REVIEW ARTICLE

Influences on the Incidence and Pathomorphological Picture of Thyroid Disease

Innocent Emmanuel[1], Mansur Aliyu Ramalan[2], Abdulazis Longwap[3], Ayuba Madachi Dauda[1]

ABSTRACT

Background: The thyroid serves the body with important endocrine functions. A variety of influences impinges on the incidence and pathomorphological picture of the thyroid gland. These influences that include: iodine deficiency; iodine sufficiency; gender and; imaging technology are elucidated further in this work. We used the Google search engine to search for literature on the subject from the internet. Iodine is associated with increased incidence of nodular goiter and follicular carcinoma. The world over the last few decades had transited from an era of iodine deficiency to its sufficiency leading to an increase in incidence of thyroiditis and papillary thyroid carcinoma. Estrogen and Estrogen receptor discovered in the thyroid is implicated in the increased frequency of thyroid disorders in females. Finally, advancement in thyroid imaging technology and its utilization has led to over-diagnosis and overtreatment of thyroid diseases.

Key words: Thyroid, Iodine, Pathomorphology, Imaging, Incidence

[1]Department of Histopathology, University of Jos, Nigeria, and Department of Histopathology, Jos University Teaching Hospital, Jos Nigeria.
[2]Department of Internal Medicine, Aminu Kano Teaching Hospital, Kano, Nigeria.
[3]Department of Chemical Pathology, University of Jos, Nigeria.

Corresponding Author:
Dr. Innocent Emmanuel,
Department of Histopathology, University of Jos, P.M.B. 2084, Jos, Nigeria, and
Department of Histopathology, Jos University Teaching Hospital, P.M.B. 2076, Jos Nigeria.
kinapele58yahoo.com, 2348065386111.

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Introduction

The thyroid is an important focus of disease. Thyroid disorders are not uncommon: they have symptoms as a result of glandular enlargement, functional effects of hormone secretion and paraneoplastic syndromes, and distant metastasis. These diseases can be morphological resolved into developmental anomalies, hyperplasia, immune/inflammatory diseases, and neoplasms.[1]

A variety of influences impinges on the incidence and pathomorphological picture of these disease conditions affecting the gland. These influences over the years that that included: iodine deficiency; iodine sufficiency; gender and; imaging technology are elucidated further in this work.

Iodine Deficiency

The mineral iodine is a trace element essential in the synthesis of thyroid hormones.[2]An estimated 28.9% (1572 million) people globally were at risk of its' deficiency.[3]It has been documented that 1/3rd of the inhabitants

of the earth are living in areas of iodine deficiency in the year 1998.[4]Also 350million Africans in 2004 were at the risk of the deficiency of this mineral.[5]In 2010 as much as 180 million people suffered from goiter as a result iodine deficiency.[6]In 1990 and 2013 respectively, this deficiency resulted in the death of 2100, and 2700 people.[7]

An expansive array of risk factors are associated with iodine deficiency and include: age (varies with disease type); female sex; oral contraceptive (protective); pregnancy; living in mountainous area; diet low in iodine; dietary goitrogens; selenium deficiency; perchlorates; thiocyanates; alcohol (protective) and tobacco smoking; and exposure to radiation.[8-13]Goitrogens acts directly (interfering with iodine uptake, thyroid hormone synthesis and release) or indirectly (interfering with thyroid hormone metabolism) on the thyroid gland.[11]The effect of goitrogen is made manifest only in the phase of low dietary iodine, or prolonged intake of the goitrogen.[9]These goitrogenic agents include: excess inorganic iodine; flavonoids/polyphenols; lithium; organic Sulfurates (e.g disulphides, isothiocyanate and thiocyanate); polybrominated (PBB) biphenyls; polychlorinated (PCB); Polycyclic aromatic hydrocarbons (PAH); Polyhydroxyphenols and phenol derivatives; Polyhydroxyphenols and phenol derivatives; and Organochlorines.[9]These goitrogenic agents are found in some food substances like tubers (e.g cassava and sweet potato), cereals (e.g sorghum and millet), legumes (e.g lima beans and soy/soya beans) and cruciferous vegetables (e.g cabbage and cauli-flower).Nutritional deficiencies of minerals-selenium, iron and vitamin A- are also goitrogenic through disparate pathways.[9]The oceans is by far the greatest repository of the earths' iodine deposit, and this is redistributed to the land through the iodine cycle in which elemental iodine is oxidized and volatilize into the atmosphere from the sea water. It combines with rain and is poured down on the soil on land.[9]Hence iodine deficient soil is commoner in mountainous areas, inland locales, and regions rife with flooding.[10]Therefore crops/plants cultivated on this soil would evidently be iodine deficient.[14]

