Biological Markers of Fluoride Exposure: A Review Article

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Biological markers or biomarkers act as indicators that signal events in biological systems (human body) or samples. The concept of biological markers of fluoride exposure came to prominence in the 1994 Technical Report on Fluorides and Oral Health. The WHO stated that a fluoride biomarker was of value primarily for identifying and monitoring deficient or excessive intakes of biologically available fluoride. Knowledge of fluoride availability during pre-eruptive periods of tooth formation allows assessment of the potential for later development of fluorosis while knowledge of its availability post-eruptively provides a guide to the potential level of protection from caries. Contemporary biological markers assess present, or very recent, exposure to fluoride, fluoride concentrations in blood, bone surface, saliva, milk, sweat, and urine have been considered. The most studied recent biomarkers are nails and hair. Both can be non-invasively obtained, although collection of nails is more accepted by the subjects. During the last two decades, there has been a rapid expansion in the availability and use of biomarkers in health care such that they now occupy a central position in the armamentarium of the clinician for screening, diagnosis, and management of the disease. Here, an attempt is made to review biomarkers of fluoride exposure.

Keywords: Biomarkers, Bone, Fingernail, Fluorosis

INTRODUCTION

Biological markers or biomarkers are defined as indicators that signal events in biological systems (human body) or samples. The biomarker is not used as diagnosis test but as an indicator of a disease or biological alteration. Biomarkers of fluoride can be arranged according to two classifications. The Committee of Biomarkers of the National Research Council divided biomarkers into biomarkers of: (1) Effect, (2) susceptibility, and (3) exposure; while the World Health Organization proposes a time-perspective classification, in which biomarkers are divided into: (1) Historical, (2) contemporary, and (3) recent markers. The present review will adopt the WHO criteria and will focus on recent (nails and hair) and historical (bone and teeth) biological markers of exposure to fluoride.

The biomarker of exposure is a substance of external origin or a metabolic derivate or the product of interaction between a biological agent and molecules. The biomarker of susceptibility is an indicator that the individual is particularly sensitive to the effect of a substance and for the fluoride, this can be a form of understanding the variation of individual dose-response for the same exhibition pattern to fluoride. The biomarkers of effect are the consequences of a previous exhibition: Dental or skeletal fluorosis.

In spite of the constant use of some biological materials as plasma and saliva in dental research, the use of these materials in pharmacokinetics models for biomarkers of exposure is still limited. One of the advantages in using biomarkers model is the possibility to simplify the collection, storage, and analysis of samples. In spite of the fact that fluoride biomarkers are regarded as important auxiliaries in the evaluation of dental fluorosis risks, it is important recognizing that the biomarker model is in a developmental phase.¹ To maximize health benefits, there has to be a balance between too little fluoride (with increased risk of dental caries and its sequelae) and too much fluoride (with increased risk of fluorosis). The “therapeutic ratio” is relatively low - the space between the two disbenefits (insufficiency and excess) is small. It is, therefore, very desirable to know what the body burden of fluoride is to assess the risk/benefit ratio and maximize benefit and minimize disbenefit.²

CONTEMPORARY MARKERS

Contemporary biomarkers might be fluoride concentrations in blood, bone surface, saliva, milk, sweat, and urine. Fluoride
toxicity can be “acute” or “chronic” - The former involving a very recent high or very high dose of fluoride, while the later might occur after modest yet excessive ingestion over a longer period. Biomarkers are needed for both situations - present exposure being assessed by “contemporary” biomarkers, while more chronic fluoride exposure might be assessed by “recent” or “historic” biomarkers.3

**Blood**
It is usual to report fluoride concentration in plasma, rather than in whole blood or serum. Blood cells contain about half the fluoride concentration recorded in plasma. Arguments for selecting plasma include: (1) Plasma concentration establishes interstitial and intracellular fluoride concentrations in soft tissues and (2) plasma is the fluid from which fluoride is filtered into the nephron. While both ionic and non-ionic fluoride forms exist in plasma, the ionic form is of far greater significance, and it is detectable by the ion specific electrode. When interpreting plasma fluoride concentration information, it is important to be aware that several factors, independent of fluoride dose, influence the concentration value. These include: Site of blood collection, age, acid-base balance, altitude, hematocrit and genetic background. The effects of circadian rhythm and hormones are rather discrete. Of these, site of blood collection, age, and hematocrit have the most influence. It is advisable to collect venous or capillary blood. Plasma fluoride concentration increases with age, and this is likely to be a reflection of increasing bone fluoride concentration with age. Hematocrit values are likely to be lower in females than males. Plasma fluoride concentration returns to the resting value about 3-6 h after ingestion of a small fluoride dose; the half-life is about 30 min. For less than optimal water intake, the resting fluoride concentrations, the resting fluoride concentrations ranged from 9.3 to 24.0 ng/ml (0.49-1.26 umol/l).4

