Post-iodination trends in thyroid pathology; 14-year experience at a single center in a goitre endemic area

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ABSTRACT

Introduction: Goitre is endemic in many parts of Sri Lanka. Universal iodination of salt was commenced in Sri Lanka in 1995 as a measure to reduce the prevalence. This study was designed to identify the pattern of thyroid pathology reported during a period of 14 years from 2002 to 2015 in a Pathology Unit serving the population in a goitre endemic area in Sri Lanka.

Methods: This descriptive cross-sectional study included all thyroidectomy specimens histologically assessed at our unit from 2002 to 2015. Data on age, gender, clinical presentation, type of resection, and histopathological diagnosis were retrieved from the records. The trend of change in thyroid pathology over time was analysed by comparing 2002-2010 cohort (615specimens) with the 2011-2015 cohort (995 specimens).

Results: This study included 1610 thyroidectomy specimens. Features of colloid goitre were present in 71.6% (1152/1610). Prevalence of chronic autoimmune thyroiditis and thyroid cancer was 41% (660/1610) and 15.3% (246/1610) respectively. There was no significant change in the gender and the age at presentation over the years. However, an upward trend in the prevalence of both focal and diffuse chronic autoimmune thyroiditis ($p<0.001$), hyperplastic nodules ($p=0.008$), papillary microcarcinoma ($p<0.001$), papillary carcinoma and colloid nodular goitre ($p=0.004$) was evident.

Conclusions: Parallel increase in the prevalence of chronic autoimmune thyroiditis and papillary carcinoma together with the upward trend in the prevalence of colloid nodular goiter was evident.

Key words: *Goitre, iodination, thyroid cancer, thyroiditis.*

Introduction

Goitre is endemic in Sri Lanka. A survey of the incidence of goitre in Sri Lanka was carried out in the years 1947-1949 and goitre was found to be endemic in the south-west sector of the Wet Zone of Sri Lanka (1). The overall prevalence was found to be 18.8% in a report published in 1989 (2). Leaching of iodine from soil due to heavy rain fall was suggested as the possible cause (1, 2). Universal iodination of salt was commenced in Sri Lanka in 1995 to reduce the iodine deficiency induced goiter (3).

The prevalence of goitre in Sri Lanka has been reported to be 6.8% between 2006 to 2007, a decade after the implementation of national policy on salt iodination (3). This figure has been an age and sex corrected island wide prevalence rate. They have recorded a widespread prevalence of goitre across the country with no evidence of a goiter belt (3).

The incidence of thyroid cancer is increasing globally, mostly due to the increasing incidence of papillary thyroid carcinoma (4). Controversies exist as to whether the increase in the incidence of thyroid cancer is due to the increased detection or due to a true increase in its incidence (5). Elevated serum thyroglobulin antibody level is associated with an increased risk of thyroid cancer (6). An increase in the incidence of autoimmune thyroiditis has been reported from many countries especially in countries where there is iodine fortification of salt done as a national policy to combat the problem of endemic goiter (7). It is well known that papillary carcinoma of thyroid is associated with autoimmune thyroiditis (8). Therefore, the incidence of papillary carcinoma is expected to increase in the post iodination era.

Incidence of thyroid cancer is increasing in Sri Lanka too. Thyroid cancer was the 6th most common cancer among females in the year 2000, and it has become the 2nd most common cancer among females by 2015. Out of all types of thyroid cancer, it is the papillary thyroid carcinoma which predominates. Thyroid cancer is the commonest cancer among females aged 15 - 34 years. The incidence of thyroid cancer among males in Sri Lanka continues to remain low (9, 10).

This changing pattern of thyroid pathology should be investigated as time trends in disease rates provide invaluable information for needs assessment, planning and evaluation of healthcare delivery and policy development activities. Examining data over time also allows a precise characterisation of changes over time permitting predictions about future frequencies and rates of occurrence. Hence, we intended to study the pattern of thyroid diseases reported during a period of 14 years from 2002 to 2015 in a Pathology Unit catering to the population of Southern Sri Lanka which is considered a goitre endemic area.

