Chapter 10
Iodine

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Abstract Iodine is an essential micronutrient for health and maintenance of thyroid function in humans and other vertebrates. The major effects of iodine in the organism are mediated by its action as a structural constituent of thyroid hormones, thyroxine and triiodothyronine, potent regulators of cellular metabolism and growth and development processes. As a component of thyroid hormones, iodine has a crucial role in prenatal and early postnatal ontogenesis due to its involvement in the regulation of neurodevelopment, maturation of the musculoskeletal and respiratory systems and the formation of cognitive function. The adequate iodine status is also an important factor in preventing thyroid disorders and maintaining proper mental and physical health in adulthood. Iodine exhibits some effects not mediated by its action in the composition of thyroid hormones and can be involved in the prevention and inhibition of tumour growth. Iodine deficiency in organism has multiple adverse health consequences, including goitre, hypothyroidism and an increased risk of developing several types of cancer. The activity of the thyroid gland changes with age, and alterations in its function can be associated with longevity; thus, peculiarities of iodine metabolism in older age are of particular interest.

Keywords Iodine · Thyroid gland · Thyroid hormones
Iodothyronine deiodinases · Iodine deficiency disorders · Goitre
Neurodevelopment · Cognitive function · Cancer prevention · Health · Aging
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10.1 Introduction

Iodine (I) [*Gr.* = violet], a halogen of atomic number 53 and atomic mass 126.9 amu, was discovered in 1811 by Bernard Courtois, who separated it from seaweed ash, and was independently identified as a chemical element in 1813 by Joseph Louis Gay-Lussac and Humphry Davy (Kendrick 2016). Along with the 200-year period of fundamental research and practical use of iodine, this element has a thousand-year history of application in medicine. Medications with iodine-rich brown algae *Sargassum* and the thyroid gland of animals were used in ancient China and the ashes of marine sponges were applied in medieval Europe, presumably for the treatment of goitre (Langer 1960). Progress in biochemistry and endocrinology from the late 19th to the middle of the 20th century and subsequent advances in molecular biology made it possible to clarify the biological role of iodine, its metabolism in human organism and the health risks associated with iodine deficiency.

The thyroid gland, which can effectively concentrate iodine from the blood, provides the accumulation and organification of iodine in humans and vertebrate animals. Thyroid tissue is unique among vertebrate tissues because of its ability to synthesize 3,5,3′,5′-tetraiodothyronine (thyroxine, T_4) and 3,5,3′-triiodothyronine (T_3), the only known to date iodine-containing natural compounds that exhibit hormonal activity (Felig et al. 1995; Nicola and Carrasco 2014). Thyroid hormones are involved in the regulation of a wide range of metabolic and physiological processes and mediate the main functions of iodine in human organism. These bioregulators are critical for growth, development, differentiation and maintenance of metabolic balance (Cheng et al. 2010). As an integral component of thyroid hormones, iodine is especially required for development and proper activity of the nervous system and brain maturation (Hetzel 2005; Bernal 2017), as well as for the maturation of the respiratory and musculoskeletal systems during the prenatal and early postnatal periods (Forhead and Fowden 2014). Thyroid hormones are also important for the maturation of the reproductive system and the maintenance of a healthy pregnancy (Krassas et al. 2010), for the functioning of cardiovascular (Klein and Danzi 2016), gastrointestinal (Sirakov and Plateroti 2011) and other vital system throughout life. Iodine exhibits some effects independently of its action in composition of thyroid hormones (such as antioxidant effect) and participates in autoregulation of thyroid functions (Gaertner 2009; Venturi and Venturi 2014). In addition, iodine exhibits an antiproliferative effect and can be involved in prevention of certain types of cancer (Venturi et al. 2000; Brown et al. 2013; Rappaport 2017).

Iodine deficiency in humans leads to metabolic and functional disturbances as a consequence of inadequate formation of thyroid hormones. The spectrum of these disease states is collectively referred to as iodine deficiency disorders, widespread in the world's population (Hetzel 1983; Zimmermann 2009). Endemic goitre is the most visible manifestation of iodine shortage in the organism; however, most severe consequences of iodine deficiency include neurodevelopmental abnormalities and infant mortality (Zimmermann 2016).

Most metabolic disorders observed in conditions of iodine deficiency can be prevented by normalizing iodine intake (Hetzel 2005; Zimmermann 2009). However, the problem of iodine deficiency in population still remains unresolved in many countries. Nearly 1.9 billion people worldwide have inadequate iodine consumption and are at a risk for iodine deficiency disorders, with children, pregnant and lactating women being the most vulnerable groups (Andersson et al. 2012; Zimmermann 2007, 2016). Thus, iodine deficiency is one of the global health problems and attracts considerable attention of the world's scientific community.

In addition, iodine is an element associated with global environmental processes, and its speciation in the atmosphere can contribute to the destruction of atmospheric ozone (Saiz-Lopez et al. 2012). Studies on the global cycle of iodine, its evolutionary significance and essentiality for living systems and various aspects of human health are among actual issues in many areas of scientific research. The aim of this chapter was to analyze the distribution of iodine in the environment, its metabolism in human organism and its importance for human health.

10.2 Iodine Distribution in the Environment

Iodine is an ultra-trace element of the Earth's crust (mean concentration is about 0.25 mg/kg) with an uneven and highly variable distribution in different compartments of the natural environment (Fuge and Johnson 2015). Its concentration is generally low in the lithosphere and reaches higher levels in seawater and in marine and oceanic sediments. Iodine occurs in different oxidation states (from −1 to +7), with I^- (iodide), IO_3^- (iodate) and organic iodine compounds being predominant in the environment (Küpper and Kroneck 2015).

A key part of the global biogeochemical cycle of iodine is its volatilization from the surface of the World Ocean to the atmosphere. Volatile iodine species include molecular iodine (I_2) and organic compounds (CH_3I, CH_2I_2 and CH_2ClI), produced by macrophytic algae, phytoplankton and bacteria (Leblanc et al. 2006). Iodine concentration in the seawater amounts on average 45–60 μg/L, while most freshwater systems contain it at a concentration of <20 μg/L with many values in the range from 0.5 to 5 μg/L (Fuge and Johnson 1986). The total concentration of iodine in the atmosphere is in the range of 10–20 ng/m^3 and includes both the organic and inorganic fractions. In wet and dry precipitation, iodine is transferred from the atmosphere to the land surface and infiltrates the soils, where its concentration varies in the wide range (0.5–50 mg/kg), depending on the soil type and location. The near-coastal soils are enriched in iodine, while those located far from marine influence are relatively depleted in this element (Fuge and Johnson 2015). Iodine is generally strongly adsorbed in soils due to its binding by organic matter and other soil components, while only small amount of the total soil iodine is available for uptake by plants. Heavy rainfalls, seasonal flooding, soil erosion and weathering, excessive use of fertilizers deplete the soil content of iodine. Agricultural cultivation of iodine

depleted soil results in the production of iodine deficient crops that increase risk of iodine deficiency in the residents of such regions.

Iodine has a strong tendency to accumulate in the biosphere and is found in all groups of terrestrial, soil and aquatic biota. Iodine content is usually low in natural vegetation (less than 1 mg/kg), but in some agricultural plants it can be significantly increased by using iodine-containing fertilizers (Medrano-Macías et al. 2016). Marine algae and invertebrates accumulate iodine in much larger quantities than terrestrial biota, with brown algae (Phaeophyceae) being the most potent iodine bioaccumulators among all living organisms. The highest iodine contents have been reported in the species of the genus *Laminaria* with the maximum levels in *Laminaria digitata* (up to 6.12–8.17 g/kg of dry weight) (Teas et al. 2004). To date, more than a hundred iodine-containing natural products have been identified, most of them derived from marine organisms (Küpper and Kroneck 2015). Many of recently discovered compounds of marine origin were found to possess biological activities, including anticancer and antibiotic properties (Gribble 2015).

Iodine is necessary for all classes of vertebrates for the synthesis of thyroid hormones that control embryonic development, postnatal growth and metabolic rate (Tata 2011; Mullur et al. 2014). In amphibians and teleost fishes, thyroid hormones are involved in the control of metamorphosis (Tata 2011). In mammals, thyroid hormones are closely related to the regulation of growth and development processes (Forhead and Fowden 2014). In homeothermal organisms, thyroid hormones play an important role in the regulation of basic metabolism and the processes of obligate and adaptive thermogenesis.

10.3 Iodine in the Human Organism

Iodine is an essential micronutrient for normal growth, metabolism and thyroid function in humans and is primarily used as a substrate for the processes of hormonogenesis in the thyroid gland (Kopp 2005). Total amount of iodine in the human body ranges from 15 to 20 mg with 70–80% of it being stored in the thyroid (Hetzel and Maberly 1987). The major part of iodine enters the human organism via the gastrointestinal tract, including more than 90% of iodine derived from food. Other routes of iodine entry (inhalation, dermal absorption) have only a minor role in iodine intake by humans.

10.3.1 Iodine Absorption in the Digestive Tract

The biologically available form of iodine for humans is an iodide anion that is readily absorbed into the bloodstream from the small intestine, mostly from the duodenum (Josefsson et al. 2002). Other forms of dietary iodine are converted into iodide in the gastrointestinal tract prior to absorption. Iodine-containing organic compounds

are usually decomposed during digestion of food with the release and subsequent absorption of iodide.

Iodide uptake in the intestine is mediated mainly by sodium iodide symporter (Na^+/I^- symporter, NIS) that is identical to the thyroidal NIS (Nicola et al. 2009, 2015). In the small intestinal epithelium, NIS is located in the brush border of enterocytes and can mediate iodide active transport from the intestinal lumen to the cells. Subsequently, iodide can reach the bloodstream, probably through the Cl^- channels (Nicola et al. 2009). Closely linked to NIS is Na^+-multivitamin transporter (SMVT), also capable of transferring iodide, but with a lower affinity. The SMVT may provide a complementary pathway for iodide uptake in the small intestine (de Carvalho and Quick 2011). Iodide is transported via the blood, being weakly bound by plasma proteins. A small fraction of the plasma iodide is in an ionic form.

10.3.2 Iodine Accumulation in the Thyroid Gland and Extrathyroidal Tissues

Iodide is absorbed by thyroid cells in an amount necessary to maintain an adequate thyroid function. In conditions of sufficient iodine intake, the adult human thyroid gland contains 12–15 mg of this element (Hetzel and Maberly 1987). Under physiological conditions, the thyroid absorbs about 60 μg of iodide per day; however, in cases of iodine deficiency, the level of daily iodide uptake by the thyroid gland can be reduced to 20 μg or less (DeGroot 1966). Iodide uptake by human foetal thyroid begins around 10–12 weeks, but increases significantly after 22 weeks of prenatal development until term. Thyroidal iodide uptake is higher in adolescents than in adults and decreases progressively with age (Verger et al. 2001).

Iodide enters the thyroid cells via two routes: (1) active transport involving membrane Na^+/I^- symporter and (2) diffusion through ion channels (McLanahan et al. 2008). The main stages of iodine metabolism in the thyroid are associated with the oxidation of iodide and its subsequent organification followed by the formation and release of thyroid hormones. The formation of iodolipids and deiodination of iodothyronines with the release of iodide also take place in thyroid cells (Köhrle et al. 2005; Gaertner 2009).

In addition to the thyroid gland, a certain amount of iodine can accumulate in some extrathyroidal tissues, mainly in the gastric mucosa, salivary glands and lactating mammary gland (Spitzweg et al. 1998; Dohan et al. 2003; Angelousi et al. 2016). All these cells express the Na^+/I^- symporter and form the major extrathyroidal iodide pool, which can be maintained depending on the level of iodide intake and the physiological status of the organism. In these tissues, as in the thyroid gland, NIS is located in the basolateral membrane of epithelial cells and mediates the uptake of iodide from the bloodstream (Nicola et al. 2009). However, unlike the thyroid gland, nonthyroidal tissues do not possess the ability to organify accumulated iodide (with the possible exception of the lactating mammary gland) (Carrasco 2005).

The mammary gland during lactation concentrates iodide almost as actively as the thyroid and secretes it into milk, providing a substrate for thyroid hormone synthesis in newborns. NIS is present in the healthy breast exclusively during late pregnancy and lactation, in contrast to its constitutive expression in the thyroid (Tazebay et al. 2000). Conversely, malignant cells of the non-lactating mammary gland have been shown to express Na^+/I^- symporter and accumulate iodide (Tazebay et al. 2000; Angelousi et al. 2016).

Iodide accumulation in the gastric mucosa and salivary glands may provide the formation of its endogenous reserve, which can be reabsorbed in conditions of low dietary iodine intake. From the gastric mucosa, iodide is released into the stomach lumen, possibly through the Cl^- channels (Josefsson et al. 2002). Iodide secreted in the saliva and gastric juice can be reabsorbed in the small intestine along with newly ingested iodide.

10.3.3 Excretion of Iodine from Human Organism

Iodine is removed from human body primarily through the excretory system in the form of iodide. Renal excretion accounts for about two thirds of iodide cleared from plasma, and urinary iodide concentration (UIC) is an indicator of recent dietary iodine intake. The remaining part of iodine is excreted through the digestive tract (about 1%), exocrine glands and in the exhaled air (Hetzel and Maberly 1987). Under conditions of strenuous physical activity, iodine can be intensively excreted through the sweat glands. In areas with low iodine intake, the loss of iodide in sweat can be equal to that in urine and can partially contribute to iodine deficiency in people who perform heavy workloads (Smyth and Duntas 2005).

The release of iodine into breast milk is an important route of iodine excretion during lactation. Iodine in milk is represented by iodide and thyroid hormones, mainly thyroxine. Breast milk iodine concentration (BMIC) is closely related to the level of iodine intake and, together with iodine concentration in urine, is considered a biomarker of iodine nutrition in lactating women (Dold et al. 2017). In conditions of iodine sufficiency, BMIC is in the range of 100–150 μg/L, but it has been reported to vary from 5.4 to 2170 μg/L in worldwide studies (Azizi and Smyth 2009). Iodine content in colostrum is significantly higher than in mature milk (Moon and Kim 1999).

