

ABSTRACTS

BIOCHEMICAL EFFECTS

CURRENT TRENDS IN FLUORINE RESEARCH

Current topics in fluorine research are presented with emphasis on findings by researchers in Szczecin and elsewhere in Poland, as well as in other places in the world. Reports are cited on the distribution of fluorine compounds in the environment, routes of penetration into living organisms, and analytical methods for the quantitative determinations of fluorine content in air, water, soil, and foods. Important contributions have been made by Polish researchers on the role and patterns of fluorides in body fluids and soft and hard tissues, which remain in direct relationship to accumulation and elimination of fluorine. So far, comprehensive studies on mutagenic effects of fluorine and its potential role in bone neoplasms, Down's syndrome, and other genetic disorders have not been carried out in Poland. Worthy of mention are reports on mechanisms of action of fluorine compounds on the cellular and subcellular level. Finally, two achievements of recent years in the field of fluorine research are discussed briefly. The first is concerned with the use in dentistry of chemical analysis for studying mineral reconstruction of teeth throughout the lifetime of an individual. The second is in the field of medicine where molecular modeling has been applied to explain the mechanism of action of aluminofluoride complexes (AlFx) as a messenger of false information during protein biosynthesis and their apparent role in the etiology of Alzheimer's disease.

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Keywords: Aluminofluoride complexes; Alzheimer's disease; Fluorine research; Polish researchers.

Source: Ann Acad Med Stetin. 2006;52 Suppl 1:73-7. [in Polish].

DENTAL EFFECTS

ASSESSMENT OF PERIODONTAL STATUS IN DENTAL FLUOROSIS SUBJECTS USING COMMUNITY PERIODONTAL INDEX OF TREATMENT NEEDS

Background: Periodontitis is multifactorial in nature. The various determinants of periodontal disease are age, sex, race, socioeconomic status and risk factors including tobacco usage and oral hygiene status. However, there are inconsistent epidemiological data on the periodontal status of subjects living in high-fluoride areas. The aim of this study was to investigate the effect of dental fluorosis on the periodontal status using community periodontal index of treatment needs (CPITN), as a clinical study in a population between residing in the high fluoridated areas of Davangere district. The possible reasons for the susceptibility of this population to periodontal disease are discussed.

Materials and Methods: 1020 subjects between ages 15 and 74 suffering from dental fluorosis were assessed for their periodontal status. Clinical parameters recorded were OHI-S to assess the oral hygiene status. Jackson's fluorosis index was used to assess the degree of fluorosis and CPITN index to assess the periodontal status where treatment need was excluded.

Results: Gingivitis and periodontitis were more common in females (65.9% and 32.8%, respectively) than in males (75.1% and 24.2%, respectively). Periodontitis was significantly more common in females. As the age advanced from 15 to 55 years and above, gingivitis reduced from 81.0 to 42.9%, and periodontitis increased steadily from 18.0 to 57.1%, which was significant. Periodontitis was high in subjects with poor oral hygiene (81.3%) compared to those with good oral hygiene (14.5%), which was significant. As the degree of fluorosis increased, severity of gingivitis was less, and periodontitis increased, i.e., with degree A

fluorosis, gingivitis was 89.4% and periodontitis was 8.5%, but with degree F fluorosis, gingivitis was 64% and periodontitis was 35.8%, which was statistically significant.

Conclusions: The results suggest that there is a strong association of occurrence of periodontal disease in high-fluoride areas. The role of plaque is well understood in contrast to the effect of fluorides on periodontal tissues. Fluoride must therefore be considered an important etiological agent in periodontal disease.

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Keywords: Community periodontal index of treatment needs (CPITN); Dental fluorosis; Oral epidemiology; Periodontal disease.

Source: Indian J Dent Res 2007;18(2):67-71.

