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Review

The role of iodine in human growth and development

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ABSTRACT

Iodine is an essential component of the hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. Iodine deficiency is a major public health problem; globally, it is estimated that two billion individuals have an insufficient iodine intake. Although goiter is the most visible sequelae of iodine deficiency, the major impact of hypothyroidism due to iodine deficiency is impaired neurodevelopment, particularly early in life. In the fetal brain, inadequate thyroid hormone impairs myelination, cell migration, differentiation and maturation. Moderate-to-severe iodine deficiency during pregnancy increases rates of spontaneous abortion, reduces birth weight, and increases infant mortality. Offspring of deficient mothers are at high risk for cognitive disability, with cretinism being the most severe manifestation. It remains unclear if development of the offspring is affected by mild maternal iodine deficiency. Moderate-to-severe iodine deficiency during childhood reduces somatic growth. Correction of mild-to-moderate iodine deficiency in primary school aged children improves cognitive and motor function. Iodine prophylaxis of deficient populations with periodic monitoring is an extremely cost effective approach to reduce the substantial adverse effects of iodine deficiency throughout the life cycle.

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Contents

1. Introduction

Iodine is an essential component of the hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. In the early 20th century, Marine and Kimball showed that endemic goiter (thyroid enlargement) was caused by iodine deficiency (ID) and could be prevented by iodine supplementation [1]. Iodine (as iodide) is widely but unevenly distributed in the earth's environment. In many regions, leaching from glaciations, flooding, and erosion have depleted surface soils of iodide. Crops grown in these soils will be low in iodine, and humans and animals consuming food grown in these soils become iodine deficient. ID has multiple adverse effects on growth and development in animals and humans. These are collectively termed the iodine deficiency disorders (Table 1), and are one of the most important and common human diseases [2,3]. They result from inadequate thyroid hormone production due to lack of sufficient iodine.

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Table 1
The iodine deficiency disorders, by age group [2,3].

Age groups	Health consequences of iodine deficiency
All ages	Goiter
	Increased susceptibility of the thyroid gland to nuclear radiation
Fetus	Abortion Stillbirth Congenital anomalies Perinatal mortality
Neonate	Infant mortality Endemic cretinism
Child and adolescent	Impaired mental function Delayed physical development
Adults	Impaired mental function Reduced work productivity Toxic nodular goiter; iodine-induced hyperthyroidism Increased occurrence of hypothyroidism in moderate-to-severe iodine deficiency; decreased occurrence of hypothyroidism in mild-to-moderate iodine deficiency

In 1980, WHO estimated up to 60% of the world's population was iodine deficient, with most of the burden in developing countries. It was realized that the consequences of ID could be averted by a low-cost intervention, universal salt iodization (USI) [3]. Since then, globally, the number of households using iodized salt has risen from <20% to >70%, dramatically reducing ID [4]. Despite this enormous progress, in 2007, WHO estimated nearly two billion individuals still have insufficient iodine intakes, including 1/3 of all school-age children [5]. Iodine requirements from the U.S. Institute of Medicine (IOM) [6] and the World Health Organization (WHO) [7] by age and population group are shown in Table 2. Because nearly all iodine is excreted by the kidney, recent dietary intake is reflected in the urinary iodine (UI) excretion. Therefore, classification of a population's iodine status as optimal, or as mildly, moderately or severely iodine deficient, is usually based on the median UI concentration (UIC), as shown in Table 3.

2. Iodine deficiency and thyroid metabolism

Dietary iodide, from sources such as iodized salt or sea foods, is rapidly and nearly completely absorbed (>90%) in the stomach and duodenum [8,9]. Iodine is cleared from the circulation mainly by the thyroid and kidney, and while renal iodine clearance is fairly constant, thyroid clearance varies with iodine intake. The body of a healthy adult contains up to 20 mg of iodine, of which 70–80% is in the thyroid [10]. In chronic ID, the iodine content of the thyroid may fall to <20 μg. In iodine-sufficient areas, the adult thyroid traps 60–80 μg of iodine/day to balance losses and maintain thyroid hormone synthesis [11,12]. Below this level of intake, the iodine content of the thyroid is depleted, and many individuals develop goiter [13]. In chronic severe ID, thyroid hormone synthesis is gradually reduced, leading to hypothyroidism and its sequelae.

