The effect of iodine prophylaxis on the frequency of thyroiditis and thyroid tumors in Southwest, Iran

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ABSTRACT

Objective: To investigate the effect of the salt iodization program, which was initiated in 1989 on frequencies of thyroiditis and papillary carcinoma in Fars province of Iran, which was previously an iodine deficient area.

Methods: Four hundred and eighty-two thyroidectomy specimens belonging to the pre-iodization period from 1983 to 1988, and 466 post iodization specimens from 1998 to 2003 were re-examined for presence of lymphocytic infiltration and types of thyroid tumors. This study was carried out in Shiraz University of Medical Sciences, Iran.

Results: The frequency of lymphocytic infiltration in non-neoplastic specimens increased from 30-60.5% after salt iodization ($p<0.001$). Background of lymphocytic infiltration in neoplastic specimens also increased from 18.5-61% after iodine prophylaxis ($p<0.001$). The frequency of papillary carcinoma in neoplastic specimens increased from 15-43% ($p=0.01$) and that of follicular adenoma decreased from 69-32.5% ($p<0.0001$).

Conclusion: Salt iodization is associated with an increased occurrence of histologic thyroiditis and papillary carcinoma.

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Supplementation of iodine by means of salt fortification has proven to be an effective method of preventing iodine deficiency disorders.[1] Iodine supplementation has been implicated as a cause of thyroid autoimmunity. Iodine induced thyroiditis is well documented in genetically susceptible animal models.[2] Some epidemiologic data also point out the role of excess iodine in human autoimmune thyroid diseases;[3] however, this issue is still controversial. There have also been reports about increased incidence of papillary carcinoma of thyroid after iodine prophylaxis.[4,5] Before 1989, Fars province, which is located in Southwest of Iran, was considered an iodine deficient area with a goiter rate up to 40%.[6] From 1989, the national salt iodization program was initiated with the aim of adding 40 mg iodine as sodium iodate to each kilogram of household salt. In 1994, a law for mandatory production of iodized salt for households was passed and since that time almost all of the population have been covered with this program. The estimated daily intake of iodine has been 100-200 micrograms and median urinary iodine is approximately 20 micrograms/dl.[7] The purpose of this study was to determine the effect of salt iodization on the frequency of lymphocytic infiltration of the thyroid gland. We presumed lymphocytic infiltration as an index of thyroid autoimmunity. The effect of iodine prophylaxis on thyroid tumor types was also investigated.

Methods. This study was carried out in hospitals affiliated with Shiraz University of Medical Sciences, which is a referral center for Fars province with a population of approximately 4.5 million. All thyroidectomy specimens from 1983 to 1988 (pre-iodization period) and all specimens from 1998 to 2003 (8-13 years after initiation of iodine prophylaxis) were selected. Information on age, gender, and final diagnosis were retrieved from the files. We grouped the specimens into neoplastic (those containing a benign or malignant tumor) and non-neoplastic. The non-neoplastic

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specimens consisted of cases of Graves' disease and goiter. For each specimen there were 6 hematoxylin and eosin stained slides, which were re-examined by a pathologist (AM). The pathologist was unaware of the date of the specimens. In histologic examination, we determined the presence and degree of lymphocytic infiltration, which was rated as mild, moderate, and severe. The extent of infiltration was stated as focal or diffuse and presence of germinal centers was also noted. The histologic criteria for the severity of chronic thyroiditis were those of Williams and Doniach:[8] None: 0-1 focus per standard representative section (2 cm^2), mild: 2-8 foci per standard section, moderate: 9-40 foci per standard section and severe: >40 foci per standard section. A focus was defined as an aggregate of ≥50 lymphocytes. In neoplastic specimens, a non-tumorous region was selected at least 5 mm from the border of the tumor to avoid reactive lymphoid cell infiltration around the tumor. In these specimens, the intensity of lymphocytic infiltration within the tumor was also compared with non-tumorous tissue. A germinal center was defined as pale areas of collection of small and large cleaved and non-cleaved cells as well as tangible body macrophages surrounded by a mantle zone of mature small lymphocytes. Lymphocytic infiltration was described as focal if it was detectable in <50% of sections examined and diffuse if it was detectable in more than half of the sections.

Statistical analysis. Categorical data were analyzed using Chi-square, Fisher's exact, Kruskal Wallis, and Mann-Whitney U tests. T-test was used to analyze parametric data. *P*-values less than 0.05 were considered significant.

Results. There were 482 thyroidectomy specimens in the pre-iodization period. The patients were 85% women and 15% men with a mean age of 35.8 ± 13.1 years. The post-iodization specimens were consisted of 466 thyroids. The patients in this period were 80.5% women and 19.5% men with a mean age of 37.0 ± 14.1 years. The differences between the age and gender of patients in the 2 periods were not statistically significant.