COMMUNITY WATER FLUORIDATION AND CARIES PREVENTION: A CRITICAL REVIEW

The aim of this paper was to critically review the current role of community water fluoridation in preventing dental caries. Original articles and reviews published in English from January 2001 to June 2006 were selected through MEDLINE database. Other sources were taken from the references in the selected papers. For the past 50 years community water fluoridation has been generally considered the milestone of caries prevention and as one of the major public health measures of the 20th century. However, it is now recognized and accepted that the primary cariostatic action of fluoride occurs after tooth eruption. Moreover, the caries reduction directly attributable to water fluoridation has declined in the last decades as the use of topical fluoride had become more widespread, whereas enamel fluorosis has been reported as an emerging problem in fluoridated areas. Several studies conducted in fluoridated and nonfluoridated communities suggested that this method of delivering fluoride may be unnecessary for caries prevention, particularly in the industrialized countries where the caries level has become low. Although water fluoridation may still be a relevant public health measure in poor and disadvantaged populations, the use of topical fluoride offers an alternative to water fluoridation to prevent caries among people living in both industrialized and developing countries.

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Keywords: Caries prevention; Dental fluorosis; Systemic fluoride; Topical fluoride; Water fluoridation review.

Source: Clin Oral Invest DOI 10.1007/s00784-007-0111-6.

HEALTH/TOXIC EFFECTS IN ANIMALS

Editor's Note: The following two abstracts evidently represent two aspects of the same research study.

PROTECTIVE EFFECTS OF VITAMINS C AND E AGAINST ENDOMETRIAL DAMAGE AND OXIDATIVE STRESS IN FLUORIDE INTOXICATION.

The aims of this study were to examine F-induced oxidative stress that promotes production of reactive oxygen species (ROS) and to investigate the role of vitamins C and E against possible F-induced endometrial impairment in rats. Rats were divided into three groups: control, F, and F plus vitamins. The F group was given 100 mg F/L orally for 60 days. Combined vitamins were also administered orally. Fluoride administration to control rats significantly increased endometrial malondialdehyde (MDA) but decreased superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) activities. Endometrial glandular and stromal apoptosis were investigated by DNAnick end-labelling (TUNEL) method on each sample, and the mean endometrial apoptotic index (AI) was calculated. Vitamin administration with F treatment caused endometrial MDA to decrease, but

SOD, GSH-Px, and CAT activities increased, all to significant levels. Vitamins showed a histopathological protection against F-induced endometrial damage. There was a significant difference in the apoptotic index AI between the groups. Lymphocyte and eosinophil infiltration in stroma in F-treated rats was greater than in the control and F +Vit groups. It can be concluded that oxidative endometrial damage plays an important role in F-induced endometrial toxicity, and the modulation of oxidative stress with vitamins reduces F-induced endometrial damage both at the biochemical and histological levels.

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Keywords: Apoptosis; Endometrial malondialdehyde; Oxidative stress; Rat reproduction; Vitamins C & E.

Source: Clin Exp Pharmacol Physiol 2007 May-Jun;34(5-6):467-74.

EFFECT OF FLUORIDE INTOXICATION ON ENDOMETRIAL APOPTOSIS AND LIPID PEROXIDATION IN RATS: ROLE OF VITAMINS E AND C

Fluoride is a strong binding anion and a cumulative toxic agent. In this work, the effect of fluoride intoxication on lipid peroxidation in endometrial tissue and the protective effects of combinations of vitamins E and C in rats were studied. Additionally, the apoptotic changes in endometrial tissue were examined. Experimental groups were as follows: control group; a group treated with 100 mg F/L (F group); and a group treated with 100 mg F/L plus vitamins E and C (F+Vit group). The F and F+Vit groups were treated orally with fluoride for 30 days. Vitamins E and C were injected simultaneously at doses of 50 mg/kg day intramuscularly and 20 mg/kg day body weight intraperitoneally. Extensive formation of DNA strand breaks, the typical biochemical feature of apoptosis, was detected with the use of the terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick and labeling (TUNEL) method. Malondialdehyde (MDA) levels were determined in uterine tissue of rats. Fluoride caused a significant increase in MDA levels (an important marker of lipid peroxidation) in the fluoride group compared with the controls ($p < 0.05$). Vitamins E and C significantly reduced the fluoride-induced lipid peroxidation in the F+Vit group compared with the F group ($p < 0.05$). Diffuse apoptosis in glandular epithelium and stromal cells was found in endometrial tissues of F treated rats by TUNEL method. The severity of these lesions was reduced by the administration of vitamins E and C. From these results, it can be concluded that subchronic fluoride administration causes endometrial apoptosis, and lipid peroxidation may be a molecular mechanism involved in fluoride-induced toxicity. Furthermore, treatment with a combination of vitamins E and C reduced endometrial apoptosis caused by fluoride.

