INTERNATIONAL DIFFERENCES IN THE RECOGNITION OF NON-SKELETAL FLUOROSIS: A COMPARISON OF INDIA AND NEW ZEALAND

ABSTRACT: In India, there has been a change from the situation present in the 1930s–1970s, when fluoride toxicity was seen to involve just the hard tissues of teeth and bones, to the situation in the 2000s–2010s when recognition was given to the occurrence of non-skeletal symptoms and that these were a key to a new approach to the prevention and treatment of fluorosis by dietary editing and dietary counselling. In New Zealand, a lack of recognition of non-skeletal fluorosis, similar to that present in India in the 1930s–1970s, was present in 1957, when a Commission of Inquiry on the Fluoridation of Public Water Supplies gave the opinion that the individual signs and symptoms of the alleged “Spira-Waldbott Syndrome” syndrome may be due to any number of unrecognised causes. A similar conclusion was reached in a 2014 New Zealand report, Health effects of water fluoridation: a review of the scientific evidence, which noted that “The only side effect of fluoridation at the levels used in NZ (0.7–1.0 mg/L) is minimal fluorosis, and this is not of major cosmetic significance. ... In particular, no effects on brain development, cancer risk or cardiovascular or metabolic risk have been substantiated, and the safety margins are such that no subset of the population is at risk because of fluoridation.” Currently, an international difference is present between India and New Zealand in the recognition of non-skeletal fluorosis. In India, recognition of this syndrome has been seen to be the key to the prevention and treatment of fluorosis while in New Zealand an authoritative panel has found that non-skeletal fluorosis is not a cause for concern. However, taking account of the recent papers by Bashash et al. (2017) and Thomas et al. (2018), a safe daily intake of F for pregnant women and children of all ages to give protection from F-induced neurotoxicity can be estimated to be approximately 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 kg woman) and 0.15 mg F/day (0.003 mg F/kg bw/day for a 45 kg child, the 90th percentile children’s body mass at 8–13 yr), respectively, which would be contained in only 72 and 214 mL, respectively, of water fluoridated at 0.7 mg/L. A consequence of this is that in order to prevent F-induced IQ loss in children, pregnant women and children, up to the age of 7 yr, should avoid the use of fluoridated community water supplies. In conclusion, the Indian view that non-skeletal fluorosis is a real problem and that for drinking water the “lesser the fluoride the better, as fluoride is injurious to health” is more consistent with the current scientific knowledge than the New Zealand view that the existence of a condition of non-skeletal fluorosis is not supported by an evidence base and that the use of drinking water fluoridated at 0.7 mg/L has no effects on brain development.

Keywords: India; New Zealand; Non-skeletal fluorosis; Treatment of fluorosis.

In a paper in the current issue, Mondal notes that a major break-through in the diagnosis of fluorosis was the recognition that, in addition to causing dental and skeletal fluorosis, fluoride ion (F) toxicity could cause non-skeletal fluorosis. Changing the clinical focus, from the effects of F on teeth and bone, to the symptoms of the soft tissue manifestations of F toxicity enabled the diagnosis to be made at an earlier stage of the disease when interventions with dietary editing and counselling enabled the patient to make a full recovery and a return to normal life. When the diagnosis of fluorosis was suspected, tests were done to see if the presence of the condition could be confirmed. The investigations involved measuring the F level in the serum, urine, and drinking water to detect if it was elevated, and taking a forearm radiograph for assessing the presence of ossification of the interosseous membrane between the radius and ulna. Mondal noted that earliest symptoms of F toxicity consisted of (i) digestive tract symptoms with inflammatory bowel disease (IBD)/non-ulcer dyspepsia (NUD), (ii) kidney problems resulting in polyuria and
polydipsia, (iii) muscle weakness and loss of muscle power, (iv) fatigue and tiredness with anaemia (a low blood haemoglobin [Hb] level), and (v) pain in the joints.

