Original Article

# Comparing Thyroid Biomarkers And The Quality Of Nuclear Scan Images Of Patients With Thyroid Cancer After Levothyroxine Withdrawal Or Receiving Thyrotropin Alfa: A Retrospective Study

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## Abstract

**Background:** Thyroid scan is a specialized imaging method for assessing thyroid cancer after thyroid gland removed. To prepare the patient before scanning the thyroid gland, levothyroxine withdrawal or injection of thyrotropin is done. The aim of the study: The present study aimed to evaluate the quality of nuclear scan images and thyroid biomarkers after levothyroxine withdrawal or receiving thyrotropin alfa. Materials and Methodology: This was a cross-sectional study. The statistical data of this research were composed of 80 female patients with thyroid cancer referred to the nuclear medicine department of the Namazi Hospital in Shiraz in 2019. To be eligible to participate in this study, the patients must have a history of thyroidectomy, a Body mass index (BMI) of between 26 and 30 kg/m$^2$, and no history of receiving radioactive iodine uptake. To nucleus scan of the thyroid gland, all patients received 150 millicuries of radioactive iodine. Patients were divided into two groups. The first group consisted of 40 patients who had discontinued levothyroxine a few weeks before the nuclear scan. The group consisted of 40 patients who continued levothyroxine and received thyrotropin alfa (Thyrogen brand name) before the nuclear scan. These two groups were compared in terms of the levels of thyroid-stimulating hormone (TSH), Triiodothyronine (T3), thyroxine (T4), and thyroglobulin (Tg) biomarkers and image quality following the opinion of nuclear medicine experts and the Region of Interest (ROI) criterion. The results: There was no statistically significant difference between the two groups in T3 and T4 levels. In contrast, the mean TSH level was 67.37±13.98 mIU/L in patients with thyroid hormone withdrawal (THW) and 72.90±16.50 mIU/L in patients who had received thyrotropin alfa injections (P<0.001). The mean Tg levels in the THW and thyrotropin alfa injection were 244.58±88.48 mIU/L and 198.40±61.76 mIU/L, respectively (P<0.001). The means of the body count parameter in the THW and thyrotropin alfa injection groups were 37629.28±9817.08 m$^2$ and 21165.25±3346.64 m$^2$ (P <0.001), respectively. Based on the comments of nuclear medicine physicians, the high qualities of the images were 27.5% and 65% in patients with THW and who had been injected with thyrotropin alfa, respectively. Discussion and Conclusion: The TSH biomarker was higher in patients who had gotten thyrotropin alfa injections, which prepared these patients for the thyroid nucleus scan without the patient's developing symptoms of hypothyroidism. Tg levels were higher in patients with THW, suggesting the likelihood of recurrence of disease, metastasis, and/or residual thyroid tissue in this group. The body count parameter was higher in patients with THW, indicating lower image quality in this group than in the group receiving thyrotropin alfa injections. Besides, the image quality was better in the thyrotropin alfa injections group. Therefore, according to the results of this study, receiving thyrotropin alfa injections was preferable to discontinuation of levothyroxine.

**Keywords:** Thyroxine, Thyroglobulin, Thyroid Cancer, Radionuclide Imaging, Thyrotropin AlfaIntroduction

## INTRODUCTION

Thyroid cancer is one of the most common endocrine cancers, which has become more prevalent in recent decades