**Sweat**
Early work suggested that the concentration of fluoride in sweat was substantial: McClurc et al., reported 0.3-1.8 mg/L, Crosby and Shepherd 0.3-0.9 mg/L, and Largent 0.3-0.9 mg/L. However, estimates made after the introduction of the ion-specific electrode were very much lower. Even after ingesting 10 mg fluoride, which raised plasma concentration to 0.2-1 mg/L (12.6 umol/ml), the concentration in sweat was only about 0.05 mg/L (2.6 umol/L). In a brief summary, Whitford stated that fluoride concentrations in sweat were similar to concentrations in plasma (1-3 umol/L; 0.019-0.057 mg/L; and 19-57 ng/ml). Presently, issues of collection, including, contamination and lack of supporting data, preclude the use of sweat as a viable marker of contemporary fluoride exposure.5

**Urine**
Urinary fluoride is considered a contemporary biomarker of fluoride exposure since varying proportions of a given fluoride dose are completely excreted with the urine in <24 h in children and adults.6

Both urinary flow and pH are involved in regulating renal clearance of fluoride from blood.3 Urinary fluoride concentrations obtained from single “spot” samples are the most accessible indicator of fluoride exposure. However, more concentrations are not a reliable marker. Fluoride may be diluted by high urinary flow, or high concentrations may occur when little fluid is drunk, resulting in the low urinary flow. Basically, urinary fluoride concentrations do not provide a direct measure of fluoride excreted via urine. However, urinary excretion does correlate very well with the plasma fluoride concentration,4 which is regarded as the most valid indicator of the fluoride supply to the organism. Research has found that for persons living in temperate climates the concentration of fluoride in urine is similar to its concentration in those persons’ drinking water. The range of urine fluoride concentrations according to Baez et al., observed throughout the 24-h period of their study was, 1.26-1.42 mg/L, confirms this rule for both daytime and nocturnal urine. Regarding the amount of fluoride excreted per hour, the nocturnal mean was less than the excretion in the morning and the afternoon. This finding is in keeping with the fact that glomerular filtration rate is a very important determinant of fluoride excretion, albeit not the only one. Urinary excretion of fluoride can be considered as a short-term indicator of fluoride exposure.2,10

**RECENT MARKERS**

**Nails and Hair**
Among the short- and long-term biomarkers studied, nails seem to be promising both for acute, subchronic, and chronic exposure to fluoride. Nail sampling has some advantages since samples can be accessed and collected in a non-invasive manner, besides the possibility of storage for long periods of time without degradation. Furthermore, the concentration of fluoride reflects the average level of intake and plasma concentration over a protracted period, in contrast to the analysis of urine, plasma, or ductal saliva, whose fluoride concentrations are more like “snapshots,” and therefore, subject to change due to recent fluoride intake and certain physiological variables. Finally, fingernail concentrations are not affected by variables such as fluoride intake within the last few hours or differences in glomerular filtration rate, urinary pH, or urinary flow rate. Such advantages make the analysis of fingernail clippings an attractive alternative to other body fluids or tissues for the purpose of monitoring fluoride exposure.5 Nails grow at about 0.1 mm/day so the average level of fluoride intake over a 1-3 weeks period can be estimated.4 Nails have been used as biomarkers of exposure to fluoride and recent data from a longitudinal study revealed that children with caries...
Fluoride in hair could be used to estimate intake over longer periods. Refinements of the sampling methods for these human tissues and improved testing technology are needed. Additional research should clarify the physiological factors that can influence fluoride uptake and accumulation in these tissues. The Authors evaluated the use of fingernails and toenails as biomarkers of subchronic exposure to fluoride (F) from fluoride dentifrice (FD) in 2-3 years old children. Ten children, 2-3 years old, used a placebo dentifrice (without F) for 28 days, FD (1,570 ppm F as monofluorophosphate) for the following 28 days, and then placebo dentifrice for an additional 28 days, then returned to their usual dentifrices. Fingernails and toenails were clipped every 2 weeks, during the experimental period and for an additional 22 weeks. Nail F was analyzed by electrode following hexamethyldisiloxane-facilitated diffusion. There were no significant differences between the fingernail and toenail F concentrations. Mean peak F concentrations occurred 16 weeks after starting the use of FD. Results suggest that fingernails and toenails may be suitable biomarkers of subchronic exposure to F from FD in small children.