Table 2
Recommendations for iodine intake (μg/day) by age or population group.

Age or population group[a]	U.S. Institute of Medicine [6]	Age or population group[c]	World Health Organization [7]
Infants 0–12 months[b]	110–130	Children 0–5 years	90
Children 1–8 years	90	Children 6–12 years	120
Children 9–13 years	120		
Adults ≥14 years	150	Adults >12 years	150
Pregnancy	220	Pregnancy	250
Lactation	290	Lactation	250

[a] Recommended daily allowance.
[b] Adequate intake.
[c] Recommended nutrient intake.

Table 3
Epidemiological criteria from the World Health Organization [7] for assessment of iodine nutrition in a population based on median or range of urinary iodine concentrations.

	Iodine intake	Iodine nutrition
School-aged children		
<20 μg/L	Insufficient	Severe iodine deficiency
20–49 μg/L	Insufficient	Moderate iodine deficiency
50–99 μg/L	Insufficient	Mild iodine deficiency
100–199 μg/L	Adequate	Optimum
200–299 μg/L	More than adequate	Risk of iodine-induced hyperthyroidism in susceptible groups
>300 μg/L	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150 μg/L	Insufficient	
150–249 μg/L	Adequate	
250–499 μg/L	More than adequate	
≥500 μg/L[a]	Excessive	
Lactating women[b]		
<100 μg/L	Insufficient	
≥100 μg/L	Adequate	
Children less than 2 years of age		
<100 μg/L	Insufficient	
≥100 μg/L	Adequate	

[a] The term excessive means in excess of the amount needed to prevent and control iodine deficiency.
[b] In lactating women, the numbers for median urinary iodine are lower than the iodine requirements, because of the iodine excreted in breast milk.

The iodine requirement during pregnancy is increased ≥50% due to: (1) an increase in maternal thyroid hormone production to maintain maternal euthyroidism and transfer thyroid hormone to the fetus early in the first trimester, before the fetal thyroid is functioning; (2) iodine transfer to the fetus, particularly in later gestation; and (3) an increase in renal iodine clearance [14]. If a chronically iodine deficient woman becomes pregnant, she has negligible thyroid iodine stores to draw from to meet these increased needs, and progressive pathological changes – goiter and hypothyroidism – occur that adversely affect maternal and fetal health.

3. The adverse effects of hypothyroxinemia on the brain

The thyroid secretes two thyroid hormones: mainly thyroxine (T4) and small amounts of triiodothyronine (T3). However, T3 is the more biological active form, and it is formed in peripheral tissues including the brain by deiodination of circulating T4 [15]. Thyroid hormone receptors (TRs) in the central nervous system (CNS) mediate most of the biological activities of T3. In the nucleus, TRs bind to thyroid hormone-responsive elements in the promoter of their target genes to regulate transcription [16]. Thyroid hormones may also have activities in nongenomic, TR-independent pathways in the cytoplasm, plasma membranes and/or organelles, including the regulation of ion channels and the activation of various signaling cascades [17]. Thyroid hormone has a myriad of important effects in the developing brain that include accelerated myelination and improved cell migration, differentiation and maturation [15,18]. They modulate expression of genes such as neurogranin/RC3, CAMKII and neuromodulin/GAP-43 involved in synaptic plasticity and memory [19–21]. The hippocampus is particularly important in learning in that it integrates spatial and contextual information [22]. In animal models, hypothyroidism *in utero* and in the early postnatal period due to ID irreversibly alters synaptic development and reduces hippocampal cell

