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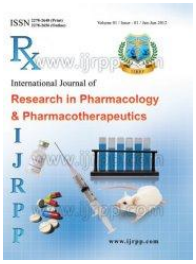

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Review article ***Open Access***

Fight the iodine deficiency: advances in the iodine supplement as life saving dot-- a critical review

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ABSTRACT

Iodine is a trace element naturally present in some foods and sea-food and available as an important nutrient and dietary supplement. Iodine deficiency is a global health issue and has multiple adverse effects on growth and development, and is the most common cause of preventable mental retardation in the world. Chronic, severe iodine deficiency *in utero* causes cretinism, a condition characterized by mental retardation, mutism, motor spasticity, stunted growth, delayed sexual maturation and other physical and neurological abnormalities and is also reported to be linked with Autism, cysts, certain Cancers along with hypo and hyper thyroidism, goiter etc. Various campaigns and awareness programs have been conducted to fight the Iodine deficiency. The Salt iodization programme in India dates back to late 50's by Ramalingaswami and his team established Iodine deficiency as the causative factor for endemic goiter and consuming salt iodized with potassium iodate as the most economic and easiest means of its prevention and control in a population. This study encouraged by the Govt. of India also helped to launch National Goiter Control Programme (NGCP). A revolutionary BINDI is a simple patch or a DOT comprising of Iodine solution in adequate quantities that works to fight against and deliver the iodine at constant and controlled rate by subdermal route throughout the month. The bindi need to be worn everyday for up to eight hours to be effective and even by the pregnant women. It contains a solution of 150-200 µg of Iodine coated on the nicotine like patch. Ground-breaking technology of life saving DOT of Bindi might work in the safe and controlled delivery of Iodine for various Iodine deficiency disorders by reducing the problems of thyroid intake and improving patients' compliance.

Keywords: Iodine, Bindi, Thyroid disorders, Mutism, Subdermal, salt iodization programme.

INTRODUCTION

Novelty of the Review

The current review summarizes the significance of Iodine, its deficiency disorders and emphasizes on various awareness programmes conducted to fight against the iodine deficiency and gives a short and innovative information of life saving DOT for the regular and continuous transdermal delivery of Iodine.

Iodine is a trace element that is naturally present in some foods and seafood, and available as an important nutrient and dietary supplement. Iodine is an essential component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Thyroid hormones regulate many important biochemical reactions, including protein synthesis and enzymatic activity, and are critical determinants of metabolic activity. They are also required for proper skeletal and central nervous system development in fetuses and infants[1]. Thyroid function is primarily regulated by thyroid-stimulating hormone (TSH), also known as thyrotropin. It is secreted by the pituitary gland to control thyroid hormone production and secretion, thereby protecting the body from hypothyroidism and hyperthyroidism. TSH secretion increases thyroidal uptake of iodine and stimulates the synthesis and release of T3 and T4 [1]. In the absence of sufficient iodine, TSH levels remain elevated, leading to goiter, an enlargement of the thyroid gland that reflects the body's attempt to trap more iodine from the circulation and produce thyroid hormones. Iodine may have other physiological functions in the body as well. For example, it appears to play a role in immune response and might have a beneficial effect on mammary dysplasia and fibrocystic breast disease [2]. The earth's soils contain varying amounts of iodine, which in turn affects the iodine content of crops. In some regions of the world, iodine-deficient soils are common, increasing the risk of iodine deficiency among people who consume foods primarily from those areas. Salt iodization programs, which many countries have implemented, have dramatically reduced the prevalence of iodine deficiency worldwide.[2, 3]

Iodine in food and iodized salt is present in several chemical forms including sodium and potassium salts, inorganic iodine (I_2), iodate, and iodide, the reduced form of iodine. Iodine rarely occurs as the element, but rather as a salt; for this reason, it is referred to as iodide and not iodine [4]. Iodide is quickly and almost completely absorbed in the stomach and duodenum. Iodate is reduced in the gastrointestinal tract and absorbed as iodide[2, 5]. When iodide enters the circulation, the thyroid gland concentrates it in appropriate amounts for thyroid hormone synthesis and most of the remaining amount is excreted in the urine. The iodine-replete healthy adult has about 15–20 mg of iodine, 70%–80% of which is contained in the thyroid [6]. Median urinary iodine concentrations of 100–199 mcg/L in children and adults, 150–249 mcg/L in pregnant women and >100 mcg/L in lactating women indicate iodine intakes are adequate. Values lower than 100 mcg/L in children and non-pregnant adults indicate insufficient iodine intake, although iodine deficiency is not classified as severe until urinary iodine levels are lower than 20 mcg/L.

