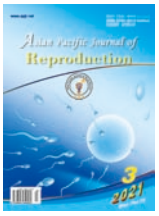

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Excess iodine exposure: An emerging area of concern for male reproductive physiology in the post-salt iodization era

Arijit Chakraborty✉

Department of Sports and Exercise Science, Somaiya Sports Academy, Somaiya Vidyavihar University, Vidyanagar, Vidya Vihar East, Vidyavihar, Mumbai, Maharashtra 400077, India

ABSTRACT

To prevent iodine deficiency disorders, the universal salt iodization programme has been introduced all over the globe, including environmentally iodine sufficient regions irrespective of their iodine status. As a result, iodine-induced thyroid dysfunctions namely hyperthyroidism, hypothyroidism, autoimmune thyroid diseases, endemic goiter and even thyroid cancer including infertility, still births, abortions and embryo toxicity have emerged as a major public health problem. In other words, the consequence of iodine deficiency and excess is almost 'U'-shaped. Hypothyroidism caused by iodine deficiency affects reproductive functions of organisms; however, such undesirable effects of iodine overload on male gonadal physiology together with hormonal profiles are yet to be adequately explored. The discovery of iodide transporter in the testis justifies an independent role of iodine in male reproductive function, which is not entirely known. Recent studies on human subjects and animal models are now revealing further perceptions into the effect of excess iodine on male infertility with euthyroid status. Excess iodine exposure has been linked with deterioration of structural and functional changes of testis leading to compromised spermatogenesis by affecting various cellular and molecular signaling pathways culminating into disrupted the blood-testis barrier and cytoskeleton. This review provides an update and summarizes various novel insights of excess iodine exposure on reproduction by establishing the independent role of iodine on male reproductive endocrinology, which might help in formulating future strategies to prevent iodine-induced male infertility, an emerging global concern, especially in the post-salt iodization era.

KEYWORDS: Iodine deficiency; Iodine excess; Reactive oxygen species; Thyroid; Testis; Lipid peroxidation level; Male infertility

1. Introduction

Iodine is an indispensable micro-nutrient required for animals as structural and functional element for biosynthesis of thyroid hormones. By virtue of thyroid hormones, iodine exerts a significant role in basal metabolic rate and on the overall expression of genes that impart many physiological functions, including embryogenesis and growth, reproduction along with advancement of neurological and cognitive functions. Iodine apart from its pivotal role for the synthesis of thyroid hormone, contributes in a number of clinically important collaborations with the functioning of thyroid gland[1]. The principal role of the thyroid gland is secretion and release of the hormones thyroxine (T_4), triiodothyronine (T_3) and calcitonin. Nearly 80% of the T_4 is converted to T_3 by peripheral organs such as the liver, kidney and spleen by deiodinases, which are selenium containing enzymes[2]. T_3 is about ten times biologically more active than T_4[3]. The total deficiency of thyroid hormones can reduce basal metabolic rate up to 50%, while in excessive production, the same can be increased by as large as 100%[4]. T_4 acts largely as a precursor to T_3, which is (with minor exceptions) the natural active hormone. Biologically active thyroid hormones have also been well known for its critical regulation of pre- and post-implantation embryo development[5].

Humans need optimum iodine for their appropriate physical, reproductive and mental development among others[6]. In an adult with sufficient iodine intake, approximately 15-20 mg iodine is concentrated in the tissues of the thyroid gland[3]. However, it has been postulated that only 30 percent of the body's iodine is concentrated in the thyroid tissue and thyroid hormones while the remaining non-hormonal iodine is found in a variety of tissues,

✉To whom correspondance may be addressed. E-mail: say.arijit22@gmail.com; arijit@somaiya.edu

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including mammary gland, eye, gastric mucosa, cervix, prostate, reproductive organs (testis and ovary) and salivary glands[4]. With the exception of mammary tissue, the function of iodine in these extra-thyroidal tissues is largely unknown[7]. However, it has been hypothesized that the relationship between iodine intake and the risk of thyroid disease is 'U'-shaped, with both low and high iodine intakes associated with altered thyroid function[8]. Indiscriminate intake of iodine resulting in hypo- and hyper-thyroidism is detrimental to thyroid function; the latter is emerging as a global concern in the present environmental scenario[9]. Altered thyroid status is known to adversely affect many organs and tissues including male and female reproduction[10]. Clinical data correlating the effects of excessive iodine supplementation on reproduction mainly male reproductive physiology is partial, probably because thyroid diseases are more common in females than in males[11]. It has also been indicated that pregnant women in excess iodine environment experience some kind of child birth related dysfunction[12]. The thyroid gland has auto- regulatory mechanism by which it can limit the entry of excess iodine through Wolff-Chaikoff effect but up-to a certain level[13]; however, no such phenomenon has not been studied on testicular tissues[14].

