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# Trends of thyroid function and autoimmunity to 5 years after the introduction of mandatory iodization in Italy

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**Summary**

**Background.** Mandatory iodine fortification of salt was introduced in Italy in 2005. The purpose of our study is to estimate the trend of thyroid diseases in Italy before and after mandatory iodization in Italy. **Methods.** 7976 patients (6802 females; 1174 males) were examined between 2003 and 2010. We divided the patients into categories according to their clinical diagnosis. Later, we evaluated for each patient if there was the positivity for antibodies anti TPO. Finally, we collected data about TSH values of all patients who did not use therapy for thyroid disease at the time of the examination. To evaluate the differences percentages for categorical variables,  $\chi^2$ -Pearson test was used; to evaluate the percentage differences of TSH values we used the Kruskal-Wallis test. Values were considered statistically significant at  $p < 0.05$ . **Results.** We considered diagnosis of "toxic adenoma / goiter", diagnosis of "Graves' disease" and diagnosis of "hyperthyroidism / thyrotoxicosis" before and after the introduction of mandatory iodization in Italy, to demonstrate the possible presence of iodine-induced hyperthyroidism. Diagnosis of toxic adenoma / goiter before 2005 were 3.7%, while after 2005 they were reduced to 3.1%. Diagnosis of Graves' disease before 2005 were 2.4%, and they remained unchanged after 2005. Finally, diagnosis of hyperthyroidism / thyrotoxicosis decreased from 2.5% to 2.1%. Comparing these results, there were no significant differences ( $P = 0.261$ ) between the percentages of diagnosis of hyperthyroidism before and after the introduction of mandatory iodization. We considered diagnosis of Hashimoto's thyroiditis before and after 2005 to demonstrate a link between the administration of iodine and thyroid autoimmunity. Prevalence of Hashimoto's thyroiditis between 2003 and 2005 was 37%; prevalence between 2006 and 2010 dropped to 34.7%. This small difference has a borderline statistical significance ( $P = 0.049$ ). Stratifying TSH values from year to year, we found a small increase in TSH value, which, in any case, remains in the normal range. TSH values passed from 1.37 in 2003, to 1.61 in 2010. Although this increase is modest, it is statistically significant ( $P$  values  $< 0.001$ ). **Conclusion.** In this study there isn't a connection between iodine fortification and iodine-induced hyperthyroidism, and between iodine fortification and Hashimoto's thyroiditis. This small increase of TSH values can not find a clear explanation yet. We considered several mechanisms to explain this phenomenon: alterations of Na/I symporter reduce intracellular levels of iodine, and cause a state of hypothyroidism; excessive levels of iodine can increase apoptosis of thyrocytes, as it is demonstrated by several studies; interference from external agents (endocrine disruptors).

The purpose of our study is to estimate the trend of thyroid diseases in Italy before and after mandatory iodization in Italy. The daily use of iodized salt has allowed a reduction of iodine deficiency disorders, as demonstrated by several studies in the literature.

Aghini-Lombardi et al. compared the prevalence of several thyroid diseases before and after mandatory iodization in Italy. The first study, carried out in 1995 (1), was conducted in Pescopagano, a small town with moderate iodine deficiency in Southern Italy. After these results, local authorities encouraged the use of iodized salt to reduce the prevalence of diseases related to iodine deficiency. In 2005, a second study was conducted in Pescopagano (2) to assess if mandatory iodization had improved thyroid function. First of all, there was a reduction of prevalence of thyroid goiter: before 1995 the prevalence was 46%, while after 2005 it was 25%. The prevalence of hyperthyroidism has decreased over time: from 2.5% it passed to 0.5% in 2005. After mandatory iodization, however, autoantibody levels increased in both male and female patients: autoantibodies have led to an increased prevalence of Hashimoto's thyroiditis which, in turn, has led to an increased prevalence of autoimmune hypothyroidism. In addition, Bonofiglio et al. (3) demonstrated a reduction of prevalence of goiter in children and young adults after mandatory iodization in a small city in Calabria, in southern Italy. On the other hand, iodine excess can modify thyroid function and common complications related to iodine fortification are iodine-induced hyperthyroidism, autoimmune thyroiditis and hypothyroidism.

Cerqueira et al. monitored the effects of mandatory iodization in Denmark (4,5). The aim of their study was to estimate the risk of hyperthyroidism after mandatory iodization, monitoring the use of antithyroid drugs. In areas with moderate iodine deficiency, the use of antithyroid drugs has increased by 45% in four years after iodine fortification. In areas with mild iodine deficiency, incidence of hyperthyroidism has increased only by 18% and only in young patients. However, it was only a temporary phenomenon.