Methods

This is a cross-sectional study with retrospective data analysis. The records of thyroid resection specimens assessed histopathologically in our unit from 2002 to 2015 were analysed for this study. Pathological and demographic data available in the histopathology worksheets were retrieved. Thyroid cancers were staged according to the dataset for thyroid cancer histopathology reporting published by the Royal College of Pathologists, UK in February 2014 (11).

Severity of thyroiditis was assessed and categorised to focal and diffuse based on the microscopic data given in the worksheets. If only the presence of focal aggregates of lymphocytes were mentioned, they were categorised as focal chronic autoimmune thyroiditis. If diffuse infiltrates were mentioned under microscopy, they were categorised as florid chronic autoimmune thyroiditis. Presence of Hürthle cell change, haemorrhages, focal calcification, fibrosis, cystic degeneration and haemosiderin laden macrophages was considered as evidence of chronicity of benign thyroid disease. To limit the number of pathological entities used for statistical analysis, some diagnoses were grouped into one; colloid nodular goitre, colloid cysts and colloid nodules were grouped under colloid nodular goitre. Follicular and Hürthle cell adenomas were grouped under adenomas. Graves' disease, toxic goitre and follicular lesions of uncertain malignant potential were categorised into one group. To eliminate duplication of data, completion thyroidectomies done as a second surgery for thyroid malignancies were excluded.

Information available on the request form on the pre-surgical assessment (clinical and serological information) was also recorded. To analyse the trend of thyroid pathology, the thyroid resection specimens received from 2002 to 2015 were divided into two cohorts (2002-2010 cohort: 615 specimens and 2011-2015 cohort: 995 specimens). A p value of <0.05 was considered significant.

The Ethics Review Committee of the Faculty of Medicine, University of Ruhuna granted ethical approval for this study.

Results:

A total of 1610 specimens received from a single surgical unit in the tertiary care hospital of the southern part of Sri Lanka had been reported during the 14-year period. The mean age was 42.35 years (range 13-73 years). Majority in the cohort were female, 1447/1610 (89.9%). More than half of the cohort, 908/1610 (56.4%) was between 31 to 50 years of age. Details of the clinical presentation were available for only 892 patients. Clinically diffuse goitre comprised 33/892 (3.7%) while solitary thyroid nodule and multinodular goitre comprised 336/892 (37.7%) and 522/892 (58.6%), respectively. The pre-surgical thyroid status was available for only 292 patients (euthyroid - 91.1%, hypothyroid - 3.4%, hyperthyroid - 5.5%). Out of the total cohort, 793/1610 (49.3%) had lobectomy while 763/1610 (47.4%) had total thyroidectomy. The rest were sub-total thyroidectomies.

Histological assessment revealed evidence of more than a single pathology in 667/1610 (42.1%) specimens in the cohort. Three different pathologies had been seen in 54/1610 (3.4%) specimens. Histological features of colloid nodular goitre were seen in 1152/1610 (71.6%) which included a few colloid nodules and colloid cysts. Either Graves' disease or toxic goitre or follicular lesions of uncertain malignant potential were present in 31/1610 (1.98%) of specimens. Details of histopathological features related to chronicity of the thyroid disease are given in the Table 1.

Histological evidence of chronic autoimmune thyroiditis was present in 660/1610 (41%). Focal aggregates of lymphocytes were seen in 468/1610 (29.1%) while 191/1610 (11.9%) had florid lymphocytic infiltrates. Lymphoid follicles were noted in 323/1610 (20.1%) which included all the specimens with florid lymphocytic infiltrates and part of specimens with focal lymphocytic infiltrates. Hyperplastic nodules were present in 215/1610 (13.4%) while follicular/ Hurthle cell adenomas were evident in 10.8% of the total cohort.