The existence of thyroid hormone receptors on germ cells suggests a probable role of thyroid hormones in sustaining differential population of cells in testicular milleu[15]. Thyroid hormone receptors are identified on different stages of developing rat germ cells *viz*. gonocyte, spermatogonia, preleptotene, leptotene, pachytene, zygotene, round and elongating spermatids[16]. Thyroid hormone receptor (TR) α and TRβ1 are mutually expressed during different stages of germ cell development as TRβ1 first appears in intermediate type spermatogonia while TRα first appears in type B spermatogonia[17]. There have been recent reports of male reproductive deterioration in type A and B spermatogonia's following excess iodine exposure having euthyroid condition[14]; also significant presence of iodine transport channels in germinal and Leydig cells[18] favour testis for a potent iodine concentrating organ. These results strongly indicate towards optimum level of iodine as an independent regulator of male reproductive functions; however, the correlation is yet to be reconnoitred in detail. Effect of excess iodide on male reproduction especially on testicular and spermatozoal morphology with functional status even in experimental models needs to be explored further to delineate its possible role in the persistence of human infertility. This review concerns those aspects of research involving excess iodine with special reference to male reproductive endocrinology. Elemental iodine is a halogen with an atomic mass of 126.9 Da which exists in the oxidation states 1 (I^- anion or iodide) to +7 (IO_4 anion or periodate) in the environment. Iodides and iodates (IO_3^-anion, oxidation state +5) occur ubiquitously in igneous rocks and soils, liberated by weathering and erosion, leached by rainwater into surface water and the seas. In many areas of the world, the surface soil becomes progressively poorer in iodine through these leaching processes[19]. Liberated elemental iodine evaporates into the atmosphere and is precipitated by rainfall into the land surface completing the environmental iodine cycle. The iodides in the sea accumulate in marine organisms, whereas, on land, small amounts of iodine are taken up by plants that are subsequently ingested by herbivores[20].

The availability of iodine is found in a wide variety of foodstuffs the richest sources being dairy products and fish. Seaweed is an intense source of iodine, but it can provide excessive amounts (particularly so in the case of brown seaweed such as kelp), and therefore consumption of seaweed more than once a week is generally not recommended, especially during pregnancy and lactation[21,22]. Milk and dairy products are the main sources of iodine for most people, irrespective of demographic and geographical variations in addition to consumption of iodized salt. Research has shown that organic milk has a 40% lower iodine content than conventional milk[4]. For implementation of universal salt iodization policy in most of the countries, iodine is added to table salt to give "iodised salt" for possible prevention from iodine deficiency disorders. Packaged iodised salt is exclusively distributed in the different countries and very popular in general supermarket chains and consumed by all strata of populations irrespective of their socio-economic status. It is further reasonable to consider that the actual amount of iodine in food varies according to the iodine content of the soil, farming practice, fish species and seasonal variations[23]. Iodine is present in nature in various forms such as inorganic sodium and potassium salts (iodides and iodates), inorganic diatomic iodine (molecular iodine or I_2) and organic monoatomic iodine. Iodides (I^-) are absorbed *via* transport protein in the gastric mucosa called the sodium-iodide symporter, found in a variety of tissues in the body that utilize and concentrate iodine such as the thyroid, mammary tissue, salivary gland, cervix including the reproductive organs[24]. However, certain generic medicines, elemental agents for water purification, topical antiseptics and iodinated radiologic contrast agents are appreciable sources of exposure to iodine in excess[25] and might be impulsive in developing hypo-/ hyper-thyroidism in selected individuals.

2. Sources of iodine excess

2.1. Iodine supplementation

Considering its importance, iodine is put into table salt to make sure that everyone has enough iodine in their bodies to form essential thyroid hormones as a part of Universal Salt Iodization Programme. Iodine has also been administrated as iodized oil orally and intramuscularly, introduced into the water supply, used in crop irrigation, incorporated into animal fodder and introduced into food, bread iodophores and other dietary products. Fortified micronutrient biscuits have also been successfully used to raise the median urinary iodine concentrations of schoolgirls (aged 10-15 years) in India[26].

2.2. Iodinated supplements

Several cases of congenital hypothyroidism caused by ingestion of excess maternal iodine tablets during pregnancy and lactation have been reported[27]. Similarly, hypothyroidism in new-borns to mothers who ingested excessive amounts of seaweed or seaweed soup during both pregnancy[28] and lactation have been reported[29] indicating risks of potential iodine-induced thyroid dysfunction .

