Adoption of TSH Reflex algorithm in an Italian clinical laboratory

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Key words: Clinical laboratory, TSH Reflex, cost effectiveness
Parole chiave: Laboratorio clinico, TSH Reflex, costo efficacia

Abstract

Background. TSH Reflex is an automated diagnostic algorithm which follows the rule “If ... then”, in which the initial determination of TSH is followed by the determination of fT4, and possibly of fT3, if TSH is not within the reference limits. The aim of our study was to evaluate the results of the introduction and implementation of the test “TSH Reflex”, which started in late 2013 in the hospital of Grosseto, comparing the requests of thyroid hormones for external patients, in 2012, 2014 and 2015.

Methods. In our study we analyzed the number of thyroid tests prescribed in 2012, 2014 and 2015 and we calculated the increase in prescription of “TSH Reflex” from 2014 to 2015; the prescriptive appropriateness, after the introduction of the “TSH Reflex”, through the ratios TSH/FT4, TSH/FT3 and the ratio “TSH Reflex”/TSH. Finally we calculated the total spending for the reagents in 2012, 2014 and 2015 and the consequent savings in euros (the costs of the reagents did not change during that time).

Results. Requests for TSH decreased by 4.6% in 2014, compared to 2012 and by 5.4% in 2015 compared to 2014, with a 9.8% reduction in 2015 compared to 2012. The requests for FT4 decreased by 11.5%, comparing 2014 with 2012, by 5.3% comparing 2015 with 2014, with a 16.2% reduction in 2015 compared to 2012. The requests for FT3 decreased by 13.3% in 2014 compared to 2012 and by 8.4% in 2015 compared to 2014, with a 20.6% reduction in 2015 compared to 2012. The appropriateness, evaluated the indicator TSH/FT4, increased by 7.6%, comparing 2014 with 2012, and remained unchanged in 2015. In 2012 71,134 euros were spent, 63,998 euros in 2014, 60,055 euros in 2015, resulting in a saving of € 11,079 in 2015 compared to 2012. The spending for “TSH Reflex” should be subtracted (1,964 Euros in 2015) from the previous savings.

Conclusions. The improvement of the efficiency and the prescriptive appropriateness was better in 2014, the first year of implementation of the “TSH Reflex”. The overall assessment suggests that the 2014 results are attributable to the letters that general practitioners received in December 2013, with a temporary increase of the use of the test. We need further analyses with the same indicators in order to assess the possibility of additional improvements in the future.
Introduction

The thyroid-stimulating hormone (TSH) is a glycoprotein produced by the pituitary gland which regulates the tropism of the thyroid gland and the production and secretion of thyroid hormones triiodothyronine (T3) and tetraiodothyronine or thyroxine (T4). The production of the thyroid hormones is subjected to a feedback regulation with TSH: the higher secretion of thyroid hormones (hyperthyroidism) determines the reduction of the production of TSH (pituitary negative feedback), while low concentrations of T3 and T4 (hypothyroidism), cause increased production of TSH (pituitary positive feedback) (1, 2).

Analyzing the number of prescriptions of tests to determine thyroid functionality TSH, fT3 (free fraction of T3) and fT4 (free fraction of T4) in different territories, the 90% of these exams are required by the outpatient setting, often inappropriately (3, 4). The inappropriate requests of exams increase the risk of false positives, leading to the execution of further unnecessary diagnostic investigations and also determines a delay in the execution of necessary diagnostic procedures, resulting in discomfort for patients and in a reduction of efficiency, due to the waste of economic resources (5-8).

According to EBLM (Evidence Based Laboratory Medicine) criteria, TSH is the recommended test for the screening of thyroid diseases, in asymptomatic patients or in patients with very nuanced symptoms suggestive of thyroid disease and, in addition, for the monitoring of chronic replacement therapy (5, 9, 10). It is not recommended, however, the use of TSH alone in pregnancy (11), in syndromes with resistance to thyroid hormones, in the central thyroid disorders, in the instability of the hypothalamic-pituitary-thyroid axis and in the early stages of thyroid hormones replacement therapy, when the stability of the hypothalamus-pituitary-thyroid axis has not been reached yet (5, 12).

TSH Reflex is a recently introduced algorithm, characterized by the initial determination of TSH and, automatically, the determination of FT4 and FT3 only when the TSH has a value outside the reference limits. If TSH is normal (0.34-3.8 mIU/L), the system stops; if TSH is less than the lower reference limit, the determination of FT4 is automatically performed, and if this is also high, the algorithm stops; if FT4 is normal, the determination of FT3 is performed (possible hyperthyroidism due to T3); if TSH is greater than the upper limit of reference, the determination of FT4 is performed. This algorithm allows the execution of these exams in an automated way, with a saving of time and reagents (5). A similar algorithm has been realized also for the identification of prostate cancers (13).

Before its introduction, the general practitioner usually prescribed TSH, FT4, FT3 (14), rarely only the TSH, with an adverse effect on costs and on prescriptive appropriateness (and no advantages for the diagnosis).

The aim of our study was to evaluate the results of the introduction of the “TSH Reflex” algorithm, in the clinical laboratory of the Hospital of Grosseto.

Methods

TSH Reflex algorithm was introduced in the Hospital of Grosseto at the end of 2013 and its prescription was promoted sending letters to the general practitioners of the province, describing the advantages of the test.

