Iodine Deficiency in the Population of Montefeltro, A Territory in Central Italy Inside the Regions of Emilia-Romagna, Tuscany and Marche

Goiter (the abnormal enlargement of the thyroid gland) is the most specific clinical marker of iodine deficiency in the human body. According to WHO, iodine deficiency is the most common cause of preventable brain damage, causing impaired cognitive development in children, and in many countries it is still a major health problem. During pregnancy, severe iodine deficiency may impair fetal development, resulting in cretinism, with irreversible mental retardation and developmental abnormalities, as well as miscarriage and stillbirth. This is a review of the endocrinological and neuropsychological studies conducted on the iodine deficient population of Montefeltro, a territory in central Italy, where the use of iodized table salt has only recently eradicated endemic malnutrition in its young population. However, in adults and the elderly scars still remain with some neuropsychiatric disorders and the last surviving cases of cretinism. I would also like to point out that research into the biochemical compounds of iodine is a new area of investigation and one which may provide insights into apoptosis, carcinogenesis and many cardiovascular and degenerative diseases.

Introduction

Iodine (I) was the first inorganic antioxidant in all the I-concentrating cells, from primitive marine algae to more recent vertebrates. Iodide (I-) acts as an electron-donor, via peroxidase enzymes, protecting the fragile molecules of the polyunsaturated fatty acids (PUFAs) in cell membranes from peroxidation (Venturi et al., 1999; Küpper et al., 2008, 2011). Roughly 500 million years ago (MYA), some primitive marine fish emerged from the I-rich sea, transferring into estuaries and the fresh water of rivers. 350 MYA, these vertebrates evolved into amphibians and reptiles, adapting to life on I-deficient land (Kelly & Snedden, 1962). Meanwhile, some I-concentrating endodermic cells, originating from the primitive foregut of vertebrates, migrated and specialized in the uptake and storage of iodine in the new follicular thyroid gland, a necessary reservoir for better adaptation to I-deficient terrestrial environments (Figures 1 & 2). At the same time, other I-concentrating ectodermic cells migrated and became the primitive nervous system and brain (Venturi, 2011). The action of thyroid hormones was made possible by the formation of T3-receptors (TH-Rs) in the cells of vertebrates. Initially, about 500 MYA, primitive TH-Rs with a metamorphosing action appeared in primitive marine
chordates, and then, about 250-350 MYA, other, more recent, TH-Rs with metabolic and thermogenetic actions were formed in birds and mammals.

Goiter is the most specific clinical marker of either the direct or indirect insufficient intake of iodine in the human body. There is evidence of goiter, and its medical treatment with I-rich algae and burnt sponges, in Chinese, Egyptian and Roman ancient medical texts. In 1848, the Italian King Carlo Alberto of Sardinia commissioned the first epidemiological study of goiter and cretinism in his Haute-Savoy territories, where hideous cases of goiters and cretinism frequently occurred in the population (Costa, 1978). In past centuries, the well reported social diseases prevalent among the poorer social classes and farmers, caused by dietary and agricultural monocultures, were: pellagra, rickets, beriberi, scurvy in long-term sailors, and the endemic goiter caused by I-deficiency. However, this disease was less mentioned because it was erroneously considered to be an aesthetic rather than a clinical disorder (Venturi, 1985).

Review of the research on the iodine deficient population of Montefeltro

In 1990s, many of the hilly and mountainous villages of Montefeltro were studied in-depth by local medical officers and researchers from Pisa University (Donati et al. 1991, 1992). Previously, Venturi (1978, 1985) and Donati et al. (1986, 1988) had shown the alarmingly high prevalence of goiter and cretinism in the population of Montefeltro, a territory in central Italy, inside the regions of Emilia-Romagna, Tuscany and the Marche. Yet most of the Italian medical books at that time reported that iodine deficiency disorders (IDD), such as endemic goiter and cretinism, had completely disappeared with the prophylactic use of iodized table salt, as had occurred in other countries. However, this problem was neglected, because iodized salt, which was produced exclusively by Italian government manufactories, was scarce and practically unavailable in Italy (Venturi, 1985).

Figure 2. Over three billion years ago in the primitive sea, blue-green algae were the first living Prokar-yota to produce oxygen in the atmosphere and fragile molecules of PUFAs in their lipid cellular membranes. About 500 million years ago (MYA), some primitive marine fish started to emerge from the I-rich sea and transferred to fresh water and then, as amphibians and reptiles, adapted to I-deficient land. Meanwhile, some I-concentrating endodermic cells, originating from the primitive foregut of vertebrates, migrated and specialized in the uptake and storage of iodine in the new follicular thyroid gland, a necessary reservoir for better adaptation to the I-deficient terrestrial environments. At the same time, other I-concentrating ectodermic cells migrated and became the primitive nervous system and brain (Venturi, 2000).
Renaissance painting: historical evidence of severe IDD in Montefeltro

Figure 3. Piero della Francesca: Artist’s self portrait.

