

## Effect of Chronic/High Iodine Intake on Thyroid Function and Fertility

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### Abstract

Micronutrients play a pivotal role in the human body. Their deficiencies and toxicities lead to many life-threatening diseases. Among them, iodine deficiency was one of the situations prevailing globally since decades. Its causes thyroid diseases and disturb fertility. To overcome this deficiency a Universal Iodization program was established in 2004. This prolonged unchecked iodized salt utilization beyond limits not only correct the deficiency but also created problems such as hypo/hyperthyroidism, thyroid autoimmunity and compromised fertility. Epidemiological studies show a huge number of fertility issues globally and unchecked iodized salt utilization may be one of the factors having a contribution in it. This slow-progressing pattern remained unchecked and needs to be addressed to ensure the provision of safe dietary iodine level. This review provides a link between high iodine intake and its effect on thyroid and fertility.

**Keywords:** Iodized Salt; Infertility; Hypothyroidism; Hyperthyroidism; Thyroid-Autoimmunity

### Introduction

Human metabolism and growth rely on a well-balanced diet constitute different micro and macronutrients. The micronutrients make a little part of the complete diet but they perform a vital role in several metabolic phenomena taking place inside the body. Excess or deficiency of these micronutrients can adversely affect the standard biochemical processes of the body.

Among many essential micronutrients, Iodine is a crucial micronutrient which performs an important function in the regulation of thyroid hormones in the body. Recommended daily iodine intake is 150 µg in adults and youngsters and 250 µg for lactating or pregnant females. Iodine insufficiency can cause obesity, goiter, hair loss, high cholesterol concentrations, and slow physical and mental development. In pregnant females, a number of problems such as stillbirth, miscarriage, and irreparable damages in the fetus and mentally retarded children can occur due to iodine deficiency. Similarly, excess iodine intake can cause hypothyroidism, hyperthyroidism and thyroid autoimmunity [1].

World health organization in 2012 found that a huge number of children having iodine deficiency are in Africa (39.3%) and Europe (43.9%), while a small number of children with iodine deficiency are in the Western Pacific (18.6%) and America (13.7%) [2].

The countries having no or little iodine deficiency-related problems are due to the utilization of iodized salt in the diet. Even though no solid policy for the supplementation of iodized salt was active in Spain and only < 50% community utilize iodized salt [3].

There was a high prevalence of goiter and a serious deficiency of iodine in the Chitral and Gilgit regions of Pakistan, first time reported in the early eighteen century. In a survey done in 1993 - 1994 shows total goiter prevalence in Pakistan was 84.9% [4].

A study showed that the Pakistani daily dietary consumption of iodine was 3.8 times low i.e. 40 µg/d than the U.S. recommended intake of dietary iodine i.e. 150 µg/d And it was five times lesser than the recommended value given by the International Commission on Radiological Protection i.e. 200 µg/d [5]. so Universal Salt Iodisation (USI) program was launched in Pakistan in 1994 to overcome iodine deficiency [6].

According to National Nutrition Survey 2011, 79% people in the Punjab province of Pakistan were consuming iodized salt, compared to only 17% in 2001 that shows a reduction in iodine deficiency in women and school children with time [6].

Most studies showed that chronic or excessive use of iodized salt has a temporary and permanent effect on thyroid function and ultimately disturbing reproduction [7]. Prolong and higher than normal level iodine intake had a bad effect on the reproductive organs and thyroid. It is highly recommended that iodine utilization should be under observation to reduce the effect of deficiency as well as excess iodine intake.

### **Iodine induced hyperthyroidism**

Excessive iodine intake, particularly in patients with thyroid disease, can cause temporary or permanent thyroid dysfunction due to hyperthyroidism or hypothyroidism [7]. The statistics illustrated that continuous utilization of iodine mixed salt has augmented  $T_4$  and  $T_3$  level, and reduced the TSH level [8]. There is a correlation between the risk of iodine-induced hyperthyroidism and a recent excessive increment of iodine supply for the rectification of iodine deficiency. A case study showed hyperthyroidism in 39-year-old woman caused by ingestion of the iodine-rich kelp [9].

A study on a children group having a mean age of 11.6 years showed that excess of iodine is associated with hyperthyroidism patients [10].

### **Iodine induced hypothyroidism**

Hypothyroidism and goiter can occur due to overconsumption of iodine as Prolonged iodine overutilization decreases thyroid gland function of iodine organic binding [11].

