Author's response to reviews

Title: Recurrent exercise-induced acute renal failure in a young Pakistani man with severe renal hypouricemia and SLC2A9 compound heterozygosity

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Author's response to reviews:

Dear Editor,

thank you for the answer to our MS.

We accepted all the suggestions from the reviewers and we resubmit the revised version of the MS accordingly.

We answered point-by-point to the criticisms and queries.

With best wishes,

Prof. Marina Colombi

Referee 1

1. Page 2. We added the patient's concentration of serum UA and FE-UA in the abstract, as requested.

2. Page 3, line 9. The sentence about RHUC2 was rewritten in order to explain more in detail the two clinical distinctions of RHUC1 and RHUC2. In particular, we added that heterozygous RHUC2 patients show UA values similar to those of patients with URAT1 mutations, whereas homozygous and/or compound heterozygous patients are characterized by considerably lower serum UA levels (near 0 mg/dL) and higher renal UA excretion (>100%).

3. Concerning the pathogenic hypothesis based on the antioxidant activity of UA, we agree with the reviewer. Since low hypouricemia is also present in classical
xantine dehydrogenase deficiency (type I and II), and these patients do not have AKI in their medical history, this suggests that hypouricemia alone, probably, could not contribute to renal failure in patients with primary renal hypouricemia, therefore, we modified the text accordingly.

4. We are conscious that not all readers are familiar with the mg/dL units. For this reason, the reference ranges for uric acid, creatinine and FE-UA were already included in Table I. Additionally, these reference ranges are now also reported in the text of the revised version.

5. Concerning the request to use CKD classification, we consider this not applicable to our patient since this is a case of Acute Renal Failure, as suggested by the normal value of serum creatinine after the second discharge (see Table I).

Minor points

1. Page 2, line 12: harbouring was used instead of "harboring" and the sentences in page 2 lines 4-5, and page 4 lines 3-4, were edited as suggested.

Referee 2

Reviewer’s report:

As requested by the reviewer the article was shortened. Concerning the relevance of exercise to renal failure, we speculated that not all exercises cause renal failure; possibly other factors like duration and strength of the exercise, environmental temperature, relative humidity, state of normal or reduced hydration of the subject, changes in urine pH due to different foods and use of some drugs could play a role. Otherwise, these patients should have ARF in all cases of strenuous exercise, or severe fever, or diarrhea, or diuretic therapy. A statement was added at the end of the discussion section, as requested.

Regarding the mechanism of ARF due in our patient to urate crystal nephropathy (loin pain, crystals and RBC in urine), we accepted the reviewer’s suggestion and added a statement in the discussion section.

Referee 3

1) We agree with the reviewer’s sentence that usually a renal biopsy in patients with EIARF with severe renal hypouricemia is unnecessary. During the first admission of our patient the renal biopsy, that was scheduled to define the diagnosis of acute renal failure (ARF), was not performed, due to the prolonged coagulation test results. During the second admission PT and activated partial thromboplastin time were at the upper limits of the normal range; therefore, ultrasound-guided renal biopsy was performed without complications. The renal biopsy did not show pathological findings. We decided to eliminate from the text that this analysis was performed, in order to avoid the misleading message to the clinicians that the diagnosis of the disorder requires a renal biopsy.

2) The necessity of prohibition of anaerobic exercise and management in patients with severe renal hypouricemia were reported in Discussion, as
Referee 4

1. Page 3, lane 18: the wrong reference 11 was changed with reference 1

2. Page 3, lane 22: Concerning the reviewer’s doubt that GLUT9S is localized to the apical membrane of proximal tubules, we explained more in detail this hypothesis citing the work of Augustin et al., [2004, reference 12], which demonstrated, using the Madin-Darby canine kidney cells model, that GLUT9L is localized to the basolateral side and GLUT9S to the apical membrane. Furthermore, several authors take for granted this specific localization of the two GLUT9 isoforms and they propose a specific model of UA handling by the proximal renal tubular cell. In particular, it is speculated that UA efflux is mediated by GLUT9L on the basolateral side, whereas UA absorption from the tubular lumen is carried out not only by URAT1, but also by GLUT9S and possibly other apical transporters [Matsuo et al., 2008; Anzai et al., 2008; Dinour et al., 2010]. We modified the text in order to clarify these sentences, as requested.

3. Page 8, lane 14: We agree with the reviewer’s observation and changed the sentence “During the patient’s first admission, his low serum UA levels, as well as the presence of UA crystals in his urine, were not taken into account, leading to a missed diagnosis.” with: “During the patient’s first admission, his low serum UA levels, as well as the presence of UA crystals in his urine, were underestimated, and did not immediately address the genetic testing for primary renal hypouricemia.”

4. Page 9, lane 8: “pumps” was replaced with “transporters”, as requested.