7 Editorial
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THE EFFECTS OF FLUORIDE ON INFLAMMATION AND CANCER

ABSTRACT: Two papers in the current issue of *Fluoride* report that (i) the insulin resistance induced by excessive fluoride intake in rats may be mediated by activation of inflammatory signaling pathways; and (ii) fluoride exposure, in humans with skeletal fluorosis, may alter the expression of two pathways relevant to cancer: pathways in cancer and proteoglycans in cancer. If the effects of fluoride on inflammation and cancer are added to the other known effects of fluoride, including those on thyroid hormone metabolism, oxidative stress, and excitotoxicity, the potential field for fluoride research becomes very broad and would include conditions commoner in fluoridated communities compared to nonfluoridated communities, particularly where the water is soft, such as asthma, chronic obstructive pulmonary disease, obesity, rheumatoid arthritis, ischaemic heart disease, sarcoidosis, osteosarcoma, prostate cancer, leukaemia, pancreatic cancer, brain cancer, skin cancer, and melanoma.

Keywords: Cancer; Fluoride; Inflammation.

Two papers in the current issue of *Fluoride* refer to the effects of fluoride on inflammation and cancer. (i) Firstly, in the paper by Chiba et al. it is noted that the adipose tissue is an endocrine organ that can influence glucose metabolism by releasing proinflammatory cytokines, which alter insulin signaling. Based on the findings of their study, they proposed that the chronic fluoride treatment-induced inhibition of insulin signaling in the periepididymal white adipose tissue of rats is related to the increase in the inhibitor of kappa B (IκB) kinase complex (IκK) phosphorylation status and tumor necrosis factor α (TNF-α) expression. They considered that these results indicated that the insulin resistance induced by excessive fluoride intake may be mediated by activation of inflammatory signaling pathways.

(ii) Secondly, in the paper by Pei et al., a high-throughput profiling of human serum carried out by using a microRNA (miRNA) array to explore the role of miRNAs in skeletal fluorosis, the results showed the expression levels of 31 and 85 miRNAs were differentially regulated between a case group with skeletal fluorosis and a control group and a high-fluoride group, respectively. Three miRNAs (miR-200c-3p, miR-3185, and miR-1231) were successfully identified by the Polymerase Chain Reaction (PCR) method. Bioinformatic analyses revealed that the target genes of the differentiated miRNAs were highly enriched in genes promoting transcription. Pathway analysis of the miRNAs by KEGG revealed that the MAPK signaling pathway, pathways in cancer, the PI3K-Akt signaling pathway, proteoglycans in cancer, and the endocytosis pathway were regulated by the differentially expressed miRNAs. Thus fluoride exposure in humans with skeletal fluorosis altered the expression of two pathways relevant to cancer: pathways in cancer and proteoglycans in cancer.

Yiamouyiannis and Burk reported in 1977 that the rate of increase in the cancer death rate in fluoridated cities in the USA, compared to nonfluoridated cities, of 15/100,000 population for persons aged 45–64 years ($p<0.02$) and of 35/100/000 for persons aged 65+ years ($p<0.05$), could not be ascribed to changes in the racial or sex compositions of the fluoridated and nonfluoridated populations.[3] In 1978 Waldbott et al. noted that the conclusions of Yiamouyiannis and Burk on cancer mortality had not been invalidated.[4] Yiamouyiannis and Burk noted that, according to the dogma current in 1977, 20–30 years must pass before a substance alters the cancer death rate. They also considered that in the case of fluoride, it appeared that a chronic low level exposure to fluoride would be optimal for producing metabolic aberrations conducive to producing a cancerous cell or selectively stimulating the growth rate of cancerous cells and that higher concentrations do not enhance these effects and may, in fact, lead to cell stasis or death.[3]

The incidence of the brain tumour meingioma in the survivors of the 1945 atomic bomb explosion in Hiroshima, Japan, increased, compared to controls, after 1975, some 30 years later (the rates in the subjects and in non-exposed controls in 1975 were 8.7 and 3.0 cases per 10^5 persons per year, respectively).[5]

For osteosarcoma, the length of time after fluoride exposure in childhood until the condition may be diagnosed in males can be shorter. For 103 patients (male=60, female=43) diagnosed before the age of 20 years (median age at diagnosis 14 years, range 6–19 years) with osteosarcoma, a significant relationship was present, compared to controls, for males, but not females, with exposure to fluoride in drinking water between the ages of 4 and 12 years, with a peak at 6–8 years. The adjusted odds ratio for the males was 5.46 (95% CI 1.50, 19.90) at age of 7 years.[6]

Moolenburgh reported in 1995 on the finding by Dr Josephien van den Berg that in 1993, 20 years after the city of Tiel, the Netherlands, had been fluoridated from 1952 to 1973, the cancer rate in women aged 56–60 years was 11.10% compared to that in the nonfluoridated control city of Culemborg which had a cancer rate of 3.10%.[7]

Moolenburgh also commented on the average weight of the people in fluoridated Tiel being 1 kg more than that in nonfluoridated Culemborg.[8] This may possibly have been related to fluoride-induced hypothyroidism and might be a contributing factor to the aetiology of fluoride-induced diabetes in addition to fluoride's effects on inflammation.

If the effects of fluoride on inflammation and cancer are added to the other known effects of fluoride, including those on thyroid hormone metabolism,[9] oxidative stress,[10] and excitotoxicity,[11] the potential field for fluoride research becomes very broad and would include conditions commoner in fluoridated communities compared to nonfluoridated communities, particularly where the water is soft, such as asthma, chronic obstructive pulmonary disease, obesity, rheumatoid arthritis, ischaemic heart disease, sarcoidosis, osteosarcoma, prostate cancer, leukaemia, pancreatic cancer, brain cancer, skin cancer, and melanoma.[12]

Bruce Spittle, Editor-in-Chief, *Fluoride*, Dunedin, New Zealand

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