2.3. Medications

Amiodarone, an iodine-rich medication used in the management of ventricular and supraventricular tachyarrhythmia, is probably the most important and common source of medication-induced thyroid dysfunction. Amiodarone is 37% iodine by weight and has some structural resemblance to the thyroid hormones T_3 and T_4[30]. Thus, one 200 mg tablet of amiodarone contains 75 mg iodine, which is several hundred-fold higher than the recommended daily intake of 150 μg in adults that may result in excess iodine intake when consumed regularly[31]. Our group has demonstrated the risk of amiodarone induced toxic changes in all the thyroid hormone responsive organs mainly because of its high iodine content[30]. Providine-iodine solutions commonly used to treat local infections is also another source for excess iodine intake especially in populations residing in environmentally iodine sufficient regions[20].

2.4. Diet

Diet is considered as one of the most effective forms of iodine nutrition. The iodine content of foods is highly variable between food categories as well as within each category. The richest sources are marine products (such as fish, shellfish, molluscs and seaweed), eggs and milk, as well as their derivatives. Iodine content of milk and eggs is also influenced by feeding and hygienic practices[19,32].

2.5. Radiologic contrast media

Use of iodinated contrast agents in diagnostic radiologic studies is a common source of excess iodine exposure in many patients. Following exposure to an iodinated contrast agent, iodine stores in the body remain elevated and provide a continuous pool that can potentially induce thyroid dysfunction which is ultimately deleterious to human body[33].

2.6. Other sources of iodine supplementation

Iodine exposure may be due to topical iodine supplementation which is frequently done in child care hospitals especially to neonates[34]. Other sources of potential excess iodine exposure include various expectorants, food preservatives and additives, prescribed medications, parenteral nutrition preparations, mouthwashes[35] and vaginal douches[36]. Some other natural sources of excess iodine exposure includes volatilization of iodine from the oceans, weathering of rock, and eruptions of volcanoes[37] also human activities like nuclear weapon testing, combustion of fossil fuel, poor waste management from municipal plants, undue combustion of iodinated waste and fossil fuels also highly aggravate the situation.

2.7. Female reproduction and developmental effects

Excess iodine has been shown to regulate serum progesterone profiles by altering the expression of androgen synthesizing enzymes as well as by down regulating progesterone responsive genes thereby leading to disrupted female reproductive system[38]. Severe structural and functional alterations in ovarian morphology and uterine wall as evidenced by decreased luminal fluid secretion and glandular morphology was observed, that resulted from critical cellular and molecular modification in steroidogenic signalling pathway[39]. Our group has experimentally demonstrated that iodine when administered 100 times excess causes hypo-estrogenic effect in female reproductive system leading to anovulatory conditions and compromised fertility maintaining euthyroid condition however iodine at 500 times excess develops hyper-estrogenic situation giving rise to altered fertility status[39]. Thus, it exhibits biphasic mode of action depending on dose and durations raising serious concerns of female reproductive health in populations consuming iodine for considerably long periods. Thyroid hormone abnormality from any cause at initial phases of development may result in severe mental retardation, neurologic abnormalities, stunted growth, and/or abnormal pubertal development[40]. Embryotoxicity and teratogenicity have been reported because of reduced body weight in fetuses along with decreased number of live births and increased incidence of resorptions especially skeletal variations in pregnancy of those women who lived in iodine excess areas or were supplemented with high amounts of iodine during gestational period. These findings strongly indicate that exposure to maternally toxic doses of iodine may have a potential developmental toxic effect in the new-borns/neonates[41].

It has been already established that oral exposure to excess stable iodine may produce hypo- or hyper-thyroidism and may cause disruption of reproductive system secondary to thyroid gland dysfunction[42]. Hypothyroidism can produce changes in the menstrual cycle in humans, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation) with incidences of abortions, stillbirths, and premature parturition[39,43]. Reproductive impairments associated with hyperthyroidism include amenorrhea, alterations in gonadotropin release and sex hormone-binding globulin, and changes in the levels and metabolism of steroid hormones in both sexes[43].