(1). According to a study by the National Cancer Institute in 2019, about 52890 people in the United States developed thyroid cancer. Also, approximately 70% of these people needed a thyroid scan, and 40% needed a thyrotropin alfa injection (2). Thyroid-stimulating hormone (TSH) is secreted by the anterior pituitary gland cells and plays a pivotal role in controlling thyroid function. It is also the most useful physiological indicator of thyroid hormone activity. Besides, TSH is the main factor determining the point of regulation in the thyroid axis.. The thyroid gland produces a hormone called triiodothyronine, known as T3. It also produces another hormone called thyroxine, known as T4. Together, these hormones regulate body temperature, metabolism, and heart rate (3-6). Iodine-131 ($I^{131}$) is an essential radioisotope that is widely used in thyroid disease. This radioisotope is used to remove the remnants of cancerous tissues after thyroidectomy. Also, flat-field imaging, which is the most popular method for determining the level of radioactive $I^{131}$ activity, is considered to identify metastatic diseases or cancerous tissues left in the thyroid gland after thyroidectomy (7). Two methods are commonly employed to prepare patients for a thyroid scan, i.e., thyroid hormone withdrawal (THW) or injection of thyrotropin alfa. After removing the thyroid gland (thyroidectomy), thyroid hormones should be replaced to avoid hypothyroidism symptoms and suppress thyroid cancer after thyroidectomy (8). The thyroid hormone cessation some weeks before scanning has long been used to prepare the patient for a nuclear scan. THW aims to increase the TSH level to enhance the uptake of radioactive iodine by healthy or metastatic thyroid cells or thyroid cancer cells. Another method for patient preparation is the injection of thyrotropin alfa that is produced by DNA recombinant technology. The advantage of this method is that it prevents the symptoms of hypothyroidism caused by the withdrawal of the thyroid hormone (9). Tg levels rise due to thyroid cancer; thus, the Tg is used as a tumor marker. In this method, the thyrotropin alfa is taken a few days before the scan, and there is no need to stop the levothyroxine to increase TSH levels (10, 11). Tg levels should be undetectable or very low after thyroid resection or after radioactive iodine treatment, provided the patient is taking thyroid hormone (levothyroxine) daily to prevent the increase of TSH. However, if Tg is still detectable in the blood after thyroid resection, the remaining thyroid tissue may either be normal or cancerous, which needs to be followed up and treated (12, 13). With the increasing use of radiotherapy medicine in clinics and animal trials, it is necessary to precisely assess the dose of the medicine absorbed by patients to assess the prognosis and side effects. Flat-field images taken by a gamma camera have been used to determine the condition and estimate the benignity or malignancy of a gland for decades. However, the difference between the estimated condition of the gland and its actual activity can be 4-6% to 10% or more for specific organs. This percentage is mainly determined by the definition of Region of Interest (ROI), context, distribution, and condition of the organ (12). To quantify flat-field imaging, the definition of ROI is a fundamental method that can affect the accuracy of quantitative results. However, studies quantifying thyroid radioactivity have not provided a consistent method for defining ROI (14). Most researchers have defined ROI based on visual specifications and depicted an area containing thyroid. Nonetheless, a visual criterion is an ambiguous concept. In addition, several researchers have proposed other methods for determining target tissue of ROI, such as selecting an 85% isocount contour of the thyroid gland or considering system spatial resolution (15, 16). To sum up, the criterion for the ROI definition is an integrated target tissue and rarely have studied have been designed precisely and simply to use an ROI definition method. Recently, with the development of image data processing workstations, ROI and more precise contexts can be defined that enable the precise quantification of flat imaging (15). To put it differently, ROI is an image or a data set that is specified for a particular purpose. It includes a surface report of the body based on the square meter in which radioactive iodine is absorbed and is specified in the image (17). The amount of ROI is calculated by counting the areas that have absorbed radioactive iodine (in square meters). Body count signifies this amount in the relevant software. There is yet no quantitative study on the effect of thyrotropin alfa and THW on ROI and nuclear scan image quality and comparison between the two. Therefore, the present study aimed to evaluate the quality of nuclear scan images, and the level of thyroid biomarkers after discontinuing levothyroxine or receiving thyrotropin alfa and compare these two methods.

## MATERIALS AND METHODS:

This study was a cross-sectional study that has been approved by the ethics committee of the Lorestan University of Medical Sciences (the ethics code number: IR.LUMS.REC.1399.173). For six months, researchers studied all medical records of patients with thyroid cancer referred to the nuclear medicine department of the Namazi Hospital in Shiraz to have a nuclear scan in 2019. A total of 150 cases was initially reviewed in six months. To participate in this research, the patients had to be females suffering from thyroid cancer who had undergone

