

## Adverse effects of fluoride towards thyroid hormone metabolism

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### ABSTRACT

An easily ionized fluoride compound like Sodium Fluoride (NaF) has been used thus far as a dental caries prevention substance. However, fluoride ions also have a negative effect because it is very toxic. Several researches on the effect of fluoride on guinea pigs and human beings indicate the presence synthesis obstruction of T3 and T4 that causes declined production, known as hypothyroidism. Hypothyroidism condition may obstruct tissue growth process and metabolism so as to impact various body organ systems. Preventive efforts against hypothyroidism caused by fluoride include avoiding diffusible fluoride compound intake, like NaF, in a long run systemic use, whereas efforts to overcome fluoride intoxication include consuming food that is rich in calcium, vitamin D, and antioxidant.

**Key words:** Fluoride, T3 synthesis, T4 synthesis, hypothyroidism

### INTRODUCTION

The use of fluoride either topically or systemically in dentistry is believed to prevent caries because it can impede plaque bacterial metabolism. A research performed to a population that usually consumes fluoride systemically (fluoridated water) with a level of 1 ppm (1 mg/L = 1 µg/mL = 0.0001% = 1 ppm {parts per million}) show that this level creates adverse effects to the thyroid gland. In addition, the adverse effects can also be seen in the nervous system, enzymes, immune system, genetic information, reproductive system, kidney, heart and digestive tract.<sup>1</sup>

Iodine is an essential element for the thyroid gland. The thyroid hormones like thyroxine has four iodine atoms m (T<sub>4</sub>) and triiodotironin has three iodine atoms (T<sub>3</sub>). The iodine transport

mechanism can be impeded by several anions that will compete with iodine to get its protein carrier. One of the anion is the fluoride that can build fluoborate (BF<sub>4</sub><sup>-</sup>), fluosulfonate (SO<sub>3</sub>F<sup>-</sup>), or difluophosphate (PO<sub>2</sub>F<sub>2</sub><sup>-</sup>) compounds that are known as antithyroid medicine. The shape of fluoride is similar to iodine because both are included into the halogen group. Fluoride can impede active transport of iodide ions into the thyroid gland.<sup>1,2</sup>

If the Iodine intake in food is decreased into less than 10 µg/day, the thyroid hormone synthesis will not be adequate and the secretion will be decreased and may eventually lead to hypothyroid. From those information it is known that the systemic used of fluoride may cause thyroid gland hypofunction. If someone is born without these hormones, a mental and physical development disorder such as dwarfism in children will occur.<sup>3</sup>

## **Overview of fluor and fluoride**

Fluoride is a toxic agent due to its reactivity with living cell molecule that affect the molecule form and cell function. The fluoride compound include two types, diffusible and non diffusible which is also non absorbable. The diffusible preparation often used in dental care products are NaF, HF,  $H_2SiF_6$ , and  $Na_2PO_3F$ . Meanwhile the non diffusible preparation include, among others,  $CaF_2$ ,  $MgF_2$ , and  $AlF_3$ . The more diffusible the preparation, the easier it is to be ionized except for  $Na_2PO_3F$  preparation that should be hydrolyzed first by an enzyme and then absorbed and enter the systemic circulation.<sup>4</sup>

The fluoride concentration in food and drink that we consume everyday rarely reaches 1 ppm concentration except for seafood and tea. In various types of dental treatment at home, fluoride concentration can reach 250-22.500 ppm.<sup>4</sup>

Fluoride use can be divided into two main subjects, i.e. topical application that we can found in toothpaste or mouthwash and systemic preparation such as drinking water fluoridation or fluoride tablet use. There are a lot of clinical experiments that show the effectiveness of fluoride topical application in reducing the caries incidence. The fluoride use shows a DMF reduction up to 50%.<sup>4</sup>

The fluoride tablet usually takes the form of sodium fluoride, phosphate fluoride, potassium fluoride and calcium fluoride. Sodium fluoride (NaF) as a topical preparation has several advantages such as chemically stable, acceptable taste, does not irritate the gingivals, and does not color the teeth as well as, surely, reduce the risk of caries. In toothpaste, the preparation usually used is the sodium monofluorophosphate ( $Na_2PO_3F$ ).<sup>4,5</sup>

Fluoride will form fluoroapatite crystal that increase enamel strength to fight acid influence that makes it more insoluble. The fluoroapatite crystal is formed because the  $OH^-$  ion in the hydroxyapatite crystal of enamel is replaced by  $F^-$  ion that the crystal structure becomes more stable. This will strengthen the hydrogen bond. In addition, fluoride can also increase the crystal size to make it stand the acid more. Three fluoride principal mechanisms happen in terms of preventing caries such as: In the pre-eruption period, fluoride reduces enamel solubility in acid condition due

to its combination with hydroxyapatite crystal. In the post eruption period, fluoride improves remineralization and prevent demineralization. Fluoride impedes bacterial metabolism activity in glycolysis.

