dysfunction occurs in the absence of clinical or histopathological evidence of chronic pancreatitis. We call this novel entity "diabetic exocrine pancreatopathy."

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Keywords

chronic pancreatitis; diabetes mellitus

Type 1 diabetes mellitus (DM), previously called juvenile-onset or insulin-dependent DM, is caused by autoimmune destruction of pancreatic beta cells; islet histopathology shows characteristic “insulitis” or islet inflammation.[1] Type 2 DM, previously called maturity-onset or non–insulin-dependent DM, is associated with metabolic syndrome and insulin resistance; islet amyloid is the characteristic histopathological finding in islets.[2] Diabetes mellitus secondary to chronic pancreatitis (CP) is due to loss of islet mass secondary to fibro-inflammatory destruction of the pancreas, and the exocrine pancreas has characteristic features in CP.[3] This review pertains to changes in the exocrine pancreas in types 1 and 2 DM, assuming a rough equivalence between current and older terminologies.

On the basis of the frequent observation that exocrine pancreatic function is abnormal in types 1 and 2 DM, it has been concluded that DM causes pancreatic exocrine insufficiency.[4–9] It has been known for more than a century that there are significant changes in exocrine pancreas in patients presenting with types 1 and 2 DM.[10] Because of both structural and functional changes in the exocrine pancreas in types 1 and 2 DM, some authors have speculated that these changes represent CP.[4,10–12] Because DM is not associated with clinical symptoms of exocrine pancreatic disease, it is postulated that the changes may represent silent CP.[4]

“Chronic pancreatitis” is the only term currently available to describe fibro-atrophic changes in the exocrine pancreas.[3] Chronic pancreatitis encompasses a wide spectrum of diseases associated with progressive fibro-inflammatory damage to the exocrine pancreas, which, if the injury is widespread, leads to failure of exocrine and endocrine pancreatic function requiring treatment. Chronic pancreatitis has a wide range of presentations depending on etiology, the most frequent being clinically acute pancreatitis, imaging evidence of calcification, dilated pancreatic duct, pancreatic atrophy, steatorrhea, diabetes, and jaundice.

To better understand the nature of exocrine pancreatic changes in types 1 and 2 DM, we performed a comprehensive review of the literature to identify studies on morphology, histopathology, and exocrine pancreatic function in DM. On the basis of this review, we conclude that DM is indeed associated with significant alterations in pancreatic exocrine structure and function, more so in type 1 DM, which share some similarities with but also have distinct differences from those described in CP. We suggest the term diabetic exocrine pancreatopathy (DEP) to describe this entity. We discuss the implications of recognizing this new entity for the study of the endocrine and exocrine pancreas and the poorly understood interactions between the two.

METHODS

Literature Review

Search Strategy—Using defined (MESH) terms and key words, MEDLINE, Scopus, EMBASE, and Web of Science were searched for studies published from database inception

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through January 2015. Search terms used included “diabetes mellitus” in combination with the key words “pancreatic volume,” “pancreatic size,” “pancreatic function,” “insulitis,” “pancreatic fibrosis,” “fatty pancreas,” “pancreatic exocrine insufficiency,” “steatorrhea,” “fecal elastase,” “secretin,” “bicarbonate,” and “cholecystokinin” (see Supplementary Appendix 1, http://links.lww.com/MPA/A487, for detailed search strategy). To complement this search, the references in the manuscripts were manually screened for additional (usually older) studies on the subject.

Study Selection—Search results from the different databases were combined, duplicates were removed electronically, and results were checked manually for accuracy. Abstracts with nonrelevant titles were excluded. Abstracts and full texts were reviewed independently by 2 reviewers (S.M. and S.M.) for inclusion. Any disagreements about inclusion or exclusion of these studies were resolved by consensus, and a third senior reviewer (S.T.C.) was consulted to resolve any remaining disagreements. Studies that seemed to fulfill the following eligibility criteria and those for which information in the abstract was not sufficient for exclusion were read in full.

Inclusion Criteria

Original articles that reported on exocrine pancreatic morphology (volume, gross morphology, and ductal morphology), histopathology, pancreatic exocrine function (tested by direct function tests [pancreatic stimulation by secretin, cholecystokinin/pancreazymin, or secretin-cholecystokinin/pancreazymin] or indirect function tests [fecal elastase 1 (FE1) concentration], coefficient of fat absorption (CFA), and steatorrhea were eligible for this review.

Exclusion Criteria

Case reports, nonsystematic reviews, non-English articles, and animal studies were excluded. Pancreatic size based on abdominal ultrasound and pancreatic volume index based on computerized tomography (CT) scan and magnetic resonance imaging (MRI) were excluded as the data were not comparable with other imaging studies. Also excluded from this review were studies of pancreatic function in patients with symptomatic pancreatobiliary disease and indirect function tests other than FE1. Histopathological studies of the pancreas in DM that focused on islet pathology and did not provide detailed description of the exocrine pancreas were also excluded.

Data Extraction, Quality Assessment, and Statistical Analysis

One reviewer extracted relevant data into a standardized form. These data were verified by a second reviewer, and discrepancies were resolved by consensus. For included studies, we abstracted data on study populations, interventions, outcomes, quality, and applicability.

Two investigators independently rated risk of bias using the Newcastle Ottawa scale for nonrandomized studies. Disagreements were adjudicated by consensus among 2 independent investigators or by obtaining a third reviewer’s opinion when consensus could not be reached. On the basis of the extracted results, textual summaries and tables were created by the reviewers. Similarities and differences across the textual summaries were further

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inspected to avoid contradiction. Figure 1 demonstrates the details of data extraction process.

Statistical pooled analysis was only applied to FE1 results measured by monoclonal antibody (Schebo); χ^2 test was used to compare percentage of subjects with decreased FE1 in type 1 DM and type 2 DM versus controls. Tables for morphological, structural, and fecal fat (FF) test abnormalities were also created for comparison, and heterogeneous data in disaggregated form were presented where appropriate in the text. As noted in the study flow diagram (Fig. 1), 8759 records were identified after duplicates were removed, and 176 abstracts were identified and screened to assess the eligibility. Of these, 50 met the final inclusion criteria for this review; some studies reported on more than 1 aspect of interest.[9,13–16]

RESULTS

Pancreatic Parenchymal Weight, Volume, and Size in DM

Type 1 DM has been consistently associated with marked (20%–50%) decrease in pancreatic weight, volume, and size compared with nondiabetic controls measured directly[17] or by computerized morphometry[18] at autopsy and CT imaging[19–21] and MRI[22–25] in living subjects (Table 1). This has been shown to occur early in the course of type 1 DM,[17] although its progression over time has not been tracked. There are conflicting reports of changes in pancreatic volume in type 2 DM; whereas some studies reported decrease in volume compared with nondiabetic controls,[20,25] others found no difference.[19] Pancreatic volume is affected by age, sex, and body mass index (BMI).[20] In 1 study[20] that controlled for these factors, there was a small (~7%) but significant decrease in total pancreas volume in 165 subjects with type 2 DM compared with age-, sex-, and BMI-matched non-DM controls. Some studies have reported no correlation between pancreatic volume with duration of DM.[19,24] A recent study[21] described decrease in pancreatic volume in DM, which correlated with low FE1 concentration or low chymotrypsin activity, suggesting a correlation between pancreatic atrophy and exocrine deficiency. However, the same study found no significant difference in pancreatic volume in type 1 versus type 2 DM.[21]

Histopathological Changes in the Exocrine Pancreas in DM

In general, histopathology studies of the pancreas in DM have tended to focus on islet pathology. We identified 7 studies[10,11,27–31] encompassing 1272 subjects with DM who commented on the changes in exocrine pancreas (see Supplementary Table 1, http://links.lww.com/MPA/A487, for details on individual studies and summary of all studies in Supplementary Table 2, http://links.lww.com/MPA/A487). Four studies included controls[27–30]; however, only in 2 studies were findings in the exocrine pancreas compared between DM versus non-DM controls[28,29] (Table 2). Collectively in all 7 studies,[10,11,27–31] 255 (59.4%) of 429 patients had pancreatic fibrosis, with all studies reporting greater than 50% prevalence of fibrosis in those with long-standing DM; Gepts[30] reported 18% prevalence of fibrosis in those with juvenile-onset DM dying less than 2 years of onset of disease. Two case-control studies provide more detailed grading of fibrosis[28,29] (Table 2). Although any amount of fibrosis (graded 1+ to 3+) without inflammation was seen equally