thyroidectomy, had a Body mass index (BMI) of 26-30 kg/$m^2$, received radioactive iodine for the first time, did not have a history of iodine therapy, received a constant amount of 150 millicuries of radioactive iodine, did not suffer from other underlying diseases, and did not take any drug other than levothyroxine. Out of the 150 reviewed cases, 80 patients were selected and later divided into two groups. The first group consisted of 40 patients who had stopped taking levothyroxine for six weeks before their nuclear scan. The second group consisted of 40 patients who received thyrotropin alfa injections (in 2 separate injections 24 hours and 48 hours before receiving radioactive iodine), did not discontinue their levothyroxine intake, and were scanned. Laboratory thyroid factors, including TSH, T3, T4, and Tg were recorded just 24 hours after the thyrod scan for patients and compared our two groups together. To evaluate the imaging quality, researchers asked and recorded the opinions of three nuclear medicine experts. These people did not know which image belonged to which patient so that their judgment would not be influenced. Furthermore, to quantitatively compare the quality of images, the average ROI was recorded in each group and compared. Quantitative variables were evaluated as mean, standard deviation, minimum, and maximum. The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test. Moreover, the two groups were compared in terms of quantitative variables using the independent t-test or the non-parametric Mann-Whitney test. A significance level of 0.05 was considered for the previously mentioned tests. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. Finally, Graphs were drawn in the GraphPad Prism software.

## RESULTS:

The mean ages of patients with THW and patients receiving thyrotropin alfa injections were 51.4±14.94 and 54.00±8.95 years. Given P=0.35, there was no significant difference between the mean ages of the two groups. Also, the mean BMIs of patients in the THW and thyrotropin alfa groups were 27.27±1.39 kg/$m^2$ and 27.18±1.43 kg/$m^2$, respectively. According to P=0.78, there was not a significant difference between the mean BMIs of the two groups. The Kolmogorov-Smirnov test was used separately for the groups to test the normality of the data. This test showed that the assumption of normal distribution of data did not apply to the variables TSH, T3, and T4 in the two groups. Therefore, the Mann-Whitney non-parametric test was used to compare the means of the variables. The mean T3 and T4 serum levels in patients with THW were 2.26±1.31 Ng/dl and 1.93±1.24 Ng/dl, respectively. The mean T3 and T4 serum levels in patients receiving thyrotropin alfa injections were 2.24±1.30 Ng/dl and 1.94±1.23 Ng/dl, respectively. Thus, according to P=0.67 and P=0.99, there was no significant difference between the mean levels of T3 and T4 between the two groups. The mean TSH and Tg levels in the THW group were 57.37±13.98 mIU/L and 244.58±88.43 mIU/L, respectively. The mean TSH and Tg levels in the thyrotropin alfa group were 72.9±16.50 mIU/L and 198.40±61.76, respectively. Given P<0.001, there was a significant difference between the two groups in terms of the mean levels of TSH and Tg, in that the TSH of patients receiving thyrotropin alfa injections was significantly higher than the TSH in patients with THW. Figure 1 Also, the Tg of patients with THW was significantly higher than that of patients receiving thyrotropin alfa injections. Figure 2. The mean ROI parameters in patients with THW and patients receiving thyrotropin alfa injections were 37629.28±9817.08 $m^2$ and 21165.25±3346.64 $m^2$, respectively. Based on P<0.001, there was a significant difference between the mean body count level of the two groups, in that the ROI of patients with THW was significantly higher than patients who had received a thyrotropin alfa injection. Figure 3. The Chi-square test and descriptive information were used to determine the frequency of the variables and compare the variable of image quality in the two groups. The results suggested that 3 patients receiving thyrotropin alfa injections (7.5%) and 13 patients with THW (32.5%) had poor image quality. Besides, 26 patients receiving a thyrotropin alfa injection (65%) and 11 patients who had stopped levothyroxine (27.5%) had good image quality. Therefore, according to P=0.001, there was a significant difference between the two groups as far as image quality was concerned. Also, the Kramer correlation coefficient value, which is used to express the degree of correlation between two nominal and ordinal variables, was 0.41, which suggested a moderate correlation value.

