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Chapter

Urinary Iodine: Biomarker for Population Iodine Nutrition

Husniza Hussain, Rusidah Selamat, Lim Kuang Kuay, Fuziah Md Zain and Muhammad Yazid Jalaludin

Abstract

Many reports or manuals had focused on the implementation of iodine deficiency disorder (IDD) elimination programme from the point of view of the programme managers. In this chapter, we will focus on the importance of urinary iodine testing, its related diagnosis and further biomarker testing suggested for further diagnosis related to thyroid health. This chapter will be relevant for the respondents to the monitoring programme, particularly the 8–10-year-old schoolchildren and pregnant women, i.e., the vulnerable targeted groups from either the iodine-deficient areas or the Universal Salt Iodization (USI) gazetted areas. USI has been proposed by the World Health Organization (WHO) as the most cost-effective programme to eliminate IDD, and it is also a way to increase the intelligent quotient (IQ) of the world population for the future. This chapter had been laid out so that the readers will know briefly the rationale behind the testing of urinary iodine among schoolchildren and pregnant women under the implementation of the USI programmes in their countries and their benefits, especially the utilisation of urinary iodine as the biomarker to portray the population iodine status. Diagnosis including iodine-induced thyroid diseases and further biomarkers measurement besides urinary iodine is also discussed briefly.

Keywords: urinary iodine, biomarker, iodine nutrition, population, thyroid status

1. Introduction

1.1 Importance of urinary iodine testing to determine population iodine nutrition

All iodine in the blood is in the iodide form either it is taken up by the thyroid and converted into thyroid hormone or being excreted in the urine. Almost 90% of the ingested iodine is excreted in the urine. Therefore, urinary iodine excretion is a good biomarker of very recent dietary iodine intake [1]. On an individual basis, 24-hour urine sample is necessary for the assessment of iodine intake as the level is more consistent in iodine-deficient populations than in those with adequate iodine intake (**Figure 1**). On a population basis, the median urinary iodine concentration (mUIC) of spot urine from sufficiently large randomly selected 8–10-year-old children or adults has been shown to provide useful information on the average iodine intake or status of a community. On an individual basis, urinary iodine varies from day to day and even within a given day. However, this variation tends to even out among population [2]. Most of the epidemiological IDD studies had emphasised on rapid inexpensive methods of urinary iodine determination that could be applied to a large number of samples [3].

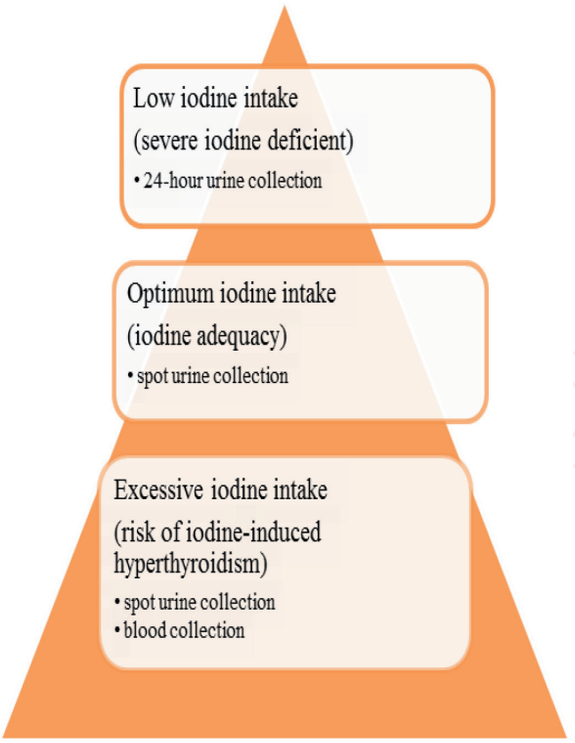


Figure 1.
Degrees of iodine intake (iodine nutrition status) and their suitable types of human sample collection to determine the median urinary iodine concentration (mUIC).

The main biochemical indicator that is widely used for the assessment of IDD is urinary iodine concentration (mUIC) [4]. The advantages of mUIC as an indicator of IDD are that the method directly reflects iodine supply of the individual, it is objective and non-invasive and urine samples can be kept for later analysis. However, the disadvantages of this method are that it requires laboratory space, special facilities and skilled technician to provide accurate determinations. In addition, this method reflects only current but not past intake of iodine [5].