In 1978, Waldbott, Burgstahler, and McKinney noted that although changes in the teeth and bones are the most conspicuous signs of chronic fluorosis, neither is an obligatory feature of the disease. Dental fluorosis involving mottling of the teeth, (with white opacities or yellow, brown, or black staining; pitting, and sometimes chipping of the edges) developed exclusively from F intake during the first 10–12 years of life when the permanent teeth were developing. Changes in the skeleton consisted mainly of increased bone density, abnormal apposition of bone substance (the laying down of bone by osteoblasts in the periosteum), and of calcifications in ligaments and joints. The authors noted that 10–20 years of continuous intake of excessive amounts of F were usually required before these effects became detectable by X-rays in radiographs. Waldbott et al. noted that the teeth and bones were not the only parts of the body affected by F. Large does of F, or the persistent intake of small amounts extending over a number of years, could adversely affect many other organs as well, as had been observed by Roholm in 1937.

Roholm reported in 1937 on 68 workers (men=47, age 20–69 yr; women=21, age 20–69 yr) exposed to cryolite dust (sodium aluminium fluoride, Na$_3$AlF$_6$) at the Øresund Chemical Works in Copenhagen, Denmark. On the whole, the men and women complained of the same symptoms. Gastrointestinal symptoms occurred in 80.9% with anorexia, nausea, and vomiting being distinctly connected to the cryolite dust exposure. The symptoms were transitory, developed after working for some time in the dusty atmosphere, and disappeared after a short time in the open air with the loss of appetite being the last to go. The workers became tolerant to the cryolite exposure and as a rule had symptoms for a period of a few days to a few weeks after starting work at the factory and then the acute gastric attacks disappeared, especially the nausea and vomiting. The frequency of the various symptoms, arranged by organ system, is shown in the Table.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Gastric symptoms (mainly acute):</strong> anorexia, heartburn, nausea, vomiting</td>
<td>80.9</td>
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<tr>
<td><strong>Intestinal symptoms (mainly chronic):</strong> disposition to diarrhoea, constipation</td>
<td>33.8</td>
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<tr>
<td><strong>Circulatory and respiratory symptoms:</strong> shortness of breath, palpitations, productive cough</td>
<td>51.5</td>
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<tr>
<td><strong>Arthritic and neuromuscular symptoms:</strong> joint pains, stiffness, indefinite or localized pain</td>
<td>35.3</td>
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<tr>
<td><strong>Neuropsychological symptoms:</strong> sleepiness, headache, giddiness, feeling indisposed</td>
<td>22.1</td>
</tr>
<tr>
<td><strong>Dermatological symptoms:</strong> rash</td>
<td>11.8</td>
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In the cryolite workers who had the 1st phase of bone changes on radiography (bone trabeculae rough, blurred, and giving deep shadows so that the bone was more prominent and more blurred at the same time), the average period of contact with the drug was 9.3 yr. In those with 3rd phase bony changes (including calcification of the forearm interosseous membrane) it was 21.1 yr.

Another 1937 study, by Shortt et al., reported on 10 patients (men=8, age 25–45 yr; female=2, age 35–45 yr) with endemic fluorosis due to a high F level in their drinking water from the Madras Presidency in India. The clinical symptoms related
chiefly to disabilities caused by calcification of ligaments, tendons and fasciae, the formation of osteophyte outgrowths of bone, and the nervous effects of mechanical pressure by encroachment of bone on the spinal canal. The radiological findings showed excessive calcification of tendons, ligaments and fasciae, the production of osteophytic formations from various bones, and the almost complete synostosis of various joints, especially those of the vertebral column. The children born and brought up in the area from which the patients came had a very high incidence of “mottled enamel” in the teeth. The enamel lost its glistening appearance and became dead white like chalk, which was present in the form of (i) horizontal bands, (ii) centrally placed areas of whiteness, or (iii) an irregular pattern of patches of whiteness. If the consumption of the high F water continued, the whiteness was replaced by chocolate coloured markings occupying exactly the same areas as were previously white. Apart from the dental condition, the children did not appear to suffer in any way from the intake of F and there appeared to be an interval, extending from childhood to about 25–30 years of age, during which few or no ill-effects were exhibited. At about 30 years of age, however, the first symptoms of intoxication appeared with a recurrent general tingling sensation, in the limbs or over the body in general, followed by pain and stiffness, especially in the lumbar region of the spine but also involving the dorsal (thoracic) and cervical regions. The stiffness increased until the entire spine, including the cervical region, appeared to be one continuous column of bone, producing the condition of “poker back.” For such patients to turn their head, they had to turn their whole body. Between the age of 30 and 40 yr, the ability to squat and to breathe, by expanding the thoracic cavity, was lost. The patient was finally bed-ridden, while the mental powers were unimpaired, and death usually occurred due to some intercurrent disease. The patients exhibited a definite cachexia with loss of appetite and general emaciation. The authors considered that the chief clinical symptoms were the physical disabilities present due to the mechanical effects of the bony growths around the spinal column and joints, and in tendinous insertions and interosseous ligaments. There was a slight degree of anaemia. The mental condition was unaffected. Nothing abnormal was noted in the endocrine system. The chest was almost immobile due to the fixation of the ribs and breathing in some cases was purely abdominal. The majority showed some tachycardia. There was generalized wasting of all the muscles, part of which, as in the case of the intercostal muscles, may have been a disuse atrophy. Kidney function was impaired in the majority of the cases. No comment was made on the gastrointestinal system.