3. Excess iodine and male reproduction

3.1. Carrier mediated iodine transport in testicular cells

Sodium-iodide symporter and pendrin are primarily involved in iodide (I) transport and entry into cells and tissues that accumulate iodine[44]. The sodium-iodide symporter is a basolateral plasma membrane transporter that facilitates active uptake of iodide into thyroidal follicular cells, the classical iodide concentrating endocrine organ[45]. Since iodide can be transported and accumulated not only in thyroid but also in many other tissues, it is predictable that presence of sodium-iodide symporter or its mRNA expression in extra-thyroidal tissues is categorically possible. Limited data are available on the sodium/iodide symporter expression in human testis, a potent thyroid hormone sensitive organ; however, recent reports have confirmed its localization and expression in both foetal and adult normal testis at various stages of development[46]. Sodium-iodide symporter is also found to be expressed in the large majority of seminomas and embryonal carcinomas of human testis, and its presence in the plasma membrane compartment of the tumor cells suggests that it may serve as potential carrier of radioiodine for an ablative treatment of cancer tissue[46]. Sodium-iodide symporter is a key plasma trans-membrane glycoprotein that catalyses the active accumulation of iodide (I) in the tissues concerned with iodide uptake; co-transports two sodium (Na^+) ions along with one iodide (I^-) ion, with the inter-membrane sodium gradient serving as the driving force for iodide uptake[47]. The sodium gradient is achieved by sodium-potassium ATPase (Na^+-K^+-ATPase) that regulates cellular Na^+ and K^+ levels by active transport of Na^+ outside the cell against the gradient, and the energy for this transfer is generated through hydrolysis of ATP[48]. However, hyperactivity of thyroid gland requires an elevated uptake of iodide, which in turn depends on the Na^+ electrochemical gradient, and dissipation of that gradient by aggressive iodide transport would be minimized if there is an accompanying increase in the Na^+-K^+-pump[49]. Na^+-K^+-ATPase has been found to be located in the conventional basolateral position in rat testicular cells and epididymis; furthermore, its presence on apical membrane of Sertoli cells has also been identified[50]. Experimental studies on mice revealed that iodine overload can cause a significant reduction in the activities of this crucial cation co-transporter when treated for longer duration, which suggested an overall detrimental effect not-only limiting to thyroid gland[51]. Similar observations have also been reported when iodine in excess induced hypothyroidism has been suggestive of decreased Na^+-K^+-ATPase in different areas of brain, leading to decreased functional status with cognitive deficits[52]. It has been well documented that further sodium-iodide symporter-mediated iodide transport is parallelly inhibited by the Na^+-K^+-ATPase inhibitor ouabain as well as by the competitive inhibitors thiocyanate and perchlorate[53] suggesting a functional interrelationship and co-localization of those two transporters. However, molecular characterisation of sodium-iodide symporter to understand its fundamental mechanisms in post-translational regulation of proteins and its role in testicular cells under excess iodine environment is a crucial area for research, following which novel therapeutic interventions and strategies for this micronutrient ingestion may be established.

Pendrin, an iodide/chloride transporter, which is expressed in the apical membrane of thyroid follicles, likely participate in the efflux of iodide into the follicular lumen[54]. Higher expression level of pendrin was found in the kidney, lungs, and reproductive tissues (including testes, ovaries, and uterus) than in the thyroid[55]. It has been confirmed from the studies of Lacroix *et al*[56] that testis contains sodium-iodide symporter and pendrin by immunohistochemistry, whereas Sertoli cells were found to have positive immunostain for the latter. Higher expression of pendrin transcripts and its products (SLC26A4 protein) has been shown to be found in testis[57], suggesting its pivotal role in regulation of iodide metabolism, transport and its relation with male steroidogenesis. It has also been reported that the consumption of high-iodine diets elevates blood-iodine concentration[58]. Maroufan[59] and May & Vardaman[60] confirmed that a significant increase in serum iodine concentration of male and female broilers was recorded when various iodide concentrations ranging between 0.3 and 5 000.0 mg/kg were used. Cao *et al*[61] reported when laying hens were fed with diets containing 50 and 100 mg I/kg for 56 days, plasma iodine rise by factors of 1.35 and 2.01 respectively. Iodine containing diets in amounts of 3.5 and 11.0 mg I/kg for 74 days to laying hens resulted in occurrence of serum iodide peaks of 4.9 and 6.5 mg/L[62]. Our study also revealed that ingestion of extra iodine may concomitantly result in elevation of plasma iodine levels besides augmented testicular accumulation[16]. In addition to plasma iodine levels, urinary iodine concentrations are a convenient but imperfectly validated marker of iodine intake. Initially, 24-hour urinary iodine excretion pattern was assumed to correspond to dietary intake of iodine; however, this is uncertain because urinary iodine content more closely relates to systemic adaptation to iodine supply, rather than being a reliable marker of the risks of iodine inadequacy. However, urinary iodine excretion may be a useful marker of adequacy or excess but its value at marginally adequate or inadequate intakes is uncertain[63]. In an recently concluded investigation on adult male animal models, it has been reported that administration of iodine in excess results in higher urinary and tissue concentrations of iodine in relation to the control[14]. Higher concentration of semen-iodine has also been associated to excess iodine intake and consequent development of infertility[64] - all these findings strongly indicating towards elemental iodine to have a promising effect on male fertility independent of thyroid hormone actions; the interrelationship of which needs to be further explored in details.

