Consequences of Suboptimal Iodine Status during the First 1,000 Days .......... 105
Iodine Metabolism and the Thyroid Hormones ..................................................... 107
    Iodine Uptake from the Gut .............................................................................. 107
    Metabolism of Iodine: The Formation and Cellular Uptake of Thyroid
    Hormones .......................................................................................................... 109
    Iodine Excretion ................................................................................................109
Iodine Metabolism and Thyroid Hormones during the First 1,000 Days .............. 109
    Pregnancy and the Fetus.................................................................................... 110
    The Neonate and the Infant ............................................................................... 111
    Iodine Requirements during the First 1,000 Days ............................................. 111
Iodine, Thyroid Hormones, and Growth during the First 1,000 Days ............... 112
    Effects of Thyroid Hormones on the Reproductive System.............................. 113
    Effects of Thyroid Hormones on Muscle, Cellular Energy Turnover,
    and Glucose Metabolism.................................................................................... 113
    Effects of Thyroid Hormones on the Cardiovascular System.......................... 114
    Effects of Thyroid Hormones on Skeletal Bone Development and Maintenance... 114
    Effects of Thyroid Hormones on Growth Hormones and Insulin-Like
    Growth Factors .................................................................................................. 115
Conclusion ............................................................................................................. 116
Suggested Additional Reading ............................................................................... 116
References .............................................................................................................. 116

CONSEQUENCES OF SUBOPTIMAL IODINE STATUS
DURING THE FIRST 1,000 DAYS

Iodine deficiency used to be highly prevalent in many parts of the world until salt
iodization programs and other prevention strategies were implemented and scaled
up, beginning in the 1980s in most countries [1]. Great progress toward reducing
iodine deficiency and its consequences has been achieved since; however, large num-
bers of people continue to be affected [2,3].
In particular, the fetus and the neonate are important at-risk groups, both with regard to physiological needs and supply from the mother, and because of the profound negative effects that iodine deficiency can have during perinatal development [4,5]. During pregnancy and lactation, maternal iodine requirements are increased to supply the fetus, neonate, and, later, infant, and iodine stores (if available at the onset of pregnancy) can become rapidly depleted if the pregnant or lactating woman does not consume sufficient dietary iodine [6–9]. Iodine requirements during these life stages are thus higher than for the general population.

Figure 7.1 summarizes the consequences of iodine deficiency during the first 1,000 days, along with a judgment of the quality of evidence for each effect and each early life stage. All effects presented are child-related and do not include adverse effects on pregnant or lactating women. Upward arrows indicate an improvement of the situation. For example, an upward arrow indicates less child cretinism if iodine is provided during pregnancy. These effects are usually stronger when intervening in populations that are severely iodine deficient, but, to some extent, they also apply in situations of moderate deficiency.

In summary, there is strong evidence as to the negative consequences of suboptimal iodine status during the first 1,000 days, such as reduced cognition, cretinism, and lower birth weight, as outlined in several recent reviews. Whereas Bougma et al. [10] concluded that iodine deficiency has an important association with the mental development in children under 5 years, Zimmermann [11] concluded that iodine supplementation at varying levels before or during early pregnancy among women living in moderate to severely iodine-deficient areas eliminates cretinism, increases cognitive development in young children, increases birth weight, and reduces infant mortality.

FIGURE 7.1 The effect of iodine interventions on known consequences of iodine deficiency during the 1,000 day window, by outcome and quality of evidence. Quality of evidence rating criteria: insufficient literature, only individual studies that are somewhat unclear or conflicting; low, small number of studies, but mostly consistent findings; medium, existing meta-analyses or systematic reviews, but somewhat conflicting findings; high, existing meta-analyses or systematic reviews, with mostly consistent findings. Outcomes reported for cretinism [10], cognition [10–12], birth weight [10,12], growth [13], perinatal and infant mortality [10], and abortion/stillbirth [14]. NA, not applicable (intervention–outcome combination not applicable for this life stage). 1Graded medium level despite only a few studies available. Studies showed consistent and clear improvements and thus, for ethical reasons, intervention studies to further corroborate findings are no longer feasible. 2Iodine supplements were given to neonate directly, not via maternal breast milk.
Similarly, Gunnarsdottir and Dahl [12] suggest that an improved prenatal iodine status is associated with improvements in cognitive function for infants and toddlers to 18 months. In contrast, there is little evidence on the effect of iodine status, or iodine supplementation or fortification on infant and child growth outcomes [13]. However, as seen in the reviews discussed above, in the case of iodine there are clear positive effects of correcting iodine status on infant morbidities, likely due to the underlying mechanisms of action of iodine in the body. Iodine plays an essential role in the synthesis of thyroid hormones; these hormones are required for many metabolic reactions essential to growth and development such as protein synthesis, and bone turnover and regulation, which will be discussed in more detail later in the chapter.