Iodine deficiency is a major problem of public health importance on a global scale.[15-17]It is the leading cause of the goitre, the enlargement of the thyroid gland.[15]Patel et al. demonstrated this relationship when an increase in thyroid volume was recorded in Fischer rats fed with diet with low dose iodine.[18]Eastman and Zimmermann[9]outlined four arguments supporting the relatedness of iodine deficiency and development of goitre: areas with low iodine deficiency have high incidence of goitre; iodine supplementation reduce incidence of goitre; patients with endemic goitre have iodine metabolism reminiscent of iodine deficiency which is reversible when iodine is replenished; and finally, the similarity in morphological changes in humans and animals with iodine deficiency.

Goitre which is the commonest morphological picture of thyroid[1] disease is a consequence of hyperplasia and hypertrophy of the thyroid epithelial cells.[19]Hyperplasia is succeeded by involution, atrophy, degeneration and repair, occurring in sequence (described as the marine cycle)[20]or in any combination at different foci in the thyroid leads to nodularity of the gland.[9,19]Pathologic hyperplasia in this case as in many other tissues is a fecund soil for malignant transformation[21], therefore a sequence of hyperplasia/goitre, adenoma and follicular carcinoma has also been described as a consequence of iodine deficiency.[19,22,23]

At the heart of the pathogenesis of the morphological picture of thyroid pathologies

arising from iodine deficiency is the increased activity of thyrotropin/thyroid stimulating hormone (TSH).[9,19,24,25,26]Lack of iodine leads to decrease synthesis of thyroid hormone with consequent excessive release of TSH.[19]In some cases, the TSH level is fairly normal but there is increased sensitivity of the gland to TSH.[9]Continuous stimulation by TSH results in hyperplasia/hypertrophy of the thyroid epithelial cells and enlargement of the gland. Hypothyroid states with concomitant increased TSH in addition to iodine deficiency including subtotal thyroidectomy and transplantation of TSH secreting tumors have been shown to be tumorigenic.[27-29]The TSH stimulation is inappropriately high for an index stimulus, owing to increase in the molecules multiple pathways, especially the two major TSH signal transduction pathways (C-AMP and Ca^{2+}) leading to sensitization of these cells to TSH stimulation.[30,31]With increasing TSH stimulation, follicular cells are prodded into and driven through the cell cycle.[32]Follicular stem cell like cells in the thyroid[33]with high proliferative capacity have been hypothesized to be the progenitors of adenomas owing to persistent TSH stimulation.[34]

Indeed, a wide range of mechanistic processes act in isolation or in concert in inducing stimulation and proliferation of follicular cells in the background of iodine deficiency.[35] Prolonged stimulations with attendant increased proliferation leads mutations involving activation of oncogenes and inhibition of tumor suppressor genes.[36,37]Affected genes inter-alia include: RAS, PIK3CA, PTEN and PAX8.[19]Furthermore, while iodination induce follicular cell production of the growth inhibitory cytokine TGF-β, iodine deficiency does the reverse.[7]Studies have shown that the lack of this inhibitory stimulus in iodine deficiency state might be contributory in follicular cell rapid growth and tumorigenesis.[38,39]

Iodine Sufficiency

The world over the last few decades had transited from an era of iodine deficiency to its sufficiency. This is as a result of an international program launched by the United Nations to eliminate the deficiency of the trace element[40], tagged USI (Universal Salt Iodization).[41]The intervention recorded great success (in reducing goitre incidence)[42-44]and gained the attribute of "a cost effective community health strategy"[41]as adding iodine to salt comes with a negligible financial burden.[45]In addition to salt, iodine was added to many other eatables in areas of its deficiency.[46]