3.2. Excess iodine and male reproductive performance

3.2.1. Tissue morphology and function

Iodine in excess has been shown to alter gross morphology of the testis[65]. Overall testicular germ cell degeneration has also been reflected by a marked reduction in all the consecutive stages of germ cells indicating impairment of spermatogenic process in experimental models[14]. Comparable results were also obtained following treatment with amiodarone, an excess iodine-containing drug, on testicular morphology, structure and function with the developed cytotoxicity ameliorated by antioxidant rich grape fruit extract[66]. Ultrastructure analysis by electron microscopy further revels testicular deterioration with relatively compressed seminiferous tubules lined with irregular outlines of the basement membrane accompanied with tubular shrinkage and altered surface architecture induced by iodine in excess[67]. Iodine at 500 times of its normal recommended dietary allowance level has also been reported to affect accessory male sex organs namely epididymis, prostrate, seminal vesicles and coagulating gland in animal models by altering their secretory functions[67] (Figure 1). The basic function of the epididymis is to store the immature sperms for their final maturation in male genetalia, and histologically it consists of lumens containing numerous sperms surrounded by columnar epithelial cells that secrete viscous fluid which provides nutrition to the sperms for their final maturation[68]. Excess iodine exposure results in shrinkage in diameter of lumens of the cauda epididymis accompanied with cellular damage and presence of very few sperms compared to the control, possible reason being the generation of cellular oxidative stress as a result of iodine in excess exposure[16]. The I^- transport system in prostate gland involves the expression of the specific sodium iodide symporter and in some cases also pendrin[69] that makes it a potent iodide concentrating organ in addition to thyroid gland. Prostate gland normally is surrounded with the luminal ducts lined by tall columnar secretary epithelial cells and the lumens were filled with prostatic fluid and in excess iodine treatment, prostatic lumens were constricted, the surrounding epithelium layer were flat, with substantial absence of prostatic fluid in the lumen resembled vacuole like appearance[14]. Studies on *in vitro* culture show that molecular iodine, or diiodine (I_2), induces cell arrest and apoptosis in cancerous cell lines of prostate[70]. In general, seminal vesicles engulf the liquid that mixes with sperm to form semen. Secretion of seminal fluid is important for semen coagulation, sperm motility, and stability of sperm chromatin and suppression of the immune activity in the female reproductive tract[71] (Figure 1). Excess iodine exposure has been shown to cause a marked reduction in the luminal space as well as reduction in the surrounding epithelial layer which may be possibly for the cellular reactive oxygen species (ROS)-induced tissue injury[16]. Coagulating glands located behind the urinary bladder of normal animals showed markeded folded epithelial invaginations surrounding the lumen. These glands produce a fluid that contains fructose which provides an energy source for the sperm, as well as contributes to the mobility and viability of the sperm[72]. Coagulating gland of excess iodide-exposed animals has been shown to be constricted with irregularly shaped lumen surrounded by less secretory flat epithelial cells demarcating deteriorated structure with altered functional characteristics[14]. Gasparich *et al*[73] showed a histopathological examination of epididymal tissues in patients on amiodarone therapy, and further reported fibrosis and lymphocytic infiltration in the seminiferous tubules leading to disturbance of spermatogenesis leading to male infertility.