10.4 Iodine Turnover in the Thyroid Gland

10.4.1 Thyroid Function and Its Regulation

The thyroid gland has a major role in the concentrating and storing of iodine and is the only specialized endocrine organ capable of synthesizing thyroid hormones, although the expression of genes involved in this process is also found in several nonthyroidal tissues (Sellitti et al. 2000; Kim et al. 2017). Thyroid-stimulating hormone (TSH, thyrotropin), produced by anterior pituitary, is the principal regulator of thyroid gland. TSH is required for the differentiation and proliferation of thyrocytes, the processes of iodide uptake and the synthesis and release of thyroid hormones. Thyrotropin itself is under the control of thyrotropin-releasing hormone (TRH) secreted from the hypothalamus (Felig et al. 1995). These hormones together with thyroxine and T_3 form the hypothalamus-pituitary-thyroid axis, which is regulated by the feedback mechanisms.

Thyrotropin controls thyroid functions and modulates the expression of thyroid-specific genes via interaction with the class A G-protein-coupled receptor located at the basolateral surface of thyrocytes (Kleinau et al. 2017). The regulatory effects of thyrotropin are mostly mediated by the cyclic adenosine 3′,5′-monophosphate (cAMP)-dependent pathway and involve protein kinase A, but TSH can induce also the phospholipase C signal transduction system (Corvilain et al. 1994). A number of additional regulatory factors, including hormones (insulin, glucocorticoids, estradiol), cytokines and growth factors (such as insulin like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β)), as well as follicular thyroglobulin and iodide itself, are involved in the regulation of thyroid functions and can interfere with TSH-stimulatory effects (Deleu et al. 1999; Santin and Furlanetto 2011; Nadolnik 2012; Pesce and Kopp 2014). The transient inhibition of thyroid hormone production by excess iodide is known as the Wolff–Chaikoff effect (Wolff and Chaikoff 1948).

In addition to the synthesis of thyroid hormones, the thyroid gland is capable of iodinating polyunsaturated fatty acids. A range of iodolipid compounds belonging to iodoaldehydes and iodolactones have been identified in human and animal thyroids, with 2-iodohexadecanal (2-IHDA) being the main compound of iodolipid fraction (Gaertner 2009; Rossich et al. 2016). It has been suggested that iodoaldehydes and iodolactones can demonstrate regulatory effects and mediate the inhibitory influence of excess iodide in the thyroid gland (Gaertner 2009).

10.4.2 Membrane Transport of Iodide in Thyrocytes

The ability of the thyroid gland to accumulate iodine was first demonstrated in 1895 by Eugen Baumann, who reported high concentrations of protein-bound iodine in thyroid extracts (Baumann 1895), and two decades later the thyroidal absorption of iodide was described (Marine and Feiss 1915). Significant progress in clarifying the

mechanism of iodide transport and its regulation in the thyroid and extrathyroidal tissues was achieved after characterization of the Na^+/I^- symporter and cloning of genes encoding NIS from rat and human in 1996 (Dai et al. 1996; Smanik et al. 1996).

The Na^+/I^- symporter, also known as SLC5A5 (solute carrier family 5, member 5) is located at the basolateral plasma membrane of thyrocytes and actively cotransports two sodium cations per each iodide anion using an electrochemical sodium gradient generated by Na^+/K^+-ATPase (Dohan et al. 2003; Carrasco 2005; Portulano et al. 2014). NIS has a high affinity for iodide, which allows the thyroid gland to concentrate this anion 20–40 times compared to its concentration in blood plasma. Besides iodide, NIS is capable of transporting other anions, including nitrate (NO_3^-), thiocyanate (SCN^-), and perchlorate (ClO_4^-) that can act as competitive inhibitors of iodide uptake (Tonacchera et al. 2004).

Spontaneous mutations of *SLC5A5* (*NIS*) gene have been identified as causes of a congenital iodine transport defect, an autosomal recessive disorder, leading to thyroid dyshormogenesis and hypothyroidism (Nicola and Carrasco 2014). Conversely, NIS expression is significantly higher in hyperfunctioning thyroid gland in patients with Graves' disease than in healthy thyroid tissue.

Membrane transport of iodide in thyrocytes is controlled primarily by TSH, which up-regulates the expression of Na^+/I^- symporter by either induction of NIS mRNA or posttranslational modification of NIS molecule (Dohan et al. 2003). Regulatory effects of TSH on NIS expression are mainly mediated by activation of adenylyl cyclase, protein kinase A and transcription factor CREB (Portulano et al. 2014). Estradiol down-regulates the expression of NIS and iodide uptake in thyroid cells that possibly explains the higher incidence of goitre in women (Santin and Furlanetto 2011). Insulin and IGF-1 down-regulate the *NIS* gene expression, with phosphatidylinositol-3-kinase (PI3K) participating in their inhibitory effects (García and Santisteban 2002). Tumour necrosis factor-α (TNF-α), TGF-β and some interleukins also inhibit NIS expression in thyrocytes (Pesce and Kopp 2014). Excess iodide was shown to reduce the iodide uptake due to down-regulation of the *NIS* gene transcription through activation of PI3K/Akt pathway (Nascimento et al. 2016).

Iodide transport through an apical membrane of the thyrocyte (iodide efflux) to the intraluminal compartment of the follicle is mediated, in part, by a transporter known as pendrin (SLC26A4, solute carrier family 26, member 4) in conjunction with several other channels such as CLCN5 (chloride channel 5) and calcium-activated anion channel anoctamin 1 (TMEM16A) (Kopp et al. 2017). Biallelic mutations in the *SLC26A4* gene lead to Pendred syndrome, an autosomal recessive disorder characterized mainly by sensorineural deafness, goitre and partial defect in iodide organification (Royaux et al. 2000).

10.4.3 Synthesis of Thyroid Hormones

The central stage in the synthesis of thyroid hormones is iodide organification that takes place in the follicular lumen. This process involves a 660 kDa homodimeric glycoprotein thyroglobulin (TG) that serves as an iodine acceptor in the process of organification, as the scaffold for the synthesis of thyroid hormones, and as an intraglandular store of iodine (Di Jeso and Arvan 2016).

Iodide, being transferred to the outer apical side of the thyrocyte, is oxidized on the cell-colloidal interface and is rapidly organified by the covalent binding to the selected tyrosyl residues of TG with formation of mono- and diiodothyrosines (MIT and DIT, respectively). This process, referred to as organification, is catalyzed by membrane-bound thyroperoxidase (TPO) in the presence of hydrogen peroxide (H_2O_2), which acts as electron acceptor (Ruf and Carayon 2006). Hydrogen peroxide is generated by two members of the NOX (NADPH-oxidase) family: dual oxidases 1 and 2 (DUOX1 and DUOX2, respectively) (Sumimoto 2008).

In the subsequent coupling reaction, also catalyzed by TPO, two iodinated tyrosyl residues within the TG molecules are coupled to form iodothyronines (either T_4 or T_3). Iodinated molecules of TG containing MIT, DIT, T_4 and T_3 are accumulated in the intraluminal colloid of the follicle. To release thyroid hormones, iodinated thyroglobulin is internalized into thyrocytes by micro- and macropinocytosis and undergoes proteolysis in lysosomes (Kopp 2005). This process is accompanied by the release of T_4 and T_3 that are secreted into the bloodstream at the basolateral membrane. The levels of T_4 and T_3 secretion from human thyroid are 80–100 μg and 3–15 μg per day, respectively (Hetzel and Maberly 1987; Nicola and Carrasco 2014). Mechanism of T_4 and T_3 secretion from the thyrocyte involves specific membrane transporters of thyroid hormones, in particular, the monocarboxylate transporter MCT8 (Visser et al. 2011).

Small amount of TG molecules (about 10%) can be subjected to the process of transcytosis (i.e., the vesicular transfer of TG from the apical to the basolateral membranes bypassing the lysosomes) that results in the release of TG into the blood (Tuma and Hubbard 2003). Megalin (gp330), a member of the family of low density lipoprotein receptors, was shown to mediate the TSH-stimulated uptake of TG in thyrocytes and its transcytosis.

Process of hormonogenesis is regulated mainly by TSH, which stimulates the expression of thyroid-specific genes, including those encoding TG and TPO expression. TSH-dependent cAMP cascade is the major regulator of hormone secretion of thyrocytes, whereas TSH-stimulated phospholipase C-dependent pathway activates the formation of H_2O_2 and TG iodination (Kopp 2005). Process of iodide organification is transiently blocked by excess iodide (Koukkou et al. 2017).

10.5 Transport of Thyroid Hormones into the Cells

The entry of thyroid hormones into target cells is mediated by transport proteins, localized in the plasma membrane. These include the Na^+/taurocholate cotransporting polypeptide (NTCP), the members of the family of Na-independent transporters of organic anions (OATP, organic anion transporter polypeptide), L-type amino acid transporters LAT1 and LAT2, and monocarboxylate transporters (MCT). However, only MCT8 and OATP1C1 exhibit a high degree of specificity for iodothyronines (Visser et al. 2011).

10.6 Deiodination of Thyroid Hormones

Studies conducted in the 1970s have shown that about 80–90% of thyroxine secreted from the thyroid gland undergoes deiodination in peripheral tissues with the formation of T_3 and reverse triiodothyronine (rT_3) (Chopra et al. 1978). Subsequently, deiodination process was recognized as an important stage in the metabolism of iodothyronines and in the iodine turnover in the organism (Leonard and Visser 1986). In humans, thyroxine deiodination produces about 80% of T_3 and almost 95% of rT_3 (Leonard and Visser 1986). In addition, about 10% of T_4 initially produced, is deiodinated intrathyroidally with formation of T_3 (Nicola and Carrasco 2014).

Catalysis of oxidation/reduction reactions of iodothyronine deiodination involves three selenium-containing enzymes: iodothyronine 5′-deiodinases type 1 and type 2 (D1 and D2, respectively) and iodothyronine 5-deiodinase type 3 (D3) (Leonard 1990; Bianco et al. 2002; Köhrle et al. 2005). The first two enzymes catalyze the deiodination of the outer (phenolic) ring of thyroxine at the 5′-position that leads to the formation of T_3 (the biologically active form of thyroid hormone). The D3 enzyme is responsible for the deiodination of the inner (tyrosyl) ring of thyroxine in the 5-position, resulting in the formation of 3,3′,5′-triiodothyronine (rT_3), which is generally considered an inactive form of thyroid hormone (although rT_3 can exhibit some local non-genomic effects). Hence, by catalytic conversion of thyroxine to T_3 or rT_3, iodothyronine deiodinases control the activation or inactivation of the thyroid hormone, respectively. The ratio between these two routes of T_4 conversion is regulated by the metabolic situation in the cells and physiological status of the organism. Expression of iodothyronine deiodinases was found to be tissue-specific and regulated by a number of factors (hormones, cytokines, growth factors, neurohumoral and alimentary factors) (Bianco et al. 2002; Antonyak et al. 2002; Köhrle et al. 2005; Bianco 2011; Antonyak and Vlizlo 2013).

These three enzymes share significant homology of the primary structure and possess the amino acid selenocysteine residue Sec (SeCys) in the active site. The Sec incorporation into enzyme molecules is determined by UGA codon and by a segment SECIS (selenocysteine insertion sequence), which is located in the 3′-untranslated region of selenoprotein mRNA. Several other factors are involved in this process,

namely: selenocysteine-specific $tRNA^{Ser(Sec)}$, specific for eukaryotes elongation factor eEFsec and the SECIS-binding protein SBP2 (SECIS binding protein 2) (Bianco et al. 2002).

D1 catalyzes primarily 5′-deiodination of T_4 and other iodothyronines, and its activity leads to the release of the main portion of T_3 into the blood. D1 is widely expressed in tissues, with the highest levels in the liver, kidneys and thyroid gland (Leonard 1990; Köhrle et al. 2005). Consequently, both the liver and kidney are the most important organs of extrathyroidal T_3 formation.

D2 specifically catalyzes deiodination of the outer ring of T_4, without showing an affinity for T_3 (Leonard 1990). The D2 enzyme is primarily responsible for the local T_3 production in target cells, and its activity is regulated by ubiquitination/deubiquitination mechanism (Bianco 2011). Expression of D2 has been found in the cerebral cortex, anterior pituitary, placenta, brown adipose tissue, thyroid gland, cardiac and skeletal muscles, skeleton, skin and haemo- and lymphopoiesis systems (Croteau et al. 1996; Soutto et al. 1998; Babych et al. 1999, 2000a, b; Antonyak et al. 2002; Bianco 2011).

The D3 enzyme, which is expressed in brain, placenta, skin and some other tissues, catalyzes T_4 conversion to rT_3 and deiodination of T_3 to 3,3′-diiodotyronine (3,3′-T_2) (Leonard 1990; Huang 2005). The physiological role of D3 is considered as the inactivation of excess thyroxine and T_3 by converting them to the inert compounds. High levels of 5-deiodination activity are found in embryonic tissues.

Alterations in the thyroid hormone deiodination system are observed in the ontogenesis of humans and animals, during pregnancy and other physiological states and in diseases (Bianco 2011; Antonyak and Vlizlo 2013). A range of studies have shown a correlation between the expression of 5′-deiodinases and cell differentiation; the changes in the deiodinase expression have been also detected in malignant cells (Schreck et al. 1994; Babych et al. 1998, 1999; Gouveia et al. 2005; Huang 2009; Miro et al. 2017).

10.7 Biological Effects of Thyroid Hormones in the Organism

Most functions of iodine in mammals are mediated by the effects of thyroid hormones, known as potent bioregulators of metabolic processes. Thyroid hormones are involved in maintaining the basic metabolism and regulation of cell proliferation, differentiation and apoptosis (Felig et al. 1995; Hulbert 2000; Babych et al. 2000c; Tata 2011; Mullur et al. 2014; Deng et al. 2017). These hormones are involved in the regulation of growth and development of the organism, tissue regeneration, maturation and maintenance of proper functioning of organ systems (Forhead and Fowden 2014). Their importance is proved for the maturation of the central nervous system (Calza et al. 2015; Bernal 2017), regulation of functions of cardiovascular (Klein and Danzi 2016), musculoskeletal (Anwar and Gibofsky 2010), gastrointestinal (Sirakov and

Plateroti 2011; Brown et al. 2013), reproductive (Krassas et al. 2010) systems. Thyroid hormones also participate in the regulation of haematopoiesis, immune function, respiratory function and blood cell metabolism (Sukhomlinov et al. 1986; Snitynsky and Antonyak 1995; Antoniak 1999; Babych et al. 2000c, d, e; Jara et al. 2017).