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Keywords: Endometrial apoptosis; Lipid peroxidation; Malondialdehyde; Rat fluoride treatment; TUNEL detection; Vitamins A & C.

Source: Toxicology 2007 Mar 7;231(2-3):215-23.

FLUOROSIS AND ITS HEMATOLOGICAL EFFECTS

Although it has been reported that fluoride ingestion has no influence on various indices of hematopoiesis, some research has been published showing that excessive fluoride leads to anemia and eosinophilia of leukocytes. Isparta is situated on the lake region of Turkey where fluorosis is endemic. Our aim was to explore the hematological effects in rats induced by fluoride. In this study, albino Wistar rats were used, divided into two groups as control and fluorized. The control group was administered commercial water (including 0.07 ppm fluoride), and the fluorized group was administered 100 ppm fluoride in commercial drinking water for four months. At the end of four months, hematological indices (Hb, Hct, MCV, MCH, RDW, RBC, WBC, and platelet counts) were measured. In addition, bone marrow samples were investigated. Mean leukocyte counts (WBC) in the control group and fluorized group were $7.7 (2.62-12.25)$ and $2.76 (1.45-3.56) \times 10^3/\text{mm}^3$, respectively. We observed

dysplastic changes on granulocytes in the bone marrow samples of the fluorized group. Although there were significant statistical changes in WBC, we did not determine red blood cell and platelet changes in the fluorized group.

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Keywords: Fluorosis study; Hematopoiesis; Leukocyte; Rat hematology.

Source: Toxicol Ind Health 2005;21(10):255-8.

SUPPRESSION OF MALE REPRODUCTION IN RATS AFTER EXPOSURE TO SODIUM FLUORIDE DURING EARLY STAGES OF DEVELOPMENT

Sodium fluoride (NaF) was given to sperm-positive female rats throughout gestation and lactation at a dose of 4.5 and 9.0 ppm via drinking water. The neonates were allowed to grow up to 90 days on tap water, and then sperm parameters, testicular steroidogenic marker enzyme activity levels, and circulatory hormone levels were studied. The sperm count, sperm motility, sperm coiling (hypo-osmotic swelling test), and sperm viability were decreased in experimental rats when compared with controls. The activity levels of testicular steroidogenic marker enzymes (3β -hydroxysteroid dehydrogenase and 17β -hydroxysteroid dehydrogenase) were significantly decreased in experimental animals indicating decreased steroidogenesis. The serum testosterone, follicle stimulating hormone, and luteinizing hormone levels were also significantly altered in experimental animals. Our data indicate that exposure to NaF during gestation and lactation affects male reproduction in adult rats by decreasing spermatogenesis and steroidogenesis.

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Keywords: Gestation and lactation; 3β -HSD and 17β -HSD activity levels; Male reproduction; Rat fluoride study; Serum testosterone; Sperm analysis.

Source: Naturwissenschaften 2007 July;94(7):607-11.

HEALTH/BIOLOGICAL EFFECTS IN HUMANS

FLUORIDE IN DRINKING WATER: A REVIEW ON THE STATUS AND STRESS EFFECTS

According to latest estimates, around 200 million people residing in 25 nations are exposed to toxic levels of fluoride in their drinking water. China and India, the two most populous countries in the world, are the worst affected. India in particular has numerous water quality problems caused by prolific fluoride contamination of geological origin. Weathering of primary rocks and leaching of fluoride minerals in soils produce fluoride-rich groundwater generally associated with low levels of calcium and bicarbonate ions. Unfettered tapping of groundwater exacerbates the failure of drinking water sources and accelerates the entry of fluoride into groundwater. Despite claims of anticaries benefits, average fluoride concentrations as low as 0.5 and 0.7 ppm have been found in India to cause dental and skeletal fluorosis, respectively, with crippling effects often seen at higher concentrations. Nearly 37,000 habitations in India are known to be affected, and the numbers continue to increase. A close association between poverty and fluorosis occurs with malnutrition playing an aggressive role in its severity. The review cites 311 references and has 13 tables and five maps, including the occurrence of endemic fluorosis globally, in India, and in several other countries.