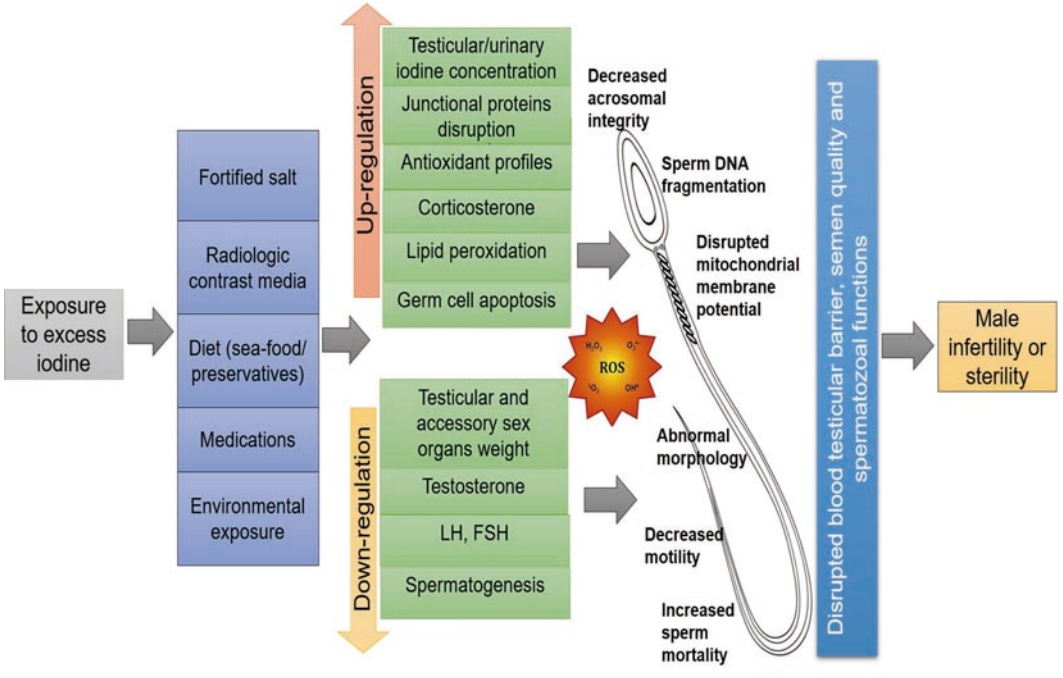

Figure 1. Schematic diagram shows the mechanistic effects of excess iodine consumption in the overall aspects of male reproductive physiology.

3.2.2. Excess iodine and spermatogenesis

Optimal thyroid function by adequate iodine intake is necessary for maintenance of spermatogenesis as the testis contains thyroid hormone receptors type 1 (TR-1)[74]. However, indiscriminate intake of iodine even in euthyroid condition can also lead to defective testicular functions and hence spermatogenesis[14]. Presence of sodium-iodide symporter on testicular cells makes iodine an important regulatory element for the control and progression of spermatogenesis, the function of which is largely unknown. Steroidogenic enzymes responsible for the biosynthesis of various steroid hormones including progestin, androgen and estrogen from cholesterol are several specific cytochrome P450 enzymes, hydroxysteroid dehydrogenases (HSDs) and steroid reductases[75] which are largely affected by excess iodine administration. The HSDs, which include the 3β-HSD and the 17β-HSD, are involved in the reduction and oxidation of steroid hormones requiring $NAD^+/NADP^+$ as acceptors and their reduced forms as donors of reducing equivalents and are considered as rate limiting enzymes for testosterone biosynthetic pathway which were altered significantly when exposed to iodine in excess[67,76]. Excess iodine has been shown to be imposing hypothyroidism in both humans and experimental animals[77,78], that reflects in a decreased plasma testosterone level and the testosterone binding globulin in plasma[79]. Chakraborty *et al*[14] reported that both acute and chronic exposure to excess iodine caused down-regulation of testicular Δ^5 3β-HSD and 17β-HSD that are considered as key enzymes of testosterone biosynthesis and suppression of testosterone level under its influence might be the possible reason for interruption of growth and differentiation of the germ cell leading to their consequal degeneration. In addition, gonadotrophins *viz.* luteinizing and follicle-stimulating hormones are necessary for quantitative normal spermatogenesis and are the pivotal endocrine factors controlling testicular functions[80]. Both the levels of luteinizing and follicle-stimulating hormone were significantly altered when iodine in excess was supplemented in experimental animals in sub-chronic durations due to interruption of hyothalamo-pituitary-gonadal axis[16] justifying the observable changes. Shoyinka *et al*[65] found that high dietary iodine leads to depressed spermatogenesis and reduces the survival period of the spermatocytes in the epididymis of iodine-supplemented rats with higher testicular organosomatic index. On the contrary, iodine supplementation at optimal doses restored fertility of sheep living in iodine deficient areas and may represent a means to achieve a silent iodine prophylaxis of local populations[81]. Lewis[82] reported that feeding of 5 000 mg I/kg diet to domestic foul resulted in delayed spermatogenesis of about 10 days when compared to control counterparts. It has been postulated that excess iodine, might act directly on gonadal cells, resulting in a inhibition of spermatogenesis and hence fertility[83]. It has been confirmed that chronic daily oral administration of iodine, in the form of tincture mixed with the food, produced regression of the seminal vesicles and testicular damage restricted to the Leydig cells[84]. There are also reports of clinical cases where transient impaired testicular function was observed following exposures to ^{131}I for ablative treatment of thyroid cancer in men that included low sperm counts, azoospermia (absence of spermatozoa), and elevated serum concentrations of follicle stimulating hormone, which persisted for more than 2 years, but were usually of much shorter duration[85]. Amiodarone, an excess iodine-containing drug, has been found to have dose-dependent degenerative and apoptotic effects on rat testes with a relatively higher number of cells positive for Terminal deoxynucleotidyl transferase dUTP nick end labelling, caspase-3, caspase-9 and Bax, suggesting a dose-dependent increase in the apoptosis under the effect of this iodinated medication[86]. Chronic ingestion of this excess iodine-containing drug has resulted in testicular dysfunction and infertility in patients along with atrophic testis and hyper-responsiveness to gonadotropin-releasing hormone[87]. The results of those studies indicate that iodine present in amiodarone may be significant factor responsible for those alterations, and the intricate details need to be explored. Blood testis barriers which are composed of cytoskeletal components are of extremely important in maintaining and progression of spermatogenesis. Excess iodine results in generation of free oxygen derived radicals that decrease the expression of adherens junctional proteins including proteins involved in Sertoli-Sertoli tight junctions or Sertoli-germ cell junctions along with downregulation of focal adhesion kinase[16] which is considered as a master regulator for blood testis barrier dynamics causing disruption of blood testis barrier and hence reduced overall spermatogenesis.