Thyroid malignancies were present in 247/1610 (15.35%) of specimens. The group of thyroid malignancies were analysed separately. Majority 128/247 (51.8%) of the patients with thyroid malignancy was in the 31-50 years age group. Females comprised the majority, 216/247 (87.5%). Details of clinical presentation were available for 132 patients (multi nodular goitre-43.9%, solitary thyroid nodule-53.0%, diffuse goitre - 3.0%). Associated chronic autoimmune thyroiditis was noted in 129/247 (52.2%) thyroid specimens with malignancy. Hyperplastic nodules were found in the background thyroid tissue in 28/247 (11.6%). Histopathological features of chronic thyroid disease were noted in the background thyroid in 6 - 24% of thyroid cancer patients (Hürthle cell change - 24.1%, haemorrhages - 15.7%, calcifications - 14.9%, fibrosis - 24.1%, cystic degeneration - 8.4%, haemosiderin laden macrophages - 6.0%).

Table 1: Percentage of thyroid specimens of the total cohort with histopathological features indicating the chronicity of the thyroid diseases

Histopathological feature	**Total Cohort** *n=1610*	**Cohort-1** *n=615*	**Cohort-2** *n=995*	***p* value**
Hürthle cell change	18.0	13.8	20.5	**0.001**
Haemorrhages	43.0	45.0	41.7	0.189
Haemosiderin laden macrophages	27.3	30.1	25.5	**0.044**
Calcification	16.5	19.2	14.9	**0.024**
Fibrosis	44.6	51.5	40.3	**<0.001**
Cystic change	29.0	26.7	30.4	0.110

Papillary carcinoma was the most common 135/247 (54.7%) subtype of cancer, of which papillary microcarcinoma comprised 16.9%. Minimally invasive follicular and Hürthle cell carcinoma together comprised 36.5% while the widely invasive carcinoma of the same category comprised 4.8% of the malignant group. The remaining 4.0% comprised medullary, poorly differentiated and anaplastic carcinoma. Tumours larger than 4 cm (stage T3) were present in 31.9% and 4% had tumours qualifying for stage T4; tumour infiltrating beyond the thyroid capsule. Staging of malignancies could be done for 229 patients (stage I - 81.7%, stage II - 9.2%, stage III - 9.2%) (11).

In order to look for any trends in thyroid pathology over the 14-year period, the total cohort was divided into two consecutive cohorts with comparable sample sizes; 2002 to 2010 (n=615) and 2011 to 2015 (n=995). Table 2 and 3 show the differences between the two cohorts.

Table 2: Comparison of clinical and histopathological features of the two cohorts

	Cohort-1 *n=615*	**Cohort-2** *n=995*	***p* value**
Gender - female *(n=1606)*	89.1	90.3	0.406
Age *(n=1600)*			0.433
< 20 years	2.6	2.2	
20 - 39	42.2	38.5	
40 - 59	46.0	49.0	
60 - 89	9.2	10.3	
Clinical presentation *(n=892)*			
Multinodular goitre	53.2	61.3	**0.022**
Solitary nodule	44.9	34.2	**0.002**
Diffuse goitre	1.4	4.8	**0.013**
Thyroid status *(n=292)*			0.054
Euthyroid	91.2	91.0	
Hypothyroid	1.4	5.5	
Hyperthyroid	7.5	3.4	
Chronic autoimmune thyroiditis			**<0.001**
Focal	22.4	33.3	
Diffuse	8.1	14.2	
Hyperplastic nodules	10.6	15.2	**0.008**
Hürthle cell change *(n=1609)*	13.8	20.5	**0.001**
Haemorrhages	45.0	41.7	0.189
Calcification	19.2	14.9	**0.024**
Fibrosis	51.5	40.3	**<0.001**
Cystic change *(n=1609)*	26.7	25.5	0.110
Haemosiderin laden macrophages	30.1	25.5	**0.044**
Colloid nodular goitre	67.5	74.2	**0.004**
Thyroid malignancy	14.0	16.1	0.256
Follicular/ Hürthle cell adenoma (*n=1605)*	12.6	9.7	0.070