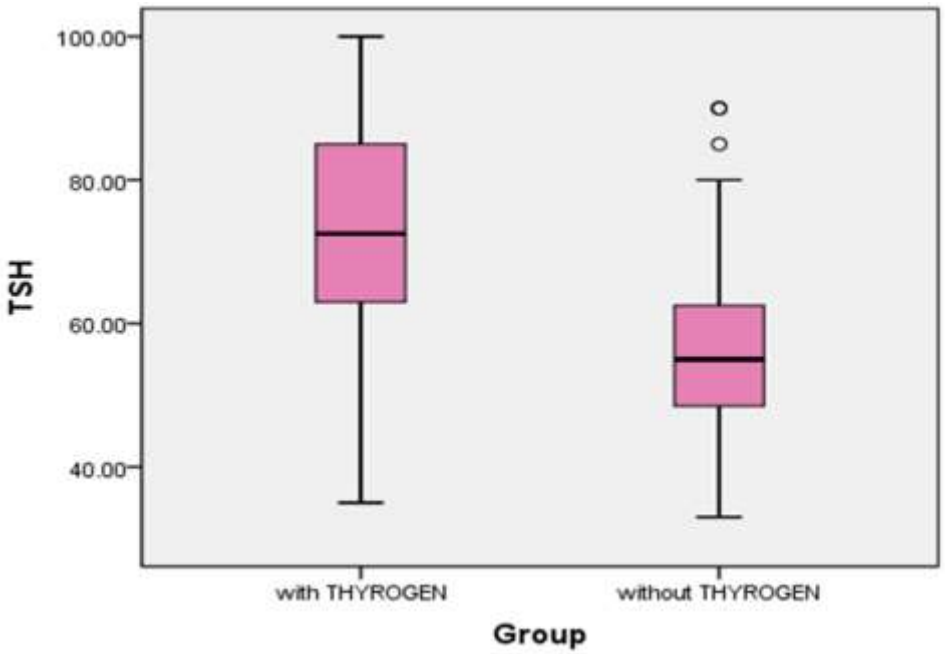


**Figure 1: Comparing blood levels of TSH in the two groups using box plots.** *TSH level is significantly higher in the patients who receiving thyrotropin alfa than the patients who had stopped levothyroxine.

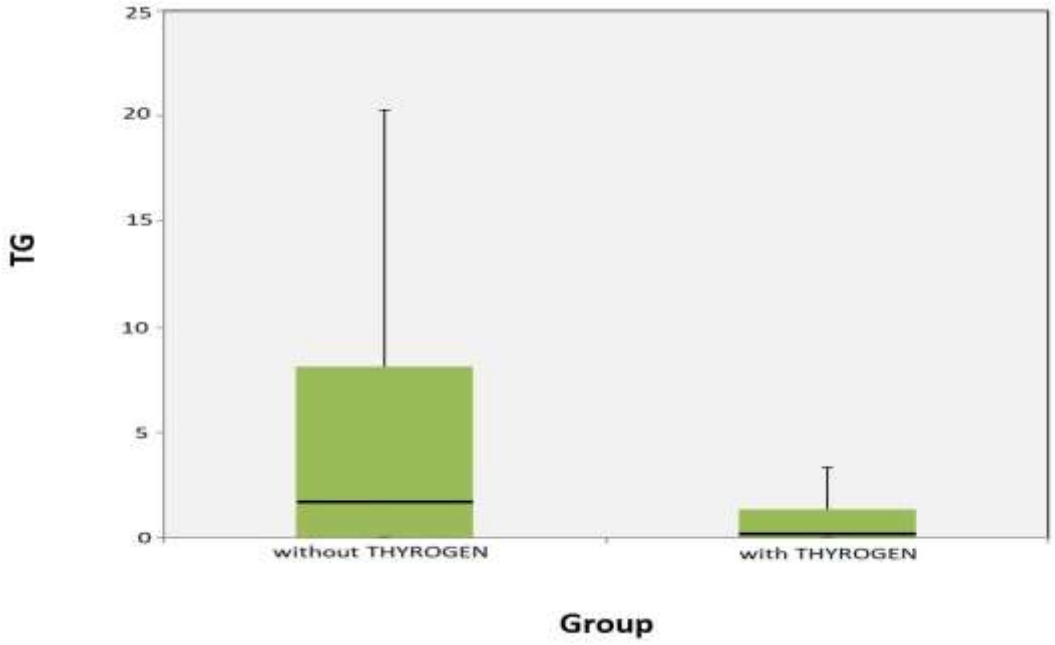


**Figure 2: Comparing blood levels of Tg in the two groups using box plots. ***Tg level is significantly higher in the patients who had stopped levothyroxine than the patients who receiving thyrotropin alfa.