Elevation of adreno-cortical pathway has also been considered as a potential inhibitor of spermatogenesis; the fundamental details have been worked out by Chakraborty *et al*[14]. Iodine in this study has been found to be associated with adrenal stress signalling mechanisms which resulted in excess production of corticosterone, a factor associated to be involved in compromised spermatogenesis. Abd-Aziz *et al*[88] reconfirmed that corticosterone-induced oxidative stress and an inhibitory effect exerted at the hypothalamic-pituitary-gonadal axis were evidenced by increased lipid peroxidation, reduced enzymatic antioxidant activities, and decreased testosterone production, which subsequently resulted in decreased fertilising capacity of epididymal sperm leading to poor pregnancy outcomes. Developmental toxicity and teratogenicity with skeletal variations after exposure of excess iodine was also noted in a study by Yang *et al*[89]; however, in a different study on sexual activity and semen characteristics on Friesian bulls, supplementation of iodine within normal ranges has a beneficial effect on semen quality and quantity, initial fructose concentration and improvement in endocrinological output of hormones along with a positive relationship with growth and maturation[90]. This confirms the biphasic action of iodine on

metabolism and developmental endocrinology *i.e.* when consumed in recommended levels, it may be beneficial to reproductive health; however, excess consumption may lead to spermatogenic arrest hence failure in the reproductive process.

Recently, it has been proposed that alterations in sperm functional status after excess iodine exposure caused a significant increase in spermatozoal DNA fragmentation and augmented the number of apoptotic sperms; however, the plasma membrane intactness/ viability was decreased with deteriorated acrosome integrity as found in one of our study[67]. It is worthwhile to note that sperm DNA fragmentation has recently emerged as a valuable tool in defining male infertility and in assessing sperm functional characteristics. Sperm chromatin integrity tests in human reproductive system and its causative relationship with oxidative stress have been increasingly disclosed[91]. One of the striking features of sperm DNA fragmentation has been its high correlation with the risk of pregnancy loss[91]. The salient observations from Chandra and Chakraborty[67] also established the depolarisation of mitochondrial membrane potential and elevation of sub-haploid cells under exposure of iodine in excess of about 500 times more than the recommended level. All these observations strongly suggest iodine to be a potential male anti-fertility agent when administered in excess for longer durations. Abnormal and reduced sperm counts with coiled tail, aberrant sperm head and disintegrated morphological features were already established by our group under varying doses of iodine excess when administered to experimental animals[14]. Increased intake in amount of iodine intake has been recommended as a probable cause of decline in sperm counts coinciding with the implementation of universal salt iodization in the United States, France and United Kingdom[92]. It would be wise to quantify the presence, number, and activity of iodine transporters in germ, Leydig and Sertoli cells for better assessment of function and its possible role in regulating steroidogenesis.