Given the paucity of available evidence about the effect of iodine deficiency on growth as an outcome measure, the objective of this chapter is to elucidate the underlying mechanisms linking iodine nutrition to growth during the life stages of the first 1,000 days.

**IODINE METABOLISM AND THE THYROID HORMONES**

The only known function of iodine in the human body is in the synthesis of thyroid hormones, of which it is a key component. This makes iodine an essential nutrient. The thyroid hormones T4 and T3 are hereafter collectively referred to as “thyroid hormones” (TH). The functions of TH in the human body are many-fold; those directly involved with somatic growth and development are discussed later in the section “Iodine Metabolism and Thyroid Hormones during the First 1,000 Days.”

The thyroid prohormone 3,5,3',5'-L-tetraiodothyronine (thyroxine, T4) and its biologically active counterpart 3,5,3'-L-triiodothyronine (T3) are small, biphenolic compounds produced by the thyroid gland in a process that is rate-limited by iodine availability. Very little T3 is secreted by the thyroid gland itself, as T3 is principally formed in the peripheral tissues by the deiodination of circulating T4 [15]. Iodine comprises 65% and 59% of T4 and T3, respectively [16]. They are structurally identical, with the exception of one less iodine at the 5' position on the outer ring of T3.

Figure 7.2 provides a visual overview of the following sections of this chapter and will be referred to frequently.

**IODINE UPTAKE FROM THE GUT**

After ingestion, iodine uptake into the bloodstream is facilitated by the sodium/iodine (Na/I) symporter (NIS), found on the apical surface of enterocytes in the stomach and duodenum [17], as shown in Figure 7.2. Uptake is autoregulated; with increasing concentrations of iodine in the gut, a regulatory mechanism is initiated that downregulates the genetic expression and, thus, production and activity of the NIS [17]. Iodine circulates in the blood in three forms: (1) inorganic iodide; (2) as TH bound to carrier proteins; and (3) to a very small extent, as part of free TH [15]. Thyroid hormones are released by the thyroid gland, which is a highly vascularized organ with a unique structure of thyroid cells surrounding a colloid. The main constituent of the colloid is thyroglobulin (Tg), a thyroid-specific, large molecular weight glycoprotein that provides the structure for thyroid hormone synthesis and iodine storage [5].
FIGURE 7.2  Overview of the role of iodine and its role in the human body, with a particular focus on the first 1,000 days. Iodine taken up via the stomach/duodenum is used for the production of TH by the thyroid gland. TH are secreted into the blood circulation, where they join free circulating iodine. TH act on almost all cells and tissues in the body to influence cellular metabolism and growth mechanisms as described later in the chapter. They do this in conjunction with GH and IGFs, which promote growth and cell survival for almost every cell in the body. During pregnancy, TH and free circulating iodine move from the maternal circulation through the placenta to the fetus where they promote growth and development, in particular an accelerated myelination of nerves in the brain and central nervous system. After birth, free circulating iodine, provided by the mother via breast milk, is critical for the continued development of neonate and infant. Any superfluous TH and free circulating iodine not removed by the placenta or mammary gland are eliminated via the liver or kidney respectively. Some free iodine is also lost in sweat. Feedback mechanisms maintain homeostasis in blood hormone levels. GH, growth hormone; GHRH, growth hormone releasing hormone; HPT-axis, hypothalamus-pituitary-thyroid axis; I–, Iodine; IGFs, insulin-like growth factors; NIS, sodium/iodine (Na/I) symporter; T3, 3,5,3′-L-triiodothyronine; T4, thyroid pro-hormone 3,5,3′,5′-L-tetraiodothyronine (thyroxine); TH, thyroid hormones; TRHs, thyroid-releasing hormones; TSHs, thyroid-stimulating hormones. (Reproduced with permission from Sabine Douxchamps.)
Metabolism of Iodine: The Formation and Cellular Uptake of Thyroid Hormones