Another potential effect of iodine excess is autoimmune thyroiditis. Pedersen et al. (6) assessed concentration of thyroid autoantibodies before and after iodine fortification. The study showed a clear increase of thyroid autoantibodies, especially in young women. Also Li et al (7) reached the same result. Anyway, there are studies that don't confirm these results: Zimmerman et al. (8) have not recorded an increase of thyroid autoantibodies.

Lastly, several authors reported an increased incidence of hypothyroidism after iodine fortification.

Pedersen et al (9) demonstrated a mild increase of hypothyroidism after mandatory iodization in Denmark. Several mechanisms can explain this phenomenon.

Firstly, a high intake of iodine can block the thyroperoxidase (Wolff-Chaikoff phenomenon). However, a normal thyroid can escape from this mechanism, modulating expression of Na/I symporter. Sometimes, this mechanism fails, the Na/I symporter is constantly activated and the excess of iodine blocks thyroid function. Secondly, high levels of iodine can increase autoimmune thyroiditis, which, in turn, leads to reduced thyroid functionality. Lastly, high levels of iodine can lead to an increased apoptosis of thyrocytes, with consequent state of hypothyroidism (10).

### Materials and methods

In this retrospective study, 7976 patients were examined at Policlinico Umberto I in Rome between 2003 and 2010. Of the total patients, 6802 were females, while 1174 were males. First of all, we divided patients into categories according to their clinical diagnosis. Clinical diagnosis were as follows:

- toxic adenoma / goiter
- Graves' disease
- Hashimoto's thyroiditis
- simple goiter
- multinodular goiter
- hypothyroidism
- hyperthyroidism / thyrotoxicosis
- single thyroid nodule
- multinodular thyroid disease
- subacute thyroiditis
- other thyroiditis
- eutiroidism
- unrelated diseases

In case of polyopathy, Hashimoto's thyroiditis prevailed over the other diseases. Secondly, we evaluated for each patient the positivity for anti-thyroid peroxidase antibodies. Finally, we collected data about TSH values of all patients who did not use therapy for thyroid disease at the time of the examination.

### Statistical method

To evaluate the differences percentages for categorical variables,  $\chi^2$ -Pearson test was used; to evaluate the percentage differences of TSH values we used the Kruskal-Wallis test. Values were considered statistically significant at  $p < 0.05$ .

### Results

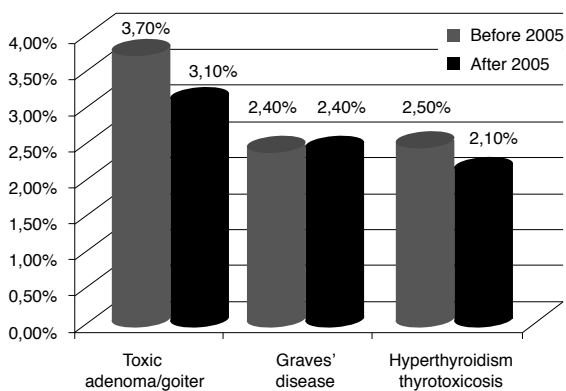
In this study, we examined 7976 patients. All patients were divided into categories according to their clinical diagnosis. Clinical categories are represented in **table 1**.

**Table 1** - Clinical diagnosis.

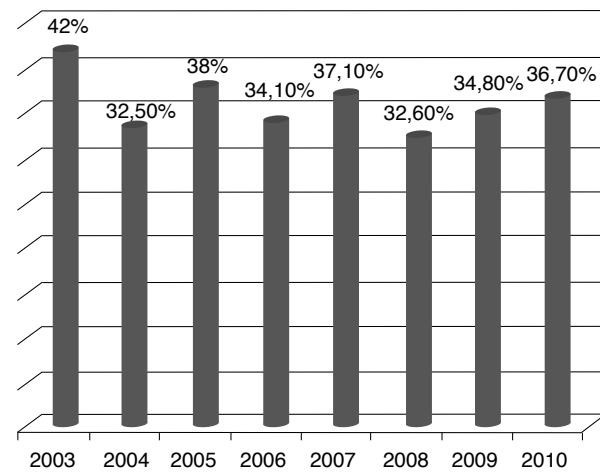
Diagnosis	Frequency	Percentage
Toxic adenoma / goiter	262	3.3
Graves' disease	193	2.4
Hashimoto's thyroiditis	2828	35.5
Simple goiter	31	0.4
Multinodular goiter	1161	14.6
Hypothyroidism	371	4.7
Hyperthyroidism / thyrotoxicosis	175	2.2
Single thyroid nodule	772	9.7
Multinodular thyroid disease	1519	19.0
Subacute thyroiditis	37	0.5
Other thyroiditis	37	0.5
Euthyroidism	368	4.6
Unrelated diseases	222	2.8
Total	7976	100%

We considered diagnosis of "toxic adenoma / goiter", diagnosis of "Graves' disease" and diagnosis of "hyperthyroidism / thyrotoxicosis" before and after the introduction of mandatory iodization in Italy to demonstrate the possible presence of iodine-induced hyperthyroidism.