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in cases and controls, moderate-to-severe fibrosis was twice as frequent in DM as in non-DM controls.[28,29] In contrast to the high prevalence of fibrosis, inflammatory infiltrates are scant and infrequent in DM (Table 2).[28,29]

Gepts[30] described a focal or diffuse lesion of acute pancreatitis in the patients with acute juvenile DM compared with less frequent involvement by the infiltrates in chronic juvenile DM. In a study from Scotland, Foulis et al[32] reported lymphocytic infiltrates in the exocrine pancreas in only 9 (9.4%) of 95 cases of type 1 DM. Lymphocytic infiltration of the exocrine pancreas was seen in 22 (46.8%) of the 47 Japanese patients with type 1 DM suggesting immune-mediated destruction of both exocrine and endocrine pancreas in the Japanese population with DM.[27] In a Danish autopsy study of 394 consecutive patients,[33] higher prevalence of DM (19% vs 7%) was reported in subjects with mild chronic inflammation compared with those without chronic inflammation.

Pancreatic Ductal Morphology in DM

One of the striking features of descriptions of pancreatic exocrine histology in DM is the complete absence of ductal changes typically seen in CP, including ductal distortion (strictures and dilatation), intraductal protein plugs, and calcification (Fig. 2). This is corroborated by the only ERP study in subjects with primary DM (25 type 1 and 15 type 2)[34] from Sudan, which showed normal pancreatogram in type 1 DM and minimal changes in 2 of 15 type 2 DM. Analysis of other ERP and magnetic resonance cholangiopancreatography (MRCP) studies in people with diabetes is confounded by the fact that they have included variable proportion of symptomatic patients with suspected pancreatobiliary disease[12,26] or did not provide any clinical history.[35] For example, Hardt et al[12] retrospectively analyzed pancreatograms of 156 symptomatic patients with DM with suspected pancreaticobiliary disease and found characteristic changes of CP in a large proportion (76.7%) of patients. Similarly, Bilgin et al[26] reported MRCP abnormalities of CP in 32% patients with pancreatobiliary disease consistent with symptoms of CP.

Pancreatic Exocrine Function in DM

Multiple studies in DM have reported high prevalence of abnormal exocrine pancreatic function both on direct[16,36–46] (Supplementary Table 3, http://links.lww.com/MPA/A487) and indirect pancreatic function test (FE1) (Table 3). The most common abnormalities observed by direct pancreatic function tests were decreased amylase and bicarbonate output and decreased maximum bicarbonate concentration. A few studies have reported mild-to-moderate reduction in lipase output.[16,39] We identified 17 studies[5–8,13–16,47–55] (Supplementary Table 4, http://links.lww.com/MPA/A487) where prevalence of decreased FE1 levels (cutoff of <200 μg/g and/or <100 μg/g) measured by monoclonal antibody (Schebo Biotech, Giessen, Germany) was reported. Collectively, these studies have included 940 non-DM controls and 3662 subjects with DM, of which 1724 had type 1 DM. A pooled analysis of these 17 studies (Table 3) shows that decreased FE1 is more prevalent in DM compared with controls ($P < 0.00001$). Furthermore, low FE1 levels are more commonly seen in type 1 DM versus type 2 DM, with a cutoff of both less than 200 μg/g (38.62% vs 28.12%, $P < 0.00001$) and less than 100 μg/g (20.11% vs 14.1%, $P < 0.00001$).

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Changes in exocrine function are nonprogressive in DM. In a German study of 20 subjects with type 1 DM, a follow-up secretin-pancreazymin test 11 years after a previously abnormal test found no significant correlation between the duration of DM and the test results for both time points of investigation.[36] In fact, only mild abnormalities in pancreatic function were observed after a mean of 22 (±10.9) years of disease. There have been conflicting results regarding FE1 levels and duration of DM; a few studies have reported that increase in the duration of DM is associated with decreased FE1 level,[50,52] but others did not find any correlation with duration of DM.[8,47,49,53] Many studies[49–51] have reported that poor glycemic control in DM was associated with greater reduction in FE1. Other reported associations with reduced FE1 in DM include BMI greater than 25[7,54] and presence of vascular disease.[54]

