Reviewer’s report

Title: Effects of iodinated contrast agents on renal oxygenation level by BOLD-MRI in a rabbit model of diabetic nephropathy

Version: 5
Date: 24 July 2014
Reviewer: Robert Menzies

Reviewer’s report:

This manuscript investigates the question of whether iodine based contrast agents can alter the BOLD signal. This is an important research question with potentially important clinical implications as has been previously explored by others, for example Heneder et al. (Invest Radiol. 2012 May;47(5):299-305). The authors present a large and commendable dataset with strong group numbers.

• Major Compulsory Revisions

The authors present a detailed description of type II and I diabetic models. However, blood and urine biochemical analysis cannot distinguish the two models. Can the authors provide a quantitative measure that clearly demonstrates insulin dependence/independence in the respective models?

Page 5, Line 1: (see above comment on insulin resistance). If these indices rose to what level exactly? Allowing for error but above an acceptable normal range? It is not clear that insulin sensitivity/insensitivity was significantly established between the two models. Rather these are two models of general ‘diabetes’. Do you have insulin measurements?

Protocol 1 looks like a dose finding study but it is not a conclusive one. This is because no maximal R2* level is observed. What would happen at 400mg/l/ml, or higher? I accept that BOLD MRI studies are expensive, and the dataset presented is already extensive. Therefore I propose that the following two limitations are fully addressed in the manuscript (ideally a more detailed limitations section). (1) The reason(s) why dose finding was performed on type II diabetic animals (and not controls or type I). (2) The reason(s) why a dose above 350mg/l/ml was not used.

There is some switching between active and passive voice, particularly in the discussion section. There are also many unclear sentence structures throughout the manuscript. I have tried to identify as many errors as possible as these issues do detract from the content and need to be addressed.

• Minor Essential Revisions

Page 2, line 2: for clarity change “…contrast agents with different concentrations…” to “…contrast agents containing increasing concentrations…”
P2, Line 5: for clarity change “performed on type II diabetic” to “performed on experimentally induced type II diabetic”

Page 3 Line 10-12: This sentence is misleading. Renal insufficiency/AKI/CKD are not necessarily the ‘most important’ risk factors for CIN (e.g. hypercholesterolemia). They are of course important, as is pointed out in the manuscripts you reference. Please revise to be explicit about this.

P3, Line 15/16: This is colloquialism. Consider changing the last sentence of the paragraph to “Early clinical detection is therefore challenging”

P3, Line 17: Sentence unclear, allows more than what? Biopsy? Consider changing “MR imaging allows more” to “MR imaging can facilitate”

P3, Line 17: MR defined on line 18 but used previously.

P3, Line 22: space missing between Wistar Kyoto

P3, Line 22: studied THE effects

Page 4, line2: procedures WERE permitted

P4, Line 2: University AND complied

P4, Line 15: sentence structure is confusing. “After 2-3 weeks, the type I diabetes...” change to “The development of type I diabetes mellitus (approximately 2-3 weeks) was considered...”

P4, Line 22: delete “for a concentration of” and place dilution in brackets

P4, Line 22: Sentence structure. “..., blood WAS COLLECTED FROM RABBITS VIA THE AURICULAR VEIN for biochemical analysis...”

Page 5, Line 4: delete ‘Overall’, delete ‘kinds of’

Page 5 Line 10: Language: ‘suffering’. Consider changing to induced with type I/II diabetes?

Page 5 Line 17: change “most influence” to “largest effect”

Page 6, line 3: through THE rabbit’s auricular

Page 6 Line 3: In rabbits is a 2ml IV injection likely to induce volume expansion? Which can change R2* value in rats (J Magn Reson Imaging. Apr 2011; 33(4): 898–901.)

Page 6 Line 11: coronary? Do you mean coronal sections?

Page 6 Line 22: change “following criteria according to the injury scoring” to “following injury scoring criteria”. Please include a sentence explaining the injury scoring criteria.
Page 7, line 4: ‘random pictures’ to ‘randomly selected images’


Page 8: It would be valuable to explicitly point out that your induction protocol successfully induced some form of diabetes (typII/I v.s. control). Then go into the description that (1) there was no difference in blood/urine results between type I/II and (2) bodyweight was constant in all groups.

Page 9, line 5: change ‘reflected’ to ‘determined’

Page 9 line 11: “tubules cells” should read “renal tubule cells” or something similar

P9 line 16: use of plural in ‘injuries’

Page 10, line 1: study OF rabbit models of

Page 10Line 6: remove first comma

Page 10Line 6: full stop should be after the reference.

Page 11, Line 5: change ‘were’ to ‘was’

Page 11, Line 7: it is not clear what you are trying to say in this sentence.

Page 11, Line 9: what do you mean by “explore the change regulation” ?

Page 11, Line 11: Consider using the word ‘increase’ or ‘decrease’ instead of ‘progress’ as it is unclear what you mean by this.

Page 11, Line 12: “renal oxygenation level reached the lowest level...” – unnecessary repetition of ‘level’

TABLE 2: abbreviations need to be described

TABLE 3: A description of the measured P-value should be given in the legend

• Discretionary Revisions

Page 8, Line 7 (and onward): for clarity consider changing “R2* bar” to mean medulla/cortex R2* value of something similar.

P9 line 9-24: To facilitate readership, when presenting non-significant P-values consider writing N.S. (or similar) instead of P>0.05.

Page 11, Line 9-13: consider splitting this sentence, it is very long.

Figures 1-4: Presumably the final manuscript would be submitted in color. They are difficult to read in black and white print out (for offline readership), the authors may wish to address this.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests