

PERSPECTIVE

The role of CFTR in diabetes-induced pancreatic ductal dysfunction

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The pancreas is a vital organ with dual functions, serving both exocrine and endocrine roles. The exocrine pancreas is responsible for the production and secretion of digestive enzymes and fluids by pancreatic acinar cells (PACs) followed by supplementation with bicarbonate (HCO_3^-) and delivery by the pancreatic duct to the duodenum, aiding food digestion (Petersen et al., 2021). The endocrine pancreas regulates blood sugar levels through the production and secretion of hormones, primarily insulin.

Despite their distinct functions and anatomical separation, there is a dynamic interaction between the exocrine and endocrine components of the pancreas. Diseases affecting one part of the pancreas can influence the other. Diabetes mellitus (DM) is a prevalent disease that primarily affects the endocrine pancreas.

The two main types of DM, type 1 (T1) and type 2 (T2), are characterized by reduced insulin production or diminished insulin sensitivity, respectively (Sakran et al., 2022). Type 1 diabetes is an autoimmune disorder where the body's immune system mistakenly attacks and destroys insulin-producing β -cells in the pancreas. This destruction leads to decreased insulin production, resulting in hyperglycaemia.

Importantly, clinical, and experimental studies have demonstrated that T1DM does not impact only the endocrine function of the pancreas (Cho et al., 2023): in T1DM, the lack of insulin adversely affects the secretion of digestive enzymes from the exocrine pancreas, leading to a condition known as exocrine pancreatic insufficiency.

This insufficiency occurs because insulin is necessary for the normal release of digestive enzymes. Consequently, the reduction in digestive enzymes can hinder the proper breakdown of nutrients in the digestive system, potentially causing malabsorption issues.

It has been reported previously that DM can cause acute pancreatitis (AP), which is a devastating life-threatening inflammatory disease associated with considerable morbidity and up to 5% mortality in severe cases (Cho et al., 2023). AP has a significant risk of progression to chronic pancreatitis and pancreatic cancer (Petersen et al., 2021). Alcohol abuse and gallstone disease are the main causes of AP with many other less common origins such as hypertriglyceridaemia and pharmaceuticals. Initial steps in AP development include aberrant calcium signalling in exocrine PACs that leads to premature intracellular activation of digestive pro-enzymes, loss of energy metabolism, and cell necrosis endorsing inflammation and persistent pancreatic failure and multiple organ malfunction (Petersen et al., 2021). Some AP aetiologies including gallstones, obesity and dyslipidaemia are thought to be a result of DM (Cho et al., 2023).

The intricate relationship between the exocrine and endocrine pancreas is highlighted in conditions like T1DM, where the autoimmune destruction of β -cells not only impairs insulin production but also affects the exocrine function, leading to exocrine pancreatic insufficiency. This connection emphasizes the need for a comprehensive understanding and management of both aspects of pancreatic function in individuals with DM.

In this issue of *The Journal of Physiology*, a well-known pancreatic research group report their findings on the mechanism of impact of DM on ductal function in the pancreas (Ébert et al., 2024). T1DM was induced in both wild-type and cystic fibrosis transmembrane conductance regulator (CFTR) knockout mice while measuring fluid and HCO_3^- secretion in pancreatic ductal epithelial cells. Ductal fluid and HCO_3^- secretion were significantly elevated in diabetic mice as well as CFTR activity and expression of CFTR. The study also observed an

increased expression and activity of other transporters such as ANO-1 (a Ca^{2+} -activated Cl^- channel) and NHE-1 (a Na^+/H^+ exchanger-1) in DM. Inhibition of CFTR significantly reduced HCO_3^- secretion in both normal and diabetic mice. These results indicate that the stimulatory effect of T1DM on ductal HCO_3^- secretion is a complex process involving multiple factors but with the main emphasis on increased CFTR activity. While it is commonly accepted that exocrine functions are mostly impaired by long-standing DM, the study by Ébert et al. challenges this view by showing that ductal secretion is affected at the initial stage of DM. The main important message from the study is that ductal HCO_3^- secretion can serve as a protective mechanism and therefore be proposed as a potential therapeutic target for the prevention or treatment of DM. Interestingly, there is also an opposite link between pancreatic disease and DM: several studies have described a type 3c pancreatogenic diabetes secondary to pancreatic disease with up to 60.2% of adult patients after AP (Sliwiska-Mosson et al., 2023). Therefore, there is a need for further studies in this area to fully understand the implications and potential therapeutic applications.

In summary, the study by Ébert et al. highlights the complexity of the relationship between DM and pancreatic ductal function, challenging conventional views and emphasising increased ductal secretion mainly due to increased CFTR activity. The authors suggest a protective role for ductal HCO_3^- secretion that could be explored for preventative or therapeutic interventions in DM.

References

- Cho, I. R., Han, K.-D., Lee, S. H., Choi, Y. H., Chung, K. H., Choi, J. H., Park, N., Lee, M. W., Paik, W. H., Ryu, J. K., & Kim, Y.-T. (2023). Association between glycemic status and the risk of acute pancreatitis: A nationwide population-based study. *Diabetology & Metabolic Syndrome*, *15*, 104.
- Ébert, A., Gál, E., Tóth, E., Szögi, T., Hegyi, P., & Venglovecz, V. (2024). Role of CFTR in diabetes-induced pancreatic ductal fluid and HCO_3^- secretion. *The Journal of Physiology*. Advance online publication. <https://doi.org/10.1113/JP285702>

- Petersen, O. H., Gerasimenko, J. V., Gerasimenko, O. V., Gryshchenko, O., & Peng, S. (2021). The roles of calcium and ATP in the physiology and pathology of the exocrine pancreas. *Physiological Reviews*, **101**(4), 1691–1744.
- Sakran, N., Graham, Y., Pintar, T., Yang, W., Kassir, R., Willigendael, E. M., Singhal, R., Kooreman, Z. E., Ramnarain, D., Mahawar, K., Parmar, C., Madhok, B., & Pouwels, S. (2022). The many faces of diabetes. Is there a need for re-classification? A narrative review. *BMC Endocrine Disorders*, **22**(1), 9.
- Śliwińska-Mossoń, M., Bil-Lula, I., & Marek, G. (2023). The cause and effect relationship of diabetes after acute pancreatitis. *Biomedicines*, **11**(3), 667.

Additional information

Competing interests

The authors declare no conflict of interest.

Author contributions

Both authors: conception or design of the work; drafting the work or revising it critically for important intellectual content. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History