Table 3: Comparison of clinical and histopathological features of thyroid malignancies in the two cohorts

	Cohort-1 *(n=91)*	**Cohort-2** *(n=158)*	***p* value**
Gender- female *(n=248)*	83.3	89.9	0.134
Age *(n=247)*			0.774
<20 years	2.2	2.5	
20 - 39	46.1	48.1	
40 - 59	37.1	39.2	
60 - 89	14.6	10.1	
Clinical presentation *(n=132)*			0.571
Multinodular goitre	37.5	46.7	
Solitary nodule	60.0	50.0	
Diffuse goitre	2.5	3.3	
Chronic autoimmune thyroiditis *(n=249)*			**0.010**
Focal	36.3	55.7	
Diffuse	5.5	2.5	
Hyperplastic nodules *(n=249)*	3.3	16.5	**0.002**
Papillary microcarcinoma *(n=245)*	8.0	26.8	**<0.001**
Papillary carcinoma *(n=249)*	44.0	60.8	**0.010**
TNM Stage *(n=229)*			0.283
I	82.6	83.6	
II	5.8	9.4	
III	11.6	6.9	
Tumour size (T) *(n=210)*			0.084
T1	11.9	28.7	
T2	34.3	23.1	
T3	32.8	31.5	
T4	20.9	16.8	

Discussion

The very first report on goitre in Sri Lanka goes back to 1967 by Mahadeva *et al.,* referring to a survey done during 1947-1949. They described a goitre belt related to iodine deficiency in diet as a result of leaching of iodine from soil (1). The wet zone of Sri Lanka receives heavy rainfall which was described to be the cause of leaching of iodine from the soil (1). At that time, potassium iodide was suggested to reduce iodine deficiency disorders. The same team one year later reported that iodine content of food grown in non-endemic areas, in most instances, was considerably higher than in goitre endemic areas supporting the first report (12). In 1998, a few years following the implementation of universal salt iodination in Sri Lanka, a research team studied the prevalence of thyroglobulin antibodies in samples of school children in low, intermediate and high goitre prevalent areas in Sri Lanka. They found a high prevalence of thyroglobulin antibodies in the group of school children indicating the onset of an increased incidence of autoimmune thyroiditis (13).

However, the same team found in their second study done in 2001, that the prevalence of goitre and thyroid autoimmunity were significantly lower than their 1998 study. They suggested the concept of reversibility of the thyroid autoimmunity in some and continuing and more aggressive autoimmunity in others (14). Later, Fernando *et al.,* reported that the prevalence of goiter was 6.8% and autoimmune thyroiditis was responsible for 16 to 20% of goiters in their study which covered the island except for two provinces, during 2007-2008 (15). They also found a high urinary excretion of iodine in the community. In 2005, Jayatissa *et al.,* reported that Sri Lanka had achieved satisfactory iodine status indicated by urinary iodine levels. The same publication also reported that the prevalence of goitre in all Provinces in Sri Lanka varied from 16.3% to 26.2% (16). A more recent publication in 2015 reported that the prevalence of goitre ranged from 5.34% to 7.93% in different areas island wide (17). A study done in the Central Province of Sri Lanka analysing clinical data of a single surgical unit spanning over a 31 year period revealed that there was a significant reduction in the prevalence of clinical nodularity of euthyroid goiters in the post-iodination era in all age groups indicating a reduction in the prevalence of clinically higher grade goiters (18).