Iodine metabolism and TH synthesis are regulated via intricate interactions between the hypothalamus, pituitary, and thyroid glands, which together form the hypothalamus-pituitary-thyroid axis (HPT) (see Figure 7.2).

The synthesis of TH starts in the hypothalamus, where thyrotropin-releasing hormones (TRHs) stimulate both the synthesis and release of thyroid-stimulating hormones (TSHs). TSHs have the same α-subunit structure as other glycoprotein hormones synthesized by the pituitary. Its β-subunit provides receptor-binding specificity and binds to TSH receptors at the thyroid cell surface. This initiates a cascade of reactions in the thyroid, resulting in the synthesis of TH, which are subsequently released into the bloodstream. Upon release into the circulation, TH are bound noncovalently to carrier proteins, mainly to thyroxine-binding globulin (75%) but also albumin (10%) and transthyretin (15%) [16,18]. TH are taken up from the blood into target tissues by active transport to a concentration of approximately 10 times that of the circulation [15]. Circulating TH exert a negative feedback effect to control the release of TSH from the pituitary gland and on the activity of the TRH-stimulating neurons in the hypothalamus. In this way, similar to the autoregulation of iodine uptake, TH regulate their own synthesis (Figure 7.2).

Once inside the cell, TH bind to a nuclear TH receptor to elicit a response. TH receptors are found throughout the body, including the liver, kidney, heart, skeletal muscle, brain, pituitary gland, adipose tissue [16], and bone [19], but not in the adult brain, spleen, testes, uterus, or thyroid gland itself. Additionally, TH can act via non-genomic mechanisms [20], or other indirect mechanisms through their influence on other endocrine systems such as the growth hormone and insulin-like growth factor axis (IGF-axis; see Figure 7.2).

Iodine Excretion

Circulating inorganic iodide is removed from the bloodstream for excretion by the kidney [16]. Renal uptake occurs by passive diffusion and is relatively constant at 85% to 90% of daily iodine intake under conditions of sufficiency [21]. There is no mechanism by which the body can reduce renal excretion to retain iodine [21]. Iodine circulating as TH is excreted hepatically through conjugation via sulfotransferase or glucuronyl-transferase. The conjugates are eliminated in the bile, and the iodine is excreted in feces along with any other iodine not absorbed from the gut [15,22]. Iodine is also lost in sweat, which may be an important factor to consider in hot environments, since these losses can contribute to a depletion of iodine stores [23]. This may be particularly pronounced in infants due to the high surface-area-to-body-mass ratio (see Figure 7.2).

Iodine Metabolism and Thyroid Hormones During the First 1,000 Days

In addition to renal and hepatic iodine excretion, both the placenta and mammary gland remove iodine and TH from the mother for the support of growth and
development of the fetus and infant, as shown in Figure 7.2. In particular, the transfer of maternal TH is important in the early stages of pregnancy until the fetal thyroid is functional and can make use of the transplacental transfer of iodine, which is the only source of iodine for the fetus during gestation, for fetal TH production. Similarly, during exclusive breastfeeding as recommended by the World Health Organization (WHO) until 6 months of age [24], the iodine in breast milk must sustain the needs of the infant (Figure 7.2), despite the wide variations in breast milk iodine concentration corresponding to the mother’s intake [25].