The proof of remineralization is shown by the re-strengthening of soften enamel caused by acid influence in vitro. This remineralization process is the most effective when the enamel experience mild demineralization such as small caries lesion characterized by white spot.<sup>4</sup>

The risk of fluoride overdose is very small. However, actions should be taken promptly when it happens. Based on the frequency of fatal fluoride intoxication, it is expected that the lethal dose of fluoride is 32-64 mg per kilogram weight in adults. If 1 mg dose per kilogram weight is given, some gastrointestinal disorders will appear (nausea, hypersalivation, stomach ache, vomiting, and diarrhea).<sup>4,5</sup>

## **Histology of thyroid gland**

Follicle consists of one epithelial layer that covers a space that is, commonly, filled by a type of rigid gel called colloid. The shape of the cell is various but it is usually cuboid. The cell height is low when the gland is hypoactive and high if it is hyperactive. The cell height in each follicle is uniform and it is neatly arranged. The lower part of the cell is situated on a thin basal lamina. The big and vesicular nucleus is located in the middle or towards the base of the cell. The cytoplasm is basophile with fine granules, mitochondria, granular endoplasm reticulum and lysosome inside. The lipid granules and other inclusions including the colloid granules are found in the cytoplasm of some cells. The follicular complex is a face-to-face cell surface form and the free surface includes fine microvilli that can be seen by electron microscope. Some cells have cilia.<sup>6</sup>

Colloid fills the follicular lumen and has the characteristic of homogenous, clear and thick. Spaces are often found between the colloid and the epithelium. The unorganized arrangement is a feature of the colloid condition that is often found in the active gland. Basophilic colloid is found in the active follicle while the weak basophilic or acidophilic colloid is found in the non active follicle.<sup>6</sup>

### **Physiology of thyroid gland**

The thyroid hormone plays a role in increasing the cell metabolism pace that it can speed up the oxygen use (calorigenic effect) and increase the amount of metabolism end product. This will lead to vasodilatation that will increase blood flow and heart flow, frequency, rate, volume and arterial pressure. The function of thyroid hormone is to improve digestive activity, neural system, muscle and other endocrine organs.<sup>3</sup>

### **Thyroid hormone metabolism**

The function of thyroid is regulated by thyroid stimulating hormone (TSH = Thyrotropine) from the anterior hypophysis. The first stage in the thyroid hormone formation is the oxidation of iodide ion that will bind the amino tyrosine acid. The iodide oxidation process is improved by the hydrogen peroxide that is attached to the apical part of the cell membrane which position the iodide right in the place of thyroglobulin molecule that initially expelled and then enter the colloid.<sup>3</sup>

The iodine binding with the thyroglobulin molecule is called the thyroglobulin organification. The iodine will bind with approximately one sixth of the amino acid from thyroglobulin with the help of the iodinase enzyme. The thyroid hormone formation is started by the iodization of tyrosine into monoiodotyrosine and then diiodotyrosine. Then, for several minutes, hours and days after, diiodotyrosine and monoiodotyrosine will couple to each other by expelling the alanine chain that change the tyrosine into thyronine. The result of this coupling reaction is the formation of thyroxin and triiodotyronine hormones which are still part of the thyroglobulin molecule. In the thyroid hormone secretion, there is 1 molecule of triiodotyronine in average for each 14 thyroxin molecules. The thyroid hormone is kept in the follicle in an amount that is sufficient for 2 to 3 months. Therefore, if the hormone synthesis is stopped, the effect of hormone deficiency will not be observable for several months.<sup>6</sup>