In our study we analyzed the number of prescribed tests for thyroid pathologies in the years 2012, 2014 and 2015. We excluded 2013, because it was the year of introduction of the new method. We calculated:

- The prescriptions of “TSH Reflex” in 2014 and in 2015;
Evaluation of the TSH Reflex algorithm

- The improvement of the prescriptive appropriateness after the introduction of the “TSH Reflex”. It was determined, according to the literature, through the increased TSH/FT4 ratio, TSH/FT3 ratio and increased “TSH Reflex”/TSH ratio (5).

- The total expenditure for reagents in the years 2012, 2014 and 2015 and the savings in Euro. The annual costs have been calculated considering only the reagents (the cost of a single test was obtained dividing the cost of the kit by the number of tests that can be done with one kit) multiplied by the number of performed tests.

Results

The TSH prescriptions were 34,985 in 2012; 33,359 in 2014; and 31,544 in 2015; the FT4 prescriptions were respectively 29,283, 25,925 and 24,548; the FT3 prescriptions were 28,260 in 2012, 24,487 in 2014 and 22,423 in 2015. The prescriptions of TSH were reduced by 4.6% in 2014 (compared to 2012) and by 5.4% in 2015 (compared to 2014), with a 9.8% reduction in 2015 compared to 2012. The prescriptions of FT4 were reduced by 11.5% in 2014 (compared with 2012), by 5.3% in 2015 (compared with 2014), with a 16.2% reduction in 2015 compared to 2012. The prescriptions of FT3 decreased by 13.3% in 2014 (compared to 2012) and by 8.4% in 2015 (compared to 2014), with a 20.6% reduction in 2015 compared to 2012 (Table 1 and Figure 1). The “TSH Reflex” prescription increased by 5% in 2015 compared to 2014 (Figure 2).

The prescriptive appropriateness evaluated

Table 1 - Prescriptions of TSH, FT4, FT3 and “TSH Reflex” in the years 2012, 2014 and 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>TSH</th>
<th>FT4</th>
<th>FT3</th>
<th>TSH Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>34,985</td>
<td>29,283</td>
<td>28,260</td>
<td>*</td>
</tr>
<tr>
<td>2014</td>
<td>33,359</td>
<td>25,925</td>
<td>24,487</td>
<td>3,224</td>
</tr>
<tr>
<td>2015</td>
<td>31,544</td>
<td>24,548</td>
<td>22,423</td>
<td>3,386</td>
</tr>
</tbody>
</table>

* In 2012, TSH Reflex had not yet been introduced

Figure 1 - Graphical representation of the decreased TSH, FT4 and FT3 prescriptions in the years 2012, 2014 and 2015
through the marker TSH/FT4(5), increased approximately by 7.6%, comparing 2014 with 2012 (year without TSH Reflex); it remained unchanged in 2015. The TSH/FT3 ratio (5) showed an increase of 10.6% comparing 2014 with 2012 and an increase of 2.9% in 2015 compared to 2014. The marker “TSH reflex”/TSH(9) showed an increase of 10% in 2015 compared to 2014 (Table 2, Figures 3 and 4).

71,134 euros were spent in 2012, 63,998 in 2014, 60,055 in 2015, with a resulting saving of € 11,079 in 2015 compared to 2012. It is necessary to subtract from this saving the total spending for “TSH Reflex” (1,964 euros).

Discussion and conclusions

We observed a better improvement of the efficiency and of the prescriptive appropriateness in 2014, the first year when the “TSH Reflex” was introduced. In 2015 the trend seems to be stable. The prescriptive appropriateness, evaluated through the ratio TSH/FT4, seems to be stationary in 2014 and in 2015, while the TSH/FT3 ratio increases by 2.9% in 2015, compared to 2014. The prescriptive appropriateness evaluated through the marker “TSH Reflex”/TSH, could not be assessed in 2012 (due to the absence of the “TSH Reflex”), while from 2014 to 2015 it shows an increase of 10%. These data seem to be attributable to the letters sent to the general practitioners in December 2013, with a temporary increase in prescription of the test.

In the following year, in fact, the prescriptions resulted to be unchanged.

However, as demonstrated by other studies (5), TSH Reflex has some limitations: it is very useful to understand the status of the thyroid if there is a stable compensation, therefore it is not recommended for situations in which the pituitary-thyroid axis is not

Table 2 - TSH/FT4, TSH/FT3 and “TSH Reflex”/TSH in the years 2012, 2014 and 2015

<table>
<thead>
<tr>
<th></th>
<th>TSH/FT4</th>
<th>TSH/FT3</th>
<th>TSH Reflex/TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>1.19</td>
<td>1.23</td>
<td>*</td>
</tr>
<tr>
<td>2014</td>
<td>1.28</td>
<td>1.36</td>
<td>0.09</td>
</tr>
<tr>
<td>2015</td>
<td>1.28</td>
<td>1.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* In 2012, TSH Reflex had not been introduced yet
intact or stable (e.g. pregnancy, central hypothyroidism, TSH-secreting pituitary adenomas). Moreover, it requires a great commitment by the laboratory managers and a lot of time to inform and educate physicians to prescribe it. There are some additional limitations in the use of TSH Reflex: in fact patients whose TSH is out of the normality range, with a following determination of FT4 and FT3 as the algorithm requires, are required to pay an economic integration, and this element could negatively affect the acceptance of it.

As other innovative laboratory techniques (15-17), although TSH Reflex could offer significant advantages, further investigations are needed about the introduction of the test, using the proposed methods and indicators, in order to assess if there are further possible improvements in the prescription of it. This method, in fact, presented certain limitations and should be used with caution, especially in patients who intend to obtain a screening or those with poorly evocative symptoms of thyroid dysfunction.

**References**


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