Figure 4. Piero della Francesca: Detail from *Polittico della Misericordia*.

Figure 5. A case of goiter recurrence in the left lobe of the thyroid of a woman from Montefeltro, ten years after a previous hemi-thyroidectomy of the right lobe, again due to lack of iodine supplementation.

Figure 6. Dissected specimen of the goiter of the above woman showing the typical aspects of multinodular goiter from I-deficiency.
Curiously, cases of goiter and cretinism in Montefeltro were never reported to the health authorities, even though they were depicted in the medieval paintings of Piero della Francesca (1416-1492), the famous artist who lived in the territory, where cases of goitrous people (including his own self portrait) were clearly represented (Figures 3 & 4). As a result of the failure to implement I-prophylaxis in Italy, endemic I-deficiency goiter and cretinism were widely present up until a few years ago, particularly in the inland, hilly and mountainous territories, where nowadays more than six million Italians are deficient in this trace element. In 1980s, IDDs were still strongly present in the territory of Montefeltro, where the prevalence of goiter in the general population was 55% and the mean urinary iodine level was 39 micrograms/g creatinine. Partial and total thyroidectomies were by far the most frequent surgical interventions carried out in women, roughly 30% of all surgical procedures (Figures 5 & 6). (Venturi, 1978, 1985, 2011, 2013). The number of patients with clinical and biochemical features of myxedematous, neurological, and mixed cretinism was about 0.4% of the local population, and researchers reported that neurological cretinism (Figures 7 & 8) was more prevalent than myxedematous and mixed forms (Figure 9 & 10). (Donati et al., 1989, 1991, 1992). The hormonal profiles of these three types of cretinism were clearly different. Nevertheless, all myxedematous cretins also had some neurological disorders (hyperreflexia, increased muscle tone, disorder of gait, Babinski sign, hypoacusia) which are typical features of neurological cretins. These findings suggest that neurological damage was very similar in all forms of endemic cretinism, reflecting a diffused assault on the developing nervous system of fetuses. The primary pathophysiological event in the different types of endemic cretinism was maternal and fetal hypothyroidism caused by I-deficiency, while differences may be explained by the extent and duration of postnatal hypothyroidism. In 1990, all the cretins were over 35 years of age, suggesting more severe I-deficiency in past decades, and progressive nutritional improvements, thanks to the ‘silent iodine prophylaxis.’ In fact, by comparing the year 1980 with 1995, one can see that the Italians increased their yearly I-rich sea-fish consumption (from 8.7 to 14.4 kg per person) (Venturi, 1999). The studies also showed a high prevalence of neurological hypoacusia and a reduction in the mental performances of ‘normal’ schoolchildren in this area, in which auxological, psychometric and audiometric parameters, and tympanograms with stapedial reflexograms, were studied. Auxological data were within the normal ranges, as were the stapedial reflexograms and tympanograms. Whereas 54.8% of the sample performed below the 25th percentile in psychometric tests (Raven test PM-47), and 22.8% was below the 5th percentile. The audiometric data revealed a neurological hearing impairment in 3.1% of the children tested, compared with 0.28% in the I-sufficient area of Pisa. Moreover, these data indicated that an impairment of the central nervous system still persisted in this area of severe endemic goiter (Donati et al., 1991). Marani and Venturi (1985, 1986) reported significant immune deficiencies caused by IDD in schoolchildren of the same territory. Indeed, iodine is still sometimes used therapeutically in various pathologies where the immune mechanism plays an important role, for example in:
Villanova-Panol panniculitis, erythema nodosum, in nodular vasculitis, erythema multiforme, and Sweet’s syndrome. Oral iodine is currently effective also in the treatment of the lymphatic-cutaneous form of sporotrichosis. 607 schoolchildren were studied: 215 were given Lugol solution (1-2 mg by drops weekly for about 8 months) and 392 were not. The immune response was assessed by the skin test method using tetanic toxoid, a test that correlates well with lymphocyte stimulation and monocyctic chemotaxis tests. The statistically significant results indicated that an adequate intake of iodine is necessary for normal immune responses. The biochemical mechanisms were still not clear then, but nowadays it is known that iodine is necessary in leucocytes for their optimal functioning (Oh & Ahn, 2012). Venturi and Venturi (2009) further suggested that a high I- concentration of fetal thymus might provide the anatomic rationale for its action in the immune system (Figure 11). With iodized salt not being available in 1982-85, Lugol’s

Figure 7. Neurological cretin with goiter. Figure 8. A family group all suffering from endemic goiter with neurological cretinism.