Steatorrhea in DM

In DM, fat balance studies to determine CFA have been performed and correlated with pancreatic function tests (Table 4). A study of 101 German subjects with type 1 DM[9] with severe reduction in FE1 (<100 μg/g) showed that 40% had normal CFA (<7 g of fat/day on a 100-g/d fat diet); the mean FF excretion (FFE) (100-CFA in grams per day) in this cohort was only 9.2 ± 5.4 g/d, and only 12% had FFE of greater than 15 g/d. Overall, 1% of 1020 subjects with diabetes had FFE of greater than 15 g/d. To understand the mechanism of steatorrhea in DM, Hahn et al[16] measured lipase output, FE1, and FFE in 33 subjects with type 1 DM. Similar to Hardt et al,[9] they found that 45.5% of subjects with type 1 DM had low FE1 (<200 μg/g) and 67% had an abnormal FFE (>7 g/d). However, in none of the subjects with abnormal FE1 or increased FFE was lipase output severely (<10% of normal) reduced. In fact, the mean reduction in lipase output was only 18%, which was not sufficient to explain the mild increase in FFE in type 1 DM. They concluded that DM is associated, at best, with only mild-moderate reduction in lipase output that is insufficient to explain mild fat malabsorption seen in DM and speculated that this may be due to small bowel bacterial overgrowth.[16] In keeping with these findings, a randomized double-blind control trial[5] of pancreatic enzyme replacement therapy (PERT) in 80 patients with low FE1 and DM showed no significant difference in clinical symptoms (stool consistency, flatulence, abdominal pain) between the PERT and placebo groups. However, there was a reduction in the frequency of hypoglycemia in patients on PERT.[5]

DISCUSSION

A comprehensive review of the published literature on the morphological, histopathological, and functional changes in the exocrine pancreas in types 1 and 2 DM reveals that a significant proportion of subjects have exocrine changes that we term DEP. Diabetic exocrine pancreatopathy is asymptomatic but is associated with (1) a marked decrease in pancreatic weight, size, and volume in type 1 DM, but mild to no decrease in type 2 DM; (2) increased interacinar fibrosis and acinar atrophy with minimal inflammation and no pancreatic ductal changes; (3) a modest reduction in pancreatic enzyme output and FE1 concentrations, more so in type 1 DM, with (4) normal to minimal decrease in CFA; and (5) lack of progression of exocrine dysfunction over time.

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Diabetic exocrine pancreatopathy differs significantly from CP in the conspicuous absence of symptoms of exocrine disease (acute pancreatitis and pain), lack of ductal changes including strictures, protein plugs and calculi, lack of significant inflammation, and lack of progression to a calcific state even in a subset of patients. Although a formal case-control study to confirm and validate the histopathological changes noted here is clearly needed, the consistency of findings across studies and the large number of autopsies included (n = 1272)[10,11,27–31] strongly support the veracity of the histopathological observations. Similarly, a large study of more than 1000 patients confirmed the abnormalities in FE1 concentrations noted in earlier studies.[8]

The fundamental significance of this study is in the conclusion that pancreatic fibrosis and exocrine dysfunction frequently occur in the absence of clinical or histopathological evidence of CP; that is, DEP is distinct from CP. This novel observation has significant implications for the study of both the exocrine and endocrine pancreas and the poorly studied interaction between the two. Similar findings have been reported in smokers[56] and alcoholics[57] without clinical pancreatic disease. The existence of EP radically challenges our perspective on the definition, pathogenesis, and diagnosis of CP. In addition, it questions the specificity of pancreatic function testing and endoscopic ultrasound for the diagnosis CP in asymptomatic subjects with risk factors for EP. A new field of research into EP will be needed to elucidate the relationship between DM and DEP and whether EP worsens DM by reducing islet cell mass. The reasons why DEP rarely progresses to clinically apparent CP also warrant study. New tests will be needed to distinguish EP from CP. In this context, the role of inflammatory markers in pancreatic juice to distinguish CP from EP will be a highly relevant field of study.