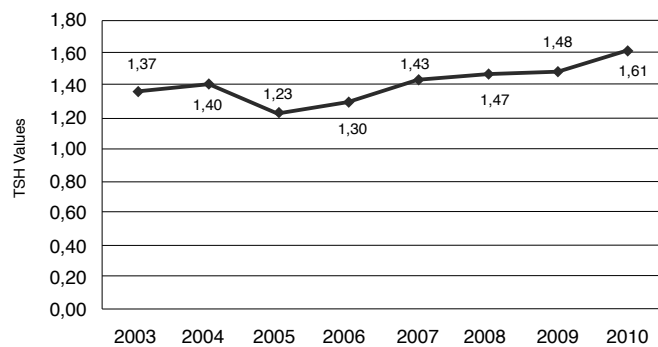
Diagnosis of toxic adenoma / goiter before 2005 were 3.7%, while after 2005 they were reduced to 3.1%. Diagnosis of Graves' disease before 2005 were 2.4% and they remained unchanged after 2005. Finally, diagnosis of hyperthyroidism / thyrotoxicosis increased from 2.5% to 2.1%. Comparing these results, there were no significant differences ( $P = 0.261$ ) between the percentages of diagnosis of hyperthyroidism before and after the introduction of mandatory iodization (**figure 1**).

**Figure 1** - Prevalence of hyperthyroidism before and after 2005.

We considered diagnosis of Hashimoto's thyroiditis before and after 2005 to demonstrate a link between the administration of iodine and thyroid autoimmunity. Prevalence of Hashimoto's thyroiditis between 2003 and 2005 was 37%; prevalence between 2006 and 2010 dropped to 34.7%. This small difference has a borderline statistical significance ( $P = 0.049$ ) (**figure 2**).

**Figure 2** - Prevalence of Hashimoto's thyroiditis.

At last, we studied TSH values, considering as normal range, TSH values between 0.4 and 4.5 mIU/ml. Stratifying TSH values from year to year, we found a small increase in TSH value, which, in any case, remains in the normal range. TSH values passed from 1.37 in 2003, to 1.61 in 2010. Although this increase is modest, it is statistically significant ( $P$  values  $< 0.001$ ) (**figure 3**).

**Figure 3** - TSH values.

## Discussion

The purpose of our study is to estimate the trend of thyroid diseases before and after mandatory iodization in Italy.

### *Iodine-induced hyperthyroidism*

Italy is an area with a moderate iodine deficiency and there was mandatory iodization in 2005. Our results confirm that iodine supplementation, in regions in which iodine deficiency is mild, would not increase the incidence of overt hyperthyroidism or Graves' disease.

These results are in agreement with the literature. Yang et al. (11) studied some areas in China with slight iodine deficiency, and they demonstrated that there wasn't a connection between iodine fortification and iodine-induced hyperthyroidism. In fact, hyperthyroidism is not related to the amount of iodine administered but it is related to iodine deficiency in the area studied, before mandatory iodization. These results are also in agreement with the study by Teng et al (12). On the other hand, Cerqueira (5) and Pedersen (13) demonstrated an increase of iodine-induced hyperthyroidism after mandatory iodization.

### *Thyroid autoimmunity*

We demonstrated a slight decrease, with borderline statistical significance, of autoimmune thyroiditis, after mandatory iodization in Italy. These data are not in agreement with the majority of studies in the literature: Pedersen et al (14), Li et al (7) and Aghini-Lombardi et al (1,2) showed an increase of thyroid autoantibodies after mandatory iodization. However, a study by Zimmermann (8) carried out in Morocco, didn't show an increase of thyroid autoantibodies after daily use of iodized salt.

### *Hypothyroidism*

The small but significant increase of TSH values can not find a clear explanation yet. These data are partially in agreement with the literature: Teng et al (12), Laurberg et al (15,16), Pedersen et al (14) (9) and Rhee et al (17) showed an increase incidence of hypothyroidism before mandatory iodization of salt. We considered several mechanisms to explain this phenomenon.