A study revealed that a small reduction in serum  $T_3$  and  $T_4$  level along with a compensatory increase in TSH concentration was noted in the persons having normal thyroid function subjected to provision of pharmacological iodine quantity (10 to 1,000 mg daily). Data revealed that iodine intake of 250 and 500 µg brings no change in thyroid function but subjects having 1500 µg daily had changes in their thyroid function indicated by the decrease in serum concentrations of  $T_3$  and  $T_4$  and a little compensatory rise in the serum concentration of TSH. It is shown that delicate changes in the function of the thyroid-pituitary axis can occur due to minor rise in dietary iodine which is possibly due to the inhibiting thyroid hormone release.

Similarly, a study shows that the patients consuming iodide-containing therapies for the treatment of bronchial asthma have developed different degrees of thyroid hypo-function and/or goiter.

A study on adults in the coastal area of Japan producing high iodine seaweed (kelp) was conducted to observe the thyroid dysfunction due to iodine intake. Results of that study indicate that the prevalence of hypothyroidism was more and marked in subjects taking excessive amounts of iodine. Thus we can consider the excessive intake of iodine as an etiology of hypothyroidism. Results of a study suggest an association of the prevalence of hypothyroidism in iodine sufficient in diet areas with the amount of iodine ingested. Hence excessive

intake of iodine can be considered as etiology of hypothyroidism as individuals taking excessive amounts of iodine have more prevalent hypothyroidism. Similarly it was illustrated that there was frequent occurrence of clinical and subclinical hypothyroidism in individuals from the iodine-rich areas [12].

A study has been done to compare the elderly women from the different geographical and ethnographical region (An iodine-deficient area and an iodine good supply area). Their results found that high thyroid antibody and subclinical/clinical hypothyroidism occurrence was observed in the region with good iodine supply.

Hypothyroidism caused by high iodine intake can be of two types, reversible and irreversible. A study on patients having hypothyroidism showed that 3 weeks iodine intake restriction made 54.5% patients euthyroid (reversible type) and remaining patients remained unaffected mean their thyroid function was not improved with the iodine intake restriction (irreversible type) [7].

Population with higher iodine utilization has more hypothyroidism cases. May be this is due to the intricate mechanism of thyroid adaptation mechanism. Higher iodine consumption inhibited many thyroid functions and increase the frequency of follicular cells apoptosis. People having thyroid autoimmunity are more prone to unusual retardation of thyroid function due to higher iodine intake. There is an age-related trend of increasing level of serum thyroid-stimulating hormone level in populations with higher iodine consumption [13].

Women having daily iodine consumption of  $\geq 200 \mu\text{g}$  have more risk of thyroid-stimulating hormone level beyond  $3 \mu\text{U/mL}$  as compared to women utilizing  $< 100 \mu\text{g/day}$ . Lowest free serum  $T_3$  level was observed in the pregnant females from the area with most supplementation coverage and maximum median of urinary iodine level ( $168 \mu\text{g/L}$ ). Hence, it is concluded that supplemented iodine consumption in initial months of pregnancy can cause thyroid dysfunction in populations with adequate iodine level or mild iodine deficiency [14].

A study on pregnant females from the area having a sufficient level of iodine was done to investigate the safe and optimum iodine consumption range in initial phases of pregnancy. Statistical analysis depicted that higher iodine consumption than adequate level brings a multifold increased risk of hypothyroidism [15].

A prospective study showed that iodine-supplemented population is prone to the risk of evident hypothyroidism even population has very moderate iodine deficiency [16].

A similar study presented that a population consuming more iodine than adequate level (MUI  $261 \mu\text{g/l}$ ) has more prevalence of subclinical cases of hypothyroidism [17].

Similarly, Results from a study propose that supplementation of iodine to an extent beyond the tolerable level in an area with the previous history of iodine deficiency can convert the subclinical hypothyroidism to clinical hypothyroidism [18].

### Iodine induced thyroid autoimmunity

In previous studies, it is concluded that iodine provision should be done to treat and avoid diseases related to iodine deficiency and iodine consumption should be maintained at an optimum safe point. Unusual level more than tolerable (MUI  $> 300 \mu\text{g}$  per liter) appear to be harmful especially in communities with insufficient iodine or thyroid autoimmunity. So, An area wise deficiency-related salt iodization and supplementation plans should be implemented. Data from the previous study illustrated that excessive iodine supplementation has a pivotal role in autoimmune diseases development in old age persons [18].

In a study on chicken strains which has genetical susceptibility to the development of autoimmune thyroid disease, were fed a diet having various quantities of potassium iodide. There was an increase in disease incidence during iodine administration in the first 10 weeks of life which was determined by histology and autoantibodies measurement against  $T_3$ ,  $T_4$  and thyroglobulin. This association between autoimmune thyroiditis and iodine is also supported by experimentation showing iodine poor régimes decrease the occurrence of disease

in chicken strain with high susceptibility for autoimmunity. A study shows that the prevalence of autoimmune thyroiditis is high in excessive iodine intake region than that of adequate iodine intake region [18].

A research illustrated that a significantly high prevalence of anti-thyroid antibodies in the population having iodine consumption more than adequate (MUI 261 µg/l) than population having adequate iodine intake (MUI 145 µg/l) [17].

A study on school children of the iodine-deficient community in northwestern Greece shows that silent iodine prophylaxis has eliminated iodine deficiency from the community but brought an increase in the prevalence of autoimmune thyroiditis [19].

A Cross-Sectional, Comparative Study suggests a trend toward a decrease in the prevalence of chronic autoimmune thyroiditis in parallel with a decrease in iodine intake [20].

Dose-dependent over-dosage of iodine brought a damaging effect to the ultrastructure of epithelial cells of the thyroid gland. With the increase in dose, the frequency of thyroiditis and infiltration of lymphocyte became high. This high iodine consumption can cause goiter which leads to adverse lymphocytes infiltration, thyroiditis and damaging follicular cell structure in mice strains prone to autoimmunity [21].

The data on the rats (BB-DP) and mice (NOD-H2h4) susceptible to autoimmune recommend that genetically susceptible individual develop thyroid autoimmunity under the effect of a high iodine dietary intake which depends on the earlier thyroid state [22].

### Effect of iodine on fertility

It is suggested that increased iodine consumption has a role in decreasing the number of sperm cells in an ejaculate [23]. In testes, high iodine concentration generates reactive oxygen species which damage the sperm genetic material [24].

Data from the experiments on rats showed that high level of dietary iodine consumption suppressed spermatogenesis as well as decreased survivability of sperms cells in the epididymis [25].

A study indicated that males who have not achieved pregnancy in more than three years were displayed a low level of  $T_4$ . A similar conclusion is made on the study that men whose has not achieved pregnancy in three years and low counts of sperm cells exhibited the greater median urinary iodine and this higher median iodine level in urine is also associated with unusual morphology of sperms [26].

Different studies associated to the use of radioactive iodine for thyroid cancer suggested that delivered cumulative dose is directly related to damage of germinal epithelium [27] and a decline in the concentration of sperm cells [28].

A case report depicts that the patient became azoospermic between a specific time periods when a patient treated with three doses of radioactive  $^{131}\text{I}$  for treating metastatic thyroid carcinoma.

A study on human thyroid cancer patients indicated that sperm density is inversely linked with total radioactive  $^{131}\text{I}$  iodine dose. Data suggest that low doses have a detectable effect on the testis but clinical effects can be reduced in an individual receiving multiple doses.

Results of another containing 103 patients indicate that radioactive  $^{131}\text{I}$  iodine therapy for thyroid carcinoma is related to a temporary reduction in cellular function of testicular germinal layer. Permanent damage due to high radiation activities year after year might be a significant risk of infertility [29].

In another trial 312 to 5000 ppm iodine in the form of KI in the diet was fed to laying hens to determine the productivity and hatchability of eggs. Egg Production was stopped upon feeding a higher level of KI in the first week and was a decline at the lower levels in the next few weeks. Reduce hatchability, delayed hatching, early embryonic death were the main results while fertility of the eggs produced remained the same. Hens started producing egg within a week after removing KI in the feed.

Female hamsters, rabbits, rats and pigs were mated to normal males and KI or NAI was added to their diet during the late pregnancy period ranges from 250 to 1000 ppm. Feeding the iodine for 2 - 5 days produced increased mortality in newborn rabbits. Rats fed with 150 mg per kg body weight had a prolonged parturition time and improper lactation. Re-mating of rabbits and rats on a normal diet leading to normal behavior.

Above experiment indicated that the high doses of iodine intake in the rat model lead to a decline in live fetus incidence and incline in the incidence of reabsorbed fetuses [30].

### Effect of hyperthyroidism on fertility

A study on young hyperthyroid male patients for the sake of infertility depict oligospermia with decline sperm motility and these abnormalities become normal after treatment of hyperthyroidism.