Epidemiological studies stated that the population distribution of urinary iodine is required rather than individual levels. The frequency distribution of urinary iodine usually skewed towards elevated values; hence, the median value is considered instead of the mean as indicating the status of iodine nutrition [1]. The mUIC of 100 μg/L and above defines a population which has no IDD; i.e. at least 50% of the sample should be >100 ug/L. In addition, not more than 20% of sample should be below 50 μg/L. Iodine nutrition status is based on six categories of urinary excretion classification (**Table 1**) [3].

Median urinary iodine concentration (μg/L)	Severity of IDD
<20	Severe deficient
20–49	Moderate deficient
50–99	Mild deficient
100–199	Optimal
200–299	More than adequate
>300	Excessive

Source: Ref. [3].

Table 1.
Epidemiological criteria for assessing IDD in a population based on median urinary iodine concentration.

1.2 Iodine role in thyroid hormone synthesis and its contribution to human body

1.2.1 Thyroid hormone synthesis

Iodine is grouped under micronutrients, and it is needed in small amount, but it is very important for the development of optimum human growth. Iodine is needed in the synthesis of thyroid hormones [6]. Through iodination, one, two, three or four iodine atoms are bound to tyrosine to form monoiodothyronine (MIT), diiodothyronine (DIT), triiodothyronine (T_3) or thyroxine (T_4), respectively, through the action of iodinase enzyme. Iodine is absorbed from the gastrointestinal system, will enter the blood circulation and will be transported into the thyroid follicle cells through the sodium/iodine (Na/I) symporter. In iodide form, it will then be transported to the thyroid follicle colloid through pendrin. Concurrently, thyroglobulin (TG) is being synthesised in the endoplasmic reticulum (ER) and being secreted into the follicle colloid through exocytosis. TG is the transporter protein of the thyroid hormones in the thyroid follicle colloid. It consists of branches of tyrosine molecules which will then be bound to iodine through the iodination process, forming the MIT and the DIT. When one MIT and one DIT bind, T_3 will be formed, while upon binding of two DITs, T_4 will then be formed. These TG-bound thyroid hormones will enter the thyroid follicular cell through endocytosis. TG will then undergo proteolysis, and T_3 and T_4 will be transported into the blood circulation through the MCT symporter [7] (**Figure 2**).

1.2.2 Iodine's contribution to human body

Iodine is a micronutrient which is present in the body in minute amount. The quantity of iodine required by an individual is about 150–200 μg/day [8]. Its main role is in the synthesis of thyroid hormone which is essential for the brain