3.2.3. Excess iodine and testicular oxidative stress

Iodine is one of the most electron-rich atoms in the diet of marine and terrestrial organisms with iodide (I^-), acting as an ancestral electron-donor through peroxidase enzymes[7]. Iodine in excess may promote oxygen free radicals to reduce the antioxidant defence capability[13]. Iodine itself is a highly active molecule which can react with proteins, lipids, and nucleic acids to generate a variety of acyclic iodo-compounds accompanied by ROS generation and lipid peroxidation in the process, resulting in the damage to the structure of the cell membrane and mitochondrial membrane[93] (Figure 1). However, when ROS are over-produced, they become toxic and bring damage to cellular components, macromolecules including lipids, proteins and nucleic acids hence causing damage to DNA and RNA. A toxic effect of iodide given to iodine-deficient laboratory animals was already noted experimentally by various research studies[94]. Similar studies have shown that 4-hydroxynonenal, a toxic product resulting from lipid peroxidation, is increased in goitrous and in iodine-induced involution glands, which indicate that oxidative stress is greatly enhanced in these conditions[95]. Testicular cells and spermatozoa are reported to have high amounts of polyunsaturated fatty acids[96]. During steroidogenesis, certain amount of ROS are generated due to leakage of electron outside the electron transfer chain that are normally counteracted by antioxidant enzyme defence system present in testis[16]. Any imbalance may thrust these radicals not only to stimulate lipid peroxidation but also produce an alteration in the level of protein and DNA causing cellular damage[13]. Excess iodine has been shown to elevate oxidative stress mediated by generation of ROS in thyroid as well as thyroid hormone sensitive organs. It has been postulated that iodide excess has pro-oxidant effects, leading to an increased lipid peroxides level and catalase activity in target tissues and blood that leads to a decreased H^+ donor ability of the sera[13]. Similar observations have also been reported with elevation of testicular lipid peroxidation levels positively correlating with upregulation in primary testicular antioxidant defence system for acute phase of the study however subsequent downregulation in those parameters were observed when excess iodine was administered for longer periods suggesting it to be a potential oxidant causing cellular oxidative stress by altering the pro-/anti-oxidant balance[13]. Testicular architecture of fertile animals are abundant in poly unsaturated fatty acids (PUFA) that serve as precursor's molecules in cell membrane glycerophospholipids and thereby serves as a protection of testicular cells against shift in fatty acid composition induced by dietary changes[97]. Ingestion of iodine in excess causes generation of iodinium (I^+) and hypoiodite (IO^-) ions as intermediate products which are extremely reactive and can cause lipid peroxidation not only in thyroid but also in extra thyroidal cells like testes[54,98]. Molecular iodine is activated into a free radical intermediate by superoxide to iodide (I^-) that forms the basis of iodination[99] and under the influence of excess iodine free radical productions are elevated for more iodination resulting in oxidative stress and hence cellular damage. It has also been reported that organs containing elevated amounts of PUFAs like testis are more vulnerable to oxidative damage[100] in addition to the fact that two high energy consuming physiological processes namely spermatogenesis and steroidogenesis yield ROS as a biproduct[101] that are particularly counteracted by the anti-oxidant defence systems present in testis; however, any imbalance can lead to free radicals-induced cellular damage causing oxidative stress[15]. Superoxide dismutase, catalase and glutathione peroxidase all have been shown to be affected by ingestion of iodine excess. Elemental iodine has been considered as an important regulator for redox balance[102] and in excess amounts acts as pro-oxidant exerting oxidative damage. Similar findings have also been reported on spermatozoal structure and function as well

where ROS were also generated as a result of excess iodine exposure in animal model[67] (Figure 1). PUFA has also been suggested to be found on sperms in addition to testis[103] and thus they are also vulnerable for oxidative damage. ROS-induced damage in sperms can also lead to their deformed structure and may be a causative factor for male infertility[104]. Generated ROS for excess iodine ingestion causes damaged acrosomal integrity, loss of mitochondrial membrane potential, reduced and motility, chromosomal aberrations, decrease in haploidy and apoptosis which all indicate towards male infertility and sterility. Recently, in a study involving infertile couples, it has been correlated that men with higher iodine levels had more morphological alteration in spermatozoa and exhibited lower motile sperm count respectively[64], indicating iodine may play a role in the quality of semen and its close association in determining the attributes of male infertility.

4. Conclusions

Role of elemental iodine has been primarily focused and attributed as an indispensable component of thyroid hormones; with its indiscriminate intake resulting in deficiencies or excess, more or less are corroborated with altered thyroidal structural and functional status. Recently, the presence of iodine transporters like sodium-iodide symporter in germ and Leydig cells; pendrin in Sertoli cells, strongly suggests a regulatory role of this trace element in male reproductive endocrinology. Therefore, considering the inadequacy of available substantial research outputs in this area, it is of high time to recognise the functions of iodine independent of thyroidal actions. Moreover, the association between iodized salt consumption, urinary iodine levels, ROS generation in testis and spermatozoa, decreased sperm number and motility with increased concentration of iodine in seminal plasma needs to be established as a cause-effect relationship to understand the role of iodine in excess on male infertility. This review provides novel insights and may serve as future strategies for establishing the independent role of iodine on male reproductive physiology, an emerging concern, which warrants further investigations.

Conflict of interest statement

The author declare no conflicts of interest.

Author's contributions

Arijit Chakraborty planned, prepared the draft of the manuscript, and supervised the entire study.

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