

*Editorial Review*

## Effects of fluoridation of community water supplies for people with chronic kidney disease

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### Introduction

Research on the effects of fluorides on oral health has been in existence for almost a century. Following the observation that communities with naturally fluoridated drinking water had a lower incidence of tooth decay, many developed countries initiated artificial water fluoridation programmes, whereby fluoride is added to the reticulated water supply, such that it reaches approximately one part fluoride per million parts water (ppm) or 1 mg fluoride per litre of water (mg/l). Recent reviews [1–5] summarizing the extensive fluoride literature have concluded that water fluoridation reduces the prevalence of dental decay, and it is estimated that a median of six people need to receive fluoridated water for one extra person to be caries-free [2]. Compared with other methods of systemic fluoridation (including fluoridated sugar, milk or salt, fluoride toothpastes, fluoride supplements), water fluoridation is argued to be the most cost-effective, equitable and safe means to provide community-wide protection against tooth decay [6]. As a result, artificial fluoridation of community water supplies is currently supported by numerous international health and dental organizations, including the World Health Organization and the International Association for Dental Research.

However, while access to fluoridated drinking water has positive effects on dental health, the characteristics of fluoride metabolism mean that fluoride consumption may have implications for the kidney. The calcified tissues in the human body contain 99% of the body burden of fluoride and most of this is non-exchangeable. Absorption of fluoride is rapid and extensive, with about 50% of the absorbed

fluoride becoming associated with calcified tissues within 24 h and the remainder being excreted in the urine. In infants and young children, the amount of fluoride retained in calcified tissues is >50% of the ingested daily amount. The renal clearance of fluoride is high, around 30–40 ml/min in healthy adults [7]. Fluoride is freely filtered by the glomerulus and then undergoes a variable amount of tubular reabsorption. Fluoride excretion falls markedly in the presence of an acid urine and is increased with higher rates of urine flow [8–10]. Considering the pivotal role of the kidney in the body's ability to metabolize fluoride, there have been surprisingly few attempts to synthesize studies relating to the relationship between fluoride consumption and kidney function. The most recent literature reviews on the health effects of fluoride intake have contained limited discussion on the potential impact on the kidneys [1–5].

Recently there has been a resurgence of interest in the artificial fluoridation of drinking water in Australia, with efforts to expand the fluoridation of public water supplies to the one remaining unfluoridated capital city (Brisbane) and several unfluoridated regional areas. With the renewed debate in Australia regarding water fluoridation, questions have been raised concerning the impact of fluoride consumption for the large proportion of the Australian population affected by chronic kidney disease (CKD). In the general Australian community over age 25, there is evidence of at least one indicator of CKD (proteinuria or reduced kidney function) in ~16% of individuals [11]. However, CKD is frequently asymptomatic, and many afflicted individuals will have significant reduction of kidney function but no overt signs or symptoms, and hence will be unaware they have the condition.

The United States National Kidney Foundation published a brief position statement on fluoridation of drinking water in the early 1980s [12], and concluded that there was insufficient evidence to recommend the use of fluoride-free drinking water for all people with CKD. This position statement was reaffirmed in 1998, but no new research or discussion was added.

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Kidney Health Australia, the leading organization promoting kidney and urinary tract health in Australia, does not have a position statement on fluoridation of community water supplies. The aim of this review is to summarize recent literature relating to the health effects of fluoridation of community water supplies for people with CKD. The findings of the review will form the Kidney Health Australia fluoride position statement.

We researched the literature to answer the following questions:

- (i) Does consumption of fluoridated drinking water increase the risk of developing CKD?
- (ii) Are there negative health effects for people with kidney disease who consume fluoridated drinking water?
- (iii) Are there particular risks for people using fluoridated water for dialysis?