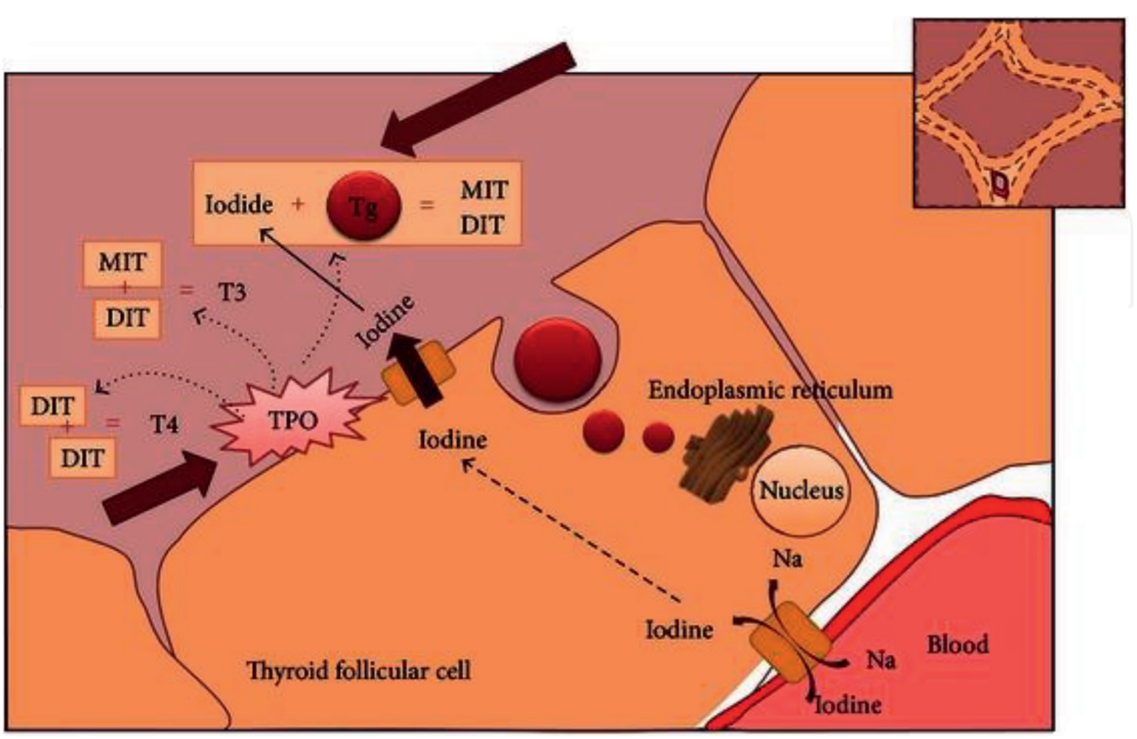


Figure 2.
Thyroid hormone synthesis in the thyroid gland (image reproduced with permission from the rights holder, Journal of Thyroid Research) [13].

and physical development [9]. The regulation of thyroid hormones is under the control of the pituitary gland through thyroid-stimulating hormone (TSH). TSH secretion is regulated by a 'feedback' mechanism related to the level of thyroid hormones thyroxine [3,5,3′,5′-tetraiodothyronine (T_4)] in the blood. Iodine is needed in the human body, and as the blood T_4 falls, the pituitary TSH secretion is increased. In severe iodine deficiency disorders (IDD), the level of T_4 remains lowered, and the level of TSH remains elevated. Both these measurements are used for diagnosis of hypothyroidism due to IDD at various stages in life particularly in neonates [10].

2. Iodine deficiency disorders (IDD) and symptoms

2.1 Causes of IDD

Most of the iodine exists in the ocean and seafood, including saltwater fish, shellfish, kelp, seaweed and seaweed products which can provide a considerable amount of iodine [11]. Iodine exists in the sea and the soil as iodide. Iodide ions are oxidised by sunlight to elemental iodine which is volatile. The iodine cycle in nature is complete if the concentration of iodide in the seawater is about 50–60 μg/L, approximately 0.7 μg/m^3 in the air, and the iodine in the atmosphere is returned to the soil through rain, with concentrations in the range of 1.8–8.5 μg/L. Iodine deficiency occurs in the soil when the return of the iodine to the soil is slow and in small amount compared to the original loss of iodine. Hence, all crops grown in this soil will be iodine deficient [12]. Low levels of iodine in the diet for people who do not get enough iodine from their food may lead to health problems collectively referred to as iodine deficiency disorders (IDD) [14].

2.2 The problem of IDD to human population

IDD is a major public health problem for population throughout the world which affects human from early foetal life through to adulthood [15]. Although IDD can affect any person of any age, pregnant women and children are the most vulnerable high-risk group for IDD [16]. Iodine requirement is high during pregnancy; it may increase by 50% because of increased maternal thyroxine production [14].

IDD in the foetus is the result of IDD in the mother, and this condition is associated with greater incidence of stillbirths, abortions, congenital abnormalities, neurological cretinism and psychomotor defects (**Figure 3**). In neonate, apart from mortality, the continuing severe IDD may affect the brain and physical development. Low birth weight is normally associated with a higher rate of congenital anomalies, and there were also evidences on substantial fall in infant mortality with improved birth weight following the iodized oil injection. IDD in the child and adolescent is associated with juvenile hypothyroidism, impaired mental function and retarded physical development. Studies on schoolchildren living in iodine-deficient areas indicated impaired school performance and IQs [17], while IDD in the adult had effects on their individual capacity, initiative and decision-making (**Figure 3**). These results indicate that IDD can be a major obstacle to human and social development of population living in an iodine-deficient environment. Therefore, correction of iodine deficiency is considered as a major contribution to population development [18].