PREGNANCY AND THE FETUS

Pregnancy induces several major changes in thyroid function and iodine metabolism. Maternal requirements are increased in pregnancy due to an increased iodine demand, and a higher than usual iodine clearance rate, as described later. The concentration of TH in utero regulates fetal growth, development, and viability via a number of factors, as discussed later. Formation of the fetal thyroid does not occur until about week 12 of gestation, and it is not capable of iodine organification until around week 20 [26]. At this point, the fetal thyroid can produce and secrete TH under the control of the HPT axis and, although it is fully functional at birth [27], during gestation the fetus is reliant on maternal TH and, later in pregnancy, iodine from the maternal circulation. At the start of gestation, therefore, maternal T4 crosses the placenta in small amounts [27]. To reflect this, in the first trimester maternal T4 production is increased by about 50% to ensure that the fetus has adequate T4 for local deiodination to the active TH, T3, for correct cerebral development [28]. An increase in circulating estrogen inhibits the breakdown of thyroid-binding globulin, maintaining higher levels of total circulating TH [26,29]. Transiently during pregnancy, there is a trend toward a reduction in free circulating TH, which stimulates a rise in TSH that in turn stimulates the synthesis of TH to maintain homeostasis in levels of unbound TH in the bloodstream [26,30]. Additional iodine is needed for the increase in TH synthesis; to compensate for this, iodine uptake and the use of maternal iodine stores are increased. Additionally, human chorionic gonadotropin, which shares the same α-subunit as TSHs and is produced in the first days of pregnancy, can also bind to TSH receptors on the maternal thyroid cells and stimulate TH synthesis [30]. Once the fetal thyroid function is established and is capable of organification of iodine from week 20, fetal iodine supply is met entirely from maternal intake [30].

From early pregnancy, there is a 30% to 50% increase in maternal glomerular filtration rate and a corresponding increase in renal blood flow, leading to a greater loss of iodine that persists until the end of the pregnancy [26,30]. To compensate, the thyroid gland increases iodine uptake [31]. In iodine-replete regions, women will typically have between 10 and 20 mg of iodine stored in their thyroid gland, and if iodine intake remains sufficient during gestation, the increased demands can be met [26]. However, if the mother’s own thyroidal iodine stores are depleted at
the start of gestation and her intake during pregnancy does not compensate for the higher need, then the risks of the effects of iodine deficiency on both mother and child are increased [31].

**THE NEONATE AND THE INFANT**

Though infants are born with a functioning thyroid gland, they have only scant iodine stores at birth. The average iodine content of the thyroid gland of a neonate is 50 to 100 μg [32], compared to 15 to 20 mg in iodine-sufficient adults [16]. Yet, in terms of iodine requirements per kilogram body weight, infants have the highest relative requirements for iodine of any life stage group [33]. There are significant changes in thyroid physiology and circulating TH concentrations after birth. There is a distinctly high turnover of T4 in infants relative to that of adults: Turnover is estimated to be about 5 to 6 μg/kg/day for infants under 3 years, compared to 1.5 μg/kg/day in adults [34].

In the neonate and young infant, excluding infants who receive formula milk (which is usually iodized), the main source of external iodine is breast milk. Breastfeeding is recommended until 2 years of age [24]. The milk must therefore contain adequate levels of iodine to ensure continued growth and development until the infant can obtain adequate iodine from food sources and iodized salt. A number of factors can influence breast milk iodine concentration: maternal iodine status, recent maternal iodine intake, duration of lactation, and maternal fluid intake [35]. In iodine-sufficient populations where the mother has had adequate intakes of iodine during pregnancy, breast milk iodine concentrations are considered adequate to meet the needs of neonates and young infants [29]. The mammary gland is able to concentrate iodine at levels 20 to 50 times higher than in plasma [36] due to the upregulated expression of NIS in breast alveoli during lactation [37]. About 20% of iodine in breast milk is present as organic iodine, including a small amount of TH, which are considered insufficient for neonatal and infant TH requirements, particularly because, via oral ingestion, the TH are likely to be destroyed during digestion [38]. The remaining 80% of the iodine present in breast milk is in the form of free iodide from the maternal bloodstream. This should cover the deficit in iodine requirement, provided that the mother’s dietary iodine intake is adequate [29], and in which case, breast milk is considered sufficient to fulfill the iodine requirements of the breastfed infant.