Thyroxin and triiodotironine are divided from the thyroglobulin molecule and these free hormones are then released into the blood stream. This process are as follow: the apical surface of the thyroid cell extends pseudopodia surrounding a small part of the colloid that forms a vesicle that enters the apical part of the thyroid cell in a

process that is called pinocytic endocytosis. Then this will combine with the lysosome to form a digestive vesicle that contains digestive enzymes from the lysosome that have been mixed with the colloid. The proteinase found among these enzymes will digest the thyroglobulin molecule and release the thyroxin and triiodotironin that will diffuse through the basal part of the cell to the surrounding capillaries. The amount of blood flow each minute is about five times higher than the weight of the thyroid gland itself.<sup>6</sup>

### **Hyperthyroidism**

Thyrotoxicosis is a hypermetabolic state due to the excess of active thyroid hormone in the tissue. When the excessive amount is caused by the thyroid hyperfunction or a tumor, it is called hyperthyroidism. The clinical symptoms of thyrotoxicosis include nervousness, menstruation disorders, unstable emotion, subtle tremor of the hands, hot and damp skin, cannot stand heat, decreased weight, increased appetite and decreased strength. The cardiopulmonary disorders are often prominent, these including difficulty to breathe, fast pulse, palpitation and in severe thyrotoxicosis a heart failure may happen.<sup>7</sup>

### **Hypothyroidism**

Hypothyroidism can be classified as a primary disorder if it is caused by a pathological process that destroy the thyroid gland or a secondary disorder if it is caused by the deficiency of TSH hypophysis secretion. When the lack of hormone is found in children, it may induce cretinism. Several hypothyroidism cases show atrophic thyroid gland or no gland due to surgery, radioisotope ablation, and destruction by autoimmune antibody or growth disorders. The clinical manifestations of hypothyroidism in adults and juvenile include fatigue, coarse voice, cannot stand cold, less sweat, cold and dry skin, swollen face, slow movement, slow motor activity and intellectual and delayed reflex.<sup>7</sup>

### **Changes in thyroid hormone level due to excessive fluoride intake**

Susheela et al.<sup>8</sup> has performed a research to 90 7-18 year old children who live in a fluoride endemic and receive sufficient iodine intake. The drinking water contains 1.1 to 14.3 ppm fluoride

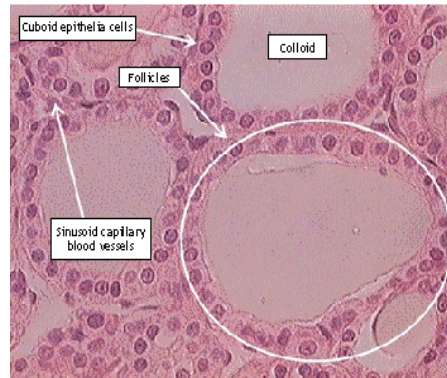


Figure 1. Histology of thyroid gland.

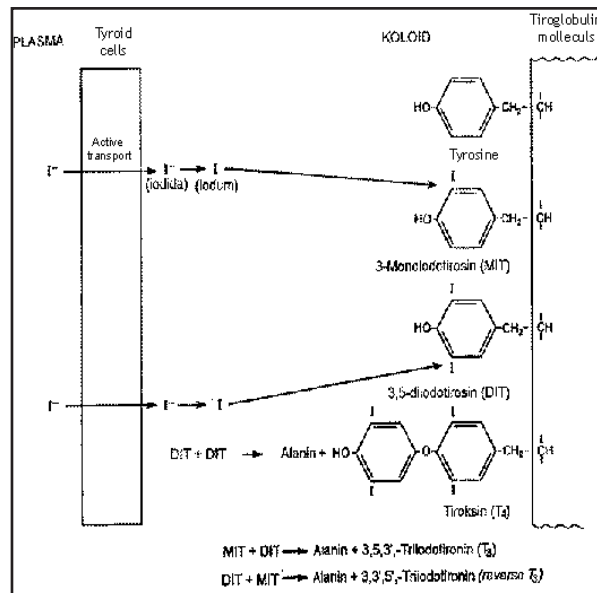


Figure 2. Scheme for thyroid hormone biosynthesis.