HISTORIC MARKERS: BONE AND TEETH

The body burden of fluoride is best reflected in the calcified tissues though enamel is not the tissue of choice because most of its fluoride were taken up during tooth formation. After tooth eruption, exposure to widely fluctuating concentrations of fluoride in the oral cavity significantly affects fluoride levels in the surface layers of enamel, where the highest concentrations of fluoride are found. The fluoride concentrations of dentin are similar to those of bone and, as in bone, they tend to increase over the years provided that fluoride intake does not decline. Dentin, especially coronal dentin, may be the best marker for the estimation of chronic fluoride intake and the most suitable indicator of the body burden. The tissue does not normally undergo resorption, it is more easily obtained than bone, it seems to continue accumulating fluoride slowly throughout life, and it is permeated by the extracellular fluid. Dentin is usually protected from exposure to fluoride in the oral cavity by the covering enamel or cementum.

Bone fluoride concentrations are much better indicators of long-term fluoride exposure and body burden though fluoride is not uniformly distributed throughout bone. For example, cancellous bone has higher fluoride concentrations than does cortical bone. Bone is more studied, but its fluoride concentrations vary according to the type of bone and subjects’ age and gender. They are also influenced by genetic background, renal function and remodeling rate, variables that complicate the establishment of a normal range of fluoride levels in bone that could indicate “desirable” exposure to fluoride. The main issue when attempting to use bone as biomarker of fluoride exposure is the difficulty and invasiveness of sample collection. In this aspect, collection of dentin, especially from 3rd molars that are commonly extracted, is advantageous. However, mean values also span a wide range and reference concentrations have not been published yet.

FLUOROSIS AS A BIOMARKER

Epidemiological studies by Dean and colleagues in the 1940s clearly demonstrated the relationship between dental fluorosis in humans and the level of fluoride in water supply. Studies suggest that fluorosis can be used as a biomarker for the level of fluoride exposure though dental fluorosis is a reflection of fluoride exposure only during the time of enamel formation. For example, an increased level of fluorosis in both fluoridated and non-fluoridated communities has been used to indicate increased exposure to fluoride in these communities, despite constant fluoride levels in the drinking water. This increased exposure to fluoride was found in part to result from unintentional ingestion of topical fluorides, underlining the value of using fluorosis as a biomarker. There are several limitations in the use of fluorosis as a biomarker for the amount of fluoride exposure.

1. Useful only for exposure to children <7 years of age
2. Varies with timing of exposure
3. Varies with duration of exposure
4. Varies with the level of exposure

Current human and animal studies seem to indicate a degree of individual variability in response to the effects of similar doses of fluoride. Therefore, it does not appear possible to use enamel fluorosis alone as a biological marker to indicate the level of fluoride exposure for an individual. However, with a known fluoride history, it may be possible to use enamel fluorosis as a biological marker indicating an individual response to fluoride. However, dental fluorosis is a reflection of fluoride exposure only during the time of enamel formation, somewhat limiting its use as a biomarker. In addition, the degree of fluorosis is dependent not only on the total fluoride dose but also on the timing and duration of fluoride exposure. At the level of an individual response to fluoride exposure, factors such as body weight, activity level, nutritional factors, and the rate of skeletal growth and remodeling are also important. These variables, along with individual variability in response to similar doses of fluoride, indicate that enamel fluorosis cannot be used as a biological marker of the level of fluoride exposure for an individual.

CONCLUSIONS

Recent total fluoride exposure of individuals or populations is most reliably monitored by assessing fluoride levels in
plasma or markers available by non-invasive methods, preferably urine, and ductal saliva. Clinical dental fluorosis is the most convenient biomarker, but it only records the effects of ingestion of fluorides in the first 6 years of life. Dental hard tissues are suitable biomarkers for long-term monitoring of fluoride intake during defined periods of life, whereas bone provides information of exposure over decades or a lifetime. Concentrations of fluoride in hair and nails as potential biomarkers for exposure during recent weeks merit further study.

REFERENCES


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