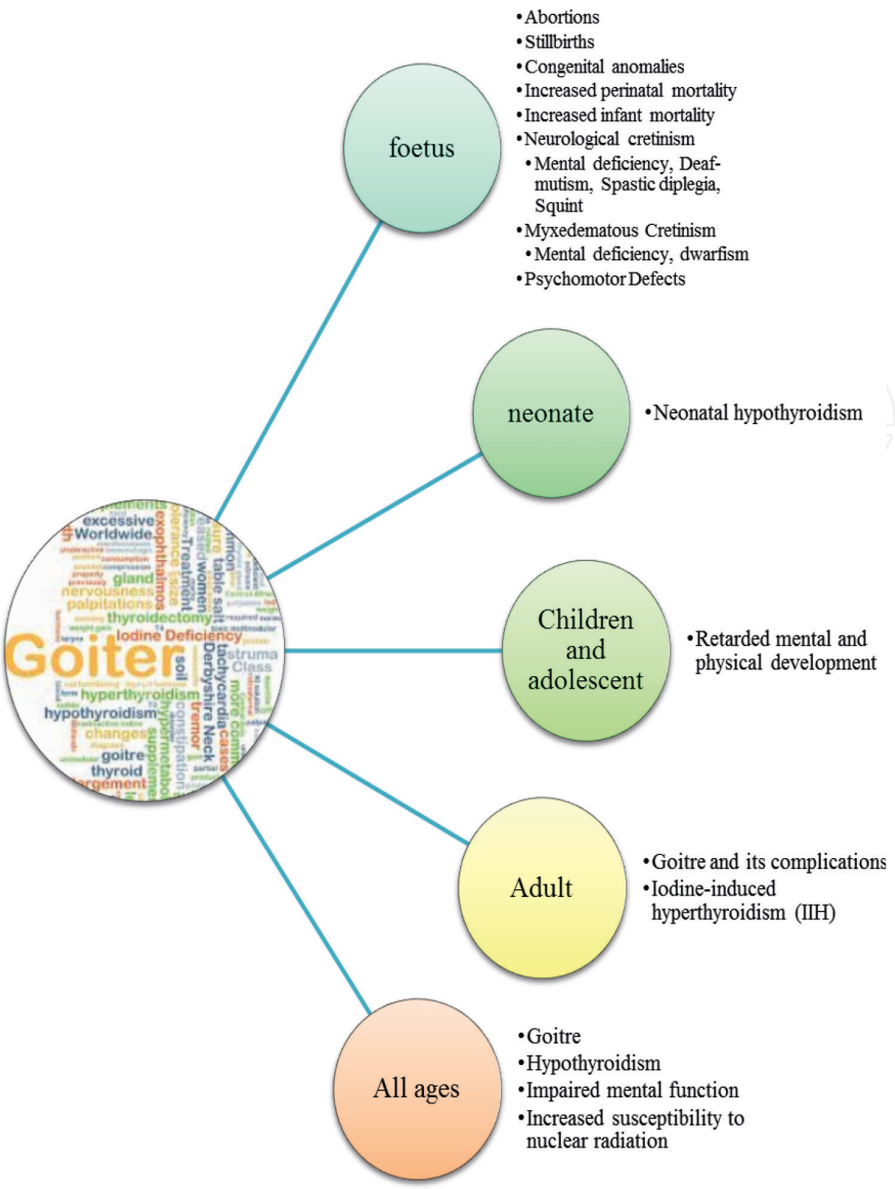


Figure 3.
Effect of iodine deficiency and the spectrum of IDD across the life span (clinical presentation) in various age groups, i.e. foetus, neonate, infant, child, adolescent and adult.

3. Iodine needs in pregnant women and their foetuses

Pregnant woman is one of the most susceptible groups for iodine deficiency. An adequate intake of iodine in the diet of pregnant woman is important to ensure normal growth and development of the foetus. During pregnancy, iodine requirement increases substantially to ensure adequate supply to the foetus particularly for healthy brain development. Iodine deficiency during pregnancy can cause maternal and foetal hypothyroidism and impairs neurological development of the foetus since it is secondary to transplacental passage of iodide. The consequences depend upon the timing and severity of hypothyroidism; the most severe manifestation is cretinism [14].