What are the possible mechanisms for the alterations in pancreatic structure and function in DM? In type 1 DM, acinar cell atrophy has been attributed to lack of trophic action of insulin. Lohr and Kloppel[18] found that exocrine atrophy is due to reduction in size rather than number of acinar cells. However, they could not find a clear relationship between the extent of exocrine atrophy and the residual insulin positivity, the duration of DM, or microangiopathy related to DM. In a study of 11 patients with recent-onset type 1 DM, Foulis and Stewart[58] demonstrated that severe pancreatic acinar cell atrophy was present surrounding the insulin-deficient islets whereas acinar cells around the insulin-containing islets were normal suggesting that the exocrine changes could be related to islet-acinar vascular connections and the loss of trophic effects of various islet hormones on pancreatic acini. Fibrosis with minimal inflammation has been attributed to diabetic vasculopathy.[28,29]

In both forms of DM, parenchymal atrophy and exocrine fibrosis is often accompanied by lesions in the smaller blood vessels and fatty atrophy of the pancreas. Lazarus and Volk[29] reported distinct arteriolosclerosis in 66% of the diabetic patients compared with 34% of non-DM controls suggesting that microangiopathy could be the primary factor causing pancreatic fibrosis and exocrine atrophy. However, Lohr and Kloppel[18] could not find any significant correlation between the extent of exocrine atrophy and microangiopathy in chronic type 1 DM. In addition, pancreatic function (ductal and acinar) has been shown to decline, secondary to hyperglycemia and hyperinsulinemia.[59] There are conflicting reports on fatty atrophy of the pancreas with some suggesting increased fatty change in DM[27,28] but

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others[20] describing increase in pancreatic fat associated with increase in BMI rather than presence of DM when compared with non-DM controls.

This retrospective review, although exhaustive, has limitations and biases. Over time, the terminology of DM (now called types 1 and 2) has changed many times, and the assumption of equivalence, for example, of terms juvenile-onset DM, insulin-dependent DM, and type 1 DM may not be wholly accurate. If there are distinct subtypes of DEP in types 1 and 2 DM, we could not identify their unique histopathological characteristics other than differences in islet pathology. Although findings from more than 1200 autopsies and more than 4600 FE1 measurements have been reported here, many of the studies did not have controls or had limited description of controls. However, findings in uncontrolled studies parallel those seen in case-control studies. Despite these limitations, the observation that more than half of the patients studied had pancreatic fibrosis, often moderate to severe, and nearly 30% to 40% had pancreatic exocrine dysfunction cannot be ignored. The observations need further study to understand its nature and mechanism.

In summary, both types 1 and 2 DM are associated with changes in the exocrine pancreas and decrease in acinar and ductal function. Although an exocrine pancreatopathy does occur in DM, its mechanism and clinical significance remain to be explored. Further studies focusing on the exocrine pancreas are clearly needed to better define DEP and distinguish it from CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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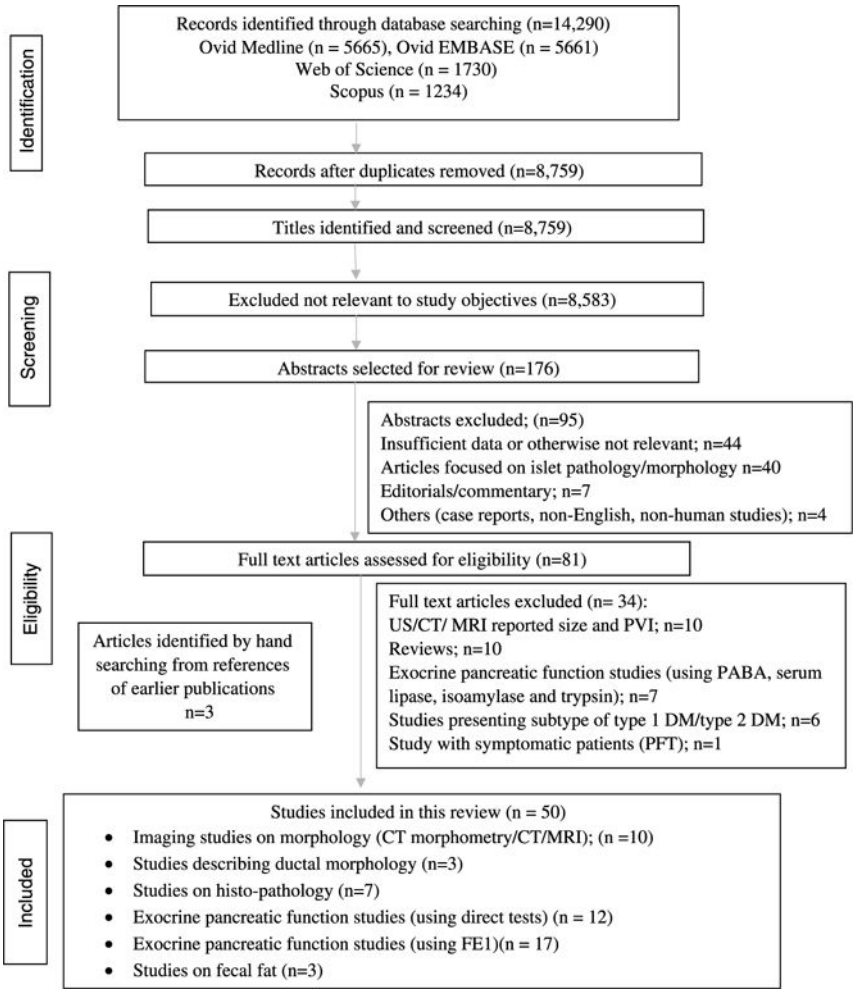