Comparison of the non-neoplastic specimens. There were 297 non-neoplastic specimens in the pre-iodization period, which consisted of 35 cases of Graves' disease and 262 cases of goiter. In the post-iodization period there were 262 non-neoplastic specimens, which included 32 cases of Graves' disease and 230 cases of goiter. The difference between frequencies of different diseases in the 2 periods was not statistically significant. The overall frequency of lymphocytic infiltration in non-neoplastic specimens was 30% in pre-iodization and 60.5% in the post-iodization period (x^2, p<0.001). There was a marked increase in all degrees of lymphocytic infiltration, focal and diffuse types, and germinal center formation (**Tables 1 & 2**).

Comparison of the neoplastic specimens. The number of neoplastic specimens was 185 in pre-

Table 1 - Comparison of frequencies of different degrees of lymphocytic infiltration in non-neoplastic specimens in pre- and post- iodization period.

Period	No. of patients (%)			
	Mild lymphocytic infiltration	Moderate lymphocytic infiltration	Severe lymphocytic infiltration	Any degree of lymphocytic infiltration
Pre-iodization (n=297)	65 (21.9)	16 (5.4)	8 (2.7)	89 (30)
Post-iodization (n=262)	90 (34.3)	49 (18.7)	20 (7.6)	159 (60.5)
P value	<0.001	<0.001	<0.01	<0.001

Table 2 - Comparison of extent of lymphocytic infiltration and presence of germinal center formation in non-neoplastic specimens in pre- and post- iodization periods.

Period	No. of patients (%)		
	Focal lymphocytic infiltration	Diffuse lymphocytic infiltration	Presence of germinal center
Pre-iodization (n=297)	41 (13.8)	40 (13.5)	48 (16.2)
Post-iodization (n=262)	82 (31.3)	77 (29.3)	90 (34.3)
P value	<0.001	<0.001	<0.001

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iodization and 204 in post-iodization period. The overall frequency of lymphocytic infiltration increased from 18.5-61% after iodine prophylaxis (x^2, p<0.001). The changes in frequencies of lymphocytic infiltration were significant in specimens containing follicular adenoma and papillary carcinoma (**Table 3**). There was also a significant decrease in frequency of follicular adenoma and an increase in occurrence of papillary carcinoma (**Table 4**).

Discussion. Iodine is an essential element for thyroid hormonogenesis and its deficiency leads to a wide variety of clinical disorders. Salt iodization is an effective method for eradication of iodine deficiency. The main side effect of iodine supplementation in iodine deficient areas is iodine-induced hyperthyroidism.[9] Another side effect, which is still debated by many, is iodine-induced autoimmunity. In our study, after iodine prophylaxis, the frequency of histologic thyroiditis, as manifested by lymphocytic infiltration, increased by 2 in non-neoplastic and by 3.5 times in neoplastic specimens. Thyroiditis increases in frequency with age and it is more prevalent in females.[3] Since there was no significant difference between the age and gender of the patients in the 2 periods, the increased frequency of lymphocytic infiltration cannot be due to the effect of age or gender. Our findings were similar to the results of a study from Argentina in which the frequency of moderate and severe thyroiditis in neoplastic specimens increased from 8-25% after iodine prophylaxis.[10] Several epidemiologic and human studies also support our findings. The prevalence of positive thyroid autoantibodies and autoimmune hypothyroidism is higher in areas with higher iodine intake.[11] An increase in thyroid antibodies and lymphocytic infiltration

Table 3 - Comparison of frequencies of lymphocytic infiltration in different types of neoplastic specimens in pre- and post-iodization periods.

Type of tumor	Pre-iodization period			Post-iodization period			*P*-value
	Total no. for each tumor	n	(%)	Total no. for each tumor	n	(%)	
Follicular adenoma	128	17	(13)	66	28	(42)	<0.001
Papillary carcinoma	28	6	(21)	88	69	(78)	<0.001
Follicular carcinoma	5	0	(0)	12	5	(41)	ns
Medullary carcinoma	11	2	(18)	15	7	(46)	ns
Hurthle cell adenoma	6	4	(66)	11	9	(82)	ns
Hurthle cell carcinoma	3	1	(33)	6	2	(33)	ns
Anaplastic carcinoma	4	4	(100)	6	5	(83)	ns
Total	**185**	**34**	**(18.5)**	**204**	**125**	**(61)**	**<0.001**

ns - not significant

Table 4 - Frequencies of different types of thyroid tumors before and after salt iodization.