Although thyroxine is the main thyroid hormone secreted by the thyroid gland, it is considered a prohormone of T_3, which is able to regulate gene expression. The T_3 was demonstrated to be present in human plasma by J. Gross and R. Pitt-Rivers in 1952, and its role in the regulation of transcription process was shown in the 1960s by J. R. Tata and colleagues (Tata 2011). A range of vitally important genes were shown to be directly activated by T_3 at the transcriptional level (Huang et al. 2008). The T_3-target genes include the genes of structural and regulatory proteins, those that participate in metabolic processes, detoxification, transduction of regulatory signals, adhesion and cell migration. In addition, a number of transcription factors and cell cycle regulators are activated by T_3 (Tarım 2011). These effects of the thyroid hormone largely mediate the influence of iodine on metabolic processes in human and vertebrate animals.

Thyroid hormone nuclear receptors (TRs) are non-histone proteins acting as ligand-dependent transcriptional activators by binding to the response-elements (TRE) in promoter regions of target genes (Zhang and Lazar 2000; Antoniak et al. 2000; Boelen et al. 2012). TR expression is determined by *TRα* and *TRβ* genes, located in humans on chromosomes 17 and 3, respectively (Yen 2001). Genomic effects of thyroid hormone are mediated by TR receptor isoforms α1, β1 and β2 that regulate target genes in the presence or absence of T_3 by involving the co-regulatory complexes (nuclear corepressors and coactivators) (Boelen et al. 2012). The TRs often act as homodimers, but also as heterodimers with the retinoid-X receptor. The TRα1 and TRβ1 are widely expressed in tissues, with high level of TRα1 expression in the cardiac and skeletal muscles and TRβ1 as the main TR isoform in the liver. Expression of TRβ2 is restricted to the anterior pituitary gland, hypothalamus, the developing brain and the inner ear (Yen 2001).

Iodothyronines can act also through non-genomic mechanisms that are not initiated by liganding of T_3 to nuclear receptors (Davis et al. 2016). These effects may be initiated by interaction of iodothyronines with the binding sites located in the plasma membrane or in cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin αvβ3 that activates mitogen-activated protein kinase (MAPK) cascade. The T_3 can also activate phosphatidylinositol 3-kinase (PI3K) pathway by a mechanism that may be cytoplasmic in origin or may begin at integrin αvβ3 (Cheng et al. 2010). These mechanisms can potentially influence gene expression. In addition, iodothyronines have effects on mitochondrial energetics by modulating the basal proton leak in mitochondria that accounts for heat production and cellular oxygen consumption (Felig et al. 1995). Thyroid hormone can also act on the mitochondrial genome via imported isoforms of nuclear TRs to affect several mitochondrial transcription factors (Cheng et al. 2010).

10.8 Iodine in Human Nutrition

10.8.1 Recommended Norms for Iodine Intake

Inadequate intake of iodine is associated with a broad spectrum of thyroid disorders related to both the deficiency and excess iodine in the organism. To prevent the development of adverse effects, especially those associated with insufficient iodine intake, and to maintain proper thyroid function, optimal levels of iodine intake have been established by international health agencies for different population subgroups. According to the recommendations of the World Health Organization (WHO) based on the propositions of the United Nation Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), the daily intake of iodine should be as follows: 90 μg for preschool children (0–59 months); 120 μg for schoolchildren (6–12 years); 150 μg for adolescents (above 12 years) and adults; 250 μg for pregnant and lactating women (WHO 2007). When assessing the level of iodine intake using the urinary iodine concentration as an indicator, iodine consumption can be considered adequate when the UIC is 100–199 μg/L in the general population and 150–249 μg/L in pregnant women (WHO 2007).

Several studies recommend a higher daily intake of iodine in pregnant and lactating women: 250–300 and 225–350 μg, respectively, because of significant increase in iodine requirements in women during pregnancy and lactation and the positive effects of this element on the development of the child in prenatal period and in infancy (Delange 2004, 2007). In particular, need for iodine increases by ≥ 50% during pregnancy (Zimmermann 2016) due to several factors: increased demand for T_4 to maintain normal metabolism in the mother; transfer of T_4 and iodide from mother to foetus; increased loss of iodide through the kidneys (Delange 2004). Since part of the maternal iodine is taken up by the growing foetus and placenta, a decrease in the amount of absorbed iodine, available to the mother, is more obvious in the second half of pregnancy (Verger et al. 2001).

10.8.2 Sources of Iodine and Levels of Iodine Intake

The estimated daily iodine intake in residents of different countries varies widely, from < 50 μg in the population of iodine deficiency areas to 500 μg and above in people who regularly consume marine foods (WHO 2004; Zava and Zava 2011; Abt et al. 2016). In several areas of Africa, Asia, Latin America, and parts of Europe, iodine consumption is insufficient and varies from 20 to 80 μg per day, while dietary intake of iodine by residents of Japan, the USA and Canada is higher compared to the population of other countries (WHO 2004). Recent findings based on iodine concentration in food samples suggest that the mean daily iodine intake for the total USA population is 216.4 μg per person (Abt et al. 2016). In contrast, iodine intake

by the population of Japan is 1–3 mg/day, but in some cases this index is significantly higher (up to 10 mg/day and above) (Zava and Zava 2011).

Food analysis shows that iodine levels in the main food groups range as follows (data indicate geometric mean for each group): marine fish (1294.6 μg/kg) > freshwater fish (102.8 μg/kg) > leafy vegetables (88.8 μg/kg) > milk and dairy products (83.9 μg/kg) > other vegetables (80.1 μg/kg) > meat (68.4 μg/kg) > cereals (56.0 μg/kg) > fresh fruits (30.6 μg/kg) > bread (18.3 μg/kg) > water (6.4 μg/L) (Fordyce 2003). In addition, iodine concentrations in edible marine invertebrate species vary from 308 μg/kg in crab tissues to 1300–1400 μg/kg in shrimp and mussels (Wayne et al. 1964), while commercially available seaweed products contain iodine averagely 16–1540 mg/kg dry weight (up to 8.17 g/kg in kelp granules made of dried algae) (Teas et al. 2004). Consequently, marine algae, fish and shellfish are the most potent natural source of iodine in human nutrition. These foods are traditionally consumed by the population in Asian countries, with seaweed accounting for 10–25% of people's diet in Japan (Yuan and Walsh 2006).

In addition to marine foods, milk and dairy products, being particularly important sources of iodine for children and pregnant women, also make a significant contribution to iodine intake by population. In some countries milk has been shown to be the principal source of dietary iodine. Contribution of milk and dairy products to the total level of iodine consumption comprises about 50% in the USA, Canada and Europe (Fordyce 2003). Iodine concentration in cow's milk was shown to vary from 50–130 μg/L to considerably higher levels (up to 2000 μg/L), depending on the stage of lactation, seasonality and composition of cattle feeds (Fordyce 2003; Flachowsky et al. 2014).

10.8.3 Inhibitors of Iodine Uptake

Regardless of iodine levels in foods, the absorption of this micronutrient in the gastrointestinal tract and in the thyroid depends on food composition and on the presence of various xenobiotics that can get into agricultural products as a result of environmental pollution (Miller et al. 2009). NIS inhibitors such as perchlorate and thiocyanate present in food can interfere with iodide uptake in the intestine, thyroid and lactating mammary gland and reduce its content in breast milk, creating a risk of iodine deficiency in infants (Pearce et al. 2007). Excess iodide inhibits iodide absorption in the intestine and in the thyroid gland (Nicola et al. 2015).

Plant secondary metabolites, such as glucosinolates and cyanogenic glycosides, can affect iodine uptake, since degradation and detoxification of these compounds in the digestive tract lead to the formation of thiocyanate (Gaitan 1990). These compounds are referred to as goitrogens, as if consumed in high amounts, can contribute to development of goitre and hypothyroidism. Several flavonoids present in plants (including soy isoflavones) also have a goitrogenic potential due to the inhibition of the iodide uptake and thyroperoxidase activity (Gonçalves et al. 2017).

10.9 Consequences of Inadequate Iodine Intake

10.9.1 Iodine Deficiency Disorders

In conditions of unbalanced nutrition of people living in areas with low content of iodine in soils (areas remote from the marine environment, mountain areas, etc.), the amount of iodine entering the body can be less than optimal demand. Long-term deficiency of iodine in the organism leads to a decrease in the synthesis of thyroid hormones and is associated with a range of metabolic and functional disorders that result from thyroid dysfunction. These include goitre, hypothyroidism, and impaired growth and development in children (Zimmermann 2009). Furthermore, the iodine deficiency increases pregnancy loss, foetal development anomalies and infant mortality and is the leading preventable cause of mental deficiency in childhood (WHO 2007; Zimmermann 2007). These disease states are generally referred to as "iodine deficiency disorders" (IDD) (Hetzel 1983; WHO 1994).

As is known, thyroid function is controlled by the dynamic interrelationships between the hypothalamus, the pituitary gland and the thyroid. Under physiological conditions, the function of the thyroid gland is tightly controlled by TSH, whose secretion typically increases when iodine intake declines below the 100 μg/day (Zimmermann 2009). TSH stimulates the thyroidal iodide uptake from the blood and its recycling within the thyroid, and increases the efficiency of thyroid hormone production by up-regulating the genes of NIS and components of the hormone synthesis system. However, this mechanism can fail in conditions when the supply of iodine is chronically too low to maintain an adequate function of the thyroid gland. A very low level of iodine intake during a certain period can reduce thyroid hormone production even in the presence of elevated TSH levels. Consequently, depending on the level of decrease in iodine intake and the duration of iodine deficiency, there may be different degrees of thyroid dysfunction. Based on the UIC measurement, the degree of iodine deficiency in the population is classified as mild (UIC 50–99 μg/L), moderate (UIC 20–49 μg/L) or severe (UIC < 20 μg/L) (WHO 2007).

In conditions of long-term iodine intake in amounts below the 50 μg/day, the stimulating effect of elevated serum TSH levels on thyrocytes leads to the enlargement of the thyroid gland, known as goitre. Goitre is usually the earliest clinical sign of iodine deficiency, and can be regarded as an adaptive disease that develops in response to an insufficient supply of dietary iodine (Stanbury et al. 1954). Goitre is 20–30 times more common in women than in men, and is most commonly observed in young girls at the age of puberty. A more severe iodine deficiency (in conditions of daily iodide intake below 10–20 μg) can lead to hypothyroidism (insufficient production of thyroid hormones). Although many people with goitre have normal thyroid hormone levels, studies have shown that more than 30% of the persons in endemic areas are hypothyroid, despite the enlargement of their thyroid gland (Kapil 2007).

Being the most common manifestation of iodine deficiency, endemic goitre has for centuries prevailed in the inhabitants of the mountainous regions, such as the

Himalayas, Alps, and Andes and in areas with frequent flooding. In addition to suffering from goitre, a certain proportion of the population in these regions was affected by endemic cretinism, manifested by mental deficiency, neurological disorders, short stature and often deafness. The relationship between iodine scarcity in environmental components and the development of endemic goitre and cretinism was established by G. A. Chatin in the 1850s (Chatin 1853).

Iodine deficiency can arise in the organism at any age, but children, pregnant women and lactating mothers are the most vulnerable groups for IDD (WHO 2007; Delange 2007; Zimmermann 2016; Nyström et al. 2016). Severe iodine deficiency in pregnant women can lead to the pregnancy loss, stillbirth and perinatal mortality, and adversely affects the development of a child (WHO 2007). This especially refers to the period before the onset of foetal thyroid function (the second trimester of pregnancy), when human foetus is entirely dependent on the maternal thyroid hormone. Subsequently, after the foetal thyroid gland begins to function, maternal iodine is necessary for the production of foetal thyroid hormones involved in the regulation of development and maturation of the brain, musculoskeletal, respiratory, auditory and other systems of the foetus (Forhead and Fowden 2014).

Daily iodide intake below about 10–20 μg in pregnant women can cause maternal and foetal hypothyroidism and result in major neurodevelopmental deficits and goitre in their offspring. The most severe consequence of iodine shortage during the prenatal period is cretinism, accompanied by an intellectual disability that arises primarily as a result of irreversible brain damage caused by a deficiency of thyroid hormones (Zimmermann 2016). The lesser degrees of iodine deficiency in pregnant and lactating women can also cause thyroid dysfunction and potentially affect neurodevelopment in infants and children with long-term adverse consequences. A study, performed in Australia has shown that even mild iodine deficiency in pregnant women was associated with lower education outcomes in their children aged 9 years (Hynes et al. 2013). The authors have concluded that the adverse impacts of maternal mild iodine deficiency on foetal neurocognitive development are not ameliorated by iodine sufficiency during childhood.

Being especially required by infants and their mothers, iodine is an important micronutrient for growth, physical and mental development of preschool and school-age children. Iodine deficiency in children is characteristically associated with goitre. Goitre rate increases with children's age and reaches a maximum in adolescence. Inadequate iodine intake during these periods of life can lead to retarded physical development, delayed puberty, weight gain, slower growth and decreased intelligence with a decline in cognitive function, including memory and thinking skills. The observational studies have reported differences in intelligence quotient (IQ) between groups of children living in iodine-sufficient areas and those from the areas of iodine deficiency (Bleichrodt and Born 1994; Qian et al. 2005). In particular, meta-analysis made in China has shown a 12–13 point lower IQ score in children of lower iodine status (Qian et al. 2005). A decrease of 6.9–10.2 IQ points is observed in iodine-deficient children of 5 years old and under in comparison with iodine replete children (Bougma et al. 2013). The lowering of intelligence due to iodine shortage affects the educational potential of children. According to Wolka et al. (2013), children with

goitre had a 1.8 times greater odds of having a below-average academic achievement than children who did not have goitre (Wolka et al. 2013). Similar negative effect of iodine deficiency on the mental performance of schoolchildren has been revealed in other studies (Pineda-Lucatero et al. 2008). The adverse health consequences of iodine deficiency in the periods of childhood and adolescence can lead to reduction in both productivity and intellectual potential in adulthood.

