



July 11, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO 4076-Review.doc).

Title: Morphological and functional evaluation of chronic pancreatitis with magnetic resonance imaging

Author: Tine Maria Hansen, Matias Nilsson, Mikkel Gram and Jens Brøndum Frøkjær

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4076

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer.

We appreciate the fast and efficient reviewing process and the constructive comments, which we have used for this revised manuscript. The comments have been carefully evaluated and we believe that they have improved the manuscript substantially. We have made a point-to-point response to the comments together with the revised paper, where the changes are highlighted with yellow.

Reviewer no. 00289406:

(1) Reviewer wrote: "With regard to the evaluation of pancreatic function it might be useful to include studies comparing MRI function tests to other non-MRI procedures (secretin test, fecal elastase 1 etc.)."

Our reply: We appreciate this comment. The s-MRCP section is now updated with reference to studies comparing s-MRCP findings with non-MRI based test for exocrine function. The section now reads: "Studies in CP by Manfredi *et al.* and Schneider *et al.* showed correlation between assessment of the pancreatic exocrine reserve by dynamic s-MRCP and exocrine function assessed by fecal elastase test and ¹³C-mixed chain triglyceride breath test [25,26]. Wathle *et al.* found correlation between endoscopic aspiration-based bicarbonate test and s-MRCP findings in healthy controls [27]. However, the use of s-MRCP has not yet been integrated as a part of the Mayo diagnostic criteria for CP and further evaluation of s-MRCP as a test for exocrine function in comparison to traditional tests is needed."

Reviewer no. 00503417:

(1) Reviewer wrote: "The sections on DWI and MR spectroscopy may be expanded a bit since these are recent innovations in practice and are not widely covered in textbooks."

Our reply: The spectroscopy section has now been improved with more details about the few studies performed on the pancreas. The section now reads: "MR spectroscopy with non-invasive *in-vivo* assessment of metabolite concentrations has been applied in a variety of different tissues (e.g. brain, prostate, breast and liver). Hence, spectroscopy of the pancreas has the potential to offer

a more accurate tissue characterization. Due to methodological challenges, the pancreas has only been studied to a very limited degree with spectroscopy. Despite of this, Su *et al.* characterized the normal pancreas at 3T and identified metabolites such as lipid, choline and cholesterol [36]. Cho *et al.* used MR spectroscopy to distinguish between patients with chronic focal pancreatitis and patients with pancreatic carcinoma and found less lipid in pancreatitis than in pancreatic carcinoma [37]. Furthermore, other studies also detected differences between normal pancreatic tissue and carcinoma tissue with alterations in lipid, choline and fatty acids [38,39]. However, to the best of our knowledge, this technique has not yet been applied in the characterization of CP patients."

The DWI section has also been improved as stated in our reply to the following comment.

(2) Reviewer wrote: "A few lines may be added to detail how DWI can help to differentiate the various cystic lesions in the pancreas (page 7 of ms)".

Our reply: We fully agree with this comment, and for clarification, the following has been added to the DWI section: "Furthermore, the technique is useful in differentiating between pancreatic cysts, inflammatory cysts and cystic neoplasms and between pancreatic adenocarcinoma and normal pancreas due to different content of cellular elements [32]. Inan *et al.* calculated ADC values and ADC cyst-to-pancreas ratios and found significant lower values for abscesses, hydatid cysts and neoplastic cysts compared to values of simple cysts and pseudocysts [33]"

Reviewer no. 00034432:

(1) Reviewer wrote: "The authors stated in the abstract section that "positron emission tomography (PET) holds a pivotal position in ruling out tumor formation." This sentence does not fit with the aim of the review."

Our reply: We agree that this is beyond the scope of the present review, and therefore the sentence has been omitted.

(2) Reviewer wrote: "The authors stated that "A few decades ago the evaluation of CP was limited to radiography depicting calcifications, which are only present in severe CP". This is the history of imaging because CT and/or US represented a clear advance in pancreatic morphology."

Our reply: We thank the reviewer for a good observation and for improved clarity, the sentence has been rephrased: "A few decades ago, before the clinical introduction of cross-sectional imaging techniques, the imaging evaluation of CP was limited to plain radiography depicting calcifications."

(3) Reviewer wrote: "The role of MRI in diagnosing autoimmune chronic pancreatitis should be added. As well as the role of this technique in differentiating chronic pancreatitis and main duct IPMN."

Our reply: This is an important issue. Information on the typical presentation of AIP has now been added to the Standard MRI section, which now reads: "MRI also has a role in diagnosing autoimmune pancreatitis (AIP) which can be a differential diagnosis to CP [13,14]. In diffuse AIP, MRCP may show a decreased diameter of the main pancreatic duct and can be accompanied by strictures and an irregular wall. However, in AIP the pancreas is typically with diffuse or localized enlargement with reduced signal on T1 and increased signal on T2-weighted images. A surrounding capsule with reduced signal in T2-weighted images can be seen."

The role of DWI in the diagnosis and evaluation of IPMN is now discussed. The DWI section is updated reading: "This technique may be useful in the diagnosis of intraductal papillary mucinous neoplasms (IPMN), which is often difficult since CP and IPMN may have overlapping imaging findings [13,34]. Patients with main duct IPMN can present with ductal dilatation and associated parenchymal atrophy, and patients with side-branch IPMN can present with cystic lesions often confused with pseudocysts. ADC values of the cystic lesions may be helpful in deciding the

malignant potential of IPMN [34,35].”

(4) Reviewer wrote: “The role of MRI in assessing the pancreatic function according to the Matos criteria should be added.”

Our reply: We agree that the Mayo criteria represent a central issue and the use of MRI in the Mayo Clinic diagnostic criteria for CP has now been addressed. The introduction now reads: “In the Mayo diagnostic criteria for CP, MRI is now an accepted method for assessing ductal pathology and concretions [1]. The s-MRCP section now reads: “However, the use of s-MRCP has not yet been integrated as a part of the Mayo diagnostic criteria for CP and further evaluation of s-MRCP as a test for exocrine function in comparison to traditional tests is needed.”

Reviewer no. 00004525:

(1) Reviewer wrote: “This is the review of MRI in CP. However, most papers are old and there are few newly important findings for readers.”

Our reply: In order to improve the review and make it more interesting for the readers we have added new information on: 1) studies comparing s-MRCP findings with non-MRI based test for exocrine function, 2) details about spectroscopy of the pancreas has the potential to offer a more accurate tissue characterization including new references, 3) details on how DWI can help to differentiate the cystic lesions (including intraductal papillary mucinous neoplasms (IPMN)), and 4) the role of MRI in relation the Mayo Clinic diagnostic criteria for CP.

3 References and typesetting were corrected. Furthermore, the manuscript has been carefully evaluated by a native speaker of English and we consider the manuscript to reach grade A.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Jens Brøndum Frøkjær, MD., PhD.
Mech-Sense, Department of Radiology
Aalborg University Hospital
9000 Aalborg
Denmark
Telephone: +45 9932 6825
Fax: +45 9932 6507
E-mail: jf@mech-sense.com