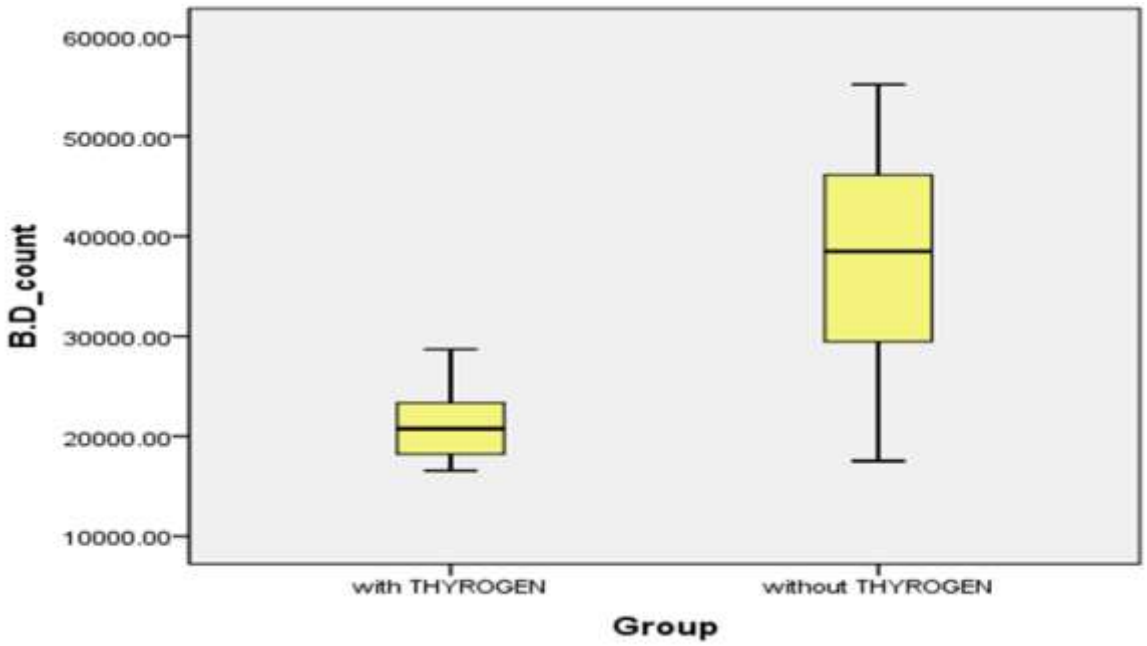


**Figure 3: Comparing image quality with the body count parameter of the two studied groups using box plots. ***Image quality is significantly higher in the patients who receiving thyrotropin alfa than the patients who had stopped levothyroxine.

## DISCUSSION:

The present study results showed patients receiving thyrotropin alfa injections had a significantly higher TSH level than patients with THW. This rise in the TSH level after the thyrotropin alfa injection resulted in better image quality. In addition, the TSH level was kept high for a few days while using thyrotropin alfa injections; whereas, TSH was kept high for a few weeks when THW was used, which has proven to be associated with a lower probability of cancer reoccurrence accompanied by lower levels of Tg. The patients with THW had a significantly higher TSH level than patients receiving thyrotropin alfa injections. The level of Tg must be very low after thyroidectomy. Therefore, if there was a detectable amount of Tg post-operation, it would be possible that a normal or cancerous thyroid tissue has remained in the patient's body or the tumor has recurred, indicating the need for additional treatment. As a result, the present study showed that the recurrence rate of the tumor was lower in patients receiving thyrotropin alfa injections than patients who had stopped consuming levothyroxine. Thyrotropin alfa is a protein produced by a recombinant DNA technique that is quite similar to TSH (18). Thyrotropin is consumed to measure thyroid activity, detect the amount of remnant thyroid after thyroidectomy, and increase the absorption of radioactive iodine by the thyroid gland (19, 20). Thyrotropin binds to thyrotropin receptors on residual thyroid cells or normal tissues, stimulating radioactive iodine uptake and improving diagnostic imaging quality with radioactive iodine (21). Measuring Tg levels can show if thyroid cancer cells are still in the body after treatment; that is, if Tg levels remain the same or increase after cancer treatment, it may indicate the presence of thyroid cancer cells in the body (22). If Tg levels decrease or disappear after treatment, it may mean that there are no normal or cancerous thyroid cells in the body. Follow-ups are performed after follicular or papillary cancer surgery by measuring Tg. The lower the Tg, the lower the chance of recurrence, and vice versa (23-25). Tg levels are directly related to the tumor volume. Tg and TSH follow-ups are performed through annual periodic ultrasounds. The body count parameter is basically the count of ROI units in square meters, and if the amount increases in the imaging, it indicates that the image quality is low. As a result, the present study showed that due to the high body count in patients with THW, the image quality in patients receiving thyroid injections was higher than those with THW. Also, in this research, the quality of images was assessed based on the comments of nuclear medicine experts. The results showed that 65% of patients with thyrogen injection and 27.5% of patients with THW had good image quality. Therefore, there was a significant difference between the image quality of the two groups. During this period, several studies have been conducted in this regard with different results. Some of the said studies and their findings will be mentioned as follows, and their findings will be

