

Clinical Aspects of Iodine and Iodine Deficiency

Research Article

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Introduction

Iodine, characterized as a trace element, is essential for the synthesis of thyroid hormones thyroxine (T₄) and triiodothyronine (T₃). These hormones are critical for the functioning of the liver, kidney, muscle, brain, and central nervous system [5]. Iodine plays a vital role in regulating overall metabolism and is crucial for fetal and child neurodevelopment, as well as organ and tissue function [1]. An average adult typically contains 15-20 mg of iodine in their body, with 70-80% stored in the thyroid gland [7]. Deficiency during pregnancy is a leading cause of preventable intellectual disability in children, underscoring the importance of monitoring iodine status in pregnant women and women of reproductive age globally [17]. Iodine, the heaviest stable halogen element, primarily exists in nature as iodide (I⁻), which is commonly used to produce supplements and iodized table salt in the form of potassium iodide (KI). Another naturally occurring form is iodate (IO₃⁻), used to fortify table salt as potassium iodate (KIO₃) [13]. Iodide is naturally present in soil and seawater, influencing the iodine content of crops. However, many regions have iodide-depleted surface soils. Since iodide is found in seawater, it can volatilize into the atmosphere and return to the soil. In non-coastal regions, this cycle is incomplete, leading to iodide depletion in plant foods and drinking water. Historically, iodine deficiency was observed in populations from inland regions (central Asia and Africa, central and eastern Europe, the central U.S.),

mountainous areas (Alps, Andes, Atlas, Himalayas), and those with frequent flooding (Southeast Asia) [19]. Early research conducted in Armenia identified the country as iodine deficient, as evidenced by the presence of endemic goiter, particularly notable in the southern regions. Despite efforts in the early 1990s by the major domestic salt producer to voluntarily iodize food salt, deficiency remained widespread [11].

Iodine Metabolism

Iodine is ingested as an inorganic ion or organically bound compound, but it is absorbed in the form of iodide after the reduction of iodine compounds in the stomach. Enteric absorption of iodide occurs primarily in the stomach and duodenum, where the enteric isoform of the sodium iodide symporter (NIS) is predominantly expressed. [20]. Iodine accumulates predominantly in the thyroid gland, which contains the largest pool of intracellular iodine in the human body. However, the most significant amount of iodide is found in the extracellular fluid, where its concentration is approximately 10–15 µg/L. Circulating iodide is cleared by the kidneys, with a small portion lost through the skin, intestinal secretions, or expired air [10]. The mammary gland can also accumulate and secrete iodide, providing an additional source of iodine clearance in lactating women. Renal clearance of iodide is estimated at 30-50 mL per minute but largely depends on the individual glomerular filtration rate, with no evidence of tubular secretion or active transport. Reabsorption

is partial and passive, and renal clearance of iodide is influenced by overall iodide status. Clearance by the kidney is constant, while uptake by the thyroid depends on iodine status and intake [19]. When iodine supply is sufficient, uptake by the thyroid may be less than 10%, but it can exceed 80% due to chronic deficiency. After active transport into the thyroid, iodide is stored in the thyroglobulin (Tg) protein before being converted into T3 and T4. These hormones enter circulation bound to carrier proteins and target tissues, with T3 being the primary physiologically active form that preferentially binds to its receptors. Both free T3 and T4 are assessed in serum by immunoassay. Iodide is also produced via intrathyroidal deiodination of iodothyronine after thyroglobulin hydrolysis. Part of the circulating iodide pool is re-organised into de novo synthesized iodothyronine, while the rest enters systemic circulation (iodide leakage). Iodine also originates from the peripheral degradation of thyroid hormones, entering circulation, where it can be recycled after subsequent thyroid uptake or ultimately excreted in urine [20].

Recommended Intake

The recommended daily iodine intake ranges from less than ten micrograms in areas with extreme iodine deficiency to several hundred milligrams in patients taking iodine-containing medications. For adults and the elderly, 150 µg of iodine is generally recommended. Pregnant or lactating women require at least 200-250 µg daily. In newborns and children, the iodine requirement per kilogram of body weight is higher than in adults, corresponding to an absolute iodine intake requirement of 70-120 µg in children and 40 µg in newborns. These recommendations are based on factors such as daily thyroid hormone turnover in healthy individuals, the mean iodine intake associated with the lowest values of thyroid-stimulating hormone in the normal range, the smallest thyroid volume, the lowest incidence of transient hypothyroidism in neonatal screening, and the mean requirement of levothyroxine to restore euthyroidism in patients with thyroid agenesis or following thyroidectomy [18].