In 1955, Waldbott noted that the symptoms of chronic fluoride poisoning were exceedingly difficult to diagnose, did not develop before many years of ingestion of the drug, and were generally not recognized by physicians.\(^5\) The principal manifestations were described as nausea, general malaise, loss of appetite, increased thirst, chronic constipation, headaches, stiffness and rheumatic pains, and similar vague symptoms of the kind which also result from a large variety of causes. More advanced symptoms were cachexia, calcifications of tendons and ligaments, and nephritis. Waldbott noted that symptoms of F toxicity were shown by seven persons in a Michigan city (Highland Park\(^2\,5\)), where the calcium and magnesium content of the water was relatively low, after 3 yr of water fluoridation with 1 mg F/L.

In 1955, Siddiqui noted that fresh arrivals into the village of Kamaguda, 50 miles from the city of Hyderabad, in the Nalgonda district, India, where the drinking water
F level was 11.8 mg/L, developed marked skeletal symptoms after 1–4 years. This was much less than the 30–40 yr found by Shortt as being the period required for a definite picture of skeletal fluorosis to develop.

In 1963, Singh et al. reported on a study of 409 cases of endemic fluorosis over a period of seven years (1956–1962) from Panjab (also spelt as Punjab), one of the Northern States of India and a highly endemic area. The chief source of water for domestic and drinking purposes was fairly shallow artificial wells from which the water, with a F content of 1.2–16.2 mg/L, was obtained with hand pumps. In 208 adults in the village of Papra of the Sangur district, where the range of F in the drinking water was 9.12–10.68 mg/L, 204 (98.1%) had dental fluorosis. The authors noted that the changes in the skeleton were the most distinctive and characteristic feature of endemic fluorosis. They commented that since the dental and skeletal manifestations can be easily demonstrated and provide reliable evidence of fluorosis, other physical abnormalities tend to be overlooked. They commented that a lengthy list of manifestations had been attributed by Spira to chronic fluorosis, based on a questionnaire given to 5,000 military personnel during World War II of whom 20% had mottled enamel, but that his hypothesis that they were due to F acting on the central nervous system and on endocrine glands had not been substantiated. Singh et al. also discussed the claim by Waldbott that fluoride toxicity could cause a number of complaints including constipation, neuralgia, headache, epileptiform and tetanus-like convulsions, furunculosis (a deep infection of a hair follicle leading to abscess formation with the accumulation of pus and necrotic tissue), urticaria, dermatoses, alopecia, and brittle nails. Singh et al. stated that Waldbott had advanced an allergic hypothesis to explain most of the symptoms but, in their view, they were non-specific minor complaints and there were no convincing data to show that there was a hypersensitivity to fluoride. Singh et al. submitted the population of Papra to a detailed questionnaire and physical examination and found no evidence of underdevelopment, undue anaemia, or any unusual nutritional deficiency among the people in the affected areas. No evidence of goitre or hypothyroidism, or abnormalities in the cardiovascular, or other systems were found.