A Prospective Controlled Study showed that half of the hyperthyroid males suffer from sexual dysfunction along with declined sex libido, which can be treated with six months of hyperthyroidism treatment. The abnormalities in sperm motility were the main indication in hyperthyroid male patients. On treatment against hyperthyroidism, these parameters gain normal values. For hyperthyroidism syndrome parameters does not depend upon the treatment for example anti-thyroid drugs or with radioactive <sup>131</sup>Iodine [31].

In another study on treatment of hyperthyroidism with radioactive <sup>131</sup>Iodine showed that 67% hyperthyroid patients had sperm motility lower than 50%, while after treatment with radioactive <sup>131</sup>Iodine significantly increase the sperm progressive motility [32].

Above studies indicated that prominent changes in the gonadotropic-prolactin axis and effect on male reproductive function are the main causes of hyperthyroidism. Bio-available testosterone measurement was very useful to diagnose hyperandrogenism in hyperthyroid patients. Asthenospermia and hypothermia were the most frequently observed changes, followed by necrospermia and oligozoospermia in this case. Patients reported erectile dysfunction associated with decreased libido in patients [33].

### Effect of hypothyroidism on fertility

Radio thyroidectomy experimentation in adult female rats revealed that hypothyroidism induces irregular and prolonged estrous cycles, an increase in Luteinizing hormone during proestrus and a reduced ovulation rate, affect steroid metabolism in corpus luteum and growing follicles [34].

Hypothyroidism was induced in the albino rat in a research trial by surgical ablation and pharmacological suppression of the gland. Results show that hypothyroidism causes a disturbance in normal reproductive functions in rats. Although experimented rats were ovulated and conceived. Their fetuses were reabsorbed at multiple levels of pregnancy.

A study shows the relationship between hypothyroidism and reproduction by the results that indicate the adverse effects of hypothyroidism on reproduction and its proper treatment decrease the risk of abortion and other complication in gestation [35].

The results of the experimentation involving *in-vitro* and *in-vivo* fertilization of rat model for fertility test depicted that impaired fertility in mature hypothyroid rats was occurred due to defected sexual behavior as well as due to testicular and epididymal functions. The complete or partial recovery in impaired fertility and sexual behavior was noted after treatment. Upon transfer, those homozygous embryos completed their development up to term without losing viability [36].

A female suffering from hypothyroidism has significant irregularities in the menstrual cycle. The menstrual disturbance could be more frequent in severe hypothyroidism in comparison with subclinical and mild hypothyroidism [37].

An experiment on rats shows hypothyroidism reduced the pups per litter and implantation site areas. Change in normal hormone profile, expression of ovarian receptors, insulin-like growth factor family, members of the growth factor and *cyp19A1* aromatase was observed in them that can favor the survival of corpus luteum which results in the pseudopregnancy unsaturation [38].

A Prospective Controlled Study shows Hypothyroidism effect adversely human spermatogenesis. Morphology of sperm greatly differs from control and post-treated with levothyroxine. Increase in sperms Motility also observed in patients after treatment but that difference was not significant [39].

Various studies showed that hyper and hypothyroidism can produce alterations in spermatogenesis, increased risk of miscarriage, menstrual abnormalities and possible long-term effects in offspring [40].

### Effect of thyroid autoimmunity on fertility

A study Compared women with positive thyroid autoimmunity had a higher (35%) miscarriage rate, a lower (41%) Live birth rate when compared to females with negative thyroid autoimmunity [41] thyroid autoimmunity has a negative role in both unexplained infertility and conception failure [42].

Hyperthyroidism and hypothyroidism are shown to be more prevalent in all females of couples facing infertility and in couples of female origin infertility having positive thyroid antibodies as compared to women without positive thyroid antibodies in the same groups [43].

The combination of thyroid autoimmunity and high TSH in the initial phase of pregnancy is linked with three times greater risk of producing low birth weight neonates and four times higher risk of gestational diabetes [44].

A prospective study on pregnant females indicated that Euthyroid pregnant women positive for thyroid peroxidase antibody impaired thyroid function linked with a higher risk of premature deliveries and abortion [45].

### Conclusion/Future Direction

Infertility of unknown cause remain a debatable issue since a long time and different factors such as dietary habits, living style, use of electromagnetic signals like cellular phone and Wi-Fi are highly debatable factors. This review gives us insight about one micronutrient and its possible effect on fertility and thyroid function. This data strongly suggest that the use of iodized salt should be subjected to individual requirement and serum level of a person. We recommend continuous uncheck iodized salt utilization should be avoided and the population's iodine requirement should be analyzed at least annually.

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