Since most foods have relatively low iodine content, Universal Salt Iodization (USI) programmes are executed. However, in countries or setting where USI is not possible, other mode of iodine supplementation needs to be implemented. It is difficult to accurately quantify iodine intakes using traditional methods of dietary assessment in terms of the contribution of iodized salt use from table and cooking to total iodine intake. In view of the limitations of dietary assessment for adequate iodine, a mUIC

of 150–249 μg/L has been established to determine the adequate iodine status among pregnant women. However, the large intra-individual variation in UIC from either spot or 24-hour urine samples means that UIC cannot be used to assess iodine status in an individual pregnant woman. Therefore, the association between iodine status in pregnancy and the developmental outcome of the individual child is rather difficult to be assessed.

4. IDD elimination programme worldwide and Universal Salt Iodization (USI) programme

Universal Salt Iodization (USI) is currently the most widely used strategy towards sustainable control and elimination of IDD. There was a significant progress since the adoption of USI as a primary strategy to address IDD in 1993. Iodizing table salt is one of the best and least expensive methods of preventing IDD. Salt is used as a key vehicle as it is widely available and consumed in a regular amount throughout the year apart from a very low cost of salt iodization with US$ 0.05 per person per year [1]. This strategy has been implemented in most countries where iodine deficiency is a public health problem.

Various concerted global efforts have also been undertaken to eliminate IDD. This includes extensive advocacy from the international partners/alliances such as the WHO, UNICEF and ICCIDD (International Council for Control of Iodine Deficiency Disorders). These alliances have been in the forefront in helping countries to set up national salt iodization programmes. As reported by WHO/UNCEF/ICCIDD, there are currently 65 countries worldwide implementing USI as an effective strategy to eliminate IDD [3]. However, an effective USI in correcting iodine deficiency adequately through iodized salt must reach the whole affected population including pregnant women and children. Therefore, close and regular monitoring of iodized salt at various levels from the production, importation, retailer and household is crucial. Such monitoring requires close collaboration between the governments, salt industries and importers. In countries or areas within countries where USI is not possible, iodine supplementation needs to be implemented and especially targeted to pregnant women and children until USI is scaled up.

5. Urinary iodine results and their implications

Upon consumption, the needed amount of iodine is retained in the body, while excess iodine is excreted. Thus, high urinary iodine concentration does not reflect a disease state yet, but if persists on repeated urine sample, further blood tests is recommended. Urinary iodine reflects the food consumption taken overnight, and it is just an immediate biomarker (short-term reflection) for iodine intake. Thus, the long-term reflection of iodine intake will be more representative by measuring blood thyroglobulin (TG) as it is synthesised parallel to the amount of iodine present in the thyroid follicular cells. The very low or high individual urinary iodine readings will usually be repeated for testing to ensure that it is replicating the first reading.

6. Other blood biomarker measurement to support iodine-deficient status determined through urinary iodine measurement

For respondents with high mUIC, other biomarkers such as blood thyroglobulin (TG), thyroid-stimulating hormone (TSH), thyroid hormones (free thyroxine, fT_4;

	Whole group (n = 870)			Constraint group (n = 453)		
Hormone	**Median**	**Minimum-Maximum**	**2.5th–97.5th percentiles[a]**	**Median**	**Minimum-Maximum**	**2.5th–97.5th percentiles[a]**
TSH, mIU/L	1.31	0.05–14.50	0.30–3.63	1.36	0.12–5.29	0.40–3.77[b]
T_4, nmol/L	101.00	52.10–209.00	71.50–158.00	98.30	61.80–173.00	70.50–157.00
T_3, nmol/L	1.77	0.89–4.00	1.23–2.80	1.77	0.89–3.96	1.27–2.79
FT_4, pmol/L	16.20	8.24–28.60	12.70–20.80	16.20	9.30–24.70	12.80–20.40
FT_3, pmol/L	5.10	2.52–9.96	3.89–6.66	5.13	2.52–9.96	4.02–6.79

[a]*Data are reported as empirical percentiles.*
[b]*The lower limit of the TSH reference interval in the constraint group was >5% different from the comparable limit of the whole group.*

Table 2.
Reference intervals for thyroid hormones from subjects with normal thyroid gland assessed sonographically (table reproduced with permission of the rights holder, Clinical Chemistry) [19].