Adequate iodine intake is necessary for health also in adult age, and iodine status is a key determinant of thyroid disorders in adults. Severe iodine deficiency in adult persons causes goitre and its complications, hypothyroidism, endemic mental deficiency, and decreased fertility rate. In conditions of mild and moderate iodine deficiency, increased thyroid activity can compensate for low iodine intake and maintain euthyroidal state in most persons, however, long-term thyroid stimulation results in an increase in the prevalence of toxic nodular goitre and hyperthyroidism in populations (Zimmermann and Boelaert 2015).

10.9.2 Hypothyroidism

Lack of iodine, leading to inadequate synthesis of thyroid hormones, is one of the common causes of hypothyroidism, which is defined as a complex of clinical symptoms caused by impaired thyroid function or insufficient action of thyroid hormones in target tissues (Almandoz and Gharib 2012). Apart to the conditions of iodine deficiency, hypothyroidism can also be caused by a disruption in the ability of the thyroid gland to absorb and organify iodide as a result of congenital defects in the expression of NIS and components of the hormone synthesis system; the harmful effects of alimentary factors, medications and environmental contaminants; because of the destructive treatment of thyrotoxicosis or due to a chronic autoimmune disease. In addition, rare cases of hypothyroidism can result from hypothalamic or pituitary dysfunction (Persani and Bonomi 2017).

The initial stage of hypothyroidism is latent (subclinical) hypothyroidism, which is defined biochemically by an elevated serum TSH concentration (above of 4.0 mU/L) and normal serum free thyroxine (fT_4) level (Almandoz and Gharib 2012; Schübel et al. 2017). Subclinical hypothyroidism often occurs asymptomatically, but nearly 30% of patients with this condition may have symptoms that are suggestive of thyroid hormone deficiency. According to epidemiologic studies, subclinical hypothyroidism occurs in 3–10% of the general population and is more common in women than in men (Schübel et al. 2017). Latent hypothyroidism can progress to overt hypothyroidism from 2–5% (Khandelwal and Tandon 2012) to about 18% of affected patients per year (Parle et al. 1991). Overt hypothyroidism is defined as a combination of low fT_4 and high TSH concentrations (Bensenor et al. 2012). In general, hypothyroidism affects 3–8% of men and 5–20% of women, and occurs most frequently in older women (Laurberg et al. 2005; Bensenor et al. 2012).

Hypothyroidism, in particular its subclinical form, is the most common pregnancy-related thyroid disorder, affecting 3–5% of all pregnant women, and is associated with

a higher risk of pregnancy loss, placental abruption, premature rupture of membranes, and neonatal mortality (Maraka et al. 2016). High TSH levels in pregnant women have been also associated with an increased risk of developing neurocognitive deficits in offspring.

10.9.3 Tumour-Promoting Effects of Iodine Deficiency

The prevalence of goitre and thyroid nodules is known to be higher in populations living in areas with iodine deficiency (Carlé et al. 2014), and in many cases goitre and nodularity precede the development of thyroid cancer. The relationship between iodine deficiency and thyroid cancer incidence was demonstrated in the 1920s by Carl Wegelin, who argued that thyroid cancer was more common in endemic goitre areas, with a frequency ranging from 1.04% in central Switzerland (the area of endemic goitre) to 0.09% in Berlin (non-endemic region) (Wegelin 1928). In animal studies, iodine deficiency induces thyroid tumours and promotes thyroid carcinogenesis under an influence of carcinogens, such as N-bis(2-hydroxypropyI)-nitrosamine (DHPN) or N-nitrosomethylurea (NMU) (Ohshima and Ward 1986; Zimmermann and Galetti 2015).

A number of studies suggest that iodine deficiency can have a causative role in the incidence of breast cancer (Stadel 1976; Aceves et al. 2013; Rappaport 2017) and increases the risk of endometrial, ovarian and stomach cancers (Stadel 1976; Gołkowski et al. 2007).

10.9.4 Prevention of Iodine Deficiency

It has been proven that most of metabolic abnormalities observed in the circumstances of iodine deficiency, are preventable and can be avoided by normalizing the iodine intake. The use of iodine to prevent iodine deficiency disorders began with the research of David Marine, who first used low doses of iodide to reduce the manifestations of goitre in schoolchildren in 1917 (Marine and Kimball 1917). Then the program of iodization of table salt was developed in the USA and Switzerland in the 1920s, and subsequently this practice was introduced in a number of countries. By the 1970s, it became apparent that iodine supplementation reduced the level of intellectual impairment and infant mortality rates (Hetzel 1983). In 1993, WHO and UNICEF recommended universal salt iodisation as the main strategy to achieve elimination of IDD in the world population (WHO 1994), with iodised salt containing iodine in an amount of 15–80 mg/kg. Since then, there has been significant progress in increasing the use of adequately iodised dietary salt worldwide, and as a result, many countries have achieved, or are now on the threshold of achieving IDD elimination. In 2015, around 100 countries had national iodized salt programs (Zimmermann and Galetti 2015).

However, despite the fact that IDD have been eliminated in most areas with severe iodine deficiency, many countries, including industrialized ones, still show a mild to moderate degree of iodine deficiency. The IDD remain a global public health problem, as approximately 1.9 billion people are at risk worldwide (Andersson et al. 2012). On the basis of current surveys performed in 152 countries, 29 are affected by iodine deficiency (Zimmermann and Boelaert 2015). Globally, 29.8% of school-age children (241 million) are estimated to have insufficient iodine intakes (Andersson et al. 2012), while in Europe this index comprises about 44% (Taylor et al. 2014). Many pregnant women in European and other countries are also at risk for IDD due to inadequate iodine intakes (Zimmermann 2007). Dietary deficiencies of the micronutrients (selenium, iron, and vitamin A) may interact with iodine deficiency and affect the response of iodine-deficient persons to iodine supplementation (Zimmermann 2009).

To date, various strategies have been developed in order to increase iodine content in people's diet and in the foodstuffs. Biofortification of food plants with iodine is considered as an effective method of iodine supply to the population and a novel strategy for the prevention of iodine deficiency in humans (Gonzali et al. 2017). The use of iodine supplements for feeding livestock and poultry remains an important way of increasing iodine concentration in dairy products and in eggs (Flachowsky et al. 2014). One way to increase iodine intake in a population is the producing of iodine-enriched food products such as bread, sweets, etc. Consumption of foods of marine origin is also important for increasing the level of iodine intake; however, a high level of consumption of iodine-rich foods, mainly seaweed, can adversely affect people with thyroid disorders.

10.9.5 Excessive Iodine Intake

Excessive iodine intake in humans occurs less often than iodine deficiency, since common diets consisting of natural foods (with the exception of marine products) usually contain less than 1 mg of iodine per day. However, such a situation can arise when the diet contains a large amount of marine fish or seaweed or when a person takes medications containing iodine such as amiodarone and diagnostic contrast agents. In particular, taking an antiarrhythmic medication amiodarone leads to an additional intake of 3–21 mg of iodine daily (Aceves et al. 2013). Intake of excess iodine can also occur when, in the context of iodine prophylaxis, salt iodisation is excessive and poorly controlled (WHO 2007).

There are a variety of data relating to people's tolerance to different doses of iodine. While some studies show that consumption of iodine at a dose of 2 mg per day should be considered harmful to humans (Wolff 1969), there are many studies suggesting that low and intermediate doses of iodine (1.5–8 and 10–32 mg/day, respectively) are well tolerated in euthyroid persons (Backer and Hollowell 2000; Bürgi 2010). High tolerance to iodine is observed in all animal species studied, pointing to a wide margin of safety for this element (WHO 1996).

On the other hand, long-term consumption of excess iodine from medical sources, foods or food additives with exceptionally high iodine content has been associated with the development of thyroid autoantibodies and may lead to alterations in thyroid function, including autoimmune thyroiditis, goitre, hyperthyroidism and hypothyroidism (Luo et al. 2014; Foppiani et al. 2016). Therefore, it is important to take into account the maximum safe level of iodine intake, especially for population subgroups at risk of developing thyroid dysfunction.

The ICCIDD has proposed that 150–299 μg iodine per day is adequate to cover the thyroid requirement, and the RDA (Recommended Dietary Allowances) suggested the maximal allowable dietary dose of iodine 1.0 mg/day for children and 2.0 mg/day for adults (Aceves et al. 2013). According to recommendation of health agencies, a tolerable upper level (the approximate threshold below which notable adverse effects are unlikely to occur in the healthy population) of iodine intake is of 1100 μg per day in adults (Leung and Braverman 2014). In Japan, a safe upper limit of iodine intake was set by the Ministry of Health, Labor and Welfare at a level of 3 mg/day (Zava and Zava 2011). When estimating iodine intake in the population, WHO recommends that UIC values ≥ 300 μg/L and ≥ 500 μg/L be considered as indicative of excessive iodine intake in children and adults, and in pregnant women, respectively (WHO 2007).

10.9.6 Effects of Excessive Iodine Intake

The organism of healthy persons possesses mechanisms of adaptation to the conditions of excess iodine, and the majority of people tolerate a wide range of dietary iodine levels. When iodide is consumed in large amounts, its absorption in the gastrointestinal tract can be reduced due to inhibition of NIS in the cells of the small intestinal mucosa (Nicola et al. 2015). At the level of the thyroid gland, the excess iodide can inhibit the production of thyroid hormones (the Wolff–Chaikoff effect) by affecting each step leading to their secretion, namely: iodide uptake, iodide organification and secretory process itself (Ferreira et al. 2005), but the rate-limiting step for these effects depends on thyroperoxidase activity. The inhibition is usually transient (lasting 24–48 h) and is followed by normalization of thyroid hormone production (the "escape" from the Wolff–Chaikoff effect). The transient inhibition of thyroid hormone production is an autoregulatory mechanism that shields organism against hyperthyroidism in conditions of abundant iodine supply, while the resumption of thyroid function provides the maintenance of euthyroid state. Mechanism for the acute Wolff–Chaikoff effect is considered to be mediated by generation of intrathyroidal iodolipid compounds (iodolactones, iodoaldehydes) and their inhibitory effects on iodide organification catalyzed by thyroperoxidase (Pramyothin et al. 2011).

Unlike to healthy individuals, the persons with thyroid disorders might fail to "escape" from the Wolff-Chaikoff effect that can lead to iodine-induced hypothyroidism. Susceptible persons include patients with the autoimmune thyroid disease, thyroiditis, amiodarone-induced thyrotoxicosis of type 2; those with a previous

surgery, treatment with radioiodine or antithyroid drugs for Graves' disease; patients treated with interferon-α, and persons concomitantly using the potential goitrogens (Leung and Braverman 2014). Exposure to high concentrations of iodide in healthy persons may also lead to a decrease in production of thyroid hormones that is accompanied by a mild increase in the serum TSH level (often to the upper limit of the normal range) (Pramyothin et al. 2011). Hypothyroid state has been also observed in infants born to mothers who consumed excessive amounts of seaweed during pregnancy and lactation (Shumer et al. 2013). There have been reports of several cases of congenital hypothyroidism in newborns caused by maternal intake of excess iodine tablets during pregnancy (Connelly et al. 2012).

In some susceptible persons, excess iodine leads to hyperthyroidism, that is, excess thyroid hormones in the circulation because of their increased production by a hyperactive thyroid gland. The elevated levels of thyroid hormones suppress TSH secretion from the pituitary in a negative feedback loop (Sharma et al. 2011). Iodine-induced hyperthyroidism, also known as the Jod–Basedow phenomenon, was first described in the early 1800s in the context of the treatment the endemic goitre. It has been observed that in patients with goitre treated with iodine, thyrotoxicosis develops more often than in persons without goitre (Coindet 1821). This type of hyperthyroidism is much more common in iodine-deficient areas than in areas where the diet contains sufficient amount of iodine. The risk factors for iodine-induced hyperthyroidism include long standing iodine deficiency, latent Graves' disease and nontoxic or diffuse nodular goitre (Leung and Braverman 2014). Iodine-induced hyperthyroidism has also been observed in euthyroid patients with nodular goitre in iodine-sufficient areas in conditions of excessive iodine supplementation. In general, hyperthyroidism is found in about 2% of women and 0.2% of men (Pearce 2006). Subclinical hyperthyroidism, defined as low serum TSH in the presence of normal thyroid hormone levels, affects about 3% of the population.

Besides iodine-induced alteration in thyroid function, excessive iodine intake also affects other aspects of thyroid health. High levels of iodine intake can increase the prevalence of autoimmune thyroiditis, as shown in animal model and in humans (Kahaly et al. 1998; Harach and Ceballos 2008; Leung and Braverman 2014). Autoimmune thyroiditis is more common in iodine-replete areas compared with areas of iodine deficiency, and its incidence increase after iodine prophylaxis both in non-goitrous and iodine-deficient areas (Harach and Ceballos 2008). In particular, a study conducted by Kahaly et al. (1998) has shown that high microsomal and thyroglobulin autoantibodies titres with marked lymphocyte infiltration in the thyroid gland were present in six of 31 goitrous patients (19%) who received iodine at a dose of 0.5 mg/day for 6 months; while iodine-induced hypo- and hyperthyroidism developed in four and two of them, respectively.

10.10 The Extrathyronine Effects of Iodine in the Organism

Apart from the participation in the structure of thyroid hormones, iodine can have some additional functions in human organism that are not mediated by iodothyronines. A number of studies have shown the antioxidant effects of iodine, its effects on cell proliferation and promotion of apoptosis, induction of cell differentiation, protective effects against some types of cancer, anti-inflammatory effects, and possible participation in mechanism of cell mediated immunity (Venturi 2011; Swietaszczyk and Pilecki 2012; Aceves et al. 2013; Venturi and Venturi 2014).