Recommended Intakes

Intake recommendations for iodine and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences)[2].

DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and gender [2], include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals.
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.
- Estimated Average Requirement (EAR): average daily level of intake estimated to meet the requirements of 50% of healthy individuals. It is usually used to assess the adequacy of nutrient intakes in populations but not individuals.
- Tolerable Upper Intake Level (UL): maximum daily intake unlikely to cause adverse health effects.

Table 1 lists the current RDAs for iodine [2]. For infants from birth to 12 months, the FNB established an AI for iodine that is equivalent to the mean intake of iodine in healthy, breastfed infants in the United States[2].

Table: 1. Recommended dietary intake chart

Recommended Dietary Allowances (RDAs) for Iodine				
Age	**Male**	**Female**	**Pregnancy**	**Lactation**
Birth to 6 months	110 mcg*	110 mcg*		
7–12 months	130 mcg*	130 mcg*		
1–3 years	90 mcg	90 mcg		
4–8 years	90 mcg	90 mcg		
9–13 years	120 mcg	120 mcg		
14–18 years	150 mcg	150 mcg	220 mcg	290 mcg
19+ years	150 mcg	150 mcg	220 mcg	290 mcg

*Adequate Intake (AI)

The World Health Organization (WHO), United Nations Children's Fund (UNICEF), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) recommend a slightly higher iodine intake for pregnant women of 250 mcg per day[3, 7]

The daily dose of Iodine would need to be higher than the regular dose during severe health conditions like cancer which is a result of mutated cells. Iodine is absolutely critical for P53 gene which is known as the "keeper of the genetic code. Without iodine and selenium it will not function to eliminate abnormal cells from the body such as cancer.

Sources of Iodine

Food

Seaweed (such as kelp, nori, kombu, and wakame) is one of the best food sources of iodine, but it is highly variable in its content (Table 2) [5]. Other good sources include seafood, dairy products (partly due to the use of iodine feed supplements and iodophor sanitizing agents in the dairy industry [8], grain products, and eggs. Dairy products, especially milk, and grain products are the major contributors of iodine to the American diet [9]. Iodine is also present in human breast milk [2, 5] and infant formulas. Fruits and vegetables contain iodine, but the amount varies depending on the iodine content of the soil, fertilizer use and irrigation practices. Iodine concentrations in plant foods can range from as little as 10 mcg/kg to 1 mg/kg dry weight. This variability in turn affects the iodine content of meat and animal products because it affects the iodine content of foods that the animals consume [10]. The iodine content of different seaweed species also varies greatly[11]. For these reasons, the values in Table 2 are approximate.

Table 2: Selected Food Sources of Iodine[10, 11, 12]

Food	**Approximate Micrograms (mcg) per serving**	**Percent DV* (*DV: Daily Value)**
Seaweed, whole or sheet, 1 g	16 to 2,984	11% to 1,989
Cod, baked, 3 ounces	99	66
Yogurt, plain, low-fat, 1 cup	75	50
Iodized salt, 1.5 g (approx. 1/4 teaspoon)	71	47
Milk, reduced fat, 1 cup	56	37
Fish sticks, 3 ounces	54	36
Bread, white, enriched, 2 slices	45	30
Fruit cocktail in heavy syrup, canned, 1/2 cup	42	28
Shrimp, 3 ounces	35	23

Ice cream, chocolate, 1/2 cup	30	20
Macaroni, enriched, boiled, 1 cup	27	18
Egg, 1 large	24	16
Tuna, canned in oil, drained, 3 ounces	17	11
Corn, cream style, canned, 1/2 cup	14	9
Prunes, dried, 5 prunes	13	9
Cheese, cheddar, 1 ounce	12	8
Raisin bran cereal, 1 cup	11	7
Lima beans, mature, boiled, 1/2 cup	8	5
Apple juice, 1 cup	7	5
Green peas, frozen, boiled, 1/2 cup	3	2
Banana, 1 medium	3	2%

DVs were developed by the U.S. Food and Drug Administration (FDA) to help consumers compare the nutrient contents of products within the context of a total diet. The DV for iodine is 150 mcg for adults and children aged 4 and older. However, the FDA does not require food labels to list iodine content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient. The U.S. Department of Agriculture's (USDA's) Nutrient Database Web site lists the nutrient content of many foods, but this list does not currently include iodine[13].