FIGURE 1.
Study flow diagram.

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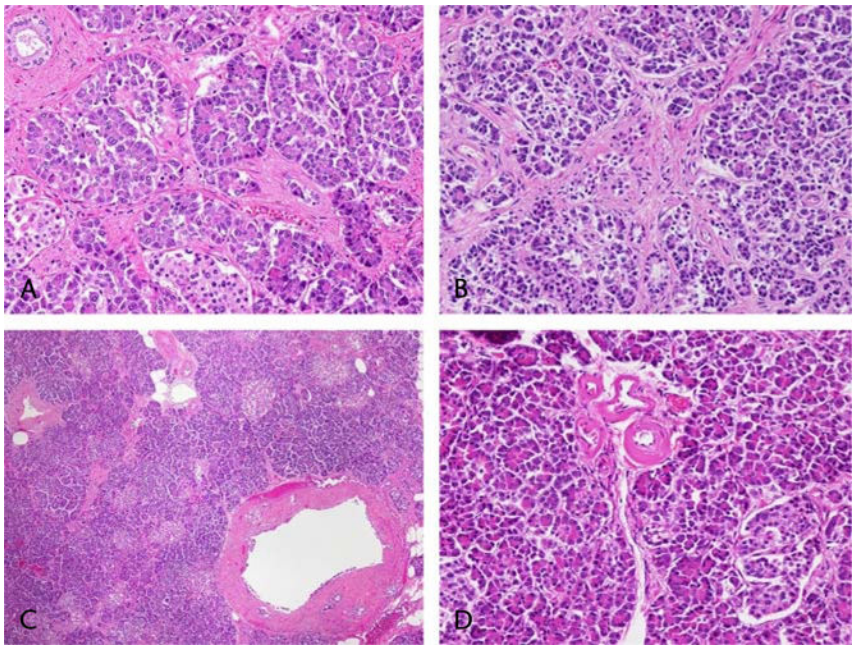

FIGURE 2.

A and B, Interacinar fibrosis without inflammation (200×) in type 2 DM. A small normal duct is present in the upper left corner of A. C, Large duct at lower right has denuded epithelium (likely artifact), but where intact, the epithelium and pancreatic duct glands are normal (40×). D, Vasculopathy: small artery branches with wall thickened by amorphous pink material (200×). **Editor's note:** A color image accompanies the online version of this article.