Figure 9. Prof. A. Pinchera from Pisa University (left) and Prof. J.T. Dunn from Virginia University (right) together with a typical subject with myxedematous cretinism with dwarfism and goiter.
drops were administered orally to the population as an I-prophylaxis. These drops were also useful in preventing damage from radio-iodine, following the nuclear disaster of Chernobyl in April 1986. In 2009, in the same schoolchildren, researchers also reported a significant correlation between dietary iodine and oral and dental health. In fact, before the I-prophylaxis, the prevalence of filled, decayed and missing teeth (DMFT index) was much higher than in non-deficient countries. The author corroborated the correlation between nutrition and oral health reported by Price in 1939, in his famous world investigation *Nutrition and Physical Degeneration: A Comparison of Primitive and Modern Diets and Their Effects*, in which he states “in fish and in sea food there are essential trace elements, such as iodine and other trace elements, which are very important for the prevention of health problems and tooth decay”. Repeating the tests after ten years of

Figure 10. Sequence of 123-iodide human scintiscans after an intravenous injection, (from left) after 30 minutes, 20 hours, and 48 hours. A high and rapid concentration of radio-iodide is evident in the periencephalic and cerebrospinal fluid, choroid plexus, salivary glands, oral mucosa and the stomach. In the thyroid gland, I-concentration is more progressive, also in the reservoir (from 1% after 30 minutes, to 5.8% after 48 hours, of the total injected dose) (Venturi, 2010).

Figure 11. Distribution of 131-I (white) in the abdomen of a pregnant mouse 24 hours after an intravenous injection. Two fetuses are evident with a high concentration of radio-iodine in their thymus, thyroid gland, placenta, gastric mucosa, in the endodermal and ectodermal tissue, and also in the milk gland of their mother (right). (Reproduced with the permission of Acta Radiologica).
I-prophylaxis, Venturi (2011) demonstrated that in Montefeltro’s schoolchildren of the same age, the previously detected mental deficits, immune deficiencies and dental caries were greatly reduced and the prevalence of goiter had fallen back to the normal range of 5%. Incidentally, researchers from the University of Krakow in Poland also reported that the mortality and survival rates after gastric cancer surgery improved in this population after I-prophylaxis (Venturi et al., 1999; Golkowski et al., 2007; Tomasz et al., 2013).

Iodine plays a role in the metabolism of serum lipids, independent of thyroid hormones. Therefore, monitoring iodine intake is extremely important for the effective prevention, and perhaps cure, of some cardiovascular diseases (Katamine et al., 1985; Zhao et al., 2011; Venturi, 2011).

Presently, IDDs cause 50 hospitalizations in Italy per 100,000 inhabitants with an estimated economic impact of over 150 million euro a year (data from the Ministry of Health, 2011).

In 2011, the pharmaceutical costs for the population of Montefeltro, when compared to the non-deficient sea-coastal population of the city of Rimini, were: 39% higher for thyroid diseases, 43% higher for neuropsychiatric disorders, 26% higher for gastric diseases, and 11% higher for heart diseases (Venturi, 2013). My own opinion is that the higher costs for treating the aforesaid diseases in the adult and elderly population, is the sad legacy of previous IDDs in the population, as well as the still surviving cases of cretinism. Indeed, the US Food and Nutrition Board of the Institute of Medicine (2001) recommended that daily allowances of iodine should range from 150 micrograms per day for adult humans to 290 micrograms per day for lactating mothers, even if the thyroid gland needs no more than 70 micrograms per day to synthesize requisite daily amounts of T4 and T3. These higher recommended levels of iodine would appear to be necessary for the optimal functioning of non-thyroid I-concentrating organs, such as the brain’s choroid plexus and neurons, salivary glands, breasts, thymus, arteries, and the stomach, etc.

