Understanding pain in chronic pancreatitis: not yet the end of the story?

Jonas Rosendahl

In *Gut*, Olesen *et al* present the first comprehensive multicentre cross-sectional study of pain in prospectively enrolled chronic pancreatitis (CP) patients.[1] It is demonstrated that pain-related factors are often overlapping in these patients and have a cumulative detrimental effect on patient-reported outcomes. One might argue that the results of this study are lacking novelty, but there are several reasons why such studies are urgently warranted.

Pain, may it be acute, recurring or chronic, is one of the cardinal symptoms of CP and impacts patients' well-being significantly.[2] Thus far, several efforts have been conducted to improve the treatment of painful CP, with variable outcome. At first it is interesting to note, that the methodology to quantify pain for most of the published efforts was not validated in CP patients before and as such results obtained in these studies might not truly reflect the patients' situation.[3] Second, the approaches to understand pain patterns seem to need evaluation of multiple aspects, since several factors are capable to aggravate pain.[4] Third, most interventional trials did not take the possibility of placebo effects into account complicating the interpretation of available data. In this regard it is well taken that the component of such an effect is difficult to assess, this, however, underscores the importance to cautiously interpret results of studies with pain as an endpoint in CP, if the relevance of such effects cannot be determined or excluded. For all these reasons, it is not astonishing that success rates or effect sizes of interventional trials were lower than we all might have initially hoped.

Consequently, studies like the one published by Olesen *et al* path the way for a better interpretation of pain in CP patients and highlight the importance of a multidisciplinary assessment. Demonstrating that quality of life is among other factors largely impacted by psychological distress implies that neuronal sensitisation is an important contributor for painful CP. Therefore, such observations should be considered before invasive procedures in patients with painful CP are undertaken in the future.[5] Of course, current treatment concepts with, for example, endoscopic interventions of pancreatic duct obstruction or surgical interventions should not be disregarded from now on as they have proven to be successful in several patients.[6–8] However, it seems reasonable that our increasing knowledge of pain development in CP patients offers strategies to better define patients that benefit most from distinct interventions may they be conservative or interventional.

Otherwise, knowledge gaps remain even after this study. It confirms pancreatic duct obstruction as a hallmark criterion for pain in CP but cannot fully answer why interventions are not successful in all these patients. Here, further work is needed to clarify whether this could be due to clinically non-overt inflammatory processes described in patients during attack-free intervals or whether other factors, like neuronal sensitisation ('the wiring theory') among others are responsible.[9 10] This knowledge in combination with the results of the current study should then lead to the development of strategies to stratify patients for distinct treatment approaches, which will need prospective evaluation thereafter.

Finally, as in most cases our approaches to treat CP patients start when the disease has progressed and morphological changes (that likewise are fundamental to diagnose CP) are overt, we need a better understanding and identification of early processes in CP development. So far, the presence of pain seems to correlate with

Martin-Luther-Universität Halle-Wittenberg, Halle, Germany

Correspondence to Dr Jonas Rosendahl, University Clinic Halle (Saale), Clinic for Internal Medicine I, Halle (Saale), Germany; jonas.rosendahl@uk-halle.de

morphological changes as demonstrated again by the importance of pancreatic duct obstruction, but only when clinical evaluation is also added into the equation. Otherwise, it is likely that even in the time before these changes are identified relevant factors define painful disease courses. For sure this effort of a better understanding will not be easily achieved but will open avenues to intervene in stages where irreversible changes are not yet prevailing.

In conclusion, the team of Olesen *et al* can be congratulated for this and their ongoing efforts to better understand the pain in CP. Hopefully, further knowledge in this regard will be obtained soon and will, as the current study, be considered when interventional studies in CP patients are performed. Moreover, current treatment plans of CP patients should be adapted, and data of success rates evaluated in future studies to improve patient care. Finally, as stressed by several authors before CP is and remains a disease to be treated in a multidisciplinary setting.

Contributors JR solely wrote this commentary.

Funding The author has not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Rosendahl J. *Gut* 2022;**71**:2378–2379.

Received 30 November 2021
Accepted 1 December 2021
Published Online First 9 December 2021

Linked

► http://dx.doi.org/10.1136/gutjnl-2021-325855

Gut 2022;**71**:2378–2379.
doi:10.1136/gutjnl-2021-326279

ORCID iD
Jonas Rosendahl http://orcid.org/0000-0003-4513-0506

REFERENCES

1 Olesen SS, Phillips AE, Faghih M. Overlap and cumulative effects of pancreatic duct obstruction, abnormal pain processing and psychological distress on patient-reported outcomes in chronic pancreatitis. *Gut* 2022;71:2518–25.
2 Löhr JM, Dominguez-Munoz E, Rosendahl J, *et al*. United European gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J* 2017;5:153–99.
3 Kuhlmann L, Teo K, Olesen SS, *et al*. Development of the comprehensive pain assessment tool short form for chronic pancreatitis: validity and reliability testing. *Clin Gastroenterol Hepatol* 2021:S1542-3565(21)00594-2.
4 Phillips AE, Faghih M, Drewes AM, *et al*. Psychiatric comorbidity in patients with chronic pancreatitis associates with pain and reduced quality of life. *Am J Gastroenterol* 2020;115:2077–85.
5 Kuhlmann L, Olesen SS, Olesen AE, *et al*. Mechanism-based pain management in chronic pancreatitis - is it time for a paradigm shift? *Expert Rev Clin Pharmacol* 2019;12:249–58.
6 Díte P, Ruzicka M, Zboril V, *et al*. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy* 2003;35:553–8.
7 Cahen DL, Gouma DJ, Nio Y, *et al*. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med* 2007;356:676–84.
8 Issa Y, Kempeneers MA, Bruno MJ, *et al*. Effect of early surgery vs Endoscopy-First approach on pain in patients with chronic pancreatitis: the escape randomized clinical trial. *JAMA* 2020;323:237–47.
9 Robinson SM, Rasch S, Beer S, *et al*. Systemic inflammation contributes to impairment of quality of life in chronic pancreatitis. *Sci Rep* 2019;9:7318.
10 Anaparthy R, Pasricha PJ. Pain and chronic pancreatitis: is it the plumbing or the wiring? *Curr Gastroenterol Rep* 2008;10:101–6.