Iodine sufficiency has changed the picture of thyroid malignancy with a switch from the erstwhile predominant follicular carcinoma (associated with iodine deficiency as discussed earlier) to papillary carcinoma which is now the most frequently diagnosed cancer of this gland.[47]This changing pattern was evident on the African continent as documented in an earlier publication.[48]Studies in Africa published between 1952 and 1998 showed follicular carcinoma predominating[49-58], while those between 1999 and 2014 had a predominant papillary carcinoma morphology.[59-68]This trend has been reported across the globe.[47,69-76]

Papillary thyroid carcinoma(PTC) in the background of iodine sufficiency has been associated with mutation in the BRAF gene.[77]This involves the substitution of valine with glutamic acid in position 600 of the BRAF protein ($BRAF^{V600E}$).[78]The outcome of this is the constitutive activation of BRAF then RAS which are important proteins in the MAPK (Mitogen Activated Protein Kinase) signal

transduction pathway.[78,79]In China, Guan et al. reported BRAF mutation in 69% of PTC in regions with high iodine content, compared to 53% in regions with normal iodination of drinking water.[77]Genrally, as much as 29-83% of PTC harbor BRAF mutation, and this mutation is rare in follicular carcinoma.[80]In an iodine replete area of Korea, Kim et al reported that 97% of thyroid cancers were PTC, and 80% of the PTC have BRAF mutation.[81,82]Iodine supplementation has also been implicated in the increase of the proportion of PTC with BRAF mutation from 54.8% to 70.6% ($p = 0.001$) over time.[83]Mohammadi-Asl et al. in Iran established a 71.4% rate of BRAF mutations in PTC.[84]

As the space gets widened with the accumulating evidence of a strong association between iodine sufficiency, papillary thyroid carcinoma and BRAF mutation, it is worthwhile to highlight the effect of this on treatment of afflicted patients. Well differentiated PTC in low risk patients has a cure rate of 80% with a combined treatment of surgery and radioiodine (131I).[85]BRAF mutation has been reported to reduce the expression of genes responsible for radioiodine uptake,[86]thereby inhibiting this treatment modality. Genes affected in this regard include: AIT (apical iodide transporter), BRAF-mut (BRAF-mutant), NIS (sodium/iodide symporter) and TPO (thyroperoxidase).[86]BRAF mutations have been demonstrated to be commoner in PTC recurrence lacking radioiodide uptake than in those showing positivity for uptake.[87]Therefore the findings that primary PTC with BRAF mutations tend to be more aggressive, have more recurrence rate and lacks radioiodide uptake.[69,88,89]Another importance of BRAF mutation is the contemplated possibility its usage as a tumor marker in areas where its prevalence is high.[84]

Another pathology that has been associated with Iodine sufficiency is thyroiditis.[90]Zois et al. established an increase in the prevalence of autoimmune thyroiditis in Greek Children following the completion of the USI program.[91]Slowinska-Klencka et al. reported an increase in cytologically diagnosed thyroiditis in Poland[92]Experimental mice fed iodinated diet developed thyroiditis with dose dependent lymphocytic infiltration.[93]In a double blind trial approximately 10% of participants (adult humans) developed thyroid dysfunction and autoimmunity after iodine supplementation.[94]Post partum thyroiditis was demonstrated to have high prevalence in a group of women with high intake of iodine compared to other two groups with relatively lower intake.[95]

Gender

Thyroid disorders, both non-neoplastic and neoplastic, in all literature reviewed in this study, and to the best of our knowledge are overwhelmingly commoner in women than men. In this gender, the disease has been seen to be more prevalent within the childbearing age group- between puberty and menopause.[96,97]Empirically, women are also more responsive to goitrogenes.[98]This gender imbalance has sparked the need for research for a possible targeted therapy.[99, 100] To this end, reproductive hormone-estrogen, has been implicated to play a role in the pathogenesis of thyroid disease,[100]and many studies undertaken to examine this effect.[101-103]

In 1981, the expression of estrogen receptor (ER) was first reported in a work by Molteni et al.,[104]and a direct action of estrogen on the thyroid has also been described.[105]Many studies have shown variable expression of ER on the thyroid,[100,106-108] and this has been attributed to methodological differences.[133]However, ER and PR