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Keywords: Crippling skeletal fluorosis; Dental caries; Dental fluorosis; Drinking water fluoride; Endemic fluorosis; Fluoride water; Fluorosis worldwide; Skeletal fluorosis.

Source: Crit Rev Environ Sci Technol 2006;36:433-87.

ADDITION OF MONOFLUOROPHOSPHATE TO ESTROGEN THERAPY IN POSTMENOPAUSAL OSTEOPOROSIS - A RANDOMIZED CONTROLLED TRIAL

Introduction: Treatment of osteoporosis with high-dose fluoride alone does not reduce fracture risk. We hypothesized that the anti-fracture efficacy of fluoride could be optimized by its use in low doses combined with an antiresorptive agent. **Experimental Subjects:** 80 women with postmenopausal osteoporosis who had been taking estrogen for 1 year or more. **Methods:** Subjects were randomized to receive monofluorophosphate (fluoride content of 20 mg/day) or placebo over 4 years in a double-blind trial. **Results and Discussion:** There were progressive increases in lumbar spine bone density (BMD) over the duration of the study (MFP 22%, placebo 6%, $P<0.0001$). In the trabecular bone of L3, these increases were even greater (MFP 49%, placebo 2.5%, $P<0.0001$). In the proximal femur there were smaller but significant treatment effects ($P=0.015$). Total body scans and their sub-regions also showed significantly greater increases in the MFP group. Bone formation markers increased significantly in the MFP group at year 1. Hyperosteoidosis was present in biopsies from 5 of 7 MFP subjects, with osteomalacia in 2 of 7. The hazards ratio for vertebral fractures was 0.20 (95% confidence interval 0.05-1.30) and the incidence rate ratio was 0.12 (95% confidence interval, 0.06-0.23, $P<0.01$). The hazards ratio for non-vertebral fractures was 3.3 (95% CI 0.8-12.0). **Conclusion:** We conclude that 20 mg F/day produces substantial increases in BMD but still interferes with bone mineralization. This indicates that most previous studies with this ion have used toxic doses, and that much lower doses should be assessed to find a safe dose window for the use of this powerful anabolic agent.

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Keywords: Double blind trial; Fluoride; Humans; Hyperosteoidosis; Monofluorophosphate; Osteomalacia; Osteoporosis; Postmenopausal osteoporosis; Vertebral fracture.

Source: J Clin Endocrinol Metab. 2007 Apr 17; [Epub ahead of print]

APOPTOTIC STUDY ON THE EFFECT OF FLUORINE AND SELENIUM ON THE HUMAN HAIR FOLLICLE IN VITRO

Objective: The aim of this study was to observe the status of human hair follicle apoptosis affected by fluorine and the antagonism effect by selenium *in vitro*. **Method:** Single hair follicles were separated and cultured. They were then added in different concentrations to sodium fluoride and sodium selenite. After choosing the appropriate concentrations, the follicles were divided into seven groups. The TUNEL method was used to investigate the apoptotic cells of different groups. The morphosis of hair follicles was observed consecutively by electron microscopy. **Results:** We found that in 1 mmol/L and 10 mmol/L sodium fluoride groups, when the human hair follicles *in vitro* were cultured on the 5th day, the apoptotic cells of outer root sheath (ORS), dermal sheath, and hair papilla and hair bulb were evidently increased. But 0.01 mmol/L sodium selenite weakened the toxicity of 1 mmol/L sodium fluoride at the outer root sheath and hair bulb ($P<0.05$). **Conclusions:** Different concentrations of sodium fluoride had different effects on the growth of human hair follicle cultured *in vitro* cultured on 5th day. Sodium fluoride at certain concentration can accelerate apoptosis of the human hair follicle *in vitro*. Sodium selenite at certain concentration acted antagonistically to the toxicity of sodium fluoride.

