The Whole Human Pancreas: An Understudied Organ in Diabetes

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Type 1 and type 2 diabetes both cause life-changing morbidity and earlier mortality, with effects on the individual, their family, and wider society. Working lives are affected, with knock-on effects for the wider economy. Many questions remain about the etiology of both types of diabetes and about disease-specific changes in the exocrine pancreas. The anatomical position of the pancreas renders it relatively inaccessible to biopsy, and the islets containing the endocrine cells are scattered throughout the large organ, which serves the very different role of supplying digestive enzymes to the gut. Diabetes of either type does not develop unless the insulin-secreting β-cells of the islets fail to perform adequately in their ambient environment. Paradoxically, even though the pancreas is the most important organ of diabetes, integration of exocrine and endocrine function of the whole organ is less often studied.

Both endocrine and exocrine tissues develop from the fetal gut, and they share genetically determined traits and remain in communication by paracrine and possibly vascular routes (1). Disease primarily of the exocrine pancreas, such as cystic fibrosis or chronic pancreatitis, commonly affects endocrine function, and conversely exocrine pancreatic function is abnormal in some people with either of the common types of diabetes (2,3). In cystic fibrosis, at least 35% of people develop diabetes (2,4). In type 2 diabetes, the increased prevalence of pancreatic cancer (5) also suggests cross talk between tissues. Given that insulin is a powerful antiapoptotic factor (6), the excess basal secretion and potential paracrine effect is likely to contribute to the link. This is supported both by the known link between pancreatic cancer and higher body weight and by the large decreases in fasting plasma insulin and incidence of all weight-related cancers brought about by bariatric surgery or dietary weight loss (7,8).

The study by Wright et al. (9) on organ donor pancreases preserved within 20 h of surgical removal is particularly welcome given the limitations otherwise imposed by postmortem autolysis. In pancreases from donors who did not have diabetes (n = 74), the range of changes with age and obesity was defined, and comparison of changes in the two common types of diabetes was described (Fig. 1). In the pancreases from individuals without diabetes, increasing age was found to be related to increased adipocyte content. There was a tendency for increasing age to be linked with intraepithelial neoplasia (a premalignant change) and metaplasia from acinar to ductal cells. Thickening of the walls of medium-sized blood vessels increased with age, but fibrosis and atrophy score did not. Higher BMI was associated with intraepithelial neoplasia but not metaplasia from acinar to ductal cells.

The quantification of notable acinar atrophy in the pancreases from individuals with type 1 diabetes (n = 20; mean diabetes duration 15.0 years) provided detailed histology about the decrease in whole-pancreas volume that is evident from early in the disease process (10). The authors speculate that this decrease in volume results from decreased exposure to peak insulin levels, and indeed the early atrophy could reflect loss of the 10- to 15-fold rise in plasma insulin following meals (11), potentially reflecting an even greater rise in interstitial insulin concentration within the pancreas. Type 1 diabetes was also characterized by an increase in fibrosis and a greater degree of blood vessel wall thickening. The revealed pattern of fibrosis could be relevant to the exocrine dysfunction of type 1 diabetes, as it affected periductal and perivascular tissues. Previous work by the authors showed fibrosis to be correlated with lower volume of the whole pancreas (12). Research on the resolution of intraorgan fibrosis in several disciplines is showing promise, and if a clinically important impact of perivascular and periductal fibrosis of the pancreas in type 1 diabetes becomes established, then development of therapeutic prevention of fibrosis may become important. No differences in either acinar to ductal metaplasia (related to premalignant change) or in premalignant change itself were observed in the pancreases from individuals with type 1 diabetes. Fewer intralobular

