Editorial

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Diabetes mellitus and Exocrine Pancreatic Function

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About one million endocrine islets are scattered throughout the human exocrine pancreas. An islet is composed of about five thousand endocrine cells and the whole body of islets accounts for 1–2% of the volume of the pancreas. An islet contains four major types of endocrine cells, a majority of insulin-producing β cells, less glucagon-producing α cells, and fewer δ (somatostatin) and pancreatic polypeptide cells. It has a certain tradition that gastroenterologists study the exocrine pancreas whereas endocrinologists study the endocrine pancreas. This goes so far that the pancreas is often regarded as two separate organs. However, clinical observations clearly show that disturbances of the exocrine gland impact on endocrine cells.

Patients with chronic pancreatitis (CP) often suffer from endocrine pancreatic dysfunction. This even leads to a distinct secondary type of diabetes [1]. Diabetes mellitus (DM) secondary to CP accounts for <1% of all diabetes cases, which is probably the reason why it is not of that much interest to most diabetologists. On the other hand, 80% of patients with CP develop an overt DM in the long run and DM is an independent risk factor for mortality in patients with CP [2–4]. This makes this form of DM relevant to the gastroenterologist. The most frequent cause of secondary DM in patients with pancreatic diseases in the Western hemisphere is chronic alcoholic pancreatitis [5]. Its occurrence is attributed to the close anatomical and functional links between the exocrine and endocrine pancreas. It is believed that CP, progressively developing fibrosis and sclerosis, alters pancreatic capillary circulation and thereby reduces islet perfusion. Interestingly, in tropical countries and India a special form of non-alcoholic tropical calcifying pancreatitis leads to DM. Although little is known about the exact etiology of this form of diabetes it has been found that the β-cell function is damaged whereas the α cells are preserved [6, 7]. This is in contrast to the non-tropical chronic pancreatitis where both cell populations are altered. In any case, two different pathogenic mechanisms have been proposed, one eliciting CP and the other selective pancreatic β-cell impairment and subsequent DM. DM caused by chronic inflammation of the exocrine pancreas develops typically in 80% of the patients within the first 10 years after the initial diagnosis of chronic pancreatitis [8]. Chronic calcifying pancreatitis (60–70%) leads to diabetes more often than non-calcifying pancreatitis (15–30%) [2, 9]. The duration of CP plays an important role: the continuing inflammatory-fibrotic disturbance of exocrine and endocrine tissue, with a significant loss of β cells and hence a progressive decrease in insulin-secretion, triggers overt DM. DM occurs when approximately 80% of the β cells are destroyed [10].

One can try to explain the occurrence of pancreatic exocrine dysfunction as a complication of preexisting diabetes. However, only in a few patients do overt DM symptoms precede a later finding of chronic pancreatitis. It is rather questionable whether DM is the reason for CP rather than CP being oligosymptomatic and allowing DM to become overt somewhat earlier. Anyway, this may lead to an initial misclassification [11, 12]. Overall, it seems

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unlikely that DM is a true risk factor of chronic pancreatitis in the vast majority of patients. Whether newly developing concepts of the pathogenesis of chronic pancreatitis will shed more light onto this question is so far only speculative [13].

However, a wealth of physiological evidence has been collected that, together with earlier morphological evidence, indicates that islet hormones regulate the exocrine pancreas [14]. The underlying observation is that an islet-acinar portal blood system exists carrying endocrine cell products such as insulin (and also other peptides) to the acinar cells. In experimental diabetes the makeup of digestive enzymes changes and solid data prove that the mRNA for insulin is reduced following a lack of insulin. In the present issue of *Digestion* an interesting follow-up study by Creutzfeldt and co-workers appears following a collective of patients with type-1 DM. More than two decades ago *Digestion* published a paper dealing with this collective [15] in whom an abnormal secretin-pancreozymin function test was found in a significant proportion of 23 of 53 patients. From the original study population 20 persons could be recruited into a follow-up examination of their exocrine pancreatic function. These data are now again being published in *Digestion* [16]. The time interval between the initial and the follow-up tests ranged from 9 to 23 years. Certainly, the present study has obvious limitations; less than 50% of the original collective were reinvestigated and no data on the metabolic control of diabetes (HBA1c, etc.) are available. Still, the data hint that exocrine pancreatic insufficiency is not a clinically relevant late complication of type-1 diabetes. It suggests that mild to moderate exocrine pancreatic insufficiency may be due to an early event in the course of autoimmune diabetes and does not progress. This early phase during the onset of type-1 diabetes with an affinity for both parts of the gland is still a matter of ongoing research.

Autoimmune events are under consideration for the development of chronic pancreatitis per se. Still, the pathophysiological mechanisms between type-1 diabetes and autoimmune chronic pancreatitis are probably distinct. In any case, when handling diabetic patients an increasing insulin deficiency is substituted by exogenous insulin delivery. The latter obviously makes up for the lack of insulin regulating exocrine pancreatic acini and exocrine function.

The data presented here stress the notion that follow-up studies of exocrine pancreatic function are unnecessary in type-1 diabetes on a routine basis.

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