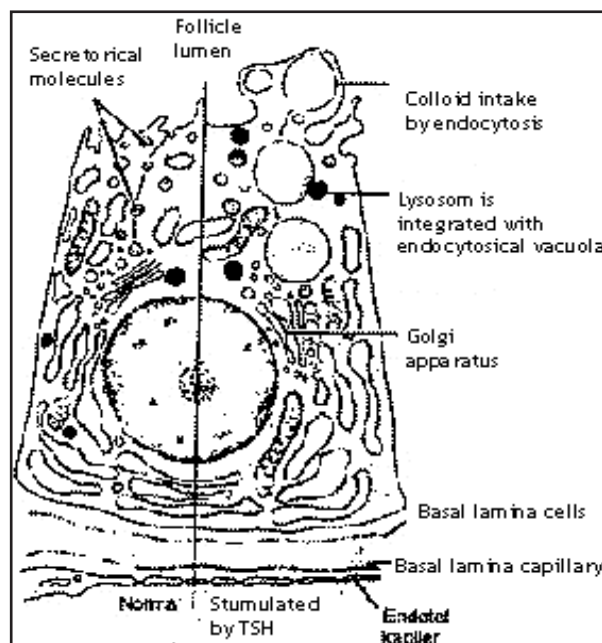


Figure 3. TSH-induced follicular cell.

level (average 4.77 ppm). The results of the observation show that the fluoride level in the blood is 0.02 to 0.41 ppm (average 0.14 ppm) and the urine fluoride level is 0.41 to 12.88 ppm (average 3.96 ppm).<sup>8</sup>

The hormone status of the 90 children shows a change in the hormone level in 49 children (54.4%) and there are 41 children in normal border. The variation of hormone level change in 49 children is categorized into five categories: T4 and T3 normal with high TSH (46.9%); T4 and TSH normal with low T3 (32.7%); T4 normal with TSH and high T3 (14.3%); T3 normal, high TSH, and low T4 (4.1%); T4 normal, high TSH, and low T3 (2%).

The results of this research show that children who are exposed to excessive fluoride may experience changes in the thyroid hormone level. The average thyroid hormone change shows a higher TSH, normal T4, and changing T3 levels.<sup>8</sup>

#### **The effect of fluoride on thyroid gland and on the development of young rat's cerebellum**

Trabelsi et al.<sup>9</sup> had done a research on adult female Wistar Strain rats. The rats were treated with a diet of  $0,72 \pm 0,012 \mu\text{g}$  iodine and NaF 0,5g/l (500 ppm) which are dissolved in their drink since 15 days of pregnancy to 14 days after the birth.

The result of the research shows that the treated young rats experience 35% weight loss, 75% decrease of thyroxin level in the blood, 27% decrease of protein in the cerebellum, and 17% decrease of protein in cerebrum. Histologically, cerebellum consists of three layers: internal granular, molecular, and external granular layers. The treated rats show a decrease in external granular layer. They also show lesser amount of the purkinje cells differentiating into internal granular layer, and apoptosis of purkinje cells increases.<sup>9</sup> The decrease in thyroxin level on treated young rats influences the growth hormones and it causes rats to loose weight. Lack of thyroid can affect functional activities of central nerve system. It can be proven by the decrease of protein content in the cerebrum and cerebellum. Most of the cells in cerebellum are formed after birth. Fluoride is proven to influence cells proliferation in cerebellum external granular layer. The damage in the external granular layer that is caused by fluoride can be indicated by neuron movement to molecular and internal granular layers.<sup>9</sup>

The increase of apoptosis on the treated rats indicates that some granular cells died because they cannot contact the purkinje cells. Purkinje cells are very sensitive to the absence of thyroid.<sup>9</sup>

#### **The effect of fluoride on thyroid gland growth and function in young pigs**

Zhan et al.<sup>10</sup> had done a research on 32 fifty-days-old pigs, each weighed 17 kg. The pigs were divided into three sample groups, 8 pigs on each group. The pigs in each group were treated by a fluoride diet that contains 100, 250, and 400 mg/kg NaF for 50 days. The comparison with 8 controls treated with 6.2 mg/kg fluoride shows weight and T4 decrease, and TSH increase. However, there is no significant change in T3.<sup>10</sup>

Iodine accumulation in thyroid gland is caused by Na/K-ATPase and Na/I symport. Inhibition of Na/K-ATPase activities by fluoride causes iodine level decrease in thyroid gland.<sup>10</sup> From this research, it can be concluded that thyroid hormone plays an important role in regulating growth, differentiation, and metabolism in almost all of the tissues. Thyroid gland is one of the organs that are very sensitive to fluoride, particularly in its histology and function. Excessive fluoride intake can cause growth retardation and hypothyroxinemia in pigs, and can change the level of thyroid hormone as in iodine deficiency condition.<sup>10</sup>