## Methods and results

The search strategy focused on the OVID platform (Medline, Pre-Medline, PsycInfo), the Cochrane Library, the National Research Registers (United Kingdom and United States) and other databases of controlled clinical trials. Databases were searched from inception until 1 July 2006. The reference list of each article retrieved by the electronic database search was hand-searched to find other relevant articles. Articles not published in the English language were not included. The Google Internet search engine and grey literature directories (such as the NY Academy of Medicine: Grey Literature Page) were also used to identify unpublished reports.

The search strategy utilized the keywords 'fluoride', 'water', 'kidney', 'renal', 'chronic renal failure', 'chronic kidney disease', 'end-stage kidney disease', 'renal replacement therapy', 'haemodialysis' and 'peritoneal dialysis' (singly and in combination). Truncated characters were used where necessary to retrieve all suffix variations of the root word (e.g. fluorid\$ retrieves fluoride, fluoridation, etc). Both American and English spellings were searched (e.g. hemodialysis and haemodialysis). Full text articles were selected, on the basis of the title and abstract, by M.L. and confirmed by G.L. We aimed to include only articles that provided relevant information to answer the questions detailed here. Where possible, a distinction was made between investigations concerning the optimal concentration of fluoride in drinking water ( $\leq 1.5$  ppm [13]), and higher than optimal fluoride levels ( $> 1.5$  ppm).

The search strategy did not identify any high-level evidence in the form of randomized (or pseudo-randomized) control trials. While there were a small number of comparative studies with concurrent or historical controls, the majority of the identified

studies were in the form of case-series or case-reports. The quality of the included studies was typically in the moderate to weak range, with a lack of methodological rigour and inadequate control of potential sources of bias. While the studies typically focussed on the concentration of fluoride in the public drinking water supply, it is important to note that nowadays, fluoride intake may also be influenced by other sources, such as ingestion of fluoride-containing dental products, the consumption of bottled water in place of tap water and the use of water purification systems in the home. Whitford [14] comprehensively reviewed this issue and stressed that the multiple sources of fluoride available today make estimations of intake based solely on the concentration of the ion in drinking water likely to be misleading.

### *Does consumption of fluoridated drinking water increase the risk of developing CKD?*

People with access to optimally fluoridated drinking water (1.5 ppm/1.5 mg/l), drinking 1.0 l of water a day will consume 1.5 mg of fluoride a day ( $< 0.021$  mg/kg for the average 70 kg person). Few studies have examined the effects of this level of fluoride consumption on kidney function. In a study by Schlesinger *et al.* [15], a 10-year follow-up revealed no difference in urinary albumin excretion between children exposed to optimally fluoridated drinking water (1.2 ppm) and children in a non-fluoridated area. Similarly, a recent investigation demonstrated no difference in protein or albumin levels in children exposed to varying levels of fluoride in drinking water (range from 0.61 ppm to 5.69 ppm) [16]. However, analysis of markers of tubular epithelial cell damage revealed that consuming water with over 2 ppm of fluoride may cause impairment to kidney function in children, and the degree of damage is increased as the water fluoride concentration increases [16].

Two other community-based studies examined the impact of exposure to drinking water with higher than optimal levels of fluoride (2.5 ppm [17] and 8 ppm [18]), and they demonstrated no relationship between consumption of this water and risk of developing kidney disease. A more recent examination of over 18 000 people living in India, exposed to water with fluoride concentrations between 3.5 ppm and 4.9 ppm, reported an increased risk of kidney stone formation in this population [19]. However, the subjects of this study were at increased risk of kidney stones due to malnutrition, and the findings of this study have not been replicated elsewhere. One case study [20] suggested a possible link between long-term consumption of a fluoride-rich commercially available mineral water (8.5 ppm of fluoride) and the development of end-stage kidney disease, but this hypothesis has not been fully investigated.