With this background data, it is apparent that the prevalence of goitre has reduced with the implementation of island wide iodine supplemen--tation. However, the success depends on absence or minimization of harmful effects as well. There are reports from Sri Lanka that a substantial proportion of iodized salt available in the market contain iodine in excess to what is recommended (14, 15). This is of concern as there is increasing evidence that chronic autoimmune thyroiditis is related to iodine supplementation (13-15, 19,20). Furthermore, the incidence of thyroiditis as well as the degree of lymphocytic infiltration in the thyroid has been reported to increase gradually and dose-dependently in experimental rats (21). Excess of iodine makes thyroglobulin highly immunogenic hence autoimmune thyroiditis has been reported by many countries which implemented universal salt iodination (7, 20).

The current study was conducted 20 years after the implementation of universal salt iodination in Sri Lanka. Our study included data from a single unit in a goitre endemic area revealing the trend in thyroid pathology during the latter 14 years of this period.

Cancer incidence data for Sri Lanka reveals a steady rise in the incidence of thyroid cancer from 1995 to 2010 where age specific rate rise from 3.1 to 7.4 per 100,000 population with a steep rise to 15.9 by 2015 (10). However, comparison of the current two cohorts did not demonstrate a statistically significant increase in the prevalence of thyroid cancers reported at our institution. In the analysis we compared the percentage of thyroidectomies with cancer out of all thyroidectomy specimens reported. However, the total number of thyroid malignancies reported during the first nine years (2002-2010) had been 91 while 160 thyroid malignancies had been reported during the period of latter 5 years (2011-2015). This substantiates that there is an increase in the thyroid cancers reported at our unit although the parallel increase in the thyroidectomy for non-malignant causes masked the true increase in the prevalence of thyroid malignancies reported.

Our data also demonstrates a significant upward trend in the prevalence of chronic autoimmune thyroiditis in the background thyroid tissue of thyroid malignancies in the two cohorts. It is well known that chronic autoimmune thyroiditis is associated with increased incidence of thyroid cancer especially papillary carcinoma (8). Our results demonstrate a parallel increase in the prevalence of papillary carcinoma. The significant increase in papillary microcarcinoma too is analogous to the increased prevalence of associated autoimmune thyroiditis. However, increased awareness and detection also may have contributed to this finding. During the past couple of decades, the morphologic spectrum identified as papillary carcinoma has also increased to a multitude of variants which may have contributed to the increase in the incidence (22).

The significant increase in the presence of hyperplastic nodules in the background thyroid tissue in thyroid cancers and in the non-malignant thyroidectomy specimens is an interesting finding of our study as currently there is emerging evidence for molecular basis of hyperplastic/ adenomatoid nodules. Lei Te *et al.,* found that 24.3%

of adenomatoid nodules carry mutually exclusive mutations, which is different from papillary thyroid carcinoma (23). The possibility of benign thyroid nodule being a precursor lesion is a topic under investigation and needs further evidence.

The tumour size and the TNM stage do not show a significant change over the 14-year period and most have been in stage I at presentation. It may be due to the improvements in detection which make the patient present at a relatively early stage. A study published in 2003 comparing thyroid cancers diagnosed before and after the universal iodination programme in Sri Lanka revealed a trend towards more differentiated thyroid cancer with lesser degree of extra-thyroid spread in the post iodination period (24). We too have not found a trend in poorly differentiated cancers apart from the upward trend in papillary carcinoma which is considered a well differentiated thyroid cancer. Although there is no significant change in the clinical presentation, a fair proportion of thyroid malignancies have presented as multi nodular goitres which has increased over the years. Such malignancies may be missed unless radiological assessment/thyroidectomy has been done.