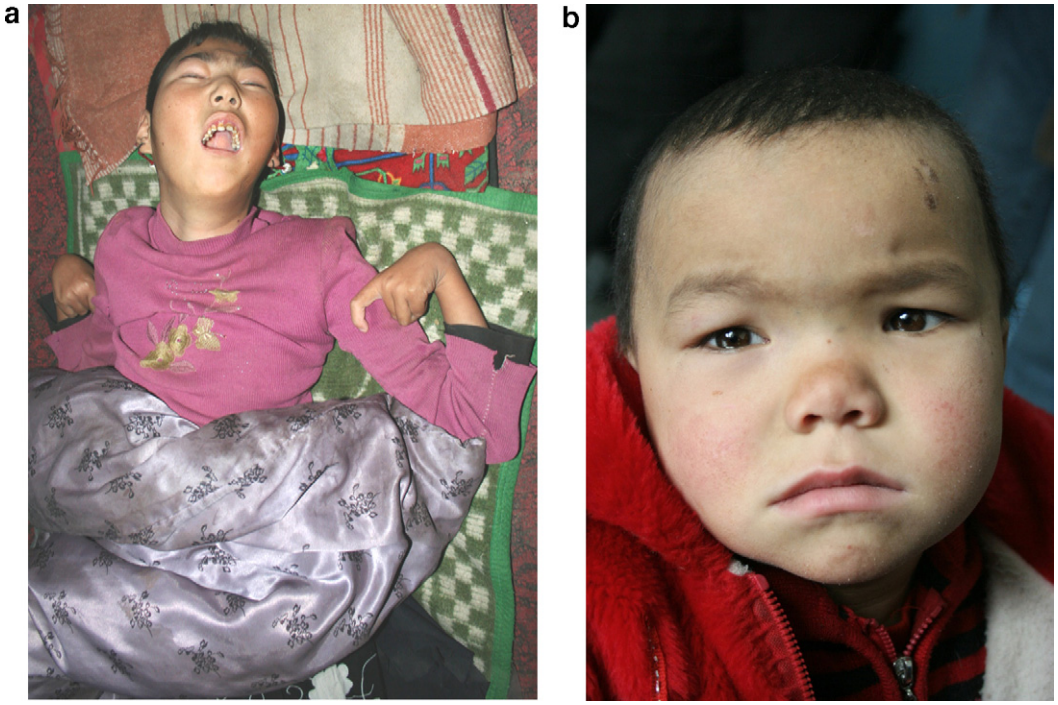

Fig. 1. (a) Neurological cretinism. This 2007 photograph of a 9-year-old girl from western China demonstrates the three characteristic features: severe mental deficiency together with squint, deaf mutism and motor spasticity of the arms and legs. The thyroid is present, and frequency of goiter and thyroid dysfunction is similar to that observed in the general population. (b) Myxedematous cretinism. This 2008 photograph of a 7-year-old girl from western China demonstrates the characteristic findings: profound hypothyroidism, short stature (height 106 cm), incomplete maturation of the features including the naso-orbital configuration, atrophy of the mandible, myxedematous, thickened, dry skin, and dry hair, eyelashes and eyebrows. The thyroid typically shows atrophic fibrosis.

numbers; it also causes a down regulation of hippocampal synatophysin, a vesicle protein involved in the release of neurotransmitters, but an upregulation of caveolin-1, a membrane protein involved in cell signaling and endocytosis [23]. Animal models have shown that the detrimental effect of hypothyroidism on the developing brain depends on its timing, magnitude and duration [18,24,25]; hypothyroidism has adverse effects on cognition throughout the life cycle [26,27].

However, the adverse effects of hypothyroidism *in utero* are particularly severe [28]. Nuclear thyroid hormone receptors are present in the fetal brain by nine weeks; this suggests CNS development may be sensitive to thyroid hormone deficiency as early as the first trimester [25]. Onset of fetal thyroid hormone secretion occurs in the second trimester, at 18–22 weeks of gestation [24]. In a healthy fetus born to an iodine sufficient mother, both fetal and maternal thyroid hormone contributes to fetal requirements. In newborns with congenital thyroid defects or thyroid agenesis, who are born to iodine-sufficient, euthyroid mothers, cord blood T4, derived from the mother, is 30–60% of concentrations in normal newborns [29]; this appears to be sufficient for normal brain development until birth. But in areas of moderate-to-severe ID, both maternal and fetal thyroid hormone production is compromised, leading to fetal hypothyroidism and impaired brain development.