In 1979, Raja Reddy discussed the preskeletal stage of fluorosis and noted that it was reported to range from 10–30 years or even longer in endemic areas and from 10–15 years or longer in cases of industrial exposure. It was usually free from any signs or symptoms in the early stages in endemic regions. He stated that the persons concerned may occasionally complain of pains in the small joints of the limbs and back, which are often mistaken for rheumatic arthritis or ankylosing spondylitis. Raja Reddy noted that various reports from Europe and America suggest that there would be symptoms corresponding to gastrointestinal, musculo-skeletal, respiratory, and other visceral symptoms during this stage. He described a number of alleged symptoms of preskeletal fluorosis and referred to publications of Roholm 1937, Waldbott 1956, Frada et. al. 1963, Waldbott and Cecilioni 1969, Zislin and Girskaya 1971, Grimbergen 1974, Petraborg 1974, Waldbott 1962, and Spira 1941. Raja Reddy concluded that since these symptoms are traceable to various other causes, it would be difficult to identify them with those of fluoride intoxication.

In 2001, Susheela noted that the conventional belief that fluoride affects only bone and tooth had been negated in recent years as the evidence on the involvement of the
soft tissues, organs, and systems of the body became convincing. She noted how investigations, including electron microscopy, had demonstrated soft tissue involvement in humans with fluorosis in skeletal muscle, erythrocytes, gastrointestinal mucosa, ligaments, and spermatozoa. In addition, there was evidence, from animal models, of involvement of the kidney, liver, adrenal gland, and the reproductive organs. She stated that the detection of fluorosis at early stages was now possible because of the understanding of soft tissue manifestations in fluorosis and that fluorosis was now an easily preventable disease. In 2009, Susheela reported that anaemia in pregnancy in India was an easily rectifiable problem which responded to a greatly reduced intake of F and the inclusion of essential nutrients in the daily diet.

In 2009, Sharma et al. published the results of a health survey on the prevalence of neurological manifestations of 2691 subjects (1145 children and 1546 adults), in Sanganer Tehsil, Rajasthan, India, exposed to varying amounts of F in drinking water (low <1.0 mg/L, medium 1.0–1.5 mg/L, and high 1.5–6.4 mg/L). Although the percentage of headache, insomnia, and lethargy among the adults was fairly small in the low and medium F villages, it was considerable in the high F endemic villages, clearly indicating a role of F in the neurological outcomes. Similarly, the authors reported on a health survey in the same region on the prevalence of gastric discomforts of 2610 subjects (1135 children and 1475 adults), exposed to varying amounts of F in drinking water (low <1.0 mg/L, medium 1.0–1.5 mg/L, and high >1.5 mg/L). The percentage of adults with symptoms (stomach ache, a bloated feeling, nausea, diarrhoea, and constipation) increased as the water F level increased. It was considered that the possible reasons for the prevalence of gastric distress in these areas included poor nutritional and socio-economic conditions, which were exacerbated by the ingestion of F through drinking water and dietary habits.

Thus, in India, there has been a change from the situation present in the 1930s–1970s when fluoride toxicity was seen to involve just the hard tissues of teeth and bones to the situation in 2000s–2010s when recognition was given to the occurrence of non-skeletal symptoms and this recognition was a key to the new approach to diet and treatment as described by Mondal.

In New Zealand, a lack of recognition of non-skeletal fluorosis, similar to that present in India in the 1930s–1970s, was present in 1957 when a report of a Commission of Inquiry on the Fluoridation of Public Water Supplies summarised their conclusions on the “Spira-Waldbott Syndrome” by noting that (i) We are of the opinion that the individual signs and symptoms of the alleged syndrome may be due to any number of unrecognised causes; and (ii) We are satisfied that there is no causal relationship between any of these signs and symptoms and the ingestion of water containing 1 ppm of fluoride and food cooked in this water. Similarly, an introductory letter by Sir Peter Gluckman, the Prime Minister’s Chief Science Advisor, and Sir David Skegg, President, Royal Society of New Zealand, in the 2014 report Health effects of water fluoridation: a review of the scientific evidence, noted that “The only side effect of fluoridation at the levels used in NZ is minimal fluorosis, and this is not of major cosmetic significance. There are no reported cases of disfiguring fluorosis associated with levels used for fluoridating water supplies in New Zealand. The use of fluoridated toothpastes does not change these conclusions.
or obviate the recommendations. Given the caveat that science can never be absolute, the panel is unanimous in its conclusion that there are no adverse effects of fluoride of any significance arising from fluoridation at the levels used in New Zealand. In particular, no effects on brain development, cancer risk or cardiovascular or metabolic risk have been substantiated, and the safety margins are such that no subset of the population is at risk because of fluoridation.”