Firstly, alteration of Na/I symporter reduce intracellular levels of iodine and it cause a state of hypothyroidism (18). High intake of iodine can block the thyroperoxidase activity (Wolff-Chaikoff phenomenon). However, a normal thyroid can escape from this mechanism, modulating expression of Na/I symporter. Sometimes, this mechanism fails, the Na/I symporter is constantly activated and the excess of iodine blocks thyroid function. Another mechanism is the link between iodine administration and thyroid autoimmunity: several studies confirm that high levels of iodine can lead to an increase of autoimmune thyroiditis, which in turn leads to a state of hypothyroidism (6,7,9). Lastly, high levels of iodine can lead to an increased apoptosis of thyrocytes, with consequent state of hypothyroidism.

Anyway, these mechanisms may explain a state of hypothyroid-

ism only in areas with severe iodine deficiency. Italy is an area with mild iodine deficiency and, for this reason, these mechanisms fail to explain the increase of TSH values. However, this small increase of TSH values, totally unexpected, is statistically significant and it can not be ignored. At the present time, it is not possible to find a clear explanation but several factors may be implicated, such as poor patients' compliance and interference by other agents (endocrine disruptors).

Endocrine disruptors can play an important role on thyroid function. Normally, there is likely to be a tight relationship between changes in circulating levels of Thyroid Hormones and changes in Thyroid Hormone action in various target tissues. This relationship is maintained by tissue-level mechanisms that include Thyroid Hormone metabolism and transport. Environmental chemicals that interfere with Thyroid Hormone signaling mechanisms (Endocrine Disrupting Chemicals, EDCs) may produce adverse effects both in the individual and in a population. Some authors underline the relationship between organic pollutants, heavy metals (lead and mercury) and thyroid function. They demonstrated that organic pollutant levels are positively related to TSH and negatively to free T<sub>4</sub>; further, anti-thyroid peroxidase antibody levels also are related to organic pollutant levels suggesting elevated risk of autoimmune disease among the exposed.

In conclusion, although iodine supplementation should be implemented to prevent and treat iodine- deficiency disorders, supplementation should be maintained at a safe level. Levels that are more than adequate or excessive do not appear to be safe, especially for susceptible populations with either potential autoimmune thyroid diseases or iodine deficiency.

### References

1. The Spectrum of Thyroid Disorders in an Iodine-Deficient Community: The Pescopagano Survey. Aghini-Lombardi F, Antonangeli L., Martino E., Vitti P, Maccherini D., Leoli F, Rago T., Grasso L., Valeriano R., Balestrieri, A., Pinchera A. 1999. *J Clin Endocrinol Metab.* 84:561-6.
2. The Effect of Voluntary Iodine Prophylaxis in a Small Rural Community: The Pescopagano Survey 15 Years Later. Aghini-Lombardi F, Fiore E., Tonacchera M., Antonangeli L., Rago T., Frigeri M., Provenzale AM., Motanelli L., Grasso L., Pinchera A., Vitti P. 2013, *J Clin Endocrinol Metab.* Vol. 98, p. 1031-9.
3. Beneficial effects of iodized salt prophylaxis on thyroid volume in a iodine deficient area of southern Italy. Bonofiglio D., Catalano S., Perri A., Baldini MP, Marsico S., Tagarelli A., Conforti D., Guido R., Andò S. 2009, *Clinical Endocrinology.* Vol. 71, p. 124-9.
4. Doubling in the use of thyroid hormone replacement therapy in Denmark association to iodization of salt? C, Cerqueira e Knudsen N., Ovesen L., LaurbergP, Perri H., Rasmussen LB., Jørgensen T. 2011, *Eur J Epidemiol.* Vol. 26, p. 629-35.
5. Association of Iodine Fortification with Incident Use of Antithyroid Medication - A Danish Nationwide Study. Cerqueira C., Knudsen N., Ovesen L., Perrild H., Rasmussen LB., Laurberg P,