4. Pregnancy outcome and neurodevelopment of the offspring

The consequences of ID during gestation depend upon the timing and severity of the hypothyroidism. Severe ID *in utero* can cause cretinism. The two classic forms of cretinism – neurological and myxedematous – were originally described in 1908 in the Himalayas [30]. Worldwide, neurological cretinism is the most common form [31]. Its clinical features include mental retardation with the following: (i) defects of hearing and speech – most neurological cretins are deaf-mutes of varying degree; (ii) squint; (iii) impaired voluntary motor activity involving spastic diplegia or paresis of the lower limbs; (iv) disorders of stance, with spastic gait and ataxia (Fig. 1a). Neurological cretins are usually euthyroid, but goiter and hypothyroidism can be seen in some cases. In myxedematous (hypothyroid) cretinism, severe or long-standing hypothyroidism is present with the following features: dwarfism, myxedema, dry, thickened skin, sparseness of hair and nails, deep hoarse voice, sexual retardation, retarded maturation of body parts, skeletal retardation, weak abdominal muscles, poor bowel function and delayed tendon reflexes. Maturation of the face is abnormal, with wide-set eyes, saddle-nose deformity with retarded maturation of naso-orbital configurations, mandibular atrophy and thickened lips (Fig. 1b).

The prevention of cretinism by iodine treatment was conclusively demonstrated in a landmark trial in an area of severe ID in Papua New Guinea [32,33]. Alternate families received saline (control) or iodized oil injection; subjects received 4 ml if aged ≥12 years and 2 ml if <12 years. Iodine supplementation was associated with a significant reduction in the prevalence of endemic cretinism: at 4 years of age, the relative risk (95% CI) was 0.27 (0.12, 0.60) and at 10 years of age, the relative risk (95% CI) was 0.17 (0.05, 0.58). The authors carried out a long term follow-up on a small sub-sample of non-cretinous children at 11 and 15 years of age [34] and found no significant differences in motor and cognitive function between the children born to supplemented families and controls. In a trial in Zaire, participants were pregnant women attending antenatal clinics in an area of severe ID with a 4% cretinism rate [35,36]. Pregnant women were randomly allocated to two groups: one received iodized oil injection without vitamins, the other an injection of vitamins without iodine. Women were on average 28 weeks pregnant when they were treated. Psychomotor development was measured in the offspring, with follow-up data to 72 months of age. The psychomotor development scores were significantly higher in the

iodine group (mean psychomotor development score, 91 ± 13 vs. 82 ± 14). However, there was a loss to follow-up of ≈50% in both groups.

In a study in western China, an area of severe ID and endemic cretinism, participants were groups of children from birth to 3 years and women at each trimester of pregnancy [37]. Untreated children 1–3 years of age, who were studied when first seen, served as controls. The intervention was administration of oral iodized oil, given either once during pregnancy or in the newborn period. Treated children and the babies born to the treated women were followed for two years. The main outcomes were neurologic examination, head circumference, and indexes of cognitive and motor development. A small subsample was followed out to ≈7 years of age [38]. The prevalence of moderate or severe neurologic abnormalities among the infants whose mothers received iodine in the first or second trimester was 2%, as compared with 9% among the infants who received iodine during the third trimester (through the treatment of their mothers) or after birth. Treatment in the third trimester of pregnancy or after delivery did not improve neurologic status, but developmental quotient improved slightly. Treatment at the end of the first trimester did improve neurologic outcome. The mean (±SD) developmental quotient at two years of age was higher in the treated than in the untreated children (90 ± 14 vs. 75 ± 18) [37].

These intervention trials were ground-breaking studies done under difficult conditions in remote areas. The Papua New Guinea study has the strongest design and clearly demonstrates that iodine treatment in a population with high levels of endemic cretinism sharply reduces or eliminates incidence of the condition. The Zaire and China trials report developmental scores were 10–20% higher in young children born to mothers treated during pregnancy or before. Although the data from the Zaire trial indicate correction of ID even at mid-to-late pregnancy improves infant cognitive development, data from the other trials suggest the full picture of neurological cretinism can only be prevented when iodine is given before or early in pregnancy.