Brief Outline on Iodine Deficiency-Diorders

Iodine deficiency is a global health issue and has multiple adverse effects on growth and development, and is the most common cause of preventable mental retardation in the world[14]. The World Health Organization (WHO) estimates over 2 billion people may be iodine deficient, with up to 50 million of them suffering from serious symptoms of iodine deficiency. Iodine deficiency disorders result from inadequate thyroid hormone production secondary to insufficient iodine [5]. During pregnancy and early infancy, iodine deficiency can cause irreversible effects. Under normal conditions, the body tightly controls thyroid hormone concentrations via Thyroid Hormone Stimulating Hormone (TSH). Typically, TSH secretion increases when iodine intake falls below about 100 mcg/day [5]. TSH increases thyroidal iodine uptake from the blood and the production of thyroid hormone. However, very low iodine intakes can reduce thyroid hormone production even in the presence of elevated TSH levels.

If iodine intake is below approximately 10–20 mcg/day, hypothyroidism occurs [1], a condition that is frequently accompanied by goiter, an earliest clinical sign of Iodine deficiency [2]. In pregnant women, iodine deficiency of this magnitude can cause major neuro developmental deficits and growth retardation in the fetus, as well as miscarriage and stillbirth [5]. Chronic, severe iodine deficiency *in utero* causes cretinism, a condition characterized by mental retardation, deaf mutism, motor spasticity, stunted growth, delayed sexual maturation, and other physical and neurological abnormalities [5].

In infants and children, less severe iodine deficiency can also cause neurodevelopmental deficits such as somewhat lower-than-average intelligence as measured by IQ [1, 5]. Mild to moderate maternal iodine deficiency has also been associated with an increased risk for attention deficit hyperactivity disorder in children [16]. In adults, mild-to-moderate iodine deficiency can cause goiter as well as impaired mental function and work productivity secondary to hypothyroidism. Chronic iodine deficiency may be associated with an increased risk of the follicular form of thyroid cancer[17]. Recently it was reported that Iodine deficiency has been linked to Autism in children. Other symptoms of Iodine deficiency include slow brain function and metabolism, low immunity, emotional upset and anxiety, compromised organ function, cysts, soreness and heaviness in the breasts etc [18, 19, 20, 21].

CAMPAIGNS AND AWARENESS: PROGRAMMES CONDUCTED IN INDIA

National Iodine Deficiency Disorders Control Program (NIDDCP)

Formerly called Salt Commissioner's Organization.The Salt iodization programme in India dates back to late 50's by Ramalingaswami and his team from 1956 to 1972 after the study by McCarrison in 1908 [23] and Stott *et al* in 1931 [24] in Kangra Valley of Himachal Pradesh established Iodine deficiency as the causative factor for endemic goiter and consuming salt iodized with potassium iodate as the most economic and easiest means of its prevention and control in a population. This study encouraged by the Govt. of India also helped to launch National Goiter Control Programme (NGCP).

National Goiter Control Programme (NGCP)

In 1962, NGCP was started with an objective to supply Iodised Salt instead of common salt to all the identified and notified goiter endemic areas in the country and the common salt being completely banned. The sustained efforts of Salt Commissionerate over the last two decades in implementing the policy initiatives and the cooperation of the salt manufacturers have resulted in significant progress on Salt Iodization Status in the country. This was called Universal Salt Iodization (USI), adopted by World Health Assembly held at Geneva in May 1990 [24]. The nomenclature of the NGCP was changed to National IDD Control Programme (NIDDCP) in 1992 to emphasize the wider implications of iodine deficiency, health education and advocacy.

The Central Council for Health and Family Welfare

In 1984 implemented compulsory consumption of iodized salt in the entire country. The Programme was effective from IstApril, 198625.

The United Nations World Summit for Children

Conducted in May 1990 and attended by 71 Heads of State and other senior officials of 15 Member States, adopted a plan of action for elimination of IDD by the year 2000 [26, 27].