Natural sources of iodine

Iodine is primarily obtained from food sources, especially vegetables grown in iodine-rich soil, with the remaining requirement typically met through drinking water. The oceans serve as the primary reservoirs of iodide, which, upon conversion to elemental iodine, follows the water cycle and is delivered to the soil through rainfall. However, in regions with high precipitation rates, such as mountainous inland areas, the iodine content of soils and consequently, of food crops is significantly reduced due to rain leaching. This leads to iodine-deficient soils and, subsequently, nutritional iodine deficiency, which is more prevalent in these mountainous inland areas but can also be found in very rainy coastal zones [3]. Seafood and saltwater fish are the most important sources of iodine, as marine fauna and flora accumulate substantial amounts of soluble iodine from seawater. Freshwater and farmed fish, in comparison to seawater organisms, contain lower levels of iodine [14]. Therefore, fish sourced from rivers or lakes typically have lower iodine content [8].

Iodine deficiency disorders

The critical importance of iodine throughout the life cycle is evident from a group of diseases that arise due to iodine deficiency

(iodine deficiency disorders, IDD) and the subsequent insufficient production of thyroid hormones. The effects of iodine deficiency vary depending on the life stage and the severity of the deficiency [9]. For instance, during pregnancy, severe iodine deficiency leads to significant mental and growth impairments, including deaf-mutism and spasticity, which are characteristic features of cretinism. Conversely, mild-to-moderate iodine deficiency in the womb is linked to neurodevelopmental issues such as decreased intelligence quotient, impaired fine motor skills, and difficulties in verbal and non-verbal communication. Iodine deficiency in the early stages of life may significantly affect brain development. Thyroid hormones are necessary for the myelination of the central nervous system, which takes place before and shortly after birth. Primary hypothyroidism related to iodine deficiency has been found to negatively affect cognitive function with potentially irreversible intellectual consequences [19]. Adequate maternal exposure to iodine in the early stages of pregnancy is essential for the proper intellectual development of the child, irrespective of hypothyroidism.

Iodine deficiency has also been associated with increased miscarriage and stillbirth rates, and congenital disabilities, including congenital hypothyroidism in the offspring [6]. Congenital hypothyroidism comprises two classical clinical features with specific phenotypes: neurological and myxedematous [15]. The first is characterized by intellectual impairment and developmental delays, and various neurological defects, including the underdevelopment of the cochlea leading to deafness, defects of the cerebral neocortex with intellectual impairment, and the underdevelopment of the corpus striatum with motor disorders. Patients do not exhibit signs of hypothyroidism, and the prevalence of goiter is similar to that observed in the general population. The hypothyroid phenotype includes dwarfism with delayed bone and sexual maturation, intellectual impairment, and overt hypothyroidism. Thyroid development is critically involved, and patients usually exhibit low thyroid volume or thyroid atrophy. The prevalence and risk factors associated with neurological cretinism is related to thyroid hormone deficiency in the early stages of embryonal development, resulting from a severe maternal iodine deficiency in a phase when thyroid development is still incomplete. Myxedematous cretinism is associated with thyroid insufficiency during late pregnancy or early infancy. Iodine deficiency remains a significant public health concern, affecting more than one billion people worldwide and leading to various levels of growth and developmental abnormalities [2].

Iodine Supplementation

Thanks to food policies permitting the addition of iodine to food items, processed foods containing notably elevated levels of iodine have become more accessible in recent decades. These foods have been utilized in nationally implemented programs to offer iodine prophylaxis, mitigating the clinical effects of iodine deficiency. The global strategy recommended for this purpose is the iodization of salt for human consumption. Iodine supplementation is an effective strategy for reducing population iodine deficiency, but care must be taken to avoid excessive intake. The goal is to increase iodine intake to the level necessary to prevent IDDs without surpassing it. The bioavailability of iodine from food varies and is challenging

to determine, and interactions between different foods in the food matrix are not well understood [14]. The most practical and cost-effective method of providing iodine supplementation to deficient populations is through the use of iodized salt, as recommended by organizations such as the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and the International Council for the Control of Iodine Deficiency Disorders. Other approaches include the consumption of iodized water, iodized oil, and iodine tablets [18]. The quantity and type of iodine used for salt fortification vary by region but typically fall within the range of 20-40 mg iodine/kg salt. The forms used for fortification globally are either potassium iodate (KIO₃), which is more stable, or potassium iodide (KI), which has a higher iodine content and solubility [7], or sodium iodide (NaI). Unlike iodization of salt and water, which can reach a larger proportion of the population, supplementation with iodized oil or tablets is more suitable for individual use and can rapidly improve iodine status, especially in regions where salt iodization is not feasible or cannot be implemented in the short term.