**IODINE REQUIREMENTS DURING THE FIRST 1,000 DAYS**

To reflect the increased nutritional needs to support normal fetal, neonatal, and infant growth and development, the daily recommended iodine intakes for pregnant and lactating women are increased. The iodine requirements for these groups, women of reproductive age, and infants are summarized in Table 7.1 [39,40].
IODINE, THYROID HORMONES, AND GROWTH DURING THE FIRST 1,000 DAYS

An adequate and continued supply of iodine is needed throughout life for the synthesis of TH, yet, as outlined earlier, the first 1,000 days are of particular importance. Iodine supplementation of mothers during pregnancy, and directly to infants, has been shown to improve infant survival [10,41], and, if undertaken before or during pregnancy, maternal iodine supplementation [10,42,43], or an adequate iodine status [44,45], has been positively associated with birth weight [10,42–45] and infant growth at 6 months [46]. Furthermore, recent analyses by Krämer et al. (2016) suggest a positive association between the absence of iodized salt availability at household level and low birth weight [47]. Additionally, they observed significant associations between household iodized salt availability and growth indicators (e.g., stunting, wasting, and underweight); however, the association was only positive for infants over 5 months of age, probably due to breastfeeding practices, although some benefit via maternal milk is proposed [47]. In toddlers, Neumann and Harrison (1994) reported that household availability of iodized salt use in Kenya was related to improvements in height [48] and, in toddlers and older infants, the use of iodized salt has been associated with increased weight-for-age z-scores and mid-upper-arm circumference in some countries in Asia [49].

During fetal development and the neonatal period, TH are responsible for a multitude of effects that include accelerated myelination in the brain, and improved

---

**TABLE 7.1**
Iodine Intake Recommendations for Individuals during the First 1,000-Day Window

<table>
<thead>
<tr>
<th>World Health Organization</th>
<th>Institute of Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Group</td>
<td>RNI (μg/day)</td>
</tr>
<tr>
<td>Women and children &gt;12 years</td>
<td>150</td>
</tr>
<tr>
<td>Children 0–5 years</td>
<td>90</td>
</tr>
<tr>
<td>Pregnant</td>
<td>250</td>
</tr>
<tr>
<td>Lactating</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*Notes:* RNI, Recommended Nutrient Intake; RDA, Recommended Dietary Allowance.

<sup>a</sup> Adequate intake.
central nervous system cell migration, differentiation, and maturation [50,51] (see Figure 7.2). TH also promote the growth and maturation of the peripheral tissues and skeleton, and they raise the basal metabolic rate [16], which provides energy for growth (see Figure 7.2). Indeed, TH may be the best surrogate biochemical markers for healthy fetal development [28,52].

The actions of TH in target tissues are mediated by thyroid hormone receptors that regulate the transcription of target genes, which can induce pathways that stimulate or inhibit protein synthesis [16]. However, the numerous effects of TH integral to human growth are not limited to TH and TH receptor interactions: Nongenomic functions of TH have also been identified. Such effects do not require gene transcription or protein synthesis, and can have a rapid onset [20]. Furthermore, and importantly, TH can also indirectly affect growth via other hormonal axes, the most consequent of which involves human growth hormone (GH). Both TH and GH are essential for normal growth and development [53]: Thyroid function and growth mechanisms are intertwined in a complex relationship; neither can be considered without the other, and iodine plays a central and fundamental role.

The impact of TH on growth mechanisms is discussed next. A detailed and fully comprehensive discussion on growth mechanisms above those directly implicated with thyroid function is beyond the scope herein. For further in-depth reading, additional publications are suggested at the end of this chapter.

**EFFECTS OF THYROID HORMONES ON THE REPRODUCTIVE SYSTEM**

Although not directly a growth mechanism, the ability to reproduce successfully is the primary determinant of the viability of a new life. Normal reproductive physiology in both women and men is dependent on having normal levels of TH, and evidence points to the association between reproductive complications or failure and TH levels. This association is mainly based upon the interrelationship between the HPT axis and the hypothalamic-pituitary-gonadal axis, which controls the release of sex steroid hormones, as both axes influence each other.

Abnormal amounts of TH can cause problems with sperm morphology and motility and induce erectile dysfunction [54]. In women, reproductive problems due to incorrect TH levels may impact menstruation, oocyte quality, and endometrial thickness [54]. In both sexes, TH abnormalities cause changes in sex hormone-binding globulin and sex steroids.