compared with the present study results. In a study, Robbins et al. (2001) compared patient preparations by recombinant human thyrotropin (rhTSH) injection and discontinuation of the thyroid hormone to detect residual thyroid carcinoma in patients with thyroid cancer. In this retrospective study, 289 patients were studied for two years. These patients were divided into two groups. One group consisted of 161 patients with thyroid hormone withdrawal (THW). The second group consisted of 128 patients with thyroid hormone residue who received a thyrogen injection (rhTSH). The Diagnostic whole-body radioiodine scanning (DxWBS) and Tg levels were measured for all patients after the rise of TSH. Sensitivity, specification, positive and negative predictive values of DxWBS and Tg stimulated after preparation were evaluated using THW and rhTSH methods. The results showed no significant difference between positive and negative predictive values of the two groups. The highest negative predictive value among patients (97%) was seen in patients with negative DxWBS, and low stimulated Tg levels after rhTSH. Overall, this study was unable to show significant differences in the diagnostic accuracy of DxWBS and/or Tg between patients prepared by THW or rhTSH. They concluded that the preparation of patients with rhTSH was diagnostically equivalent to preparation with THW (26). In contrast, the result of our study showed image quality of patients with thyrotropin alfa injections method was pereferd.

In another study by Dontas et al. (2003), the use of thyrotropin alfa was examined in the treatment and diagnosis of thyroid cancer patients. They concluded that the introduction of rhTSH in the diagnosis of thyroid cancer improved the patient's quality of life by preventing debilitating hypothyroidism. They reported seven cases intending to update the use of thyrotropin alfa. All these seven cases were treated with thyrotropin alfa for diagnostic or therapeutic purposes. All seven patients underwent thyroidectomy, and the remnant thyroid cells were removed by radioactive iodine, and all had basal serum thyroglobulin levels (b-Tg) [1 ng/ml <]. Thyroid stimulation resulted in an increase in Tg (s-Tg) in all patients. Five patients had a negative whole body scan (WBS) and had no clinical or radiological symptoms. Two patients with Tg of 5 ng/ml and 11 ng/ml showed Tg of 17 ng/ml and 84 ng/ml, respectively, while their WBS was negative. Both patients received 100 mCi $I^{131}$. Patients with positive values of Tg and WBS with cranial, lung, and liver metastases received $I^{131}$ after preparation with thyrotropin alfa. Six months later, one of these patients was disease-free, and the other was evaluated in the coming months. As a result, thyrotropin alfa appeared as a reliable factor in the diagnosis of thyroid cancer. In addition, it seemed that thyrogen could be used to metastasis as an alternative for THW. The result of this study indicated that the use of thyrotropin alfa was reliable and safe, and thyrotropin alfa was also a very good alternative for THW to treat metastatic thyroid cancer (27). Lipp (2014) conducted a study on the sensitivity of preparations with rhTSH and THW using an $I^{131}$ WBS to detect thyroid cancer metastases. They based their study on a report that stated that rhTSH was more sensitive to the diagnosis of differentiated thyroid cancer (DTC) metastases than THW. The goal of their study was to confirm this reported difference in sensitivity using whole body scan (WBS). In this retrospective study, 43 patients with evidence or suspicion of metastatic DTC (assessed by Tg or abnormal findings in the previous WBS) underwent WBS 24 hours after oral consumption of 370 MBq $I^{131}$. Two independent observers interpreted WBS, and then categorized the findings as positive or negative for metastatic diseases. Findings were controlled by measuring stimulated Tg and a two-year follow-up. Of the studied patients, preparations were done for 14 patients with rhTSH and 29 patients with THW. According to the results, there was no statistical difference between the characteristics of the patients in the two groups (age, sex, Tg level, TSH level, and type of cancer). In this study, no difference was observed between the WBS sensitivity of patients treated with rhTSH and patients with THW. Out of the studied 14 patients, 11 individuals (78%) were positive for rhTSH, and 19 out of 29 patients (65%) were positive for THW. Metastatic patients were confirmed by assessment and follow-up of stimulated Tg. The results of this study showed that, unlike previously published data, no difference was in the sensitivity of rhTSH or THW for the preparation of DTC patients under $I^{131}$ imaging (28). Park et al. (2017) did a study on early stimulation of Tg after administration of thyrogen. It is generally recommended to measure the Tg stimulated by rhTSH 72 hours after the second rhTSH injection. However, due to the acute effect of $I^{131}$ on thyrocytes, Tg is measured after radioiodine therapy (RIT) and is not accurately reflective of the load on thyroid tissue. Their study aimed to determine the predictive value of serum Tg levels measured before RIT with the help of rhTSH and compare the post-RIT results in patients with disseminated thyroid carcinoma (DTC). In this study, patients with DTC after a complete thyroidectomy were studied between 2009 and 2014. The serum Tg level of these patients was measured 24 hours (primary Tg) and 72 (or 96) hours (Delayed or secondary Tg) after the rhTSH injection. An excellent response was defined according to the latest guidelines of the American Thyroid Association. Univariate and multivariate analyzes were performed for primary Tg, delayed Tg, and other