- Jørgensen T. 2009, *J Clin Endocrinol Metab.* Vol. 94, p. 2400-5.
6. A cautious iodization programme bringing iodine intake to a low recommended level is associated with an increase in the prevalence of thyroid autoantibodies in the population. Pedersen IB., Knudsen N., Carlè A., Vejbjerg P., Jørgensen T., Perrild H., Ovesen L., Rasmussen LB., Laurberg P. 2011, *Clinical Endocrinology.* Vol. 75, p. 120-6.
  7. Antithyroperoxidase and Antithyroglobulin Antibodies in a Five-Year Follow-Up Survey of Populations with Different Iodine Intakes. Li Y., Teng D., Shan Z., Teng X., Guan H., Yu X., Fan C., Chong W., Yang F., Dai H., Gu X., Yu Y., Mao J., Zhao D., Li J., Chen Y., Yang R., Li C., Teng W. 2008, *J Clin Endocrinol Metab.* Vol. 93, p. 1751-7.
  8. Introduction of Iodized Salt to Severely Iodine-Deficient Children Does Not Provoke Thyroid Autoimmunity: A One-Year Prospective Trial in Northern Morocco. Zimmermann MB., Moretti D., Chaouki N., Torresani T. 2003, *Thyroid.* Vol. 13.
  9. An Increased Incidence of Overt Hypothyroidism after Iodine Fortification of Salt in Denmark: A Prospective Population Study. Pedersen IB., Laurberg P., Knudsen N., Jørgensen T., Perrild H., Ovesen L., Rasmussen LB. 2007, *J Clin Endocrinol Metab.* Vol. 92, p. 3122-7.
  10. Iodide Excess Induces Apoptosis in Thyroid Cells through a p53-Independent Mechanism Involving Oxidative Stress. Vitale M., DiMatola T., D'Ascoli F., Salzano S., Bogazzi F., Fenzi G., Martino E., Rossi G. 2000, *Endocrinology.* Vol. 141, p. 598-605.
  11. Chronic iodine excess does not increase the incidence of hyperthyroidism: a prospective community-based epidemiological survey in China. Yang F., Shan Z., Teng X., Li Y., Guan H., Chong W., Teng D., Yu X., Fan C., Dai H., Yang Y., Yang R., Li J., Chen Y., Zhao D., Mao J., Teng T. 2007, *Eur J Endocrinol.* Vol. 156, p. 403-8.
  12. Effect of Iodine Intake on Thyroid Diseases in China. Teng W., Shan Z., Teng X., Guan H., Li Y., Teng D., Jin Y., Yu X., Fan C., Chong W., Yang F., Dai H., Yu Y., Li J., Chen Y., Zhao D., Shi X., Hu F., Mao J., Gu X., Yang R., Tong Y., Wang W., Gao T., Li C. 2006, *N Engl J Med.* Vol. 354, p. 2783-93.
  13. Increase in Incidence of Hyperthyroidism Predominantly Occurs in Young People after Iodine Fortification of Salt in Denmark. Pedersen IB., Laurberg P., Knudsen N., Jørgensen T., Perrild H., Ovesen P., Rasmussen LB. 2006, *J Clin Endocrinol Metab.* Vol. 91, p. 3830-4.
  14. Large Differences in Incidences of Overt Hyper- and Hypothyroidism Associated with a Small Difference in Iodine Intake: A Prospective Comparative Register- Based Population Survey. Pedersen IB., Knudsen N., Jørgensen T., Perrild H., Ovesen L., Laurberg P. 2002, *J Clin Endocrinol Metab.* Vol. 87, p. 4462-9.
  15. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. Laurberg P., Jørgensen T., Perrild H., Ovesen L., Knudsen N., Pedersen IB., Rasmussen LB., Carlè A., Vejbjerg P. 2006, *Eur J Endocrinol.* Vol. 155, p. 219-28.
  16. Iodine Intake and the Pattern of Thyroid Disorders: A Comparative Epidemiological Study of Thyroid Abnormalities in the Elderly in Iceland and in Jutland, Denmark. Laurberg P., Pedersen KM., Hreidarsson A., Sigfusson N., Iversen E., Knudsen PR. 1998, *J Clin Endocrinol Metab.* Vol. 83, p. 765-9.
  17. Association Between Iodinated Contrast Media Exposure and Incident Hyperthyroidism and Hypothyroidism. Rhee CM., Bhan I., Alexander EK., Brunelli SM. 2012, *Arch Intern Med.* Vol. 172 (2), p. 153-9.
  18. Escape from the Acute Wolff-Chaikoff Effect Is Associated with a Decrease in Thyroid Sodium/Iodide Symporter Messenger Ribonucleic Acid and Protein. Eng PEK., Cardona GR., Fang SL., Previti M., Alex S., Carrasco N., Chin WW. 1999, *Endocrinology.* Vol. 140, p. 3404-10.
  19. Relationships of putative endocrine disruptors to human sexual maturation and thyroid activity in youth. Lawrence M. Schell and Mia V. Gallo. *Physiol Behav.* 2010;99(2):246.
  20. Environmental chemicals targeting thyroid. Thomas R. Zoeller. *Hormones.* 2010;9(1):2-40.
  21. Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. Miller MD, Crofton KM, Rice DC, Zoeller RT. *Environ Health Perspect.* 2009;117(7):1033-41.