**EFFECTS OF THYROID HORMONES ON MUSCLE, CELLULAR ENERGY TURNOVER, AND GLUCOSE METABOLISM**

Skeletal muscle is a principal target of TH signaling, and TH regulate the expression of a broad range of genes with key roles in skeletal muscle development, homeostasis, function, and metabolism [55]. TH transporter proteins and deiodination enzymes that are required for TH binding and the conversion of the inactive T4 to the active metabolite T3 are expressed in skeletal muscle tissue [55], and provide the means to control TH uptake and activation. Starting with early embryonic development of the trunk and limbs, the development of fetal skeletal muscle is dependent
upon TH, a process that continues postnatally with the transition from fetal muscle fiber phenotypes to adult phenotypes [55]. Furthermore, muscle is one of the major tissues involved in glucose uptake, and TH can control glucose uptake both from the gut and also by skeletal muscle, thereby influencing the overall glucose homeostasis of the body. This is particularly important since the fetus is highly reliant upon glucose, not only for energy but also as a precursor for biochemical reactions promoting tissue growth.

TH are unique in their ability to affect the resting metabolic rate [20], primarily through their actions on skeletal muscle both at rest and while active. The sodium/potassium (Na+/K+) adenosine triphosphatase (ATP) pump, responsible for the maintenance of the resting cellular membrane potential, is a direct target gene for T3. The ability of TH to regulate energy utilization is closely linked to effects on the function of mitochondria, which provide about 90% of intracellular energy in the form of ATP [56], and actions can also be via nongenomic influences of TH directly on mitochondria [20]. TH can also increase the number of mitochondria in a cell [57], thereby increasing the capacity to generate ATP. These factors influence fetal growth and metabolism, and hypothyroid fetuses will obtain less ATP, and therefore have less energy available for growth of non-essential tissues [27].

Last, TH have an important role to play in the survival of the neonate at birth. After delivery, the neonate must expend ATP to maintain the extrauterine body temperature, which requires the generation of more heat than while in the protective environment of the uterus. Activation of this thermogenesis in brown adipose tissue is reliant on T3 [27,55].

**Effects of Thyroid Hormones on the Cardiovascular System**

TH are critical regulators of cardiac development during fetal and postnatal life. Cardiac functions, such as heart rate, cardiac output, and contraction force, are linked to TH. In the fetus, TH are responsible for the maturation of the cardiovascular system adaptation of the heart at birth, when the ventricles switch from pumping in parallel to pumping in series [27].

**Effects of Thyroid Hormones on Skeletal Bone Development and Maintenance**

The dependence of bone maturation, growth, and development on thyroid function is well recognized [19,58], and the association between myxedematous cretinism and short stature is confirmed [59]. A euthyroid state is essential for normal skeletal development. Thyroid hormone receptors (THRs) have been identified in bone cells (osteoblasts, osteoclasts) and cartilage cells (chondrocytes) [19,58], and TH have been shown to accelerate osteoblastic differentiation [60]. In response to TH, bone cells stop proliferating and develop differentiated functions including production of growth factors, cytokines, prostaglandins, and structural proteins [60]. Osteoblasts are stimulated directly by T3 and, indirectly, via the action of
T3 on growth factors, such as insulin-like growth factor-1 (see next section) [61]. Furthermore, TSH receptors, expressed predominantly on thyroid cells, have also been identified in bone, suggesting that TSH may have a direct effect on bone and cartilage itself [62].

**Effects of Thyroid Hormones on Growth Hormones and Insulin-Like Growth Factors**

The human growth hormone (GH) is the most abundant hormone secreted from the anterior pituitary. It is secreted in response to a stimulus on the anterior pituitary by growth hormone releasing hormone, which itself is secreted from the hypothalamus. GH is essential for normal growth and development, and exerts its effects on almost all tissues in the body. TH promotes GH synthesis and secretion from the pituitary, and has a permissive effect on the anabolic and metabolic effects of GH. In turn, GH also affects TH activity: GH depresses the secretion of TSH from the pituitary, which in turn will dampen the cascade of reactions initiated by TSH to produce TH.

