WATER-BORNE FLUORIDE AND PRIMARY HYPERTENSION

SUMMARY: Despite mixed results with laboratory animals, recent studies indicate that elevated intake of fluoride in drinking water may, depending on circumstances, cause high blood pressure (hypertension) in humans. Although primary or essential hypertension has various causes and is known to be associated with higher levels of vasoconstrictors like endothelin 1 and thromboxane 2, increased oxidative stress, vascular inflammation, aortic stiffness, and magnesium deficiency, new evidence connecting this most common form of hypertension with increased intake of fluoride clearly deserves further investigation.

Keywords: Aortic stiffness; Endothelin 1; Fluoride intake; Oxidative stress; Magnesium deficiency; Primary hypertension; Thromboxane 2; Vascular inflammation.

Various effects of chronic fluorosis on different human and animal organ systems have been investigated, but comparatively few studies have dealt with the potential impact of excessive fluoride intake on the cardiovascular system. Hypertension in humans (systolic BP >140 with diastolic >90 mm/Hg) is one of the most common cardiovascular diseases, and it is an important identifiable and modifiable risk factor for atherosclerotic heart disease and stroke. In our research, we have been especially interested in the possible relationship between fluoride intake from drinking water and hypertension. Laboratory studies on animals, however, have given conflicting results. Recently, Yan, Wang, and Li reported that administration of sodium fluoride to mice significantly modulated the pulse rate and cardiac output of the heart in a dose-dependent manner, with a reduced heart rate and diminished cardiac output from high dosages of NaF.[1] Their results also suggested that fluoride reduced contractile function of the heart in response to ischemic stress. However, they did not report measurement of blood pressure in the mice. In another animal study, Bera et al. demonstrated a significant correlation between the blood pressure of male rats and perinatal exposure to NaF that resulted in a chronic, dose-dependent functional impairment of hemodynamic control.[2] In a earlier experimental study, Susheela et al. reported calcification and degeneration of smooth muscle fibers in the tunica media in the aorta of rabbits after being administered fluoride for 17–24 months.[3] Calcification and degeneration of aortic smooth muscle fibers obviously might decrease aortic elasticity, which in turn might cause an increase in blood pressure.

Several human studies have also examined the relationship between excessive fluoride intake from drinking water and hypertension (HT). Over 20 years ago, Singh et al. reported higher systolic blood pressure and increased left atrial diameter in patients with endemic skeletal fluorosis.[4] In 2012, Sun et al. published their investigation of the effect on HT of high water fluoride and plasma endothelin 1 (ET-1) levels.[5] A randomly recruited group of 487 residents aged 40 to 75 living in an endemic fluorosis area of China was divided into four groups according to the concentration of fluoride in their drinking water. The water fluoride levels of the normal, mild, moderate, and high fluoride exposure groups were 0.84±0.26, 1.55±0.22, 2.49±0.30, and 4.06±1.15 mg/L, respectively. The percentages of HT in these groups increased from 20.16%, 24.54%, 32.30%, and 49.23%, respectively. The plasma ET-1 levels also increased significantly from

normal to high fluoride exposure groups. The authors concluded that high levels of fluoride in drinking water can increase blood pressure and plasma ET-1 levels in subjects living in endemic fluorosis areas.

In 2011, Amini et al. reported an ecological study on the relationship between fluoride concentrations in ground water and blood pressure in an Iranian population.[6] They noted an overall statistically significant positive correlation between the mean concentrations of fluoride in the ground water resources and the prevalence of HT. They also found a statistically significant positive correlation between the mean concentrations of fluoride in the groundwater sources and the mean systolic blood pressure of men and a borderline correlation with women. They speculated that there might be a gender-specific difference. However, Sun et al.[5] found the effect is similar in both men and women.