free triiodothyronine, fT_3) and thyroid antibodies, thyroid peroxidase antibodies (TPO Ab) and thyroglobulin antibodies (TgAb) are thus suggested for further diagnosis. Brief information on these biomarkers is as stated below:

6.1 Free thyroxine (fT_4) and free triiodothyronine (fT_3)

T_4 is a molecule of thyronine bond to four atoms of iodine, while T_3 has three iodine atoms. T_4 is more abundant than T_3, but through deiodinase activity, the more potent T_3 is synthesised. Low level of T_4 usually indicates hypothyroidism. For clinical biochemistry free T_4 (fT_4) and free T_3 (fT_3) are usually measured as these are the biologically active forms. Reference intervals for fT_4 and fT_3 are as stated in **Table 2**.

6.2 Thyroid-stimulating hormone (TSH)

TSH is released upon the induction by thyrotropin-releasing hormone (TRH), secreted from the hypothalamus. TRH is secreted when serum T_3 and/or T_4 is low. TSH induces the production of thyroid hormones T_3 and T_4. Low level of TSH usually indicates hyperthyroidism (parallel to high levels of T_3 and/or T_4) [17]. Reference interval for TSH is as stated in **Table 2**.

6.3 Thyroglobulin (TG)

TG is the globulin where binding of iodine to tyrosine to form thyroid hormones takes place. It is the long-term biomarker for iodine status in a human, besides urinary iodine as the short-term biomarker for iodine nutrition.

The median for reference interval for dried blood spot (DBS) TG from 5- to 14-year-old children before intervention of iodized salt is 49 g/L. After using iodized salt for 5 months, the DBS-TG decreased to 13 g/L and further decreases to 8 g/L after 10 months of consumption of iodized salt [20].

6.4 Thyroid antibodies [thyroid peroxidase antibodies (TPO Ab) and thyroglobulin antibodies (TgAb)]

This antibody is for binding to the antigen thyroid peroxidase (TPO) enzyme which is responsible for thyroid hormones synthesis. Once the enzyme is bound to the antibody, less free unbound enzymes are available for thyroid hormone

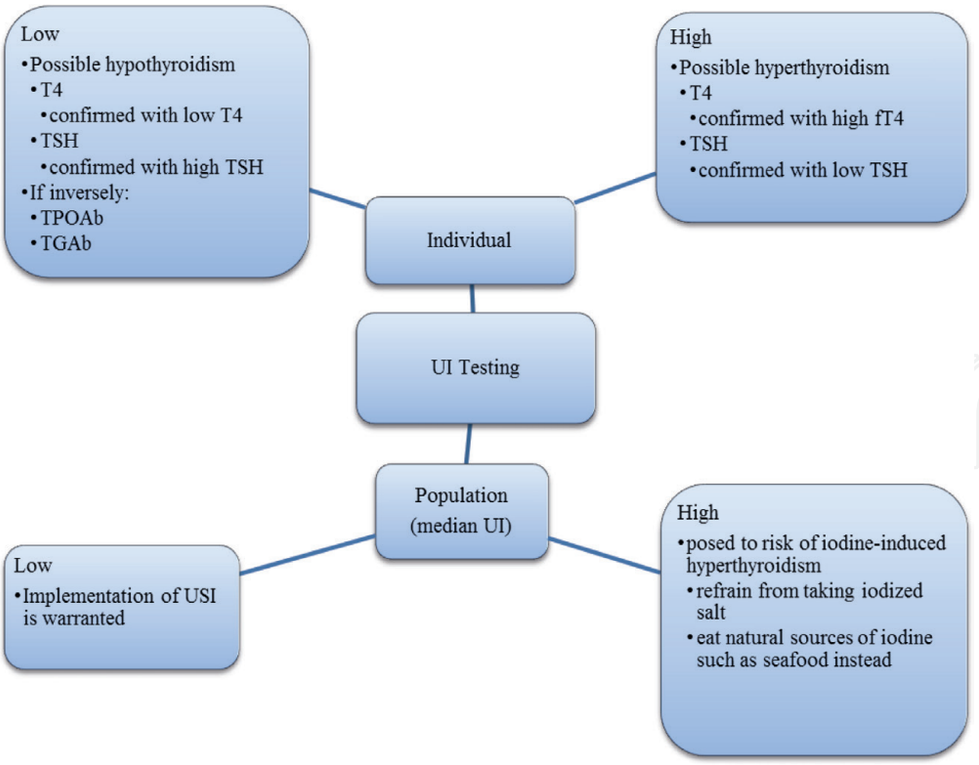


Figure 4.
Subsequent biomarker testing and further action for individual and population urinary iodine estimation.