The main function of GH is to promote the synthesis and secretion of IGFs, which mediate the effects of GH. IGFs cause cell growth and multiplication by increasing the uptake of amino acids into the cell, thereby promoting protein synthesis. GH acts on muscle, cartilage, bone, and other tissues and, indirectly, on the liver, to promote IGF secretion. IGFs circulate in the plasma in complexes with structurally related binding proteins, called IGF-binding proteins. IGF-binding protein-3 is the most common and has the highest binding affinity for IGF-1, binding approximately 95% of the growth factor [63].

Via IGFs, GH promotes accelerated protein growth, an increase in cell size, an increase in cell mitosis, and a corresponding increase in cell number. It promotes the specific differentiation of certain types of cells, for example, bone growth cells and early muscle cells. In infants and children, in whom the bone has not yet reached its adult length, GH increases the growth rate of the skeleton and skeletal muscles.

GH stimulates the increased deposition of proteins around the body, yet the most visible effect is on somatic growth, the stimulation of growth of the skeletal frame. This impact on skeletal growth occurs as a result of multiple effects on bone, including (1) an increased deposition of protein by chondrocytic and osteogenic cells that cause bone growth; (2) an increased rate of reproduction of these cells; and (3) the specific effect of converting chondrocytes into osteogenic cells, thus causing specific deposition of new bone.

Indeed, the growth-promoting actions of GH and IGF-1 are critical for growth during early life: IGFs are widely expressed in fetal tissues and have major influences on fetal growth [27,53], and in neonates and infants, where a deficiency of GH is established by 6 months of age, growth failure may result in stunted growth of up to 3 or 4 standard deviations below the mean [53].

An adequate iodine status and euthyroid state can thereby promote growth, through the promotion of the secretion of GH. The secretion of GH, IGF-1, and IGFBP-3 is dependent on thyroid function, both directly and indirectly via the effects of TH on pituitary secretion [63].
CONCLUSION

Iodine is an essential micronutrient for optimal health, being the principal component of thyroid hormones. Thyroid hormones are implicated in nearly all cells in the body, and control a vast array of biochemical reactions. During the first 1,000 days, iodine and thyroid hormones are indispensable for the viability of the developing fetus and for perinatal survival, including brain formation and cognitive development, and thereafter for the growth and ongoing development of the child.

Whereas the biological mechanisms are well characterized for iodine to have a clear impact on growth processes and growth outcomes, measurable effects of thyroid hormones on growth are principally seen in situations of severe or moderate deficiency. In situations of mild iodine deficiency, where the body’s regulatory mechanisms are better prepared to maintain homeostasis, we may be unlikely to see a measurable impact on growth. That said, there is a distinct lack of literature on the effects of iodine status, or supplementation or fortification strategies, on infant and child growth outcomes [13]. The available data are mainly cross-sectional, which are limited in scope since they make assumptions that current iodine status is reflective of past status, and may not control for socioeconomic confounders [63]. The little evidence from iodine intervention strategies on growth is of low quality: There are few randomized controlled trials, and those conducted have generally been underpowered to study growth outcomes [13,64,65]. Furthermore, growth as an outcome is difficult to measure in single nutrient nutritional studies, since the factors impacting growth are vast and spread beyond the reach of a single nutrient or even nutrition alone, and studies need to be of sufficient duration to detect a measurable difference. There is a clear need for well-designed, long-term controlled trials with adequate sample sizes to appropriately assess the impact of iodine status on growth outcomes.

SUGGESTED ADDITIONAL READING


REFERENCES


33. Andersson M, Aeberli I, Wust N et al. The Swiss iodized salt program provides adequate iodine for school children and pregnant women, but weaning infants not receiving iodine-containing complementary foods as well as their mothers are iodine deficient. *J Clin Endocrinol Metab* 2010; 95:5217–24.


45. Rydbeck F, Rahman A, Grander M et al. Maternal urinary iodine concentration up to 1.0 mg/L is positively associated with birth weight, length, and head circumference of male offspring. *J Nutr* 2014; 144:1438–44.


65. Farebrother J, Naude CE, Nicol L et al. Effects of iodized salt and iodine supplements on prenatal and postnatal growth: A systematic review. (Submitted.)