clinical variables. In multivariate analysis, tumor size [odds ratio (OR) of 1.716; confidence interval (CI) of 95%; 1.019–2.882 p=0.042] and the primary Tg level (or 2.012; 95% CI; 1.384-2 0.925 CI, p<0.001) independently predicted excellent responses. The best primary Tg level was 2.0 Ng/ml for predicting an excellent response. The delayed Tg was not significantly predictive (OR=0.992; 95% CI 0.969-1 .015; p=0.492). Primary Tg stimulation after RIT significantly predicted therapeutic response in patients with DTC with the aid of rhTSH. Therefore, to predict therapeutic responses, serum Tg should be measured before RIT. Furthermore, it was concluded that injection of thyrotropin alfa had a significant effect on the amount of Tg reaching the therapeutic value (29). Klubo-Gwiezdzinska et al. (2013) studied the use of recombinant human thyrotropin in the treatment of distant metastases in patients with DTC. To effectively treat DTC with radioactive iodine (RAI), it is necessary to increase serum TSH levels through THW or by prescribing rhTSH. The objective of this study was to provide current data on the relative impact and specifications of the side effects of THW with the help of rhTSH and RAI for the treatment of patients with DTC metastases. They searched the PubMed database for articles containing the keywords "rhTSH," "thyroid cancer," and "distant metastases" published between Jan 1, 1996, and Jan 7, 2012. They utilized a collection of clinical cases, reports, articles, and practical guidelines as resources. According to their findings, an increase in the TSH level with the injection of thyrotropin alfa was associated with a better quality of life because it eliminated the signs and symptoms of hypothyroidism caused by an increase in TSH through the THW method. The rate of neurological complications after RAI treatment with rhTSH and THW was similar for brain and spinal metastases. The rates of leukopenia, thrombocytopenia, pulmonary dryness, and fibrosis after preparation were also similar after preparation with rhTSH and THW for the RAI treatment. Currently, there is a discrepancy in some studies on the RAI uptake in metastatic lesions after preparation with rhTSH versus THW. Some studies argue that the uptake is equal for both methods and others emphasize the superiority of THW. Analyzing the existing retrospective studies comparing survival, progression-free survival, and biochemical and structural responses to set RAI dosimetry reported similar effects after preparation through rhTSH and THW. Stimulation of rhTSH is currently approved by the FDA as preparation for adjuvant therapy with RAI in patients with metastatic DTC. Data on rhTSH stimulation show that rhTSH stimulation is as effective as THW as preparation for dosimetry-based RAI in treating distant metastases in patients with DTC (30).

## CONCLUSION

The TSH biomarker was higher in patients receiving thyrotropin alfa injections, which properly prepared them for a thyroid nuclear scan without the patients' developing symptoms of hypothyroidism. The Tg level was higher in patients who had discontinued levothyroxine, indicating the probability of recurrence of the disease, metastasis, and/or residual thyroid tissue. The body count parameter was higher in patients with THW, which showed that the image quality was lower in this group than the group receiving thyrotropin alfa injections. Besides, the image quality was better in the thyrotropin alfa injections group. Therefore, based on the research results, receiving Thyrogen injections was preferable to discontinuation of levothyroxine.

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