In many patho-physiological conditions, effects of iodine are mediated by iodolipid compounds, formed in the thyroid gland. In addition to the involvement of iodolipids in mediating the Wolff–Chaikoff effect, these compounds can mediate the inhibitory effects of excess iodide on thyroid cell proliferation and modulate the signals of TSH and cytokines (Gaertner 2009; Soriguer et al. 2011; Swietaszczyk and Pilecki 2012; Rossich et al. 2016). In particular, 2-IHDA has a suppressive effect on adenylyl cyclase, which participates in cAMP formation, whereas 6-iodo-5-hydroxyeicosatrienoic acid δ-iodolactone (6-IL) can inhibit calcium-dependent protein kinase C and signaling pathways induced by local growth factors. Iodolipid compounds also show antiproliferative effects and trigger apoptosis in thyrocytes and some other types of cells (Swietaszczyk and Pilecki 2012; Rossich et al. 2016).

10.10.1 Antioxidant Function of Iodide

Iodine can act both as the oxidizing and reducing agent, depending on its chemical form and surrounding milieu. In the thyroid, iodide oxidation underlies the processes of tyrosine iodination and the formation of thyroid hormones. At the same time, iodide, by releasing electrons, is a reducing agent and, hence, can perform an antioxidant function. As electron donor, iodide can quench $^{\cdot}OH$–radical and H_2O_2; however, iodide can also act as a free radical capable of iodinating tyrosine, histidine and some polyunsaturated fatty acids in cell membranes making them less reactive with oxygen radicals (Smyth 2003; Aceves et al. 2013).

Together with peroxidases that transfer electrons to hydrogen peroxide, iodide can contribute to H_2O_2 detoxification and reduce cell damage (Venturi 2011). Iodide has been suggested to have an antioxidant function in the thyroid, mammary gland, stomach and salivary glands, where it is accumulated (Venturi et al. 2000; Smyth 2003; Venturi and Venturi 2014), while insufficient iodide intake leads to accumulation of malondialdehyde and other products of lipid peroxidation. In addition, iodide increase the total antioxidant status in human serum (Soriguer et al. 2011), and protect brain cells from lipid peroxidation (Venturi and Venturi 2014).

Some authors hypothesize that iodide together with peroxidases plays an antioxidant role in all organisms containing cells capable of concentrating iodine—from

algae to vertebrates and can be considered the most ancient antioxidant in the evolutionary sense (Venturi et al. 2000; Venturi and Venturi 2014).

10.10.2 Antitumor Effects of Iodine

It has been demonstrated that iodine exhibits an antiproliferative/cytotoxic effect on a number of malignant cells and has a protective role in several types of cancer, including thyroid, breast and stomach cancer (Venturi et al. 2000; Brown et al. 2013; Rösner et al. 2016; Rappaport 2017). Since the 1920s, there are a number of studies suggesting a lower risk of developing thyroid cancer with a higher level of iodine intake (Zimmermann and Galetti 2015). At the same time, a moderately elevated level of iodine consumption can contribute to reducing risk of several extrathyroidal cancers. In animal and human studies, iodine administration has been shown to cause regression of both iodine-deficient goitre and benign pathological breast tissue (Cann et al. 2000). The evidence of the antineoplastic effect of iodine in extrathyroidal tissues was obtained in the 1990s (Kato et al. 1994). Subsequently, it has been found that molecular iodine, which can be taken by cells through a pathway not mediated by NIS, reduces tissue neoplasia much more effectively than iodide. Clinical data and animal studies suggest that I_2 has a suppressive effect on the development of both benign and cancerous pathologies in mammary and prostate glands and is less thyrotoxic than iodide (Anguiano et al. 2007; Aceves et al. 2013). Dose-response studies in humans have shown that iodine at concentrations of 3, 5, and 6 mg/day, mainly in the form of I_2, has significant beneficial actions in benign pathologies (mastalgia or prostatic hyperplasia) and exhibits antineoplastic effects in early and advanced breast cancer, without the side effects of these doses (Ghent et al. 1993; Kessler 2009; Anguiano et al. 2010; Aceves et al. 2013). Higher concentrations of iodine (9 and 12 mg/day) resulted in the same benefits, but caused transient hypothyroidism in 20% of the studied patients with minor side effects that disappeared when the high iodine supplementation was stopped (Kessler 2009).

The antitumor effects of iodine can be mediated by different mechanisms, including direct actions in which oxidized iodine dissipates the potential of the mitochondrial membrane, thus inducing mitochondria-mediated apoptosis, and indirect effects through the formation of iodolipid compounds (Aceves et al. 2013). Iodolipids can alter both expression and action of peroxisome proliferator-activated receptors (PPARs) type gamma that, in turn, trigger apoptotic or differentiation pathways (Nuñez-Anita et al. 2009; Aceves et al. 2013).

10.10.3 Anti-Inflammatory Effects of Iodine

The available data suggest that iodine has an anti-inflammatory effect (Soriguer et al. 2011), which can be mediated, in part, by its ability to neutralize the reactive oxygen

species. Molecular iodine has been also shown to inhibit the NO generation and expression of TNF-α in monocytes/macrophages (Moore et al. 1997).

10.11 Beneficial Effects of Iodine in Human Health and Longevity

Iodine is essential for health at every stage of human life mainly because of its indispensable role in the production of thyroid hormones that control the key metabolic processes in the organism. In addition, iodine is involved in the processes of thyroid autoregulation and can have some functions in human body that are not mediated by iodothyronines (Fig. 10.1). As above mentioned, iodine in the thyroid gland can participate in formation of iodolipids that exhibit regulatory and antiproliferative effects; such compounds may also play a role in the proliferative control of extrathyroidal tissues. However, with the exception of the effects of iodine as a component of thyroid hormones, other mechanisms of iodine regulatory action have not been extensively studied. The available data on the long lifespan of people who traditionally consume iodine in moderately high amounts (for example, the population of Japan) indicate the important role of this micronutrient in human health, but it is difficult to analyze the role of iodine in longevity, because of physiological changes in thyroid function with age.

It can be considered that the most significant effects of iodine as a component of iodothyronines are manifested in the early period of development of human organism (prenatal period, infancy and childhood). The essentiality of iodine at these ontogenetic stages is proved by data on the improvement of foetal and neonatal neurodevelopment and the reduction of infant mortality after iodine prophylaxis in pregnant women. In particular, iodine supplementation before or during early pregnancy increases birth weight, reduces perinatal and infant mortality rates, eliminates the cases of cretinism and generally increases developmental scores in young children by 10–20% (Zimmermann 2016). Improvement of neurocognitive function in infants and children after iodine supplementation in pregnant and lactating mothers is associated with the indispensability of thyroid hormones for normal neuronal migration and myelination of the brain during foetal and early postnatal life. Iodine supplementation in moderately iodine-deficient children improves their mental performance due to the effect of iodine on cognition and increases their motor function and somatic growth (Zimmermann 2007).

Iodine also has an important role in the mental and physical health of adult and older persons. Adequate iodine intake is necessary for the proper functioning of the central nervous system, cardiovascular, gastrointestinal, immune, hematopoietic and endocrine systems throughout life. The available data show that adult population living in areas with iodine deficiency are characterized by a high degree of apathy, low educability, poor performance, lack of physical energy and reduced work output that contribute to poor quality of life (Ahad and Ganie 2010). Insufficient formation of

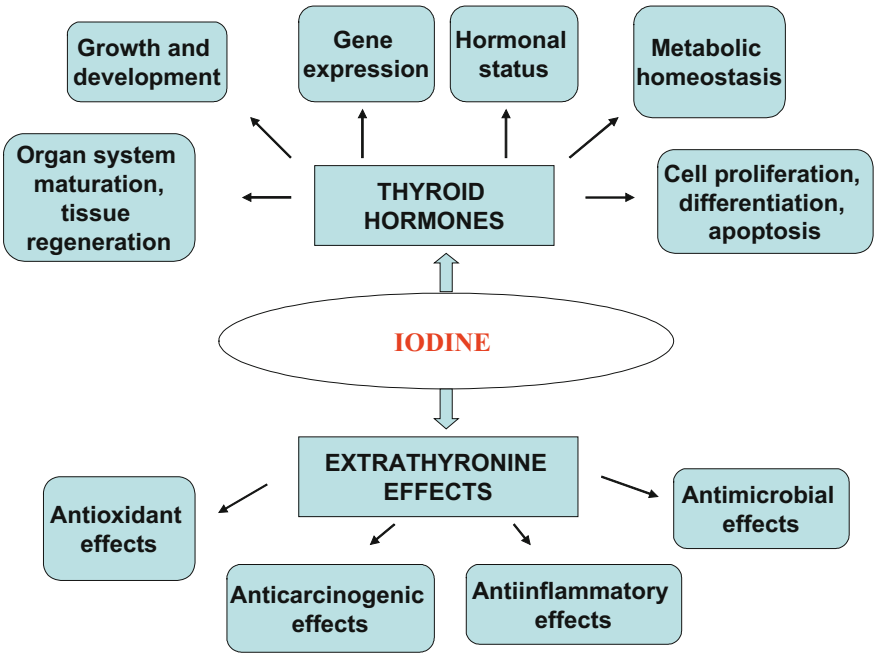

Fig. 10.1 Effects of iodine, associated with its beneficial influence on health

thyroid hormones, particularly in older persons, is often accompanied by hypertension, cardiac insufficiency, adverse lipid profile, insulin resistance, and endothelial dysfunction (Stabouli et al. 2010; Sara et al. 2015). These metabolic alterations create an increased risk of atherosclerosis, cardiovascular diseases, diabetes, cognitive impairment and depression. Thus, iodine is important for the prevention of disorders that arise mainly in adult and older age and are linked to higher mortality in older persons.

There are experimental and clinical data suggesting the association of hypothyroidism with obesity (Knudsen et al. 2005; Longhi and Radetti 2013). This is due to involvement of thyroid hormones in the regulation of basal metabolism and thermogenesis, lipid and carbohydrate metabolism and fat oxidation. Overweight is often accompanied by elevated TSH level (Laurberg et al. 2012). In addition, there is an inverse correlation between free thyroxine values and body mass index, even when fT_4 values remain in the normal range (Knudsen et al. 2005). Obesity, in turn, is associated with the presence of insulin resistance (Cali and Caprio 2008), contributes to the pathogenesis of diabetes and cardiovascular diseases, hence, increases the health risks and worsens the quality of life of people with iodine-deficiency.

Hypothyroidism, including its subclinical form, also has cognitive and neuropsychiatric consequences in adult and older people. In particular, subclinical hypothyroidism may be a predisposing factor for depression, cognitive impairment, and dementia (Davis et al. 2003; Resta et al. 2012; Joffe et al. 2013). Older adults,

particularly women, may be more vulnerable to the effects of subclinical hypothyroidism, given age-related changes to the hypothalamic-pituitary-thyroid axis, and some studies suggest the possible association between subclinical hypothyroid status and depression and cognitive decline in the elderly (Chuiere et al. 2007; Joffe et al. 2013). However, there are reports suggesting that conditions of hyperthyroidism can also lead to mental deficiency in older persons (Kalmijn et al. 2000). In particular, the findings of Kalmijn et al (2000) have shown that persons with subclinical hyperthyroidism, manifested by the reduced TSH levels, had a more than threefold increased risk of dementia and Alzheimer's disease.

It is suggested that an adequate intake of iodine is necessary to prevent several types of cancer, while iodine deficiency increases the risk of thyroid and extrathyroidal cancers (breast, endometrial, ovarian, and stomach cancers) (Stadel 1976; Venturi et al. 2000; Gołkowski et al. 2007; Aceves et al. 2013; Zimmermann and Galetti 2015; Rappaport 2017). Iodine supplementation has been shown to diminish tissue neoplasia and can ameliorate physiopathologies of several organs that take up iodine, primarily the thyroid, mammary, and prostate glands and potentially the pancreas and gastric system (Anguiano et al. 2007; Aceves et al. 2013). This especially refers to the molecular iodine, which, if ingested in milligram amounts, has a suppressive effect on both benign and cancer neoplasias (Aceves et al. 2013). Clinical and experimental data on the antitumor effects of iodine are consistent with epidemiological reports suggesting a direct association in the Japanese population between the low incidence of breast and prostate pathologies and moderately high dietary intake of iodine (Cann et al. 2000; Rappaport 2017).

The limits for iodine intake of 1–2 mg per day have been established by international agencies, given the fact that individuals with underlying thyroid pathologies can develop the hyper- or hypothyroidism if they are exposed to doses higher than 1.5 mg/day (Aceves et al. 2013). However, the available data suggest that only very high doses (>30 mg/day), mainly as iodide, consumed by humans lead to hypothyroidism and goitre, while low (1.5–8 mg/day) and intermediate doses (10–32 mg/day), ingested from various sources, are well-tolerated in euthyroid persons, maintaining levels of thyroid hormones and TSH within normal limits (Bürgi 2010; Aceves et al. 2013; Leung and Braverman 2014). It has been also shown that iodine may act as an antioxidant in the whole organism if this element is ingested at concentrations higher than 3 mg/day (Aceves et al. 2013).

In this aspect, the traditional diet of residents of Japan, which includes iodine-rich products of marine origin, attract considerable attention. Seaweed, which is widely consumed in Japan and other Asian countries, contains a large amount of iodine in the forms of iodide, I_2 and iodate, and the average iodine intake in the Japanese population is 1200–5280 μg/day (Cann et al. 2000; Teas et al. 2004; Zava and Zava 2011). At the same time, despite the high level of iodine consumption in food, Asian population does not differ from the rest of the world in the prevalence of thyroid disorders (Kamangar et al. 2006; Aceves et al. 2013). The studies, conducted in Japan, have shown that normal subjects can maintain normal thyroid function, even if they consume several milligrams per day of dietary iodine (about 30 mg/day); moreover,

the incidences of nontoxic diffuse goitre and toxic nodular goitre is markedly reduced with high dietary iodine (WHO 1996).

In Japan, the average life expectancy of the population is 83 years, that is, higher than in other countries, an extraordinarily low incidence of certain cancers, low infant mortality and a lower mortality rate from cardiovascular diseases compared to residents of other countries (WHO 2010). The main dietary difference that distinguishes Japan from other countries is high consumption of iodine, with seaweed the most common source (Zava and Zava 2011). Given the involvement of iodine in the metabolic processes that underlie the normal functioning of the cardiovascular system, cancer prevention, the maintenance of a healthy pregnancy and infant health, it can be assumed that statistic indices of Japanese people health may be related to the high level of iodine consumption.