Evaluation of Iodine Levels

Multiple indicators are utilized to assess iodine status, including urinary iodine concentration (UIC), thyroid volume (TV), serum thyroid-stimulating hormone (TSH), thyroid hormones, and serum Tg. Median UIC in spot urine samples is the preferred indicator to assess iodine status in populations. UIC serves as a reliable marker of short-term iodine status. Although UIC at the individual level fluctuates with recent food intake and hydration status, the median UIC is a valid marker of iodine intake at the group level [21]. UIC is not suitable for determining the proportion of the population with iodine deficiency or excess. Having two independent spot samples from a subset of the study population can be used to estimate the habitual long-term iodine intake and the prevalence of deficiency and excess [22]. For school-aged children and non-pregnant adults, iodine intake is considered sufficient when the median UIC in the population falls within the range of 100–299 µg/L. In pregnant women, iodine intake is considered sufficient when the median UIC ranges from 150 - 249 µg/L. Estimating daily iodine intake for population estimates can be done by extrapolating from UIC, using estimates of mean 24-hour urine volume with the equation: $UIC (\mu\text{g/L}) \times 0.0235 \times \text{body weight (kg)} = \text{iodine intake } (\mu\text{g/day})$, assuming 90% excretion and 1.5 liters urine per 24 hours. Therefore, a median UIC of 100 µg/L in an adult corresponds roughly to an average daily intake of 150 µg. However, this approach does not consider iodine uptake in the thyroid and is less reliable in iodine-deficient situations and during pregnancy and lactation [18].

TSH is a direct marker of thyroid function and can be considered reflective of iodine status to some extent. It is utilized as part of newborn screening in many developed countries to detect cases of congenital hypothyroidism. Neonates have higher iodine turnover in the thyroid compared to children and adults, and neonatal TSH is expected to be a sensitive indicator of population iodine deficiency. However, upon closer examination, it has been concluded that the increase in TSH observed is not significant enough for it to be a useful marker [4]. Furthermore, in children and adults, TSH levels may elevate slightly in cases of iodine deficiency, but they typically

remain within the reference range, making it a relatively insensitive marker [16].

The primary biologically active thyroid hormones are T₄ and T₃, serving as direct indicators of thyroid function. However, they are ineffective as biomarkers for iodine status at both population and individual levels. Thyroid hormone levels often fluctuate within the reference range in response to iodine status, making them insufficiently sensitive to reliably reflect iodine status except in severely iodine-deficient regions.

Tg is an iodoglyco protein produced in the follicular cells of the thyroid gland in response to TSH. It serves as the precursor to thyroid hormones. Its primary clinical use is as a tumor marker in patients who have undergone total thyroidectomy for differentiated thyroid cancer. Tg concentration generally reflects the overall mass of thyroid cells. Therefore, it has been proposed that it could be used as an indicator of iodine status in populations living in areas with endemic goiter. Indeed, studies have shown that Tg levels decrease at a population level following the implementation of a salt iodization program [12].

Material and Methods

We carried out a study involving pediatric patients (ages 0–17 years) from 2023 to May 2024. All patients were evaluated at the Division of Pediatric Endocrinology at “Muratsan” Hospital Complex. Blood samples were collected in the morning. The thyroid hormone levels are expressed in the following units: TSH in µU/mL, T₄ in ng/dL. The normal values (nv) for T₄ are 0.8–1.8 ng/dL. The immunological tests were conducted using clinical routine analysis instruments at “Muratsan” Hospital Complex, employing accredited techniques. The immunological analyses were performed using the Cobas analyzer.