synthesis, thus causing lower thyroid hormone production. TgAb is the antibody for the globulin TG. With the presence of elevated amount of TgAb, the thyroglobulin (TG) will bind to its antibody, and lesser TG is available to bind to the thyroid hormones for transportation in the blood vessels, thus causing lesser thyroid hormones being circulated in the human body [21]. The reference intervals are 15 kIU/L for TPOAb and 31 kIU/L for TgAb [22] (**Figure 4**).

7. Diagnosis for the iodine-induced thyroid dysfunction in respondents

Both insufficient and excessive iodine intake can result in thyroid dysfunctional diseases. If the thyroid diseases are due to iodine-induced phenomena, the main management is to avoid or reduce iodine intake, followed by the appropriate drugs if symptomatic or there is abnormality with the thyroid function test (TFT) results.

7.1 Iodine-induced hypothyroidism

Iodine-induced hypothyroidism can occur in normal individuals and in those with chronic systemic disease and underlying thyroid disorders. It has been seen in patients who had a history of post-partum thyroiditis and subacute thyroiditis and in those treated with recombinant interferon-alpha. The hypothyroidism was described as transient, and thyroid function returns to normal in 2–3 weeks after iodide withdrawal. Some patients may require transient T_4 replacement therapy [23].

7.1.1 Clinical presentation

The presenting clinical features of hypothyroidism depend on the duration and severity, the nature of its onset and the patient's psychological characteristics [24]. The following are the signs and symptoms of hypothyroidism:

- Fatigue
- Weight gain from fluid retention
- Dry skin and cold intolerance
- Yellow skin
- Coarseness or loss of hair
- Hoarseness
- Goitre
- Reflex delay, relaxation phase
- Ataxia
- Constipation
- Memory and mental impairment
- Decreased concentration
- Depression
- Irregular or heavy menses and infertility
- Myalgias
- Hyperlipidaemia
- Bradycardia and hypothermia
- Myxoedema fluid infiltration of tissues

7.1.2 Diagnosis

When there is clinical suspicion of hypothyroidism, a thyroid function test should be performed. Measurement of TSH level is the primary test to confirm primary hypothyroidism. Other laboratory evaluation may include free T_4 and thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin autoantibodies). Imaging studies to evaluate any structural thyroid abnormalities include a thyroid scan, ultrasonography or both [24]. When iodine deficiency occurs during pregnancy, it is associated with foetal hypothyroidism, mental impairment and increased neonatal and infant mortality [25]. In adults, iodine-induced hypothyroidism is rare. The most common manifestation is goitre. Low iodine intake leads to reduced T_4 and T_3 production which results in increased TSH secretion in an attempt to restore normal T_4 and T_3 production. TSH also stimulates thyroid growth leading to goitre. The goitre is initially diffuse but progresses to nodular goitre and eventually to thyroid autonomy and possible hyperthyroidism [26]. Excess iodine ingestion or exposure above the limit of the recommended daily iodine intake induces thyroid dysfunction. Iodine-induced thyroid dysfunction may be subclinical or overt. Excess iodine is generally well tolerated. However,

individuals with underlying thyroid disease or other risk factors may be susceptible to iodine-induced thyroid dysfunction following acute or chronic exposure.

7.1.2.1. Predisposing risk factors in iodine-induced hypothyroidism

Individuals with underlying thyroid disease:

a. Euthyroid Graves' disease previously treated by radioactive iodine, thyroidectomy or anti-thyroid drugs

b. Hashimoto's thyroiditis

c. Euthyroid with a history of subacute thyroiditis

d. Euthyroid with a history of post-partum thyroiditis

e. Euthyroid with a history of type 2 amiodarone-induced thyrotoxicosis

f. Euthyroid posthemithyroidectomy

g. Euthyroid after interferon-alpha therapy

The spectrum of iodine deficiency disorders (IDD) is seen across the life span in various age groups, i.e. foetus, neonate, infants, child, adolescent and adult. They include endemic goitre and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death and infant mortality and varying degrees of other growth and developmental abnormalities (**Table 3**) [27, 28]. Hypothyroidism due to very low iodine intake is now extremely rare. Adults usually have the typical clinical manifestations of hypothyroidism and goitres [29].