The range of the daily F intake for the adult New Zealand population given in the 2016 New Zealand Total Diet Study was 0.5–2.2 mg/day, although the caveat was given that a full dietary intake of F could not be made because the analytic method for F allowed testing of only a proportion of the foods sampled. The mean F content of tea sold in New Zealand was 3.97 mg/kg, range 1.12–6.49 mg/kg. Despite the 2014 report giving the reassurance that the additional F added to drinking water in New Zealand will not cause adverse effects other than dental fluorosis, a case has been reported of dyspepsia related to the use of fluoridated water. In addition, probable skeletal fluorosis has been reported in a 79-year-old female with a history of the daily drinking of at least six cups of black tea daily since childhood. The range of the F content of tea infusions in New Zealand made with 18 brands of tea bag, weighing 1.7–3.3 g, with fluoridated water with 0.7 mg F/L was 0.9–3.9 mg F/L and when made with deionized water, with 0.0 mg F/L, it was 0.4–3.2 mg F/L. The tea was brewed for 5 minutes with 200 mL of water, initially at 100°C. After 5 minutes the tea bag was removed and the infusion cooled to the room temperature of 18–20°C. The range of F intake from six 250 mL cups of tea, 1.5 L, with nonfluoridated water was 0.6–4.8 mg F/day and for cups of tea made with water fluoridated at 0.7 mg/L was 1.4–5.9 mg F/L.

The 2014 report observed that “New Zealand water supplies generally have naturally low concentrations of fluoride.” Fluoridation of public drinking-water supplies involves the deliberate adjustment of fluoride concentrations in drinking water from their naturally low levels (~0.1–0.2 mg/L [or ppm] in most parts of New Zealand), upwards to between 0.7 and 1 mg/L.” In India, for the F level in drinking water, there is a requirement (acceptable limit) of 1.0 ppm (mg/L) and a permissible limit in the absence of an alternate source of 1.5 ppm. A rider to the Indian limit is that the “lesser the fluoride the better, as fluoride is injurious to health.”

Currently, an international difference is present between India and New Zealand in the recognition of non-skeletal fluorosis. In India, recognition of this syndrome has been seen to be the key to the prevention and treatment of fluorosis while in New Zealand an authoritative panel has found that non-skeletal fluorosis is not a cause for concern. However, by taking account of the recent papers by Bashash et al. (2107) and Thomas et al. (2018), a safe daily intake of F for pregnant women and children of all ages to give protection from F-induced neurotoxicity can been estimated to be approximately 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 kg woman) and 0.15 mg F/day (0.003 mg F/kg bw/day for a 45 kg child, the 90th percentile children’s body mass at 8–13 yr), respectively. The quantities of water, fluoridated with 0.7 mg F/L (0.7 ppm) which contain 0.04 and 0.15 mg of F are 72 and 214 mL, respectively, approximately a third of a cupful and a cupful (1 cup = 8 oz = 237 mL). With this being less than 30% of the mean daily water intake for persons aged <0.5–6, 7–19, and ≥20 yr, in order to prevent F-induced IQ loss in children, pregnant
women and children, up to the age of 7 yr, should avoid the use of fluoridated community water supplies and other dietary sources high in F including tea and fluoridated dental products that may be swallowed such as fluoridated toothpaste and professionally applied fluoride gels and varnishes.

In conclusion, the Indian view that non-skeletal fluorosis is a real problem and that for drinking water the “lesser the fluoride the better, as fluoride is injurious to health” is more consistent with the current scientific knowledge than the New Zealand view that the existence of a condition of non-skeletal fluorosis is not supported by an evidence base and that the use of drinking water fluoridated at 0.7 mg/L has no effects on brain development.

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