Results and Discussion

T₄ circulates in the bloodstream as an equilibrium mixture of free and serum bound hormone. Free T₄ is the unbound and biologically active form, which represents only 0.03 % of the total T₄. The remaining T₄ is inactive and bound to serum proteins such as T₄ binding globulin (75%), pre-albumin (15%), and albumin (10%). Therefore, free T₄ is a useful tool in clinical routine diagnostics for the assessment of the thyroid status. It should be measured together with TSH if thyroid disorders are suspected and is also suitable for monitoring thyrosuppressive therapy [22].

The Diagnostic Laboratory of the “Muratsan” Hospital Complex at the Yerevan State Medical University named after M. Heratsi conducts modern complex studies for children and adolescents with acute and subacute diseases, both inpatient and outpatient. The investigations of the thyroid hormone T₄ are of key importance in Armenia. Laboratory diagnostic tests for T₄ allow for the early detection of thyroid pathologies in children and adolescents. In 2023 alone, the laboratory conducted 1,114 free T₄ tests among children, and during the period from January to May 2024, more than 1,025 children were tested. The number of patients is trending upward, which is due to several factors. Free T₄ screening is among the strategically important issues for Armenia. Diagnostic laboratory measures among socially

vulnerable patients allow for the regulation of tissue growth in children through early endocrinological interventions, normalizing the metabolism of proteins, carbohydrates, and lipids.

The diagram schematically presents the effectiveness of the studies, which has almost doubled over the course of 1.5 years. Laboratory diagnostic tests allow for the early detection of hyperthyroidism or hypothyroidism in children, enabling targeted treatment for children and adolescents (Figure 1).

The diagram clearly shows a doubling in the number of patient visits in January. The growth trend continues in the following months as well (Figure 2).

Thyroid function disorders in children lead to either hyperthyroidism or hypothyroidism. According to the analysis of screening test results, in cases of hyperthyroidism, children show an increase in T4 concentration in the blood, a sharp decrease in calcium (Ca) levels (while the amount of calcitonin remains normal), presence of hyperglycemia and glycosuria, and low cholesterol concentration in the blood serum.

Primary hypothyroidism is caused by a thyroid gland dysfunction, while secondary hypothyroidism is due to a pituitary gland functional disorder. Primary hypothyroidism is diagnosed in newborns and is a result of fetal intrauterine developmental disturbances. The widespread occurrence of hypothyroidism in neonatal-age children is dangerous because it has no clinical manifestations in the first days of life. Hypothyroidism in neonatal-age children can only be detected through laboratory diagnostic tests. Due to this, screening tests for the detection of congenital hypothyroidism are conducted in several leading countries and now also in Armenia. T4 screening

reveals the presence of the disease in the preclinical stage, allowing for therapeutic interventions. Hypothyroidism is accompanied by high concentrations of cholesterol, triglycerides, and T4 in the blood serum.

Ensuring adequate iodine intake is essential for maintaining optimal health, particularly in areas where iodine deficiency is common. Therefore, supplementation programs, such as the use of iodized salt or iodine supplements, are effective strategies for preventing and addressing iodine deficiency, leading to better health outcomes and a reduced risk of related health issues.

Conclusion

Ensuring adequate iodine intake is essential for maintaining optimal health, particularly in areas where iodine deficiency is common. Continued efforts to address iodine deficiency through supplementation programs and public health initiatives are essential to reduce the global burden of iodine deficiency disorders and improve health outcomes for populations at risk.

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Figure 1: Hyperthyroidism or hypothyroidism in children

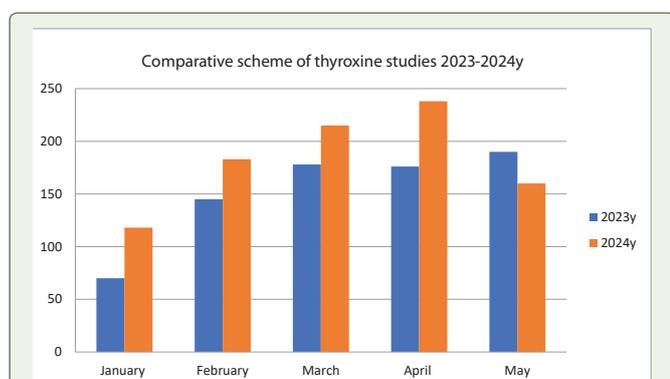


Figure 2: Diagram. Comparative scheme of T4 studies 2023-2024y.

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