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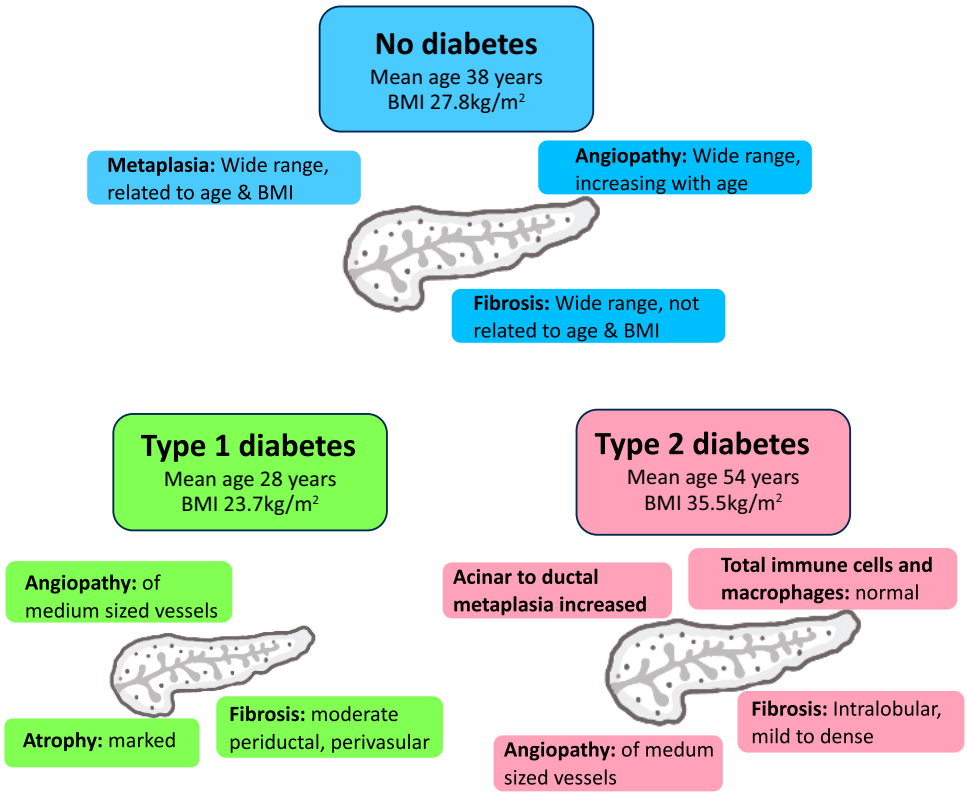

Figure 1—Summary of the principal findings in pancreases from a control group of individuals who did not have diabetes and groups of individuals with type 1 or type 2 diabetes. Subgroups of age- and sex-matched pancreases were used to determine disease-related features.

adipocytes were detected, presumably reflecting the considerably lower BMI.

In the type 2 diabetes group (n = 25), the notable absence of atrophy of the exocrine pancreas in this study contrasts with in vivo imaging studies of pancreas volume and exocrine insufficiency (2,13). This may be partially explained by the short duration (3.4 years) of known diabetes in the group studied, as pancreas volume is known to decrease with increasing duration of diabetes (14). Although there was a marked difference in BMI between the entire type 2 diabetes group (mean BMI 35.5 kg/m^2) and the control group that did not have diabetes (27.5 kg/m^2), which would affect pancreas weight, expression of pancreas weight relative to body weight was also similar to that of the pancreases of the individuals who did not have diabetes. The number and size of adipocytes in the pancreases of individuals with type 2 diabetes were not increased, although the authors point out that it is the increased intracellular levels of lipid in both endocrine and exocrine pancreatic cells (15–18) that is correctable by weight loss with remission of type 2 diabetes (19,20) and not the presence of adipocytes. There were no differences in pancreatic total immune cells, macrophage number or orientation, or T-lymphocyte subtypes. This suggests that inflammation does not have major role, especially as the progressive β-cell dysfunction is underway in type 2 diabetes in the early phase studied. Observations of proinflammatory cytokines in plasma originally led to suggestions of an immune basis for β-cell dysfunction in type 2 diabetes, although anti-inflammatory treatment has no effect on the deterioration in β-cell function (21,22). There was an increase in fibrosis restricted to intralobular spaces, although this was not severe, with all but one pancreas having less fibrosis than the highest level observed in the pancreases of the individuals who did not have diabetes. In individuals with type 2 diabetes there was a greater degree of medium-sized blood vessel wall thickening, to a degree similar to that for individuals with type 1 diabetes.

These observations highlight the need for further studies of both whole pancreas and perifused or cultured human islets to define aspects of the β-cell defect now known to be reversible in short-duration type 2 diabetes (23). Few studies of the effect of saturated fatty acids have been conducted since the groundbreaking observations of Unger and colleagues (24), even though the clinical effects upon β-cell function are now well established (19,25–27). Bearing in mind that 73% of people with BMI >40 kg/m^2 do not have diabetes, future studies should focus precisely on islets from humans or animals genetically predisposed to type 2 diabetes (28). A further area for future research concerns the observations by Wright et al. (9) on pancreas volume, which are consistent with imaging findings in type 1 diabetes (29,30) but not type 2 diabetes (13,31).

The study of fresh donor pancreases by Wright et al. (9) has generated useful novel findings. It advances knowledge of disease-specific pancreas histology and permits formulation of testable hypotheses.

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