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Keywords: Apoptosis; Human hair follicle; Sodium fluoride; Sodium selenite.

Source: Zhonghua Zheng Xing Wai Ke Za Zhi. 2007 Jan;23(1):59-61. [in Chinese]

IMPACT OF ANTIOXIDATIVE THERAPY ON THE ACTIVITY OF SALIVARY GLUTATHIONE-DEPENDENT ENZYMES IN PATIENTS WITH FLUOROSIS

Fluorosis caused by long-term intake of high fluoride levels is characterized by clinical bone and tooth manifestations. The adverse impact of high fluoride intake is also observed in

soft tissues. Although fluorosis is irreversible it can be prevented by appropriate and timely interventions through understanding the process at biochemical and molecular levels. Increased production of reactive oxygen species (ROS) and lipid peroxidation are considered to play an important role in the pathogenesis of chronic fluoride toxicity. Saliva as a biological fluid of the human organism may reflect the metabolic state. Salivary indices are clinical diagnostic indicators. The purpose of this investigation was to make a comparatively study of the salivary antioxidative defense system, including glutathione, glutathione reductase, glutathione-S-transferase, and glucose-6-phosphate dehydrogenase in adult patients with fluorosis before and after complex antioxidative therapy. Analysis indicated that there was a negative correlation between the level of glutathione and the clinical characteristics of the disease in patients with fluorosis. There was a direct relationship between the activity of glutathione-S-transferase and clinical manifestations in the patients. These results reflected dose-dependent fluoride intoxication and metabolic imbalance. The imbalanced salivary antioxidative defense system was in part corrected by complex antioxidative therapy.

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Keywords: Antioxidative therapy; Fluoride toxicity; Glucose-6-phosphate dehydrogenase; Glutathione-dependent enzymes; Salivary indices. Source: *Klin Lab Diagn.* 2007 Jan;(1);22:35-7. [in Russian].

DOSE-EFFECT RELATIONSHIP BETWEEN DRINKING WATER FLUORIDE LEVELS AND DAMAGE TO LIVER AND KIDNEY FUNCTIONS IN CHILDREN

Although a dose-effect relationship between water fluoride levels and damage to liver and kidney functions has been reported in animals, it apparently has not been clearly demonstrated in humans. To evaluate the effects of drinking water fluoride levels on the liver and kidney functions in children with and without dental fluorosis, we identified 210 children who were divided into seven groups with 30 each based on different drinking water fluoride levels in the same residential area. We found that the fluoride levels in serum and urine of these children increased as the levels of drinking water fluoride increased. There were no significant differences in the levels of total protein (TP), albumin (ALB), aspartate transaminase (AST), and alanine transaminase (ALT) in serum among these groups. However, the activities of serum lactic dehydrogenase (LDH), urine N-acetyl-beta-glucosaminidase (NAG), and urine gamma-glutamyltranspeptidase (gamma-GT) in children with dental fluorosis and having water fluoride of 2.15–2.96 mg/L and in children having water fluoride of 3.15–5.69 mg/L, regardless of dental fluorosis, were significantly higher than in children exposed to water fluoride of 0.61–0.87 mg/L in a dose-response manner. In contrast to children with dental fluorosis and having water fluoride of 2.15–2.96 and 3.10–5.69 mg/L, the serum LDH activity of children without dental fluorosis but exposed to the same levels of water fluoride as those with dental fluorosis was also markedly lower, but the activities of NAG and gamma-GT in their urine were not. Therefore, our results suggest that drinking water fluoride levels above 2.0 mg/L can cause damage to liver and kidney functions in children and that dental fluorosis was independent of damage to the liver but not the kidney. Further studies on the mechanisms and significance underlying damage to the liver without dental fluorosis in the exposed children are warranted.

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Keywords: Children; Dental fluorosis; Drinking water; Fluoride; Kidney function; Liver function; Serum enzymes; Urine enzymes.

Source: *Environ Res* 2007 Jan;103(1):112-6.