Cretinism is the extreme expression of the abnormalities in development caused by ID, but the cognitive deficits associated with ID may not be limited to remote, severely iodine deficient areas. Several experts have argued that even mild-to-moderate ID in pregnancy, still present in many countries around the world, may affect cognitive function of the offspring. However, this remains uncertain. In areas of iodine-sufficiency, two prospective case–control studies using different measures of impaired maternal thyroid function have reported developmental impairment in offspring of affected mothers. In a study by Haddow et al. [39], the IQ scores of 7–9-year-old children of mothers with subclinical hypothyroidism during pregnancy (an increased TSH in the 2nd trimester) were 4 points lower compared to children from mothers with normal thyroid function during pregnancy. In another study, Pop et al. [40] reported impaired infant development to 2 years in children of women with hypothyroxinemia (free T4 below the tenth percentile at 12 weeks' gestation) compared to controls. Despite the limitations of their case–control designs, these studies suggest cognitive deficits may occur in the offspring even if maternal hypothyroidism is mild and asymptomatic. However, maternal thyroid dysfunction in these studies was presumably not due to ID, as they were done in the USA [39] and in the Netherlands [40]. In healthy infants in an iodine-sufficient area in the U.S. (n = 500), newborn T4 concentrations within the normal reference range were not correlated with maternal thyroid function and did not predict cognitive outcome at ages 6 months and 3 years [41]. It is unclear if maternal hypothyroxinemia and/or subclinical hypothyroidism occurs in otherwise healthy pregnant women with mild-to-moderate ID. The available evidence suggests that in areas of mild-to-moderate ID, the maternal thyroid is able to adapt to meet the increased thyroid hormone requirements of pregnancy [42]. Controlled studies in mildly iodine deficient pregnant women have shown that supplementation was generally effective in minimizing an increase in thyroid size during pregnancy, but only two of the six studies reported maternal TSH was lower (within the normal reference range) with supplementation, and none of the studies showed a clear impact of supplementation on maternal and newborn total or free thyroid hormone concentrations [42]. Thyroid hormone concentrations may be the best surrogate biochemical marker for healthy fetal development [43]. Thus, the results of these trials are reassuring. However, because none of the trials measured long-term clinical outcomes such as maternal goiter or infant development, the potential adverse effects of mild-to-moderate ID during pregnancy remain unclear.

5. Birth weight, infant mortality and infant growth

In a severely iodine-deficient area of western China [37], iodine repletion of pregnant women (n = 295) improved head circumference and reduced the prevalence of microcephaly from 27% to 11% (P = 0.006). In a region of endemic goiter area in Algeria, treatment of pregnant women with oral iodized oil just before conception or during the first trimester significantly increased placental and birth weights [44]. In mildly iodine deficient Spanish pregnant women (n = 239), women with a third trimester UI between 100 and 149 μg/l had lower risk of having an SGA newborn than women with a UI below 50 μg/l (adjusted OR (95%CI): 0.15 (0.03–0.76)) [45]. In iodine deficient Nigerian pregnant women at term delivery (38–40 weeks of gestation) (n = 72), better maternal and cord serum thyroid parameters predicted higher birth weight [46]. In contrast, Mason et al. [47] reported iodized oil capsules given during pregnancy in Sri Lanka and the Philippines had a negative effect on birth weight when used with high levels of iodine in salt.

Infant survival is improved in infants born to women whose ID is corrected before or during pregnancy. Delong et al. [48] added potassium iodate to irrigation water over a 2–4-week period in three area of severe ID in China and found a large reduction in both neonatal and infant mortality in the following 2–3 years compared with areas that did not receive iodine. The median UI increased in women of child-bearing age from <10 μg/L to 55 μg/L, while the infant mortality rate (IMR) decreased in the three treated areas from a mean of 58.2 to 28.7/1000 births, from 47.4 to 19.1/1000, and from 106.2 to 57.3/1000. Similar results were also observed for neonatal mortality; the odds of neonatal death are reduced by about 65% in the population who had iodine treatment. Iodized oil given intramuscularly to iodine-deficient pregnant women in Zaire at ≈28 weeks of gestation decreased infant mortality [36]. In severely iodine deficient women, the IMR in infants of treated and untreated mothers was 113/1000 and 243/1000 births, respectively, and in women with mild or moderate ID, the IMR with and without treatment was 146/1000 and 204/1000 births. In Algeria, rates of abortion, stillbirth and prematurity were significantly lower among women given oral iodized oil 1–3 months before conception or during pregnancy than among untreated women [44]. In areas of severe ID, there is an inverse relationship between levels of maternal T4 during pregnancy and death rates in the offspring [49].