In Turkey, although fluorosis in animals and people from high fluoride groundwater is well established,[7] the effect of chronic fluoride exposure on the cardiovascular system is not yet clear. In our previous two studies,[8,9] we examined the effect of chronic fluoride exposure on the cardiovascular system of fluorosis patients living in an endemic fluorosis area in our province. We found that aortic elasticity was impaired in patients with endemic fluorosis,[8] and we also observed that the left ventricular diastolic and global functions were impaired in such patients.[9] The assessment of aortic stiffness which is calculated from pulsatile changes in ascending aorta by echocardiography is an important determinant of vascular changes and left ventricular function. Aortic stiffness is a marker of cardiovascular disease including HT and is considered an independent risk factor for cardiovascular mortality.

In its most prevalent form, HT generally has a gradual onset associated with age, genetic make-up, diet, environmental factors, and lack of physical exercise, and it is designated as primary or essential HT. When it arises from specific functional disorders, usually fairly rapidly, it is considered secondary HT and is less common than primary HT. These associated conditions include renal, endocrine, cardiac, and neurological causes. In considering our studies mentioned above and in this review, we have, as far as possible, excluded secondary causes of HT for lack of sufficient detailed clinical and laboratory investigations. For example, we have not performed echocardiographic and renovascular Doppler ultrasonographic examination to eliminate cardiac and renovascular causes of HT in relation to fluoride.

Oxidative stress is a recognized feature of fluoride exposure that has been observed *in vitro* in several types of cell and tissue cultures and also *in vivo* in different organ systems in animals and in people living in areas of endemic fluorosis.[10] Recently, oxidative stress has been implicated in chronic diseases including HT.[11] Although oxidative stress may not always be involved in HT, it amplifies blood pressure elevation in the presence of other pro-hypertensive factors (salt, renin-angiotensin system, sympathetic hyperactivity). Oxidative stress is therefore an important factor in the molecular mechanisms associated with cardiovascular and renal injury in HT. Hence it is reasonable to conclude that

oxidative stress present in F toxicity can also contribute to an increase in blood pressure.

Admittedly, the mechanism of fluoride toxicity on the cardiovascular system is complex. In addition to oxidative stress, inflammatory mechanisms contribute to atherosclerosis, endothelial dysfunction, vascular stiffness, and, consequently, to hypertension.[10] Sun et al. also showed for the first time that plasma ET-1 levels in the moderate and high fluoride exposure groups were significantly higher than in the normal and mild fluoride exposure groups.[5] However, no statistically significant difference in ET-1 levels was found between the moderate and high fluoride exposure groups and between the normal and mild fluoride exposure groups. This shows that ET-1 might play a role in fluoride-induced HT. However, moderate to high fluoride intake with drinking water also causes this effect. Recently, Bian et al., in an experimental study, showed that plasma levels of thromboxane B2 and ET-1 are increased and total nitric oxide synthase (NOS) activities in serum decrease in New Zealand rabbits exposed to high fluoride.[11] Thromboxane B2 is as potent a vasoconstrictor as ET-1, and NO is a powerful vasodilator with a short half-life of a few seconds in the blood. As a result, thromboxane and nitric oxide mediated mechanisms might also play a role in fluoride-related HT.

Among its other effects, ingestion of fluoride increases the requirement for certain nutrients. For example, the metabolic requirement for magnesium is increased by fluoride, sequestering it into the skeleton and thereby making magnesium less available to other tissues. Ophaug and Singer reported that fluoride exerted a significant effect in retarding the mobilization of skeletal magnesium in rats.[13] It has also been reported that fluoride has a biological interaction with magnesium and that excessive fluoride intake causes magnesium deficiency by decreasing its absorption from the intestine by forming magnesium fluoride.[14] In addition, previous studies have shown that subjects with chronic fluorosis had lower serum magnesium levels.[15,16] Magnesium deficiency has been implicated in the pathogenesis of HT, with epidemiological and experimental studies demonstrating an inverse correlation between blood pressure and serum magnesium levels.[17] Magnesium affects blood pressure by modulating vascular tone and reactivity. It acts as a calcium channel antagonist, it stimulates production of vasodilator prostacyclins and NO, and it alters vascular responses to vasoactive agonists.

In summary, from what is now known, excess fluoride intake from drinking water appears to exert an increase in primary HT. However, it is also clear that the association of fluoride with toxic effects on the cardiovascular system needs more experimental and epidemiological studies, including adequate control of confounding cofactors.

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