

## Reviewer's report

**Title:** Selenium may be adversely associated with kidney function and kidney length in adult offspring of parents with Balkan Endemic Nephropathy and controls. A two-year follow-up study.

**Version:** 1 **Date:** 26 August 2007

**Reviewer:** vecihi batuman

### Reviewer's report:

#### General

This is an important study evaluating the possible role of cadmium, lead, arsenic and selenium in Balkan Endemic Nephropathy (BEN). The study is well designed and examines in a longitudinal manner the role of these metals and metalloids in a well-defined population, 102 adult offspring of patients with an established diagnosis of BEN, a population clearly at risk of developing BEN. A control group of 99 patients, the adult offspring of hospitalized patients without BEN served as controls. The investigators evaluated blood levels of Pb and Se and urinary Cd and As along with creatinine clearance, kidney dimensions, blood pressure, urine total protein, and #2-microglobulin at two different time periods, in 2003-4, and 2004-5. Although the results of these investigations essentially are negative, i.e., without significant association between these metals/metalloids with possible exception of selenium and kidney parameters, the manuscript is significant because it is helpful in putting to rest the question whether environmental contaminants play a role in the pathogenesis of BEN.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors tested five hypotheses on the potential role of these metals/metalloids, and concluded that Cd, Pb, or As does not pose a risk for the development of BEN, nor that Se is protective. This is one of the best studies and the most recent one that have reached this conclusion, and is helpful in resting the metal/metalloid hypothesis and guiding investigators into different avenues in their search of the etiology of BEN. I am concerned however on the authors' emphasis on Se, and their conclusion that Se may adversely affect kidney function. Although their statistical analysis supports this statement, a sweeping conclusion is premature, and does not deserve to be featured in the title. I therefore propose the authors temper their discussion of the Se findings using more cautious language on this apparently contradictory finding, and focus more on the important finding that Se is not protective. It would also be appropriate to delete reference to Se in the title and change it to something like, "On the association of metals and metalloids with kidney size and function in the adult offspring of patients with Balkan endemic nephropathy. A two-year follow-up

study.”

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. In table 1, moderate hypertension is defined as systolic blood pressure # 140 and/or diastolic # 90 mm Hg. This obviously needs an upper limit and should probably be systolic 140-159 and/or diastolic 90-99, the definition of stage 1 hypertension by JNC-7.

2. Correlations with individual dimensions of kidney may not be meaningful. A better measure for kidney size is kidney volume calculated from kidney length, width, and depth using the ellipsoid volume formula. The investigators have kept these measurements; could the correlations with kidney size be recalculated using kidney volume?

3. The glomerular filtration rates estimated from the 4-h urine collections are nearly 50% lower than the rates calculated using the Cockcroft-Gault formula. Is there an explanation for this discrepancy? Also, by either measure, GFRs are significantly lower during the 2004/05 period compared to the 2003/04 period suggesting a trend. Such a trend, if real, would be of interest especially in the BEN offspring. Was the decline in GFR more marked in the BEN group compared with the controls?

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Discretionary Revisions (which the author can choose to ignore)

**What next?:** Accept after minor essential revisions

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.