Infant survival may also be improved by iodine supplementation in the newborn period. A randomized, placebo-controlled trial of oral iodized oil (100 mg iodine) was conducted in an area of presumed ID in Indonesia to evaluate the effect on mortality [50]. The iodine or placebo was given in conjunction with oral poliovirus vaccine; infants (n = 617) were treated at ≈6 weeks of age and were followed to 6 months of age. There was a significant 72% decrease in risk of infant death during the first 2 months of follow-up [50].

In a large cross-sectional study in Indonesia, use of adequately iodized salt was associated with a significantly lower prevalence of child malnutrition and mortality in neonates, infants, and children aged <5 years [51]. Taken together, these results indicate iodine prophylaxis in severely iodine deficient populations, or iodine supplementation of pregnant women or infants, may reduce the IMR by ≥50%.

6. Childhood cognition and growth

There have been many cross-sectional studies comparing cognition and/or motor function in children from chronically iodine deficient and iodine sufficient areas, including children from Asian and European backgrounds [52–61]. These cross-sectional studies, with few exceptions, report impaired intellectual function and motor skills in children from iodine deficient areas. However, observational studies are often confounded by other factors that affect child development [62]. Also, these studies could not distinguish between the persistent effects of *in utero* ID and the effects of current iodine status.

Several randomized, controlled trials in school aged children have tried to measure the effect of iodized oil on cognition [63–66]. Three of the studies found no effect [63–65], while one found cognition improved with treatment [66]. However, methodological problems limit their interpretation, as two of the studies were confounded by a significant improvement in iodine status in the control group [63,65], while in the other two, the treated group remained iodine deficient at retesting [64,66]. In a placebo controlled, double-blind 6-month intervention trial, moderately iodine deficient 10–12-year-old children ($n = 310$) in Albania were randomized to receive either 400 mg of iodine as oral iodized oil or placebo [67]. The children were given a battery of seven cognitive and motor tests which included measures of information processing, working memory, visual problem solving, visual search, and fine motor skills. Treatment with iodine markedly improved iodine and thyroid status: at 24 weeks, median UI in the treated group was 172 μg/L and mean circulating T4 increased ≈40%. Compared to placebo, iodine treatment significantly improved performance on 4 out of 7 tests, suggesting information processing, fine motor skills, and visual problem solving were improved. Thus, in children born and raised in areas of ID, cognitive impairment is at least partially reversible by iodine repletion [67]. A randomized controlled trial in 10–13-year children ($n = 184$) in New Zealand [68] gave a daily tablet containing 150 μg iodine as KI or placebo for 28 weeks. Cognitive performance was assessed through 4 subtests from the Wechsler Intelligence Scale for Children after 28 weeks. Thyroid hormone concentrations were in the normal range at baseline for all children. Despite this, iodine improved scores on 2 of the cognitive tests: picture concepts ($P = 0.023$) and matrix reasoning ($P = 0.040$). Overall cognitive score of the iodine group was 0.19 SDs higher than that of the placebo group ($P = 0.011$). In these two studies [67,68], increasing iodine intakes over several months improved cognition in older children who presumably grew up under conditions of ID. This short-term beneficial effect may have been due to improvements in myelination of central nervous system mediated by an increased supply of thyroid hormone [69,70]. Myelinization continues throughout childhood particularly in the frontal cortex, the brain area responsible for higher-order cognition and fluid intelligence. Alternatively, better thyroid function could improve cognition by effects on neurotransmitters and/or glucose metabolism [71]. Interestingly, while in the Albania study iodine treatment improved thyroid function, in the New Zealand study, cognition improved with iodine repletion, despite having no discernible effect on circulating thyroid hormones.

