Fluoridation of drinking water and chronic kidney disease: absence of evidence is not evidence of absence

Sir,

Ludlow et al. [1] only confirmed that our knowledge of the potential adverse effects of chronic low fluoride supplementation of drinking water on normal or diseased kidneys is insufficient. More than 60 years after water fluoridation, there is no high-level evidence as most published studies are small, have methodological deficiencies or are otherwise flawed.

There are two areas of concern regarding the nephrotoxic potential of fluoride. A small and inclusive amount of research suggests that fluoridation of community water actually causes kidney disease. Kidney damage to tubular function and structure, and reduction in glomerular filtration rate occurred in residents of endemic fluoride areas [2] and anecdotal cases of fluoride intoxication [3] suggested a causal relationship between fluoride intake and renal failure. Ludlow et al. are correct that no evidence of an increased frequency of kidney disease or tubular dysfunction has been observed in early US epidemiological studies, comparing non-fluoridated areas (0.3 mg/dl) to up to 8 mg/l fluoride in drinking water. None of these studies described renal function of the participants or serial changes in simple urinalysis. Of interest, the data of a recently published study suggested that drinking water contains fluoride levels over 2.0 mg/l—half of the fluoride concentration deemed safe by the US Environmental Protection Agency (EPA)—could cause damage to renal tubular structures in children. This conclusion is based on an investigation of 210 children living in areas of China with varying levels of fluoride in the community water (0.6–5.7 ppm). Children drinking water with more than 2 ppm fluoridwater were found to have increased levels of NAG and yGT in their urine—both markers of renal tubular damage [4].

It may be stated that there are no known adverse effects associated with the ingestion of relatively low levels of fluoride (1–2 ppm in drinking water) on a chronic basis. However, the actual levels of intake have to include fluoride not only in water, but also in the diet and in other fluoride containing products.

Moreover, a fairly substantial body of research indicates that patients with chronic renal insufficiency are at an increased risk of chronic fluoride toxicity. Patients with reduced glomerular filtration rates have a decreased ability to excrete fluoride in the urine. These patients may develop skeletal fluorosis even at 1 ppm fluoride in the drinking water [5]. Whether or not the body burden of fluoride may further damage the diseased kidneys is unknown. The National Kidney Foundation in its ‘Position Paper on Fluoride—1980’ as well as the Kidney Health Australia express concern about fluoride retention in kidney patients. They caution physicians to monitor the fluoride intake of patients with advanced stages of kidney diseases. However, a number of reasons will account for the failure to monitor fluoride intake in patients with stages 4 and 5 of chronic kidney diseases and to detect early effects of fluoride retention on kidneys and bone. The safety margin for exposure to fluoride by renal patients is unknown, measurements of fluoride levels are not routine, the onset of skeletal fluorosis is slow and insidious, clinical symptoms of this skeletal disorder are vague, progression of renal functional decline is multifactorial and physicians are unaware of side effects of fluoride on kidneys or bone.

Sir,

We read with interest the case report of a 13-year-old boy who presented with recurrent uric acid stone, which did not respond to a conventional regimen of potassium citrate (Kcit) therapy [1]. In this patient, the authors found that the urine was significantly acidic during the night, despite daytime Kcit therapy, and that excessively acidic nocturnal urine could cause uric acid precipitation at night. However, in addition to uric acid nephrolithiasis, calcium oxalate lithogenic risk is highest at late night–early morning [2]. Urine is hyperconcentrated at night time, since both urine production and renal excretion rate of solutes are at their highest during the day and show their minimum values at night. In healthy subjects, the amplitude of the circadian variation of glomerular filtration rate has been estimated at up to 33%, and this circadian variation is not directly related to blood pressure or cardiac output changes [3]. Moreover, it is possible that this pattern may be affected by age, since older patients do not exhibit such diurnal variations [4].

A retrospective study on a large population referred to the Emergency Department for renal colic [5], found the existence of a highly significant circadian variation of symptoms onset, characterized by a main peak in the morning (from 3 to 6 AM), independent of sex and presence/absence of kidney stones. The authors do not mention, in their 13-year-old boy with recurrent uric acid nephrolithiasis, whether onset of acute events showed a night preference or not. However, it is possible that a series of underlying factors, related to the circadian physiology of the renal system, may favour lithogenic risk and occurrence of renal colic during the late night–early morning hours. Thus, the capacity to modify diurnal variations in urine composition may have practical interest for a therapeutic approach.

Conflict of interest statement. None declared.


**Note:** Dr Cameron et al. had been invited to reply to this letter, but we did not receive a response.

doi:10.1093/ndt/gfm716

Advance Access publication 19 October 2007

---

**Haemoglobin and erythropoietin levels in polycystic kidney disease**

Sir, Artunc and Risler [1] recently proposed a nomogram allowing an easy interpretation of serum erythropoietin values (EPO) by plotting them against haemoglobin using percentiles. They found that EPO correlated inversely with haemoglobin and patients with chronic kidney disease (CKD) of various aetiologies preserved the feedback loop although at a lower level, with most patients below the 25th percentile.

Interestingly, patients with polycystic kidney disease (PKD) were excluded based on the assumption that this entity is associated with increased EPO concentration irrespective of renal function. Although there are several reports claiming that patients with PKD had higher levels of haemoglobin and EPO [2,3], our data only partially support this view. In fact, in a cohort of 259 patients with PKD, in several stages of CKD, haemoglobin levels were only significantly higher in PKD patients in stages 3 and 4, when compared to 87 patients with other causes of CKD (Figure 1). In addition, in our practice, many patients with PKD have to start an erythropoietic-stimulating agent (ESA) in order to treat renal anaemia. We performed a radio-immunocassay determination of serum EPO (DSL1100EPOkit) in 107 patients with PKD and in 35 patients with CKD of other aetiologies, at various stages of CKD; none was on ESA, nor had other causes for anaemia. In PKD patients in stage 2, there is a significant rise in serum EPO levels that is not accompanied by a similar elevation of haemoglobin. In later stages, there is a continuous fall in haemoglobin. In early stages of CKD of other aetiologies, there is a significant negative correlation between EPO and haemoglobin that is lost in stages 4 and 5, but no correlation was found, in any stage, in patients with PKD. By plotting EPO against haemoglobin (Figure 2), it is clear that most values are below the 25th percentile and that there is no difference between PKD and other causes of CKD.

It has been demonstrated that cystic fluid and interstitial cells produce erythropoietin independent to the oxygen

---

**Fig. 1.** Boxplot representing haemoglobin levels in different stages of chronic kidney disease.

**Fig. 2.** Scatterplot of serum erythropoietin versus haemoglobin in patients with PKD and other chronic kidney diseases.