#### **The level of thyroxin, triioditronine, and iodine binding protein in cows that develop fluorosis**

Cinar and Selcuk<sup>11</sup> had done a research on 20 cows that developed chronic fluorosis in a volcanic area of Tendurek that is located 2000 m from the sea surface, in East Anatolia, Turkey. The research was done in the volcanic area because this area has a high level of fluoride, and a fluorosis endemic has occurred for a long time in this area. Fluoride level in the volcanic area ranges from 5.7 to 15.2 ppm, which particularly influences on milk-producing cows. The high level of fluoride causes fluorosis, thyroid dysfunction, growth retardation, and decreased milk production.<sup>11</sup>

Twenty Tendurek-cows which are older than three years were compared with ten healthy control cows of the same age. The T3 and T4 levels were measured by RIA (radioimmunoassay).

Table 1. The comparison of weight increase in pigs with 50 days fluoride treatment<sup>10</sup>

	Group			
	1	2	3	4
Weight (before) (kg)	17.16	17.25	17.18	17.31
Weight (after) (kg)	42.85	40.93	39.08	38.41

Note: The values above are the average weight of eight pigs in each group. Group 1, 2, 3 and 4 are treated by fluoride with a level of 6.2, 100, 250, and 400 NaF mg/kg weight, respectively.

Table 2. The comparison of T3, T4, TSH level of the pigs with 50 days fluoride treatment<sup>10</sup>

	Group			
	1	2	3	4
T3 (ng/mL)	0.66	0.60	0.61	0.57
T4 (ng/mL)	35.93	29.44	28.30	27.88
TSH (µIU/mL)	0.98	0.91	1.31	1.32

Note: The values above are T3, T4, and TSH average level of eight pigs on each group. Group 1, 2, 3 and 4 are treated by fluoride with the level of 6.2, 100, 250, and 400 NaF mg/kg weight, respectively.

Table 3. The comparison of Na/K-ATPase and TPO levels of the pigs with 50 days fluoride treatment<sup>10</sup>

	Group			
	1	2	3	4
Na/K-ATPase (µmoles P <sub>i</sub> /mg/h)	0.92	0.76	0.74	0.72
TPO (GU/mg)	0.52	0.55	0.39	0.34

Table 4. The comparison of T4, T3, and pbi levels in healthy cow serum and fluorosis cow serum<sup>11</sup>

	T4 µg/dL	T3 ng/mL	PBI µg/d
Control	5,7±0,48	1,53±0,038	3,8±0,29
Sample	3,7±0,45	0,97±0,051	2,6±0,23
Range of normal value	4,2 - 8,6	1,4 - 4	2,7 - 4,1

Note: The values above are Na/K-ATPase and TPO average level of eight pigs in each group. Group 1, 2, 3, and 4 are treated by fluoride with the level of 6.2, 100, 250, and 400 NaF mg/kg of weight, respectively.

The PBI (protein-bound iodine) level was measured using spectrophotometer.<sup>11</sup>

The result of the research shows the decrease of T4, T3, and PBI in the serum. This result is consistent with the result of the research on the other experimental animals, such as sheep and rat. Supposedly, the decrease of T3, T4, and PBI level is because of: Absorption inhibition of

iodine and some amino acids such as tyrosine in digestive tube. Lack of synthesis and secretion of oxidized tiroglobulin and iodine in thyroid gland. Lack of iodine intake in Tendurek-cows.

### Long-term effects of various doses of fluoride and iodine on the damages in thyroid gland and on fluorosis in rats

Zhao et al.<sup>12</sup> had done a research using nine kinds of drinking water, with different iodine and fluoride levels. Iodine used in this research was potassium iodide (KIO<sub>3</sub>) and fluoride supply used was sodium fluoride (NaF). Iodine and fluoride levels used in the research were: ID (Iodine Deficiency) with 0 µg/l iodine level. IN (Iodine Normal) with 20 µg/l iodine level. IE (Iodine Excess) with 2500 µg/l iodine level. FD (Fluoride Deficiency) with 0 mg/l fluoride level. FN (Fluoride Normal) with 0.6 mg/l fluoride level. FE (Fluoride Excess) with 30 mg/l fluoride level.