A meta-analysis was done of the effect of ID on mental development [72]. It pooled data from 21 observational and experimental studies that had included a control group. Of these, 16 studies were in children, 4 included adults, and 2 included infants; the age range was 2–45 years. The final meta-analysis included 2214 participants (mainly children) and IQ was used as the main outcome measure. The studies were all done in areas of moderate-to-severe ID. The IQs of non-ID groups were on average 13.5 IQ points higher than those of the ID groups. However, the studies included in this analysis were of varying quality; much of the data came from observational studies and only 6 of the papers cited were published in peer-reviewed journals. In a second meta-analysis by Qian et al. [73], inclusion criteria included all studies conducted in China, comparing children (<16-year-old) living in naturally iodine sufficient (IS) areas with those: (a) in severely ID areas; (b) children in ID areas born before the introduction of iodine prophylaxis; and (c) children in ID areas born after the introduction of iodine prophylaxis. IQ was measured using the Binet or Raven's Scales. The effect size was an increase of 12.45, 12.3, 4.8 IQ points, respectively, for the iodine sufficient group and the later two groups, compared to those in iodine deficient areas. Compared to severely ID children, there was an increase of ≈12 IQ points for children born more than 3.5 years after iodine prophylaxis was introduced. Although it is stated that the iodine sufficient control groups were comparable socially, economically, and educationally, it is difficult to judge the overall quality of the studies reported in Chinese included in this meta-analysis. Despite the clear limitations of the mainly cross-sectional data included in these two meta-analyses [72,73], their overall conclusions are similar. They estimate that populations, and particularly children, with chronic, severe ID experience a mean reduction in IQ of 12–13.5 points.

7. Somatic growth

Cross-sectional studies on ID and child growth have reported mixed results. In Greece [74], school-age children in areas of endemic goiter had decreased height and weight and delayed bone maturation compared to children in nonendemic areas, but there was no correlation of goiter with somatic growth. Goiter was also not associated with growth in children in Bolivia [75] and Malaysia [76]. Children in iodine deficient areas in Iran [52] and India [77] showed retarded height and bone maturation; in Iran, impaired growth was inversely correlated with TSH [52]. Mason et al. [47], reviewing studies from Sri Lanka, Nepal, Bangladesh, India and the Philippines, found use of iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in children less than 3 years of age. Similarly, household use of iodized salt was directly correlated with height in preschool children in Kenya [78]. In contrast, a study in 6–12-year-old Thai children found an inverse correlation between UI concentration and HAZ score [79]. However, these cross-sectional data have limitations. They compare current anthropometry with current iodine status, but because body size reflects earlier conditions, they assume iodine status at the time of survey reflects earlier iodine status. Also, households with access to iodized salt may have better socioeconomic and environmental conditions that would favor better child growth.

There are few intervention studies examining the effect of iodine repletion on growth of school-age children. In 5-year-old Chinese children, median UI increased from <10 to 176 μg/L after iodine addition to irrigation water, and this reduced childhood stunting [80]. As part of a selenium supplementation trial in Tibet, 5–15-year-old children with Kashin–Beck disease received intramuscular iodized oil before being randomly assigned to receive selenium or placebo, and a control group did not receive iodine. Iodine treatment increased median UI from 10 to 50–250 μg/L and increased HAZ score, while weight-for-height and WAZ scores decreased, suggesting that linear growth was not accompanied by appropriate

weight gain [81]. In a 1-year placebo-controlled Mexican study of a daily multiple-micronutrient food supplement containing 90 μg iodine, there was no increase in length gain in treated children older than 1 year of age [82]. In a controlled trial in South Africa, a daily multiple-micronutrient-fortified biscuit containing 60 μg iodine was given to iodine-deficient children aged 6–11 years for 43 weeks [83]. Median UI increased to >100 μg/L in both treated and control groups, and the intervention had no significant effect on growth. In moderately iodine-deficient Bangladeshi schoolchildren, a 4-month controlled trial of 400 mg of iodine as oral iodized oil did not affect weight gain, but the treated children remained iodine deficient [64]. In 22-month, placebo-controlled trial in iodine-deficient Bolivian schoolchildren, 475 mg iodine as oral iodized oil had no significant effect on growth; however, iodine status significantly improved in the placebo group [63].

Improved growth in iodine deficient children receiving iodine is likely due to improved thyroid function; both thyroid hormone and growth hormone (GH) are essential for normal growth and development [84,85], even during fetal life [86]. Thyroid hormone is required for normal GH expression in vitro [87,88] and in vivo [89], and, in animal studies, promotes GH secretion and modulates the effects of GH at its receptor [89–91]. Thyroid hormone also directly affects epiphyseal growth, bone maturation and stature [85,92]. Hypothyroidism is a well-recognized cause of short stature in children, and in mildly hypothyroid Colombian children with minimal thyroid dysfunction, T4 administration increased growth [93].