Life stage	Spectrum of IDD
Foetus	Abortions Deaf mutism Stillbirths Congenital anomalies Increased perinatal mortality Endemic cretinism
Neonate	Neonatal goitre Neonatal hypothyroidism Endemic mental retardation Increased susceptibility of the thyroid gland to nuclear radiation
Child and adolescent	Goitre Subclinical hypothyroidism Impaired mental retardation Retarded physical development Increased susceptibility of the thyroid gland to nuclear radiation
Adult	Goitre with its complications Hypothyroidism Impaired mental function Hyperthyroidism in the elderly (after iodized salt)

Source: Refs. [27, 28].

Table 3.
The spectrum of IDD across the life span.

7.2 Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism can occur after intake of excess iodine in the diet, exposure to radiographic contrast media for imaging procedures or medications [30]. In iodine-sufficient areas, iodine can induce hyperthyroidism in euthyroid patients with previous thyroid diseases. These include patients who were treated with anti-thyroid drugs for Grave's disease and post-partum thyroiditis [31, 32].

7.2.1 Clinical presentation

The severity and spectrum of symptoms and signs of hyperthyroidism may be related to the duration of the illness, the effects of excess thyroid hormone and the age of the patient [24].

The symptoms and signs include the following:

- Nervousness and irritability
- Palpitations and tachycardia
- Heat intolerance or increased sweating
- Tremor
- Weight loss or gain
- Alterations in appetite
- Frequent bowel movements or diarrhoea
- Dependent lower-extremity oedema
- Sudden paralysis
- Exertional intolerance and dyspnoea
- Menstrual disturbance (decrease flow)
- Impaired fertility
- Mental disturbances
- Sleep disturbances (including insomnia)
- Changes in vision, photophobia, eye irritation, diplopia or exophthalmos
- Fatigue and muscle weakness
- Goitre (depending on cause)
- Pretibial myxoedema

8. Novel strategies for the vulnerable group

In the Iodine Global Network newsletter published on its website, Prof. Dr. Zimmermann had laid out the strategies needed for the vulnerable groups, i.e., the newborns, infants and the children. He had suggested that these tests should be done on these groups respectively: blood thyroid-stimulating hormone, urinary iodine and blood spot thyroglobulin (http://www.ign.org/zimmermann-calls-for-new-strategies-against-idd.htm). He also suggested using the TSH measurement in the newborn screening for iodine assessment. Commonly, iodine-deficient newborns present with elevated TSH. The WHO reported that if the TSH level is greater than 5 mIU/L from the whole blood of 3% of the newborns measured after 3–4 days post-birth, this would indicate that the population is iodine deficient. Another suggestion made by him was to use the newborns' urinary iodine as a marker of IDD in addition to the current practise of measuring the median urinary iodine of the schoolchildren. Using a non-invasive system, urine was collected from infants, and study had shown that in 1200 infants, the baseline TSH of 77 μg/L had increased to 100 μg/L after 4 days post-birth. In addition to that, a system for collecting young children blood spot was done to measure their TG concentration, and a reference range of 4–40 μg/L had been determined. Noteworthy, there are challenges in order to establish a specific international reference range among newborns as there will be differences between the population from the USI areas and the non-USI areas.

9. Conclusion

Excess urinary iodine is generally well tolerated, but individuals with underlying thyroid disease or other risk factors may be susceptible to iodine-induced thyroid dysfunction following acute or chronic exposure. Increased iodine exposure including the global public health efforts of iodine supplementation, the escalating use of iodinated contrast radiologic studies, amiodarone administration in vulnerable patients, excess seaweed consumption and various miscellaneous sources should be looked for.

Iodine-induced thyroid dysfunction may be subclinical or overt. Recognition of the association between iodine excess and iodine-induced hypothyroidism or hyperthyroidism is important in the differential diagnosis of patients who present without a known cause of thyroid dysfunction.

Conflict of interest

It is declared that there is no conflict of interest involved in the publication of this book chapter.

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