On the other hand, the available data suggest that thyroid activity changes with age, but the complex manner of its changes makes a real challenge an understanding its role in aging, as well as the level of iodine required by organism in older age. However, there is common agreement around the fact that some kind of reduced thyroid function tend to associate with increased longevity in a number of species (Gesing et al. 2012; Jansen et al. 2015). Studies conducted in people of the older age suggest that maintaining an elevated TSH level and lower concentrations of thyroid hormones in the serum might be favourable in the oldest-old persons and is related to longevity. In particular, studies on thyroid disease-free population of Ashkenazi Jews, characterized by exceptional longevity (centenarians) have shown the higher serum TSH level in these individuals (median age, 98 year) in comparison to the control group consisted of younger Ashkenazi Jews (median age, 72 year) and to another control group (median age, 68 year) from the U.S. National Health and Nutrition Examination Survey (NHANES) program (Atzmon et al. 2009). The authors have observed an inverse correlation between fT4 and TSH levels in centenarians that may suggest a potential role of decreased thyroid function in lifespan regulation, leading to extended longevity. The association of higher TSH with familial longevity was shown in nonagenarians from the Leiden Longevity Study (Rozing et al. 2010). It has been also found that nonagenarians from families with the lowest family mortality history score had relatively lower levels of thyroid hormones (Rozing et al. 2010). In animal studies, a reduced thyroid function with low thyroid hormone levels also appears to be associated with extended longevity.

Although greater longevity has been associated with higher TSH and lower levels of thyroid hormones, mechanisms underlying TSH/TH differences and longevity remain unknown. The study conducted by Jansen et al. (2015) have shown that offspring of nonagenarians have increased TSH secretion but similar bioactivity of TSH and similar thyroid hormone levels compared to controls as well as similar resting metabolic rate and core body temperature. Hence it is possible that pleiotropic effects of the hypothalamic-pituitary-thyroid axis may favour longevity without altering energy metabolism (Jansen et al. 2015).

Taking into account the above mentioned data, the peculiarities of iodine metabolism in older age are of particular interest. However, to date, there are no particular recommendations on the level of iodine intake in the older people.

10.12 Conclusions

Chemical element iodine is unevenly distributed in an abiotic environment with a relatively low concentration in soils and terrestrial vegetation and a high level of bioconcentration in marine organisms. In humans and vertebrate animals, iodine is a vital micronutrient, required primarily for the processes of hormonogenesis in the thyroid gland. Being an indispensable component of thyroid hormones, iodine is involved in the regulation of growth and development of the organism, in maintaining the metabolic balance and in controlling the key intracellular processes underlying human health and longevity. Iodine is of crucial importance during the early stages of ontogenesis, since thyroid hormones participate in the regulation of neurodevelopment, maturation and formation of functions of organ systems. In periods of childhood and adolescence, iodine is necessary for growth, physical development and cognitive function. An adequate iodine status is also a key factor in the prevention of thyroid disorders in adulthood and is important for the maintaining proper functioning of the endocrine system, central nervous system, cardiovascular, gastrointestinal, haemopoietic and immune systems throughout life. Participation of iodine (as a component of thyroid hormone) in the control of gene expression, the mechanisms of cell proliferation, differentiation and apoptosis underlies its regulatory effects in human organism. Iodine deficiency in the organism at any stage of development is associated with a wide spectrum of metabolic and functional alterations secondary to an insufficient synthesis of thyroid hormones, and is often manifested by goitre. The severe iodine deficiency can lead to hypothyroidism, which is associated with profound changes in the hormonal status and adversely affects virtually all metabolic processes; moreover, it can contribute to the development of tissue malignancies.

In addition to the effects of iodine in the composition of thyroid hormones, this element also exhibits direct antioxidant and anti-inflammatory effects and can be involved in the prevention of benign an malignant tumours, including several types of thyroid and breast cancers. Therefore, adequate intake of iodine is necessary to maintain the hormonal balance and metabolic homeostasis and contributes to the prevention of thyroid dysfunction, metabolic disorders and tissue neoplasia. However, iodine deficiency is one of the most prevalent micronutrient deficiencies worldwide, and its elimination is still a public health problem in many countries.

Along with emphasizing the need for iodine for health and adequate thyroid function throughout life, it should be noted, that thyroid activity changes with age, and alterations in its function can be associated with increased longevity.

References

Abt E, Spungen J, Pouillot R et al (2016) Update on dietary intake of perchlorate and iodine from U.S. food and drug administration's total diet study: 2008-2012. J Expo Sci Environ Epidemiol. https://doi.org/10.1038/jes.2016.78

Aceves C, Anguiano B, Delgado G (2013) The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. Thyroid 23(8):938–946. https://doi.org/10.1089/thy.2012.0579

Ahad F, Ganie SA (2010) Iodine, Iodine metabolism and Iodine deficiency disorders revisited. Indian J Endocrinol Metab 14(1):13–17

Almandoz JP, Gharib H (2012) Hypothyroidism: etiology, diagnosis, and management. Med Clin North Am 96(2):203–221. https://doi.org/10.1016/j.mcna.2012.01.005

Andersson M, Karumbunathan B, Zimmermann MB (2012) Global iodine status in 2011 and trends over the past decade. J Nutr 142:744–750. https://doi.org/10.3945/jn.111.149393

Angelousi A, Nonni A, Kassi E et al (2016) Expression of sodium iodide symporter in human breast tissues. J BUON 21(1):53–60

Anguiano B, García-Solís P, Delgado G et al (2007) Uptake and gene expression of antitumoral doses of iodine in thyroid and mammary gland: evidence that chronic administration has no harmful effects. Thyroid 17:851–859

Anguiano B, Ledezma O, Juárez MA et al (2010) Therapeutic effect of iodine on human benign prostatic hyperplasia. In: Abstracts of the 14th international thyroid congress, Paris, 11–16 September 2010

Antoniak GL (1999) The effect of thyroxine and insulin on the hemopoiesis in animals during neonatal development. Tsitologiia 41(6):512–515

Antoniak GL, Ignatenko IuV, Babich NO et al (2000) Structure and function of thyroid hormone receptors. Tsitol Genet 34(5):67–80

Antonyak HL, Vlizlo VV (2013) Biochemical role and geochemistry of iodine. Ivan Franko National University of Lviv, Lviv, pp 1–392

Antonyak HL, Babych NO, Solohub LI et al (2002) Role of iodothyronine-deiodinase in thyroid hormone mechanisms in animal and human cells. Ukr Biokhim Zh 74(1):5–18

Anwar S, Gibofsky A (2010) Musculoskeletal manifestations of thyroid disease. Rheum Dis Clin North Am 36(4):637–646. https://doi.org/10.1016/j.rdc.2010.09.001

Atzmon G, Barzilai N, Hollowell JG et al (2009) Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab 94(4):1251–1254. https://doi.org/10.1210/jc.2008-2325

Azizi F, Smyth P (2009) Breastfeeding and maternal and infant iodine nutrition. Clin Endocrinol (Oxf) 70(5):803–809. https://doi.org/10.1111/j.1365-2265.2008.03442.x

Babych N, Antonyak H, Snitynski V et al (1998) The participation of iodothyronine-5′-deiodinase in the regulatory mechanisms of myelopoiesis and immunogenesis. In: Abstracts of the 3rd international conference on farm animal endocrinology, Brussels, 1998

Babych N, Antonyak H, Sklyarov A (1999) Developmental switches in the functioning of iodothyronine-5′-deiodinase in haemopoietic tissue. FASEB J 13(5):784.4

Babych N, Antonyak H, Lacka K et al (2000a) Type 2 iodothyronine deiodinase mRNA levels in peripheral blood lymphocytes of hypo- and hyperthyroid patients. In: Abstracts of the 3rd Parnas conference "Mechanisms of Cellular Signal Transduction and Communication", Lviv, Ukraine, 14–18 October 2000

Babych N, Antonyak H, Lecybyl R et al (2000b) Thyroid hormone regulates type 2 iodothyronine deiodinase mRNA levels in cultured human peripheral blood lymphocytes. In: Abstracts of the 3rd Parnas conference "Mechanisms of Cellular Signal Transduction and Communication", Lviv, Ukraine, 14–18 October 2000

Babych N, Antonyak H, Sklyarov AYa (2000c) The influence of thyroxine on intensity of energy metabolism in bone marrow myeloid cells and neutrophilic polymorphonuclear leukocytes of neonatal pig. Endocr Regul 34(2):73–81

Babych NO, Antoniak GL, Tymochko MF (2000d) Effect of thyroxine on the activity of some enzymes of energy metabolism in bone marrow myeloid cells and blood neutrophils from piglets. Vopr Med Khim 46(2):162–167

Babych NO, Antoniak HL, Tymochko MF et al (2000e) The effect of thyroxine on the enzymatic activity of the energy metabolism and antioxidant system in the neutrophilic granulocytes of piglets. Fiziol Zh 46(3):84–91
Backer H, Hollowell J (2000) Use of iodine for water disinfection: iodine toxicity and maximum recommended dose. Environ Health Perspect 108(8):679–684
Baumann E (1895) Ueber das normale Vorkommen von Jod im Thierkörper. Hoppe-Seylers Z Physiol Chem 21:319–330
Bensenor IM, Olmos RD, Lotufo PA (2012) Hypothyroidism in the elderly: diagnosis and management. Clin Interv Aging 7:97–111. https://doi.org/10.2147/CIA.S23966
Bernal J (2017) Thyroid hormone regulated genes in cerebral cortex development. J Endocrinol 232(2):R83–R97
Bianco AC (2011) Minireview: cracking the metabolic code for thyroid hormone signaling. Endocrinology 152(9):3306–3311. https://doi.org/10.1210/en.2011-1104
Bianco AC, Salvatore D, Gereben B et al (2002) Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 23(1):38–89
Bleichrodt N, Born MP (1994) A meta-analysis on iodine and its relationship to cognitive development. In: Stanbury JB (ed) The damaged brain of iodine deficiency. Cognizant Communications, New York, pp 195–200
Boelen A, Kwakkel J, Fliers E (2012) Thyroid hormone receptors in health and disease. Minerva Endocrinol 37(4):291–304
Bougma K, Aboud FE, Harding KB et al (2013) Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis. Nutrients 5(4):1384–1416. https://doi.org/10.3390/nu5041384
Brown AR, Simmen RC, Simmen FA (2013) The role of thyroid hormone signaling in the prevention of digestive system cancers. Int J Mol Sci 14(8):16240–16257. https://doi.org/10.3390/ijms140816240
Bürgi H (2010) Iodine excess. Best Pract Res Clin Endocrinol Metab 24(1):107–115. https://doi.org/10.1016/j.beem.2009.08.010
Cali AM, Caprio S (2008) Obesity in children and adolescents. J Clin Endocrinol Metab 93(11 Suppl 1):S31–S36. https://doi.org/10.1210/jc.2008-1363
Calza L, Fernandez M, Giardino L (2015) Role of the thyroid system in myelination and neural connectivity. Compr Physiol 5(3):1405–1421. https://doi.org/10.1002/cphy.c140035
Cann SA, van Netten JP, van Netten C (2000) Hypothesis: iodine, selenium and the development of breast cancer. Cancer Causes Control 11(2):121–127
Carlé A, Krejbjerg A, Laurberg P (2014) Epidemiology of nodular goitre. Influence of iodine intake. Best Pract Res Clin Endocrinol Metab 28(4):465–479. https://doi.org/10.1016/j.beem.2014.01.001
Carrasco N (2005) Thyroid iodine transport. In: Braverman LE, Utiger RD (eds) Werner and Ingbar's the thyroid: a fundamental and clinical text, 9th edn. Lippincott Williams Wilkins, New York, pp 37–52
Chatin A (1853) Un fait dans la question du goître et du crétinisme. Impr. W. Remquet, Paris
Cheng SY, Leonard JL, Davis PJ (2010) Molecular aspects of thyroid hormone actions. Endocr Rev 31(2):139–170. https://doi.org/10.1210/er.2009-0007
Chopra IJ, Solomon DH, Chopra U et al (1978) Pathways of metabolism of thyroid hormones. Recent Prog Horm Res 34:521–567
Chueire VB, Romaldini JH, Ward LS (2007) Subclinical hypothyroidism increases the risk for depression in the elderly. Arch Gerontol Geriatr 44(1):21–28
Coindet JF (1821) Nouvelles recherches sur les effets de l'iode, et sur les precautions a suivre dans le traitement de goitre par le nouveau remede. Ann Chim Phys 16:252–256
Connelly KJ, Boston BA, Pearce EN et al (2012) Congenital hypothyroidism caused by excess prenatal maternal iodine ingestion. J Pediatr 161(4):760–762. https://doi.org/10.1016/j.jpeds.2012.05.057

Corvilain B, Laurent E, Lecomte M et al (1994) Role of the cyclic adenosine 3′,5′- monophosphate and the phosphatidylinositol-Ca2 + cascades in mediating the effects of thyrotropin and iodide on hormone synthesis and secretion in human thyroid slices. J Clin Endocrinol Metab 79:152–159

Croteau W, Davey JC, Galton VA et al (1996) Cloning of the mammalian type II iodothyronine deiodinase. A selenoprotein differently expressed and regulated in human and rat brain and other tissues. J Clin Invest 98(2):405–417

Dai G, Levy O, Carrasco N (1996) Cloning and characterization of the thyroid iodide transporter. Nature 379(6564):458–460

Davis JD, Stern RA, Flashman LA (2003) Cognitive and neuropsychiatric aspects of subclinical hypothyroidism: significance in the elderly. Curr Psychiatry Rep 5(5):384–390

Davis PJ, Goglia F, Leonard JL (2016) Nongenomic actions of thyroid hormone. Nat Rev Endocrinol 12(2):111–121. https://doi.org/10.1038/nrendo.2015.205

de Carvalho FD, Quick M (2011) Surprising substrate versatility in SLC5A6: Na^+–coupled I^- transport by the human Na^+/multivitamin transporter (hSMVT). J Biol Chem 286(1):131–137. https://doi.org/10.1074/jbc.M110.167197