Type of tumor	Pre-iodization period		Post-iodization period		*P*-value
	n	(%)	n	(%)	
Follicular adenoma	128	(69)	66	(32.5)	<0.001
Papillary carcinoma	28	(15)	88	(43)	0.0139
Follicular carcinoma	5	(2.5)	12	(6)	ns
Medullary carcinoma	11	(6)	15	(7.5)	ns
Hurthle cell adenoma	6	(3)	11	(5.5)	ns
Hurthle cell carcinoma	3	(1.5)	6	(3)	0.0303
Anaplastic carcinoma	4	(2)	6	(3)	ns
Total	**185**	**(4)**	**204**	**(6)**	

ns - not significant

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of thyroid was reported in 19% of patients with endemic goiter after taking 500 µg/day iodine for 6 months and these changes subsided after cessation of iodine intake.[12] In a study from Greece, there was an increase in thyroid autoantibodies 3 months after administration of iodized oil to patients with goiter.[13] Some in vitro and animal studies also suggest a role for iodine in thyroid autoimmunity. Highly iodinated thyroglobulin is more immunogenic.[14,15] Excess iodine causes oxidative damage to thyrocytes[18] and enhances immunoglobulin G synthesis by peripheral lymphocytes[17] and promotes inducibility of 72-kD heat shock protein by stressed thyroid cells.[18] Contrary to our results and the previously mentioned studies, there are some reports from Latin America[19] and Africa[20-22] that failed to find an association between iodine and thyroid autoimmunity. This difference may be due to some genetic and environmental factors. As in animal models, genetic factors are important in the development of thyroid autoimmunity[23] and different populations have variable predispositions to thyroiditis.[24] Among the environmental factors, the role of other nutrients especially antioxidants and selenium may be important. In animal models, antioxidants delay the onset of iodine induced thyroiditis.[16] In patients with autoimmune thyroiditis, selenium supplementation decreases thyroid autoantibody concentration.[25] The previous level of iodine intake is also important. A striking increase in thyroid antibody was reported after the use of the high iodine content drug amiodarone in Portugal, an area of low iodine intake[26] but no such effect was observed in the iodine sufficient in the United Kingdom.[27] In some experimental studies, the effect of iodine on thyroid autoimmunity was reported to be transient and thyroid autoantibody titers decreased from 12 months after administration of iodine.[28] The results of our study and the report from Argentina[4] demonstrate that this effect is long lasting and histologic thyroiditis remains for years after initiation of iodine prophylaxis. Another finding was a sharp increase in cases with papillary carcinoma in the post-iodization period. The number of cases with papillary carcinoma and its relative frequency almost tripled after iodine prophylaxis. Fine needle aspiration of the thyroid was introduced to our institution in the early 1980's and since that time there has been no significant change in the diagnostic approach to thyroid disease. The sharp increase in cases with papillary carcinoma cannot be attributed to changes in diagnostic approach. Our finding is in agreement with the result of study from Argentina in which the incidence of papillary carcinoma increased from 3.9 per year to 7.21 per year and the ratio of papillary to follicular carcinoma rose from 1.7 is to 1 to 3.1 is to 1 after iodine prophylaxis.[4] Some epidemiologic studies have also suggested that there was an increased incidence of papillary carcinoma in iodine replete areas.[29] In our study, the frequency of lymphocytic infiltration in papillary carcinoma was significantly higher than follicular adenoma and carcinoma, suggesting an association between the 2 conditions. This association became stronger after iodine prophylaxis (**Table 3**). The coincidence of thyroiditis and papillary carcinoma has been reported in some other studies and it has been suggested that autoimmune thyroiditis acts as a predisposing factor for papillary carcinoma.[30,31] However, this issue remains controversial and some authors believe that lymphocytic thyroiditis is a form of immune reaction to the tumor rather than a predisposing factor.[32] In our study, the severity of lymphocytic infiltration within the tumor was lower than the non-tumorous thyroid tissue in majority of cases of papillary carcinoma and lymphoid infiltration in tumor was always associated with non-tumoral tissue thyroiditis. This suggests that lymphocytic infiltration into the tumor was secondary to a background chronic thyroiditis rather than an immune reaction to the tumor. Molecular studies have also confirmed a close relationship between chronic thyroiditis and papillary carcinoma. In Hashimoto thyroiditis, the prototype of chronic lymphocytic thyroiditis, there is almost always the Rearranged during Transfection (RET)/papillary thyroid carcinoma (PTC) gene rearrangement, which is highly specific for papillary thyroid carcinoma suggesting that submicroscopic foci of papillary carcinoma are present in Hashimoto thyroiditis.[33]

In conclusion, our findings suggest that the incidence of histologic thyroiditis and papillary carcinoma increased after salt iodization and may be these 2 conditions were etiologically linked together. However, we do not argue against salt iodization program whose benefits far outweigh its side effects.

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