Two hundred eighty eight male rats were divided into 9 groups, 32 rats in each group. Afterwards, 9 mixtures of iodine and fluoride were made, such as: ID+FD, ID+FN, ID+FE, IN+FD, IN+FN, IN+FE, IE+FD, IE+FN, and IE+FE. From 32 rats in each group, 16 rats were treated for 100 days and the rest were treated for 150 days.<sup>12</sup>

The result of the research shows that in either ID or IE conditions, the rats can develop goiter. FE condition can increase fluoride level in bone and tooth. Adding ID or IE to fluoride can also affect the activity of thyroid gland. In 100 day-treatment, fluoride shows the tendency of the hormone T3 secretion inhibition in ID and IE conditions, and a slight effect of stimulation in IN condition. Meanwhile, for T4 hormone secretion in 100 day-treatment, FE gives stimulation effect on the secretion.<sup>12</sup>

In 150 day-treatment, fluoride shows a contrary effect compared to the 100 day-treatment. Fluoride can increase iodine uptake in 100 day-treatment, but the uptake is inhibited when given the same dose in 150 days-treatment. This shows that fluoride effects on iodine uptake for thyroid secretion are various according to the changes in concentration and treatment duration. The same is true for iodine effects on thyroid hormone formation. Thyroid gland in infant is more sensitive towards IE.<sup>12</sup> From the research of Zhao et al.<sup>12</sup>, it is concluded that iodine and

fluoride influence each other in terms of goiter and fluorosis in experimental rats. Fluoride level in the bone in ID+FE condition appears to be higher than in IE+FE condition. ID or IE can improve the tendency of fluorosis. IE shows T3 level decrease in the serum. Histological changes in rats treated by FE show hyperplasia in 100 day-treatment. After 100 days, T4 level in ID+FE is still high with the weight of thyroid gland and height of follicular cells lowered. However, the diameter of follicular cells increases. This indicates that fluoride effect on thyroid gland begins to decrease.<sup>12</sup>

### Proliferative changes in thyroid caused by fluoride and the recovery process in female rats and their children

Bouaziz et al.<sup>13</sup> had researched 30 pregnant female rats that were divided into 3 groups, 10 rats in each group. There was no treatment given to group A and this group is used as control. The other 20 rats were treated by 500 ppm NaF, which is dissolved in their drinking water since 15 days of pregnancy until 14 days after the birth (for group B) and until 4 days after birth (for group C). In group C, during the rest 10 days of their life, the rats were given water without fluoride. In the 14<sup>th</sup> day, the rats were sacrificed and then observed. The result shows that there is a 15% weight decrease in the young rats compared to controls. It also shows 15% decrease in T4 level, and 6% decrease in T3 level. There are 68% decrease in iodine level in the thyroid gland of the female rats, and 55% in the young rats. Besides, 29% thyroid gland hypertrophy occur in the young rats and 41% occurs in the female rats, which may be caused by TSH increase, which is in line with the histological changes including thyroid follicle increase and colloid volume decrease. When fluoride was eliminated from their drinking water in the 4<sup>th</sup> day after the birth, the recovery process appeared to occur during the rest of the ten days before the death that takes form of increasing weight, increasing thyroid gland weight, and decreasing TSH.

The decrease in thyroid hormone level can be caused by transplacental movement of fluoride from the mother to the child, or by the lack of prolactin effect due to the accumulation of iodine in mammary glands. Histological changes of thyroid gland include the increased vascularization, decreased of colloid volume, and

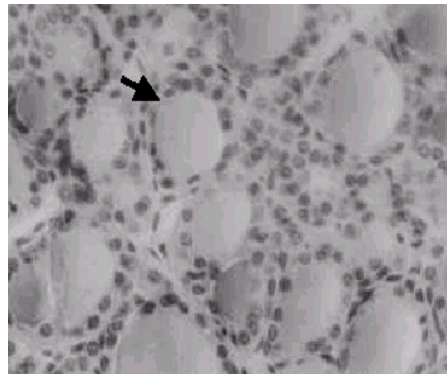


Figure 4. Histological features of normal thyroid in group A.<sup>13</sup>

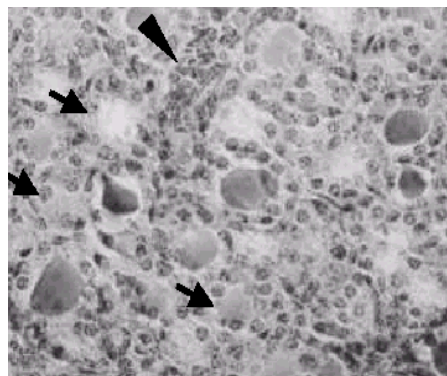


Figure 5. Histological features of the damages in thyroid in group B.<sup>13</sup>