United Nations General Assembly Special Session (UNGASS)

On children conducted in 2002 adopted new goal for IDD elimination by 2005[28].

PROBLEMS ASSOCIATED WITH THE IODINE RICH MEDICATIONS AND EXCESS IODINE EXPOSURE

Thyrotoxicosis

High Iodine content in Amiodarone (One 200 mg tablet contains 75mg iodine) which is several hundred-fold higher than the recommended daily intake of 150 µg in adults. Due to its long half life of 100 days and its lipophilic nature, the drug gets accumulated in various tissues including adipose tissue, liver and lungs thus leading to thyrotoxicosis.

Thyroid dysfunction

Use of iodinated contrast agents in diagnostic radiologic studies is a common source of excess iodine exposure in many patients. A single dose of iodinated contrast can contain up to 13,500 µg of free iodine and 15–60 g of bound iodine (which is more than several thousand times above the recommended daily intake). Following exposure to an iodinated contrast agent, iodine stores in the body remain raised and provide a continuous pool that can potentially induce thyroid dysfunction[29].

Topical iodine

The use of transdermal iodine and thyroid dysfunction associated with this practice is often seen in hospitalized neonates [30]. A study in Israel reported significantly higher serum levels of TSH in preterm neonates on whom topical iodinated antiseptic cleansers had been used than in preterm neonates on whom alcohol-based topical cleansers had been used (15.4 mIU/l versus 7.8 mIU/l, P<0.01)[31]. Iodine is also frequently used as a topical antiseptic in many surgical settings and for burn victims, whose ability to absorb topical iodine might be increased.[32] Iodine-induced thyrotoxicosis has been described in a paraplegic woman in the USA who had applied topical povidone-iodine prior to urinary self-catheterization several times daily for many years.[7]

Other sources of excess iodine exposure

Other sources of potential excess iodine exposure include various expectorants, food preservatives, prescribed medications, parenteral nutrition preparations, mouthwashes [33] and vaginal douches [34]. Reversible increases in serum levels of TSH have been observed among US astronauts drinking iodinated water as purified drinking water[35] and individuals ingesting water purified with iodinated tablets [36]. In the 1990s, due to the use of a faulty iodine-based water filtration system, small increases in serum levels of TSH were detected in American Peace Corp workers in Niger; these changes resolved when the iodinated water source was no longer used[37]

Strategies for the development of BINDI

Bindi or the colorful dot which adorns the forehead of Indian women is often associated to the Indian beauty. However, Indian women are deficient in their iodine consumption. In spite of the presence of iodized salt, there are many women in many tribal communities who suffer from the deficiency and suffer from diseases like goitre, hypothyroidism, possible brain damage etc. The authorities of the 'Grey for Good' have decided to curb this problem in an innovative fashion. They have come up with a product called '*JeevanBindi*'. *Bindi* is usually used by women irrespective of their social strata or background. The *bindi* or the dot that tries to suffice the iodine deficiency to some extent[39]

HOW BINDI WORKS

Iodine patch test done by applying a certain amount of iodine solution on the skin reveals the iodine deficiency if the skin absorbs the iodine. The bindi need to be worn everyday for up to eight hours to be effective and can be worn at night and even by the pregnant women. The Bindi contains a solution of 150-200 µg of Iodine coated on the nicotine like patch. The drug is absorbed by sub-dermal route. However, medical literature is also replete with references to how most of any iodine solution applied to the skin evaporates and less than 12% is actually absorbed by the body. If 150 micrograms had to be available in the thyroid gland and other tissues where iodine is processed, and a higher dose may be required. Also it has been proved that body takes up the required quantity of Iodine and the rest is excreted in urine[39].

FUTURE CONSIDERATIONS

Controlled clinical trials could be developed to study the efficiency of the Bindi or Life saving DOT in the controlled delivery of Iodine. The scope of developing the Bindi using various formulation strategies and evaluation methods are yet to be developed.

CONCLUSION

Ground-breaking technology of life saving DOT of Bindi might work in the safe and controlled delivery of Iodine for various Iodine deficiency disorders. It might work successfully by reducing the problems of thyroid intake by improving patients' compliance. Further studies are recommended for the development of life saving DOT-to fight thyroid deficiency.

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