**Recent studies on iodine and the brain: the biochemical action of iodine on neuronal lipid membranes**

Iodine is the primary brain selective nutrient (Cunnane, 2005; Venturi & Bégin, 2010; Küpper et al., 2011; Stroev & Churilov, 2012). Recently Stenzel and Huttner (2013) reported the important role of maternal thyroid hormones in the developing neocortex and during human evolution, showing that iodine intake has been related to the expansion of the brain and associated with the increased cognitive capacities during human evolution, because thyroid hormones regulate transcriptional activity of target genes via their nuclear thyroid hormone receptors (THRs), even mild and transient changes in maternal thyroid hormone levels can directly affect and alter the gene expression profile, and thus disturb fetal brain development.
A few minutes after an intravenous injection, radio-iodide is strongly present in the choroid plexus and in cerebrospinal fluid, and it is quickly taken up by brain’s neurons. The phospholipid membranes of the neuronal cells of the hypothalamus and retina and cerebrospinal fluid have the highest accumulation of radio-iodide (Pellerin, 1961; Venturi, 2011, 2012). About 60% of the dry weight of the brain is lipid, for which a dietary source of PUFAs is required in order to maintain the structural complexity, function and size of the human brain. Iodine protects the fragile and easily oxidable double bonds of the PUFAs from reactive oxygen species (ROS) forming specific iodolipids, and iodide (I-) also has an important antioxidant, apoptotic and antiproliferative action (Venturi & Venturi, 2007, 2011). Human babies have an enormous need for two dietary PUFAs: arachidonic acid (AA) and eicosapentaenoic acid (DHA) and their derivatives, such as 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid, to fuel the normal growth of the foetal and infant brain and retina (Crawford, 2010; Arroyo-Helguera et al., 2008; Tomasz et al., 2010). Aceves et al. (2005) reported that in the cellular homogenate of the breasts of virgin rats, iodine is about 40% in lipid fraction, where it exerts an important antitumor action against mammary cancer. The liposome membranes of brain neurons show a maximal accumulation of these iodolipids and thyroid hormones in the middle of phospholipid bilayer. The choroid plexus of the brain shows an active radioiodine uptake by sodium/iodide symporter (NIS) (Dickson et al., 1987), and, via the choroid plexus, iodine and thyroid hormones reach the cerebrospinal fluid and then the neuronal cells of the brain. In this way, the antioxidant actions of thyroxine (Ware & Wishner, 1968) and iodides protect the brain cells, making the neuronal transmission more efficient. The retinal pigment epithelium and the choroid of the eye also have a high uptake of iodine. The outer segment of retina harboring visual pigments is mostly composed of PUFAs, mainly DHA, which plays a crucial role in the development, survival and functioning of retinal photoreceptors. These photoreceptors are very susceptible to ROS which cause many retinal diseases, such as macular degeneration and diabetic retinopathy (Roy et al., 2011). Wu et al. (2003) showed that in I-deficient rats iodine may have an effect on the antioxidative ability of retinal cells, and that rats supplemented with potassium iodide, at normal doses, showed higher antioxidative ability. In 1985, Katamine et al. reported that oral iodides protect the brain cells of rats from ROS, which after a 19-month dietary treatment, showed higher tissue lipoprotein lipase activity, a lower lipid peroxide level in the brain, and a trend towards lower serum triacylglycerol levels and body fat storage, without alterations of thyroid hormones.

Peroxidases and deiodinases can take electrons from iodides, and the latter enzymes can take iodides from iodothyronines. Iodide and T4 trigger amphibian metamorphosis, which transforms vegetarian tadpoles into adult carnivorous frogs, with the better neurological, visuospatial, olfactory and cognitive abilities necessary for hunting, characteristics of carnivorous and predatory animals. Similarly, if iodine is not introduced to neotenic amphibian salamanders, they do not transform into terrestrial adults and continue to live and reproduce in the larval form of aquatic axotolt. In amphibian metamorphosis,
iodine and T4 stimulate the apoptosis (programmed cell death) of the cells of the larval gills, tail and fins, transforming aquatic tadpoles into ‘more developed’ terrestrial frogs (Venturi, 2011). Conversely, in mammals, thyroidectomy and hypothyroidism may be considered a sort of phylogenetic and metabolic regression to a former stage of reptilian life. Indeed, many of the disorders that afflict people with hypothyroidism seem to resemble features of reptiles, such as scaly, dry, hairless, cold skin, lethargic cerebration, a general slowdown of metabolism, digestion, heart rate and nervous reflexes, hyperuricemia and hypothermia (Venturi, 2000).

**Conclusion**

Goiter is the most specific clinical marker of iodine deficiency in the human body. According to WHO, iodine deficiency is the main cause of impaired cognitive development in children and is still a major public health problem in many countries. During pregnancy, severe iodine deficiency may impair fetal development, resulting in cretinism, with irreversible mental retardation and developmental abnormalities, as well as miscarriages and stillbirths. Efforts are required to strengthen sustainable salt iodization programmes. The study of iodine, and its compounds, are new areas of investigation, which might also provide insights into apoptosis, carcinogenesis and many cardiovascular and degenerative diseases.

**Conflicts of Interest**

The author declares that there are no conflicts of interest.

**References**


http://www.omceoar.it/cgi-bin/docs/cesalpino/n.%2032%20dicembre%202012.pdf


