Reviewer's report

Title: Bone resorption and environmental exposure to cadmium in children

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Reviewer: Frank Thevenod

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This study on 179 school children from Lahore, Pakistan, with low level environmental exposure to cadmium (Cd) investigates the association between markers of bone demineralization [urinary calcium (Ca) and deoxypyridinoline (DPD) excretion] and urinary Cd excretion (as an index of lifetime body burden). Because of the age range of the children (8-12 years) kidney damage is thought irrelevant. Highly significant associations between urinary Cd, urinary DPD and urinary Ca are observed. The authors conclude that even in young children, low-level environmental exposure to Cd is associated with evidence of bone resorption, suggesting a direct osteotoxic effect of Cd that may have clinical significance at older age.

General:

This study is very important for the field. It is the first study demonstrating a possible toxic impact of low level environmental Cd exposure on bone occurring already in children and has at least three major consequences: 1) DPD may represent an early biomarker of environmental exposure to low levels of Cd, particularly at a stage where the kidney is not affected; 2) Cd-induced bone damage may occur early in life and impact on subsequent osteoporosis in adulthood, particularly in older people; 3) More experimental studies in vitro and in vivo describing direct osteotoxic effects of Cd on bone are necessary to complement this epidemiological study. Refs 24 and 25 are simply not sufficient and published in vitro studies are not convincing enough.

Major Compulsory Revisions:

1. Though it is assumed that the children population studied was healthy and had no kidney damage, is there any evidence from the literature that the incidence of renal damage is similar in children from Pakistan compared to children from Western countries?

Minor Essential Revisions:

1. First paragraph of results section should read “(Figure 1 a & b)”.

Discretionary Revisions:

1. The higher urinary DPD and Cd concentrations in girls is striking, but is not well discussed. The comparison to the situation in mature women, who have lower iron stores due to menstrual bleeding and subsequent intestinal upregulation of divalent metal transporter-1, suggests that a significant proportion
of the girls had already reached puberty and went through menstrual cycles. Though this may not have been properly investigated for cultural reasons, this could be commented on. Otherwise, alternative speculations may arise, such as different roles of boys and girls, the latter being more exposed to household chores (cleaning, gardening) and hence to Cd containing dust, etc.

**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.

**Declaration of competing interests:**

'I declare that I have no competing interests'