



BAISHIDENG PUBLISHING GROUP INC

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 14465

Title: Magnetic resonance imaging of the pancreas in streptozotocin-induced diabetic rats: Gadofluorine P and Gd-DOTA

Reviewer's code: 00503608

Reviewer's country: United States

Science editor: Ya-Juan Ma

Date sent for review: 2014-10-06 20:15

Date reviewed: 2014-11-19 08:33

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|--|--|--|--|
| <input type="checkbox"/> Grade A: Excellent | <input checked="" type="checkbox"/> Grade A: Priority publishing | PubMed Search: | <input checked="" type="checkbox"/> Accept |
| <input checked="" type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Duplicate publication | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade D: Rejected | <input checked="" type="checkbox"/> No | <input type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E: Poor | | BPG Search: | <input type="checkbox"/> Major revision |
| | | <input type="checkbox"/> The same title | |
| | | <input type="checkbox"/> Duplicate publication | |
| | | <input type="checkbox"/> Plagiarism | |
| | | <input checked="" type="checkbox"/> No | |

COMMENTS TO AUTHORS

1. One does wonder why the various contrast agents were evaluated in a linear fashion rather than using additional groups. This would probably bolster the argument that Gadolinium P is superior to Gd-DOTA for the diagnosis of DM. This was addressed briefly in the discussion, but perhaps this could be expanded upon. It is entirely feasible that the changes identified may have been associated with the timing of the MRI evaluation rather than the agent used. 2. Please discuss the clinical implications in much greater detail. How will this test be helpful and who would we use it for? It is hard to believe that an x-ray would be superior to blood testing for the diagnosis of diabetes, although it is a very interesting idea. What are the cost considerations? Would there be any role for the evaluation of other pancreatic disease (chronic pancreatitis and pancreatic cancer) that have a known association with DM?

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 14465

Title: Magnetic resonance imaging of the pancreas in streptozotocin-induced diabetic rats: Gadofluorine P and Gd-DOTA

Reviewer's code: 00503542

Reviewer's country: Japan

Science editor: Ya-Juan Ma

Date sent for review: 2014-10-06 20:15

Date reviewed: 2014-10-28 18:29

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|--|--|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | PubMed Search: | <input type="checkbox"/> Accept |
| <input type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C: Good | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Duplicate publication | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade D: Rejected | <input checked="" type="checkbox"/> No | <input type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E: Poor | | BPG Search: | <input checked="" type="checkbox"/> Major revision |
| | | <input type="checkbox"/> The same title | |
| | | <input type="checkbox"/> Duplicate publication | |
| | | <input type="checkbox"/> Plagiarism | |
| | | <input checked="" type="checkbox"/> No | |

COMMENTS TO AUTHORS

This study seems to have tried to compare two MRI enhancers to detect early onset of type 1 diabetes mellitus (DM) in rats. The aim of this study seems quite reasonable and potentially important. However, the authors seem to have failed to draw a scientifically robust conclusion because of several reasons as follows. 1. As authors mentioned in the text, two enhancers are tested at different time points, which make direct comparison impossible. Results of two enhancers can be compared in control rats, because there may not be significantly different conditions in normal pancreas at the different time points. However, comparison cannot be regarded as proper at the different time points with different glucose levels in diabetic rats. This observation should have been done at the same time point in different animal groups after the same DM-induction. 2. From the description of the introduction, it is concerned that the authors may not have a right definition of "blood flow" of a tissue. Most references they cited reported increased vascular permeability or vascular dysfunction in the diabetic islets. However, in such situation, microsphere technique of blood flow measurement (for example, ref. #9) may show false positive increase because of congestion that accumulates more



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blood to the inflammatory tissue. However, this is not a true increase in blood flow. Tissue blood flow is estimated based on the blood volume that comes in to and goes out from the unit tissue volume in a unit time duration. 3. Again, as the authors mentioned in the text, the DM model employed in this study is difficult to be regarded as that of typical type 1 DM, because of the lack of classic insulinitis. 4. The histological parameters of islet diameter and islet number may not be suitable because, from Fig. 7, atypically long and narrow tissues seem to be regarded as islets. This should be examined by more specific staining like insulin staining. From the photographs like Fig. 7, islet area may be a better parameter. 5. From the above consideration (#2) of increased vascular permeability together with the result shown in Fig. 9, the negative correlation of SI and islet number may reflect an important, but yet unproven finding of less islets in the pancreas with more extravasation of the enhancer. 6. The authors' attempt to minimize the number of used animals is important. However, more important thing is to plan experiments properly to draw scientific conclusion in order to make good use of experimental animals. 7. "progeoglycans" (page 13, line 18) should be "proteoglycans".



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 14465

Title: Magnetic resonance imaging of the pancreas in streptozotocin-induced diabetic rats: Gadofluorine P and Gd-DOTA

Reviewer's code: 00503540

Reviewer's country: Japan

Science editor: Ya-Juan Ma

Date sent for review: 2014-10-06 20:15

Date reviewed: 2014-10-23 07:46

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|--|--|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | PubMed Search: | <input type="checkbox"/> Accept |
| <input type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Duplicate publication | <input type="checkbox"/> Rejection |
| <input checked="" type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade D: Rejected | <input checked="" type="checkbox"/> Plagiarism | <input type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E: Poor | | [Y] No | <input type="checkbox"/> Major revision |
| | | BPG Search: | |
| | | <input type="checkbox"/> The same title | |
| | | <input type="checkbox"/> Duplicate publication | |
| | | <input type="checkbox"/> Plagiarism | |
| | | [Y] No | |

COMMENTS TO AUTHORS

1. I have no idea why the diabetic pancreas was enhanced more prominently by gadofluorine P comparing with normal pancreas. This study is not well designed to prove the mechanism. Histological assessment is not sufficient because there is only HE data. Immunostaining for vascular network using vWF or CD31 is necessary. Is the reason for the enhancement is reflected on hypervascularization of the pancreas or leakage of the contrast agent due to destruction of the vascular network? Please have additional examinations to reveal that. 2. STZ-induced Diabetes is NOT the model for type 1 DM. If the authors use the word "type 1 DM", please change the model to spontaneously induced diabetic rat. Or, should change the word to "drug-induced diabetic rat".