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TABLE 1

Pancreatic Volume by MR or CT in DM

Author (Year)	No. Subjects With DM			Imaging Test	Pancreatic Volume, mL			Volume/Size* (Percentage Decrease vs Controls)	*P*, Controls vs Type 1 DM/Type 2 DM
	Type 1	Type 2	Controls		Type 1	Type 2	Controls		
Bilgin et al[26] (2009)	28	—	21	MRI/MRCP	—	—	—	4*	<0.0001/—
Williams et al[24] (2007)	12	—	12	MRI	52.4 ± 17.1	—	101 ± 19.5	48	<0.001/—
Sequeiros et al[23] (2010)	12	—	12	MRI	52.5	—	104.8	—	<0.0001/—
Williams et al[22] (2012)	20	—	24	MRI	91.9 ± 6.4	—	121.3 ± 6.5	26	0.003/—
Burute et al[25] (2014)	—	32	50	MRI	—	72.7 ± 20.7	89.6 ± 22.7	—	—/<0.001
Goda et al[19] (2001)	26	29	22	CT	45.2 ± 19.5	68.7 ± 18.8	71.5 ± 18.7	20	<0.001/NS
Saisho et al[20] (2007)	—	165	1721	CT	—	70.0 ± 26.5	74.9 ± 27.0	7	—/<0.05
Philippe et al[21] (2011)	24	28	—	CT	42		—	—	—

*The table excludes studies based on autopsy.[17,18]

NS indicates not significant.

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TABLE 2

Histopathological Findings in DM Versus Controls

	Kim[28] (1977)			Lazarus and Volk[29] (1961)		
Histologic Features,* N (%)	**DM (n = 95)**	**Controls (n = 95)**	***P***	**Maturity-Onset DM (n = 50)**	**Controls (n = 50)**	***P***
Interacinar fibrosis	36 (38)	16 (17)	0.004	15 (30)	8 (16)	0.09
Interlobular fibrosis	24 (36)	14 (15)	0.004	19 (38)	4 (8)	0.0003
Periductular fibrosis	33 (35)	1 (1)	0.004	—	—	
Acinar atrophy	21 (22)	7 (7)	0.004	24 (48)	12 (24)	0.001
Inflammation	13 (14)	10 (11)	NS	†	†	
Lipomatosis	13 (14)	12 (13)	NS	25 (50)	20 (40)	NS
Arteriosclerosis	37 (39)	14 (15)	0.004	11 (22)	4 (8)	0.05

Age range (years) for cases/controls: Kim et al,[28] 12–85/not stated; Lazarus and Volk,[29] 40–85/matched for age and sex.

*Both studies graded features as mild, moderate, and severe (1+ to 3+): data shown are prevalence of moderate or higher.

†Reported as found in “some,” equally in diabetic and nondiabetic pancreases.

NS indicates Not Significant.

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TABLE 3

Pooled Analysis of Studies of FE1 in DM

Type of Subjects (No. Studies)	Total No. Subjects Evaluated for Decreased FE1 (<200/<100 μg/g)	Percentage of Subjects With Decreased FE1 (<200/<100 μg/g)	*P*,* DM vs Control
Type 1 DM (14)	1178/1566	39%/20%	<0.001
Type 2 DM (7)	1938/1928	28%/14%	<0.001
Controls (6)	940/940	13%/3%	—

Total excludes studies by Nunes et al[7] (no DM subtypes), Ewald et al[5] (percentage for <200 μg/g not available), Hahn et al,[16] Laass et al,[6] and Vesterhus et al[14] (percentage for <100 μg/g unavailable).

*P values for types 1 and 2 DM versus controls are <0.00001 and <0.00001 for <200 and <100 μg/g, respectively.

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TABLE 4

FFE in DM

	No. Subjects With DM Studied			No. (%) Subjects With DM With Normal and Abnormal FF Estimation				% With Abnormal FFE in FE1 Groups	
Author (Year)	**Type 1**	**Type2**	**Mean FFE, g/d**	**Normal, <7 g/d**	**Mild, >7–10 g/d**	**Moderate, 10–15 g/d**	**Severe, >15 g/d**	**<200 μg/g**	**100 μg/g**
Hardt et al[9] (2003)	30	71	9.19 ± 5.39	41 (41.3)	20 (19.8)	28 (27.7)	12 (11.9)	—	60/101 (59.4)
Cavalot et al[15] (2006)	66	—	6 ± 3.2	47 (71.2)		19 (28.8)		8/17 (47.0)	5/7 (71.4)
Hahn et al[16] (2008)	33	—	—	11 (33.3)	7 (21.2)	11 (33.3)	4 (12.1)	9/15 (60.0)	—
Total	200			99/200 (49.5)		101/200 (50.5)		17/32 (53.1)	65/107 (60.7)

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