DeGroot LJ (1966) Kinetic analysis of iodine metabolism. J Clin Endocrinol Metab 26(2):149–173

Delange F (2004) Optimal iodine nutrition during pregnancy, lactation and the neonatal period. Int J Endocrinol Metab 2:1–12

Delange F (2007) Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition. Pub Health Nutr 10(12A):1571–1580. https://doi.org/10.1017/S1368980007360941

Deleu S, Pirson I, Coulonval K et al (1999) IGF-1 or insulin, and the TSH cyclic AMP cascade separately control dog and human thyroid cell growth and DNA synthesis, and complement each other in inducing mitogenesis. Mol Cell Endocrinol 149(1–2):41–51

Deng SB, Jing XD, Wei XM et al (2017) Triiodothyronine promotes the proliferation of epicardial progenitor cells through the MAPK/ERK pathway. Biochem Biophys Res Commun 486(2):372–377. https://doi.org/10.1016/j.bbrc.2017.03.048

Di Jeso B, Arvan P (2016) Thyroglobulin from molecular and cellular biology to clinical endocrinology. Endocr Rev 37(1):2–36. https://doi.org/10.1210/er.2015-1090

Dohán O, De la Vieja A, Paroder V et al (2003) The sodium/iodide symporter (NIS): characterization, regulation, and medical significance. Endocr Rev 24(1):48–77

Dold S, Zimmermann MB, Aboussad A et al (2017) Breast milk iodine concentration is a more accurate biomarker of iodine status than urinary iodine concentration in exclusively breastfeeding women. J Nutr 147(4):528–537. https://doi.org/10.3945/jn.116.242560

Felig P, Baxter JD, Frohman LA (eds) (1995) Endocrinology and metabolism, 3rd edn. McGraw-Hill, Inc. Health Professions Division

Ferreira AC, Lima LP, Araújo RL et al (2005) Rapid regulation of thyroid sodium-iodide symporter activity by thyrotrophin and iodine. J Endocrinol 184:69–76. https://doi.org/10.1677/joe.1.05643

Flachowsky G, Franke K, Meyer U et al (2014) Influencing factors on iodine content of cow milk. Eur J Nutr 53(2):351–365. https://doi.org/10.1007/s00394-013-0597-4

Foppiani L, Cascio C, Lo Pinto G (2016) Iodine-induced hyperthyroidism as combination of different etiologies: an overlooked entity in the elderly. Aging Clin Exp Res 28(5):1023–1027. https://doi.org/10.1007/s40520-015-0483-4

Fordyce FM (2003) Database of the iodine content of food and diets populated with data from published literature. British Geological Survey Commissioned Report, CR/03/84N

Forhead AJ, Fowden AL (2014) Thyroid hormones in fetal growth and prepartum maturation. J Endocrinol 221(3):R87–R103. https://doi.org/10.1530/JOE-14-0025

Fuge R, Johnson CC (1986) The geochemistry of iodine—a review. Environ Geochem Health 8:31–54

Fuge R, Johnson CC (2015) Iodine and human health, the role of environmental geochemistry and diet, a review. Appl Geochem 63:282–302

Gaertner R (2009) Autoregulation of thyroid growth and function by iodine: independent regulation of the thyroid gland by iodocompounds. In: Preedy VR, Burrow GN, Watson RR (eds) Com-

prehensive handbook of iodine: nutritional, biochemical, pathological and therapeutic aspects, Academic Press, pp 243–248
Gaitan E (1990) Goitrogens in food and water. Annu Rev Nutr 10:21–39
García B, Santisteban P (2002) PI3K is involved in the IGF-I inhibition of TSH-induced sodium/iodide symporter gene expression. Mol Endocrinol 16:342–352. https://doi.org/10.1210/mend.16.2.0774
Gesing A, Lewiński A, Karbownik-Lewińska M (2012) The thyroid gland and the process of aging; what is new? Thyroid Res 5(1):16. https://doi.org/10.1186/1756-6614-5-16
Ghent WR, Eskin BA, Low DA et al (1993) Iodine replacement in fibrocystic breast disease. Canad J Surg 36(5):453–460
Gołkowski F, Szybiński Z, Rachtan J et al (2007) Iodine prophylaxis—the protective factor against stomach cancer in iodine deficient areas. Eur J Nutr 46(5):251–256
Gonçalves CFL, de Freitas ML, Ferreira ACF (2017) Flavonoids, thyroid iodide uptake and thyroid cancer—a review. Int J Mol Sci 18(6) pii:E1247. https://doi.org/10.3390/ijms18061247
Gonzali S, Kiferle C, Perata P (2017) Iodine biofortification of crops: agronomic biofortification, metabolic engineering and iodine bioavailability. Cur Opin Biotechnol 44:16–26. https://doi.org/10.1016/j.copbio.2016.10.004
Gouveia CH, Christoffolete MA, Zaitune CR et al (2005) Type 2 iodothyronine selenodeiodinase is expressed throughout the mouse skeleton and in the MC3T3-E1 mouse osteoblastic cell line during differentiation. Endocrinology 146(1):195–200
Gribble GW (2015) Biological activity of recently discovered halogenated marine natural products. Mar Drugs 13(7):4044–4136. https://doi.org/10.3390/md13074044
Harach HR, Ceballos GA (2008) Thyroid cancer, thyroiditis and dietary iodine: a review based on the Salta, Argentina model. Endocr Pathol 19(4):209–220. https://doi.org/10.1007/s12022-008-9038-y
Hetzel BS (1983) Iodine deficiency disorders (IDD) and their eradication. Lancet 322(8359):1126–1129
Hetzel BS (2005) Towards the global elimination of brain damage due to iodine deficiency—the role of the International Council for Control of Iodine Deficiency Disorders. Int J Epidemiol 34(4):762–764
Hetzel BS, Maberly GF (1987) Iodine. In: Mertz W (ed) Trace elements in human and animal nutrition, vol 2. Acad Press, NY, pp 139–208
Huang SA (2005) Physiology and pathophysiology of type 3 deiodinase in humans. Thyroid 15(8):875–881
Huang SA (2009) Deiodination and cellular proliferation: parallels between development, differentiation, tumorigenesis, and regeneration. Endocrinology 150(1):3–4. https://doi.org/10.1210/en.2008-1460
Huang YH, Tsai MM, Lin KH (2008) Thyroid hormone dependent regulation of target genes and their physiological significance. Chang Gung Med J 31(4):325–334
Hulbert AJ (2000) Thyroid hormones and their effects: a new perspective. Biol Rev Camb Philos Soc 75(4):519–631
Hynes KL, Otahal P, Hay I et al (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. J Clin Endocrinol Metab 98(5):1954–1962. https://doi.org/10.1210/jc.2012-4249
Jansen SW, Akintola AA, Roelfsema F et al (2015) Human longevity is characterised by high thyroid stimulating hormone secretion without altered energy metabolism. Sci Rep 5:11525. https://doi.org/10.1038/srep11525
Jara EL, Muñoz-Durango N, Llanos C et al (2017) Modulating the function of the immune system by thyroid hormones and thyrotropin. Immunol Lett 184:76–83. https://doi.org/10.1016/j.imlet.2017.02.010
Joffe RT, Pearce EN, Hennessey JV et al (2013) Subclinical hypothyroidism, mood, and cognition in the elderly: a review. Int J Geriatr Psychiatry 28(2):111–118. https://doi.org/10.1002/gps.3796

Josefsson M, Grunditz T, Ohlsson T et al (2002) Sodium/iodide-symporter: distribution in different mammals and role in entero-thyroid circulation of iodide. Acta Physiol Scand 175(2):129–137
Kahaly GJ, Dienes HP, Beyer J et al (1998) Iodide induces thyroid autoimmunity in patients with endemic goitre: a randomised, double-blind, placebo-controlled trial. Eur J Endocrinol 139(3):290–297
Kalmijn S, Mehta KM, Pols HA et al (2000) Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. Clin Endocrinol (Oxf) 53(6):733–737
Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24(14):2137–2150
Kapil U (2007) Health consequences of iodine deficiency. Sultan Qaboos Univ Med J 7(3):267–272
Kato N, Funahashi H, Ando K et al (1994) Suppressive effect of iodine preparations on proliferation of DMBA-induced breast cancer in rat. J Jpn Soc Cancer Ther 29:582–588
Kendrick MA (2016) Halogens. In: White WM (ed) Encyclopedia of geochemistry. Springer International Publishing AG, pp 1–5. https://doi.org/10.1007/978-3-319-39193-9_95-1
Kessler J (2009) Are there side effects when using supraphysiological levels of iodine in treatment regimens. In: Preedy VR, Burrow GN, Watson RR (eds) Comprehensive handbook of iodine. Nutritional, endocrine and pathological aspects. Academic Press, San Diego, pp 801–810
Khandelwal D, Tandon N (2012) Overt and subclinical hypothyroidism: who to treat and how. Drugs 72(1):17–33. https://doi.org/10.2165/11598070-000000000-00000
Kim MJ, Oh SW, Youn H et al (2017) Thyroid-related protein expression in the human thymus. Int J Endocrinol 2017:8159892. https://doi.org/10.1155/2017/8159892
Klein I, Danzi S (2016) Thyroid disease and the heart. Curr Probl Cardiol 41(2):65–92. https://doi.org/10.1016/j.cpcardiol.2015.04.002
Kleinau G, Worth CL, Kreuchwig A et al (2017) Structural-functional features of the thyrotropin receptor: a class A G-protein-coupled receptor at work. Front Endocrinol (Lausanne) 8:86. https://doi.org/10.3389/fendo.2017.00086
Knudsen N, Laurberg P, Rasmussen LB et al (2005) Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90(7):4019–4024
Köhrle J, Jakob F, Contempré B et al (2005) Selenium, the thyroid, and the endocrine system. Endocr Rev 26(7):944–984
Kopp P (2005) Thyroid hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD (eds) Werner and Ingbar's the thyroid: a fundamental and clinical text, 9th edn. Lippincott Williams Wilkins, New York, pp 52–76
Kopp P, Bizhanova A, Pesce L (2017) The controversial role of pendrin in thyroid cell function and in the thyroid phenotype in Pendred syndrome. In: Dossena S, Paulmichl M (eds) The role of pendrin in health and disease. Molecular and functional aspects of the SLC26A4 anion exchanger. Springer, pp 107–118. https://doi.org/10.1007/978-3-319-43287-8_7
Koukkou EG, Roupas ND, Markou KB (2017) Effect of excess iodine intake on thyroid on human health. Minerva Med 108(2):136–146. https://doi.org/10.23736/S0026-4806.17.04923-0
Krassas GE, Poppe K, Glinoer D (2010) Thyroid function and human reproductive health. Endocr Rev 31(5):702–755. https://doi.org/10.1210/er.2009-0041
Küpper FC, Kroneck PMH (2015) Iodine bioinorganic chemistry: physiology, structures, and mechanisms. In: Kaiho T (ed) Iodine chemistry and applications, 5th edn. Wiley, Inc., pp 537–589
Langer P (1960) History of goitre. In: Endemic goitre. Monograph Series, No. 44. World Health Organization, Geneva, pp 9–25
Laurberg P, Andersen S, Bülow Pedersen I et al (2005) Hypothyroidism in the elderly: pathophysiology, diagnosis and treatment. Drugs Aging 22(1):23–38
Laurberg P, Knudsen N, Andersen S et al (2012) Thyroid function and obesity. Eur Thyroid J 1:159–167. https://doi.org/10.1159/000342994

Leblanc C, Colin C, Cosse A et al (2006) Iodine transfers in the coastal marine environment: the key role of brown algae and of their vanadium-dependent haloperoxidases. Biochimie 88(11):1773–1785

Leonard JL (1990) Identification and structure analysis of iodothyronine deiodinases. In: Greer MA (ed) The thyroid gland. Raven Press, New York, pp 286–305

Leonard JL, Visser TJ (1986) Biochemistry of deiodination. In: Henneman G (ed) Thyroid hormone metabolism. Marcel Dekker Press, New York, pp 189–229

Leung AM, Braverman LE (2014) Consequences of excess iodine. Nat Rev Endocrinol 10(3):136–142. https://doi.org/10.1038/nrendo.2013.251

Longhi S, Radetti G (2013) Thyroid function and obesity. J Clin Res Pediatr Endocrinol 5(Suppl 1):40–44. https://doi.org/10.4274/Jcrpe.856

Luo Y, Kawashima A, Ishido Y et al (2014) Iodine excess as an environmental risk factor for autoimmune thyroid disease. Int J Mol Sci 15(7):12895–12912. https://doi.org/10.3390/ijms150712895

Maraka S, Ospina NM, O'Keeffe DT et al (2016) Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid 26(4):580–590. https://doi.org/10.1089/thy.2015.0418

Marine D, Feiss HO (1915) The absorption of potassium iodide by perfused thyroid glands and some of the factors modifying it. J Pharmacol Exp Ther 7:557–576

Marine D, Kimball OP (1917) The prevention of simple goiter in man. J Lab Clin Med 3:40–48

McLanahan ED, Andersen M, Fisher J (2008) A biologically based dose-response model for dietary iodide and the hypothalamic-pituitary-thyroid axis in the adult rat: evaluation of iodide deficiency. Toxicol Sci 102(2):241–253. https://doi.org/10.1093/toxsci/kfm312

Medrano-Macías J, Leija-Martínez P, González-Morales S et al (2016) Use of iodine to biofortify and promote growth and stress tolerance in crops. Front Plant Sci 7:1146. https://doi.org/10.3389/fpls.2016.01146

Miller MD, Crofton KM, Rice DC et al (2009) Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. Environ Health Perspect 117(7):1033–1041. https://doi.org/10.1289/ehp.0800247

Miro C, Ambrosio R, De Stefano MA et al (2017) The concerted action of type 2 and type 3 deiodinases regulates the cell cycle and survival of basal cell carcinoma cells. Thyroid 27(4):567–576. https://doi.org/10.1089/thy.2016.0532

Moon S, Kim J (1999) Iodine content of human milk and dietary iodine intake of Korean lactating mothers. Int J Food Sci Nutr 50(3):165–171