Female preponderance in benign thyroid diseases and thyroid malignancies has not changed over the 14 years under consideration; neither is there a significant change in the age group affected. Our institutional data shows an increase in the nodular colloid goitre contrary to the expectation of reduction in the prevalence of goitre caused by iodine deficiency. Since all available edible salt in the market are iodized, it is worthwhile finding out whether there are other factors operating in increasing the trend in prevalence of nodular colloid goitre. Insufficient iodine intake could be due to consumption of inadequately iodized salt, iodine loss due to indigenous cooking practices or due to regular consumption of food containing goitrogens. Fernando et al carried out an island wide survey on consumption of six food items considered to be goitrogenic food and found no significant association with the prevalence of goiter in the cohort studied (25). But the six food types did not include red rice which is consumed by most Sri Lankans and recently described as a goitrogenic food (26). The concept of leaching of iodine from wet zone soil has been challenged recently by Fernando et al in their report on goiter incidence in an endemic area in wet zone. They identified iodine deficiency to be the major cause of goiter, but no correlation between iodine in water and goitre distribution was identified. Average iodine concentrations in subsurface water of goiter endemic regions had been 28.25 (± 15.47) µg/L whereas non-goiter regions had identical values at 24.74 (± 18.29) µg/L. They also found selenium levels of the water to be low and none of their samples exceeded the desired limit of 10 µg/L (27). Selenium, a micronutrient plays an important role in the thyroid metabolism (28). These findings shift the focus from leaching of iodine in the soil to reduced bioavailability of the micronutrients and new goitrogenic food items to be further investigated.

The prevalence of chronic autoimmune thyroiditis shows an upward trend during the 14 years. Increasing prevalence of both focal and diffuse lymphocytic infiltrates matches the increase in prevalence of autoimmune thyroiditis. Although we have not being able to collect sufficient data to comment on functional status of the thyroid in this patient cohort, it is not unreasonable to infer that hypothyroidism has been a significant problem in the study population owing to the high prevalence of auto immune thyroiditis especially with diffuse lymphocytic infiltrates which destruct most of the thyroid follicles.

Features of chronic thyroid disease; focal calcification, fibrosis and evidence of old haemorrhages show a statistically significant reduction in prevalence over the years. This may probably be due to the early detection and intervention reducing the chances of developing into more chronic disease or due to the iodine fortification of salt. Finding of decrease in clinical nodularity of euthyroid goiters during the post-iodination era, by Ratnatunga *et al.,* also substantiates our finding of lower chronicity (18). The significant increase in the trend of Hürthle cell change is expected due to the increased prevalence of chronic autoimmune thyroiditis over the years.

Most of the studies done on the problem of goitre in Sri Lanka are based on clinical and serological parameters. We have looked at it at a different

angle and tried to reveal the true trend in thyroid pathology in an endemic area using patient data from a single institution. The histopathological aspect of the trend can only be revealed in a set of patient data for reasons which are obvious. We believe that the prevalence of chronic autoimmune thyroiditis still may be underestimated as a substantial number of patients are managed medically without being referred for surgical management.

Conclusions and recommendations

Parallel increase in the prevalence of chronic autoimmune thyroiditis and papillary carcinoma together with the upward trend in the prevalence of colloid nodular goiter was evident from the findings of our study. Despite universal iodination for over 20 years, colloid nodular goitre still remains a health problem in goitre endemic southern Sri Lanka. Assessing the success of the iodination programme was not the objective of this study. We intended to describe the changes in thyroid pathology and to find out whether there is any trend during the post iodination era.

However, the specific concerns are now different to what it was in 1995. The upward trend in the prevalence of colloid nodular goitre and the twofold effect of chronic autoimmune thyroiditis on the morbidity requires urgent attention of policy planners. It is recommended to establish a proper monitoring system which looks into the effect of over 20 years long universal salt iodination programme on the good thyroid function and health of population at large.

Limitations

The current study describes the changes in thyroid pathology during the post iodination era reported at a single centre in a goitre endemic area. The findings of the study cannot be used to interpret the outcome of the national program without considering findings of several centers. Without dividing the cohorts at 5-year intervals which seems logical, we used cross-sections at two points in time to examine change over time. Dividing into more as the latter makes the total numbers be less for each feature masking any effect.

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Competing interests

None declared.

Ethical approval

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