(progesterone receptor) were concluded in a study to be a common findings in thyroid tumor tissue.[107]Two isoforms of ER have been described in the thyroid, the alpha (ER-α) and beta (ER-β).[100,105,107,108]While ER-α promotes growth of thyroid follicular cells thereby promoting growth and tumorigenesis, ER-β is pro-apoptotic in addition to other inhibitory functions.[108,109]The expression differential pattern, distribution and proportion of ER-α to beta ER-β have been shown to be important the proliferation and outcome of thyroid malignancies.[100]Also differential expression ER-α in papillary thyroid cancers and nodular goitre has been proposed to be utilizable in the immunohistochemical determination of this malignancy.[108]

Oestrogen, a lipophilic ligand traverse the cell membrane and binds to ER-an intracellular nuclear receptor of thyroid cells, forming a stable dimer that induce transcription of target genes via the oestrogen response elements (EREs).[105]Transcriped genes results in the proliferation and/or differentiation of affected cells.[100,105]An important effect is the non-genomic effects of oestrogen mediated by signal transduction through the RTK, MAPK and PI3K pathways.[99,100,105]Estrogen has been shown to increase the expression of Cyclin D1 and important regulator of the G1/S restriction point in the cell cycle, thereby favouring increased proliferation.[100,105]All these effects of oestrogen are physiological mechanisms exploited by benign and malignant disease conditions of the thyroid gland.

Imaging Technology

There has been significant advancement in thyroid imaging technology, and this has been implicated in improvement in diagnostic ability with attended increased incidence of thyroid cancer.[110-117]These techniques include Radionuclide Imaging (RNI) (Positron Emission Tomography-PET and Single-Photon Emission Computed Tomography (SPECT), Ultrasonography (US), Ultrasound Elastography (USE), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Optical Coherence Tomography (OCT) and Optical Coherence Microscopy (OCM).[111,118,119]Areas with low usage of these technologies have not experienced this increase in incidence.[120,121]Many of these tumors diagnosed by imaging are tagged as "incidentalomas" owing to the incidental nature of their discovery in the course of investigating for a different indication.[111,112]It therefore follows that these lesions are indolent/asymptomatic. A report in 2004 estimated that 30% of the USA population (approximately 900million people) have an asymptomatic nodule.[122]Similarly an autopsy revealed that as much as 38million were unknowingly living with papillary thyroid carcinoma.[117]Also it has been reported that the increased incidence of thyroid cancer has not been associated with increased mortality.[113,123,124]Indeed a necropsy study had revealed that a third of people that died from other causes had subclinical papillary thyroid cancers.[111]This bring to the fore the concept of "over-diagnosis" and "over-treatment". [112,121] While the former exerts an economic toll, the later increases physical and psychological burden with attendant risk of morbidity and mortality to the patient.[112, 121]

Imaging plays a crucial role in the screening, diagnosis, evaluation, treatment and follow-up of patients with thyroid pathologies.[110, 120] It guarantees visual representation, characterization and quantification of the tumor.[110]It also helps in the detection of residual disease, metastatic deposits and recurrence.[120]It is worthy of note that histology of thyroid cancers gives the most important prognostic indicator.[111]

Another school of thought has attributed the global increase of thyroid cancers to an actual increase in new cancer cases from other etiological factors, than the issue of improvement in imaging technology, it accessibility and increased utilization.[112, 121]It therefore confronts the implication that "if doctors just stop looking for thyroid cancer, the epidemic will disappear". [125]Exposure to radiation has been suggested as an important etiological agent to this end.[110, 113, 121, 126-135] Iatrogenic radiation via imaging for an any indication is an important source of this mutagenic radiation.[127-135]

Conclusion

There have been perturbations on the incidence and pathomorphologic picture of thyroid disease over the years. Iodine has played significant role in this regard as the world moves past an era of its deficiency to its sufficiency. While the former is associated with increased incidence of nodular goitre and follicular carcinoma, the later leads to an increase in incidence of thyroiditis and papillary thyroid carcinoma. Also oestrogen and oestrogen receptor discovered in the thyroid is implicated in the increased frequency of thyroid disorders in females. Finally, advancement in thyroid imaging technology and its utilization has led to over diagnosis and overtreatment of thyroid diseases. Ultimately, imaging is associated with radiations that are mutagenic to the gland.

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