*Are there negative health effects for people with CKD who consume fluoridated drinking water?*

The available literature suggests that impaired kidney function results in changes in fluoride retention and distribution in the body. Animal studies [21,22] have shown that nephrectomized rats retain significantly greater amounts of fluoride in both serum and bone, and the accumulated fluoride levels increase as the level of fluoride consumption increases [21]. Numerous human studies have also demonstrated a correlation between degree of kidney impairment, reduced urine fluoride and a rise in serum and/or bone fluoride, for individuals ingesting low amounts of fluoride as well as optimally fluoridated drinking water [10,22–35]. Serum fluoride levels of people with end-stage kidney disease may be up to three times as high as the healthy population [31,33,34]. However, Parsons *et al.* [23] demonstrated that normal levels of fluoride excretion were reached within 3 months following successful kidney transplantation, suggesting that the fluoride loading in end-stage kidney disease and during regular dialysis is not excessive and is reversible. Reduced renal clearance of fluoride has also been reported in children with kidney dysfunction [28,29], although children have an enhanced capacity for extrarenal fluoride clearance into the growing skeleton.

While there is considerable evidence to suggest that decreased kidney function is associated with increased retention of fluoride, two studies have shown that fluoride accumulation does not begin until stage 4 or 5 CKD (glomerular filtration rate (GFR) <29 ml/min) [36] is present. Schiffli and Binswanger [10] demonstrated that serum levels of fluoride did not rise until the creatinine clearance dropped below 25 ml/min, while Parsons *et al.* [23] reported that the mean level of creatinine clearance, when a normal dietary load of fluoride has a 90% chance of being excreted, is ~16 ml/min. These findings suggest that people with early stages of CKD (stages 1–3, GFR >30 ml/min) [36] who consume optimally fluoridated drinking water are not at risk of fluoride retention. It is possible that during these early stages of CKD, extrarenal clearance of fluoride (via the skeleton or fecal excretion [24]) provides a sufficient safety margin, but this remains to be fully investigated.

There is no consistent evidence that the retention of fluoride in people with stage 4 or 5 CKD who consume optimally fluoridated drinking water results in any negative health consequences. Animal studies have demonstrated that rats with compromised kidney function that are exposed to the level of fluoride that is commonly encountered by human populations (1 ppm in drinking water) do not develop any clinically adverse extraskeletal physiological, biochemical or genetic outcomes [21]. In addition, in rats with surgically induced renal deficiency, consumption of fluoridated water in concentrations equivalent to 3 and

10 ppm is required to cause osteomalacia and reduced bone strength [37]. Changes in the function of normal rat kidneys occur only following administration of extremely high doses of fluoride, equivalent to severe fluoride intoxication [38].

In humans, a comparative study by Al-Wakeel *et al.* [33] demonstrated that 39% of people undergoing peritoneal dialysis or haemodialysis had levels of fluoride at levels posing risks for renal osteodystrophy, but the authors did not report any evidence of the presence of this condition. Studies of people with end-stage kidney disease by Cohen-Solal *et al.* [35] and Erben *et al.* [27] also failed to show any relationship between increased levels of fluoride in serum and bone and the presence of bone conditions such as osteomalacia or osteodystrophy. Similarly, in a small study of infants receiving peritoneal dialysis, significantly increased serum fluoride levels were not associated with dental fluorosis or abnormal bone mineralization [29].

There is some low-level evidence to suggest that people with stage 4 or 5 CKD, exposed to drinking water containing higher than optimal concentrations of fluoride, may be at increased risk of deleterious health effects. Nicolay *et al.* [39] reported a link between consumption of a fluoride-rich (9 ppm) mineral water and increased risk of hyperkalaemia in six people undergoing haemodialysis. Johnson *et al.* [40] described evidence of dental fluorosis and bone disease in six people on haemodialysis who had been exposed to suboptimal levels of naturally occurring fluoride in their drinking water (1.7–2 ppm). Two cases of skeletal fluorosis have also been reported in people with kidney dysfunction who had consumed water with fluoride levels of 1.7 and 2.6 ppm [41].