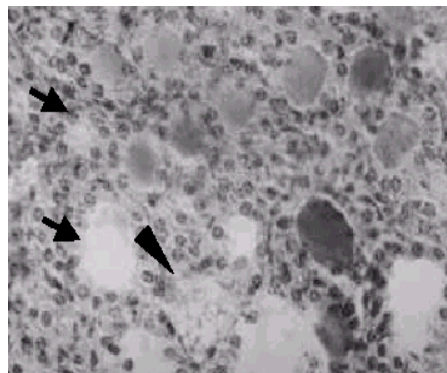


Figure 6. Histological feature of thyroid recovery in group C.<sup>13</sup>

- ▶ Indicates the thyroid follicle.
- ➔ Indicates the vascular.

follicular cell hyperplasia leading to increased thyroid gland weight.<sup>13</sup>

From the research, it can be concluded that sodium fluoride in drinking water can cause hypothyroidism in female rats and their breastfed children. The process of thyroid gland recovery can be observed during the 10 days when fluoride is eliminated from the drinking water.<sup>13</sup>

### **The damage in thyroid gland DNA in rats that are given high level fluoride and low level iodine intake**

Yaming Ge et al.<sup>14</sup> had done a research on 32 wistar albino rats. The rats were 1-month old and had 50 g weight. They were divided into 4 group, 6 female rats and 2 male rats in each group. Group 1 were the control, and treated with normal iodine (0.3543 mg/kg) and low fluoride (<0.6 ppm). Group 2 were treated by high level fluoride in their drinking water (100 mg NaF/L or 45 ppm F). Group 3 were treated by low level iodine (0.0855 mg/kg). Group 4 were treated by combination of the treatments given to group 3 and 4, i.e. high level fluoride and low level iodine. When the rats were 20 months old, the observation of the damage was done using SCGE (Single Cell Gel Electrophoresis) or comet assay. Those methods were used because they can measure the damage in a simple, fast, and sensitive way.<sup>14</sup>

The result of the research shows that the intake of high level fluoride, low level iodine, or combination of both can cause damages in thyroid gland DNA. The most serious damage occurs in the group with high level fluoride and low level iodine. Fluoride causes damages in thyroid gland cells and can break DNA chains. This will eventually lead to thyroid gland dysfunction. Iodine deficiency can also trigger damages in DNA chain.<sup>14</sup>

Thyroid gland has a capacity to absorb and accumulate fluoride. Fluoride level in thyroid gland is the second highest fluoride level in soft tissues after the aorta. Fluoride can cause the damages in the cell structure of thyroid follicle with the reduced cytoplasm followed by cariopcnosis (decreased nucleus size due to chromatin), decreased number of microvilli, and enlarged vacuole. Fluoride can also inhibit the activity of the enzymes that changes T4 into T3.

### **DISCUSSION**

Fluoride intake, either less or more than 1 ppm, combined with iodine intake, either enough or insufficient, can cause disturbances in thyroid gland, such as increased TSH, decreased Na/K-ATPase, decreased peroxide enzyme, decreased iodine binding protein, and may damage thyroid follicle cell DNA. These disturbances may eventually inhibit thyroid hormone synthesis.

Fluoride toxicity can be overcome by calcium diet for binding fluoride into a non diffusible compound, antioxidant diet such as ascorbic acid and vitamin E to support recovery, and vitamin D for supporting calcium and phosphate absorption in digestive track and to keep the optimum level in the blood.

### **CONCLUSION**

Systemically used fluoride, either less or more than 1 ppm can cause hypothyroidism and fluoride compound that is usually used as an anti-caries substance has high toxicity, particularly in the form of diffusible compound such as NaF.

### **SUGGESTION**

Fluoride is better used with in a non diffusible form such as CaF<sub>2</sub>. Avoid the use of systemic fluoride and prolong fluoride use and if fluoride poisoning occurs, it can be overcome by high-calcium, vitamin D, and antioxidant diet.

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