Moore K, Thomas A, Harding KG (1997) Iodine released from the wound dressing Iodosorb modulates the secretion of cytokines by human macrophages responding to bacterial lipopolysaccharide. Int J Biochem Cell Biol 29(1):163–171

Mullur R, Liu YY, Brent GA (2014) Thyroid hormone regulation of metabolism. Physiol Rev 94(2):355–382. https://doi.org/10.1152/physrev.00030.2013

Nadolnik L (2012) Role of glucocorticoids in regulation of iodine metabolism in thyroid gland: effects of hyper-and hypocorticism. In: Qian X (ed) Glucocorticoids—new recognition of our familiar friend. InTech, pp 265–302. https://doi.org/10.5772/52043

Nascimento C, Nicola JP, Teixeira SDS et al (2016) Excess iodide downregulates Na^+/I^- symporter gene transcription through activation of PI3K/Akt pathway. Mol Cell Endocrinol 426:73–90. https://doi.org/10.1016/j.mce.2016.02.006

Nicola JP, Carrasco N (2014) The Na^+/I^- symporter (NIS) and thyroid hormone biosynthesis. In: Ulloa-Aguirre A, Conn PM (eds) Cellular endocrinology in health and disease. Elsevier, pp 65–83

Nicola JP, Basquin C, Portulano C et al (2009) The Na^+/I^- symporter mediates active iodide uptake in the intestine. Am J Physiol Cell Physiol 296(4):C654–C662. https://doi.org/10.1152/ajpcell.00509.2008

Nicola JP, Carrasco N, Masini-Repiso AM (2015) Dietary I(-) absorption: expression and regulation of the Na(+)/I(-) symporter in the intestine. Vitam Horm 98:1–31. https://doi.org/10.1016/bs.vh.2014.12.002

Nuñez-Anita RE, Arroyo-Helguera O, Cajero-Juárez M et al (2009) A complex between 6-iodolactone and the peroxisome proliferator-activated receptor type gamma may mediate the anti-neoplastic effect of iodine in mammary cancer. Prostaglandins Other Lipid Mediat 89(1–2):34–42. https://doi.org/10.1016/j.prostaglandins.2009.04.001

Nyström HF, Brantsæter AL, Erlund I et al (2016) Iodine status in the Nordic countries—past and present. Food Nutr Res 60. https://doi.org/10.3402/fnr.v60.31969

Ohshima M, Ward JM (1986) Dietary iodine deficiency as a tumor promoter and carcinogen in male F344/Ncr rats. Cancer Res 46(2):877–883

Parle JV, Franklyn JA, Cross KW (1991) Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf) 34:77–83

Pearce EN (2006) Diagnosis and management of thyrotoxicosis. BMJ 332(7554):1369–1373

Pearce EN, Leung AM, Blount BC et al (2007) Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab 92(5):1673–1677

Persani L, Bonomi M (2017) The multiple genetic causes of central hypothyroidism. Best Pract Res Clin Endocrinol Metab 31(2):255–263. https://doi.org/10.1016/j.beem.2017.04.003

Pesce L, Kopp P (2014) Iodide transport: implications for health and disease. Int J Pediatr Endocrinol 1:8. https://doi.org/10.1186/1687-9856-2014-8

Pineda-Lucatero A, Avila-Jimenez L, Ramos-Hernandez RI et al (2008) Iodine deficiency and its association with intelligence quotient in school children from Colima, Mexico. Pub Health Nutr 11(7):690–698. https://doi.org/10.1017/S1368980007001243

Portulano C, Paroder-Belenitsky M, Carrasco N (2014) The $Na^+/I-$ symporter (NIS): mechanism and medical impact. Endocr Rev 35(1):106–149. https://doi.org/10.1210/er.2012-1036

Pramyothin P, Leung AM, Pearce EN et al (2011) Clinical problem-solving. A hidden solution. N Engl J Med 365(22):2123–2127. https://doi.org/10.1056/nejmcps1008908

Qian M, Wang D, Watkins WE et al (2005) The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. Asia Pac J Clin Nutr 14(1):32–42

Rappaport J (2017) Changes in dietary iodine explains increasing incidence of breast cancer with distant involvement in young women. J Cancer 8(2):174–177. https://doi.org/10.7150/jca.17835

Resta F, Triggiani V, Barile G et al (2012) Subclinical hypothyroidism and cognitive dysfunction in the elderly. Endocr Metab Immune Disord Drug Targets 12(3):260–267

Rösner H, Möller W, Groebner S et al (2016) Antiproliferative cytotoxic effects of molecular iodine, povidone-iodine and Lugol's solution in different human carcinoma cell lines. Oncol Lett 12(3):2159–2162. https://doi.org/10.3892/ol.2016.4811

Rossich LE, Thomasz L, Nicola JP et al (2016) Effects of 2-iodohexadecanal in the physiology of thyroid cells. Mol Cell Endocrinol 437:292–301. https://doi.org/10.1016/j.mce.2016.08.036

Royaux IE, Suzuki K, Mori A et al (2000) Pendrin, the protein encoded by the Pendred syndrome gene (PDS), is an apical porter of iodide in the thyroid and is regulated by thyroglobulin in FRTL-5 cells. Endocrinology 141(2):839–845

Rozing MP, Houwing-Duistermaat JJ, Slagboom PE et al (2010) Familial longevity is associated with decreased thyroid function. J Clin Endocrinol Metab 95(11):4979–4984. https://doi.org/10.1210/jc.2010-0875

Ruf J, Carayon P (2006) Structural and functional aspects of thyroid peroxidase. Arch Biochem Biophys 445(2):269–277

Saiz-Lopez A, Plane JMC, Baker AR et al (2012) Atmospheric chemistry of iodine. Chem Rev 112(3):1773–1804. https://doi.org/10.1021/cr200029u

Santin AP, Furlanetto TW (2011) Role of estrogen in thyroid function and growth regulation. J Thyroid Res 2011:875125. https://doi.org/10.4061/2011/875125

Sara JD, Zhang M, Gharib H et al (2015) Hypothyroidism is associated with coronary endothelial dysfunction in women. J Am Heart Assoc 4(8):e002225. https://doi.org/10.1161/JAHA.115.002225

Schreck R, Schnieders F, Schmultzler C et al (1994) Retinoids stimulate type I iodothyronine 5′-deiodinase activity in human follicular thyroid carcinoma cell lines. J Clin Endocrinol Metab 79(3):791–798

Schübel J, Feldkamp J, Bergmann A et al (2017) Latent hypothyroidism in adults. Dtsch Arztebl Int 114(25):430–438. https://doi.org/10.3238/arztebl.2017.0430
Sellitti DF, Akamizu T, Doi SQ et al (2000) Renal expression of two 'thyroid-specific' genes: thyrotropin receptor and thyroglobulin. Exp Nephrol 8(4–5):235–243
Sharma M, Aronow WS, Patel L et al (2011) Hyperthyroidism. Med Sci Monit 17(4):RA85–91
Shumer DE, Mehringer JE, Braverman LE et al (2013) Acquired hypothyroidism in an infant related to excessive maternal iodine intake: food for thought. Endocr Pract 19(4):729–731. https://doi.org/10.4158/EP13017.CO
Sirakov M, Plateroti M (2011) The thyroid hormones and their nuclear receptors in the gut: from developmental biology to cancer. Biochim Biophys Acta 1812(8):938–946. https://doi.org/10.1016/j.bbadis.2010.12.020
Smanik PA, Liu Q, Furminger TL et al (1996) Cloning of the human sodium iodide symporter. Biochem Biophys Res Commun 226(2):339–345
Smyth PPA (2003) Role of iodine in antioxidant defence in thyroid and breast disease. BioFactors 19(3–4):121–130
Smyth PP, Duntas LH (2005) Iodine uptake and loss-can frequent strenuous exercise induce iodine deficiency? Horm Metab Res 37(9):555–558
Snitynsky V, Antonyak H (1995) The hormonal regulation of blood respiratory function in cattle during the neonatal period. Ann Zootech 44(Suppl1):281
Soriguer F, Gutiérrez-Repiso C, Rubio-Martin E et al (2011) Iodine intakes of 100–300 μg/d do not modify thyroid function and have modest anti-inflammatory effects Br J Nutr 105(12):1783–1790. https://doi.org/10.1017/s0007114510005568
Soutto M, Guerro JM, Osuna C et al (1998) Nocturnal increases in the triiodothyronine/thyroxine ratio in the rat thymus and pineal gland follow increases of type II 5′-deiodinase activity. Int J Biochem Cell Biol 30(2):235–241
Spitzweg C, Joba W, Eisenmenger W et al (1998) Analysis of human sodium iodide symporter gene expression in extrathyroidal tissues and cloning of its complementary deoxyribonucleic acids from salivary gland, mammary gland, and gastric mucosa. J Clin Endocrinol Metab 83(5):1746–1751
Stabouli S, Papakatsika S, Kotsis V (2010) Hypothyroidism and hypertension. Expert Rev Cardiovasc Ther 8(11):1559–1565. https://doi.org/10.1586/erc.10.141
Stadel BV (1976) Dietary iodine and risk of breast, endometrial, and ovarian cancer. Lancet 1(7965):890–891
Stanbury JB, Brownell GL, Riggs DS et al (1954) Endemic goiter. The adaptation of man to iodine deficiency. Harvard University Press, Cambridge, pp 1–209
Sukhomlinov BF, Antoniak GL, Trikulenko AV (1986) Effect of thyroxine on the hemoglobin affinity to oxygen and 2,3-diphosphoglycerate level in rat erythrocytes. Ukr Biokhim Zh 58(2):84–86
Sumimoto H (2008) Structure, regulation and evolution of Nox-family NADPH oxidases that produce reactive oxygen species. FEBS J 275(13):3249–3277. https://doi.org/10.1111/j.1742-4658.2008.06488.x
Swietaszczyk C, Pilecki SE (2012) Two hundred years after discovery of iodine—less known functions of the element in human organism. Przegl Lek 69(12):1280–1282
Tarım Ö (2011) Thyroid hormones and growth in health and disease. J Clin Res Pediatr Endocrinol 3(2):51–55. https://doi.org/10.4274/jcrpe.v3i2.11
Tata JR (2011) Looking for the mechanism of action of thyroid hormone. J Thyroid Res 2011(730630). https://doi.org/10.4061/2011/730630
Taylor PN, Okosieme OE, Dayan CM et al (2014) Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. Eur J Endocrinol 170:R1–R15. https://doi.org/10.1530/EJE-13-0651
Tazebay UH, Wapnir IL, Levy O et al (2000) The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nat Med 6(8):871–878
Teas J, Pino S, Critchley A et al (2004) Variability of iodine content in common commercially available edible seaweeds. Thyroid 14(10):836–841

Tonacchera M, Pinchera A, Dimida A et al (2004) Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid 14(12):1012–1019
Tuma PL, Hubbard AL (2003) Transcytosis: crossing cellular barriers. Physiol Rev 83(3):871–932
Venturi S (2011) Evolutionary significance of iodine. Cur Chem Biol 5:155–162. https://doi.org/10.2174/2212796811105030155
Venturi S, Venturi M (2014) Iodine, PUFAs and iodolipids in health and diseases: an evolutionary perspective. Human Evolution 29(1–3):185–205
Venturi S, Donati FM, Venturi M et al (2000) Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. Adv Clin Pathol 4(1):11–17
Verger P, Aurengo A, Geoffroy B et al (2001) Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. Thyroid 11(4):353–360
Visser WE, Friesema EC, Visser TJ (2011) Minireview: thyroid hormone transporters: the knowns and the unknowns. Mol Endocrinol 25(1):1–14. https://doi.org/10.1210/me.2010-0095
Wayne EJ, Koutras DA, Alexander WD (1964) Clinical aspects of iodine metabolism. Blackwell Publ, Oxford, pp 1–303
Wegelin C (1928) Malignant disease of the thyroid gland and its relation to goiter in man and animals. Cancer Rev 3:297
WHO (1996) Iodine. In: Trace elements in human nutrition and health. World Health Organization Geneva, pp 49–71
WHO (2004) Vitamin and mineral requirements in human nutrition, 2nd edn. WHO, Geneva, pp 303–317
WHO (2010) World health statistics 2010. Geneva. http://www.who.int/gho/database/WHS2010_Part2.xls
WHO, UNICEF, ICCIDD (1994) Indicators for assessing iodine deficiency disorders and their control through salt iodization. WHO, Geneva, pp 1–66
WHO, UNICEF, ICCIDD (2007) Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers, 3rd edn. WHO, Geneva, pp 1–98
Wolff J (1969) Iodide goiter and the pharmacologic effects of excess iodide. Am J Med 47(1):101–124
Wolff J, Chaikoff IL (1948) Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem 174:555–564
Wolka E, Shiferaw S, Biadgilign S (2013) The effect of iodine-deficiency disorders on academic achievement of schoolchildren in Southern Ethiopia. Publ Health Nutr 17(5):1–5. https://doi.org/10.1017/S1368980013000931
Yen PM (2001) Physiological and molecular basis of thyroid hormone action. Physiol Rev 81(3):1097–1142
Yuan YV, Walsh NA (2006) Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. Food Chem Toxicol 44(7):1144–1150
Zava TT, Zava DT (2011) Assessment of Japanese iodine intake based on seaweed consumption in Japan: a literature-based analysis. Thyroid Res 4:14. https://doi.org/10.1186/1756-6614-4-14
Zhang J, Lazar MA (2000) The mechanism of action of thyroid hormones. Annu Rev Physiol 62:439–466
Zimmermann MB (2007) The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review. Thyroid 17(9):829–835
Zimmermann MB (2009) Iodine deficiency. Endocr Rev 30(4):376–408. https://doi.org/10.1210/er.2009-0011
Zimmermann MB (2016) The importance of adequate iodine during pregnancy and infancy. World Rev Nutr Diet 115:118–124. https://doi.org/10.1159/000442078
Zimmermann MB, Boelaert K (2015) Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 3:286–295. https://doi.org/10.1016/S2213-8587(14)70225-6
Zimmermann MB, Galetti V (2015) Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Res 8:8. https://doi.org/10.1186/s13044-015-0020-8