It is unclear at what level of serum fluoride accumulation people with stage 4 or 5 CKD should curtail their ingestion of fluoride. A study of nephrectomized rats [37] indicated that serum fluoride levels below 7.6  $\mu\text{M}$  did not affect bone strength, however re-analysis of this data (D. Taves personal communication 15 January 2006) did not rule out significant changes in the range of 3–5  $\mu\text{M}$ . The aforementioned Johnson *et al.* case-reports [40] demonstrated evidence of skeletal fluorosis in people with end-stage kidney disease and serum fluoride levels of 5  $\mu\text{M}$ , and recommended that fluoride intake should be modified at this point. However, a more recent study by Lau and Baylink [42] indicates that the effects of fluoride on bone-cell proliferation are not evident until serum fluoride levels reach ~10  $\mu\text{M}$ . While animal studies have demonstrated that serum levels as low as 2  $\mu\text{M}$  begin to affect the amount of calcium-pump protein in the kidney membranes [43], the threshold for nephrotoxicity after use of fluoridated anaesthetics is considered to be a serum fluoride concentration of 50  $\mu\text{M}$  [44]. It is apparent that more clinical studies are required to reliably determine the safe level of serum fluoride for people with advanced CKD.



*Are there particular risks of fluorosis for people using fluoridated water for dialysis?*

People with end-stage kidney disease who undergo dialysis with fluoridated water receive an additional load of fluoride from the dialysate. Compared with the average gastrointestinal uptake, fluoride absorption increases by 20- to 30-fold during a single pass of dialysis [5]. Recommendations for the suitability of water to be used for dialysis are available from the Australian and New Zealand Society of Nephrology [45] and the Caring for Australasians with Renal Impairment (CARI) guidelines [46]. These directives endorse investigation of local water supplies for normal quality and seasonal variation, analysis of water samples for fluoride and removal of fluoride by water treatment systems (including deionizers or reverse osmosis), to ensure that fluoride concentrations in the final feed water to the dialysis machine do not exceed concentrations defined in the Association for the Advancement of Medical Instrumentation (AAMI) guidelines. Failure to comply with standards for dialysis water quality may result in serious health consequences for people undergoing dialysis. For example, Arnow *et al.* [47] reported an outbreak of fluoride intoxication, where 12 cases of severe illness or death were linked to the failure of a deionization system to purify the dialysis feed water.

## Conclusion

With increasing recognition of the role of the kidney in the metabolism and elimination of fluoride, the recent public fluoride debate in Australia has raised questions regarding the consequences of fluoridation of community drinking water supplies for the sizeable proportion of the population who experience reduced kidney function. The aim of this review was to summarize recent literature relating to the health effects of fluoridation of community water supplies for people with CKD.

The review identified a distinct lack of high-level evidence in the form of randomized controlled trials, with the majority of studies consisting of case-series, case-reports or comparative studies utilizing historical controls. The poor evidence quality and deficient methodological rigour of the identified studies means that no definitive conclusions regarding the association between consumption of optimally fluoridated community water and CKD can be made.

On the basis of the available evidence, Kidney Health Australia has developed the following position statement regarding fluoridation of community water supplies:

- There is no evidence that consumption of optimally fluoridated drinking water increases the risk of developing CKD, although only limited studies addressing this issue are available
- There is consistent evidence that impairment of kidney function results in changes to the way in which fluoride is metabolized and eliminated from the body, resulting in an increased burden of fluoride
- There is no evidence that consumption of optimally fluoridated drinking water poses any health risks for people with CKD, although only limited studies addressing this issue are available
- There is limited evidence that people with stage 4 or 5 CKD who ingest substances with a high concentration of fluoride may be at risk of fluorosis
- Monitoring of fluoride intake and avoidance of fluoride-rich substances would be prudent for people with stage 4 or 5 CKD, in addition to regular investigations for possible signs of fluorosis
- Fluoride concentrations in the final feed water to the dialysis machine must comply with established water quality guidelines.

*Conflict of interest statement.* None declared.

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