Insulin-like growth factor (IGF)-1 is a growth factor that mediates many of the effects of GH [94,95]. Approximately 95% of circulating IGF-1 is bound to insulin-like growth factor binding protein (IGFBP)-3; binding prolongs the half-life of circulating IGF-1 and may target IGF-I towards growth stimulation and away from glucose metabolism [94,96]. IGFBP-3 can promote or inhibit growth, and its effects can be either IGF-mediated or IGF-independent [96]. Circulating IGF-1 and IGFBP-3 are dependent on thyroid status [97–100], both indirectly through effects on pituitary GH secretion and by a direct effect [101]. In adults, hypothyroidism decreases serum levels of IGF-1 and IGFBP-3, and thyroid hormone replacement increases them [99,102]. In malnourished, iodine-deficient Malaysian children, there was a positive correlation between T4 concentrations and IGF-1 and IGFBP-3 concentrations [103], and Turkish children from areas of endemic goiter had low IGF-1 and IGFBP-3 concentrations [104,105]. In a previous study examining the effect of iodine supplementation on IGF-1 and IGFBP-3 concentrations, 5–15-year-old Turkish children who received 400 mg iodine showed decreased free (F)T4, IGF-I and IGFBP-3 concentrations after six months [106]. However, the study was not controlled, and many of the children remained iodine deficient after treatment [106].

The aim of a recent study [107] was to determine if iodine repletion improves growth in school age children, and to investigate the role of IGF-1 and IGFBP-3 in this effect. Three prospective, double blind intervention studies were done in areas of varying ID. In a study in Morocco, children ($n = 71$) were enrolled from households that were using either iodized or noniodized salt. The children at baseline had a median UI concentration of 14–18 μg/L indicating severe ID, mean total (T)T4 concentration was in the low-normal range, and 21% of children were hypothyroxinemic. After 10 months, in the children consuming iodized salt, there were significant increases in TT4 and IGF-1 concentrations (median IGF-1 increased >100%), as well as median HAZ and WAZ scores. An Albanian study randomized children ($n = 310$) to two groups; one group received iodized oil and one group a placebo; they were followed for 6 months. At baseline, the children had a median UI concentration of 42–44 μg/L indicating moderate ID, mean TT4 concentration was in the low-normal range, and 30% of children were hypothyroxinemic. In the group receiving the iodized oil, there were significant increases in mean TT4 concentration, median HAZ and WAZ scores, as well as median IGF-1 and IGFBP-3 concentrations. In South African children ($n = 188$) randomized to receive either iodized oil or placebo and followed for 6 months, baseline median UI concentration was 70–78 μg/L indicating mild ID, and mean TT4 concentration was near the midpoint of the normal range. In the group receiving the iodized oil, there were no significant changes in mean TT4 concentration, in median HAZ and WAZ scores, or median IGFBP-3 concentration. However, median IGF-1 concentration increased significantly with treatment. These controlled studies [107] clearly demonstrate that iodine repletion in school-age children can increase IGF-1 and IGFBP-3 concentrations. In the children who were only mildly iodine deficient, there was no significant change in TT4 with iodine repletion, and no measurable effect on growth. In contrast, in the children who were moderate-to-severely iodine deficient, iodine repletion increased mean TT4 concentrations by 40–50% and somatic growth improved.

8. Conclusions

The major impact of hypothyroidism due to iodine deficiency is impaired neurodevelopment, particularly early in life. In the fetal brain, inadequate thyroid hormone impairs myelination, cell migration, differentiation and maturation. Offspring of iodine deficient mothers are at high risk for cognitive disability, with cretinism being the most severe manifestation. Iodine deficiency during childhood reduces somatic growth and impairs cognitive and motor function. Thus, with a focus on vulnerable groups such as pregnant women and young children, iodine prophylaxis of deficient populations is essential to avoid the many adverse effects of ID on growth and development.

Conflicts of interest statement

The author has no conflicts of interest to disclose.

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