Original Article, Endocrine

Three Weeks Withdrawal of T4 Prior to I131 whole Body Scan Can Achieve the Required Serum TSH Level with Significantly Less Hypothyroidism

Wagieh Sh[*], Al Salman Kh[*], Al Munshy T[*], Kandeel A[**] and Abou-Gabal M[**].

*Nuclear Medicine Departments: *King Abdullah Medical city, Saudi Arabia and **NEMROCK, Kasr Al-Eini Hospital, Cairo University, Egypt.*

ABSTRACT

Introduction: I131 whole body scan (WBS) is used in follow–up of patients with well differentiated thyroid cancer (WDTC) post total thyroidectomy and I131 ablation therapy. Traditionally, it is performed after withdrawal of Thyroxine (T4) for at least 4-6 weeks to stimulate endogenous TSH to a level more than 30mIU/L. T4 withdrawal is associated with significant symptoms of hypothyroidism. In clinical practice, several studies report that serum TSH rapidly reaches the level of >30mIU/L at a mean of 17 to 18.1 days after T4 withdrawal in 96.2% of patients, reducing the duration of hypothyroidism and improving acceptance of scanning with I131 with minimal impact on health related quality of life (QOL).

Aim of the study: The aim of the current study is to compare effects of T4 withdrawal for 3 weeks versus traditional withdrawal for 4 weeks on serum TSH level and hypothyroid symptoms in patients with WDTC presenting for I131 follow up WBS post total thyroidectomy and successful I131 ablation therapy.

Patients and methods: One hundred patients with WDTC presented for I131 WBS post successful complete ablation of residual functioning thyroid tissue in the neck, all had suppressed or within normal TSH level. They were divided into 2 equal groups. Group I, instructed to withdraw Thyroxine for 3 weeks and group II, instructed to stop thyroxine for 4 weeks. Serum TSH level was estimated for all patients prior to oral intake of I131. Also, a questionnaire of main hypothyroid symptoms was filled by all patients about presence or absence of the symptoms and their severities that were divided into mild, moderate and severe.

Results: For group I, 49 patients (98%) had TSH level >30 mIU/ml (mean=77.4±27.9), while all patients in group II (100%) achieved significantly higher TSH level (mean=119.1±42.1). There was a highly significant positive correlation ($p<0.001$) between number of symptoms and late serum TSH level within each group. The number of symptomatic patients was 39 patients (78%) in group I having a total number of 100 symptoms, with a mean of 2.0±1.5; out of them 60 mild, 29 moderate and 11 severe representing 60%, 29% and 11%, respectively. While for group II, number

of polysymptomatic patients was 46(92%) with a total number of 233 symptoms with a mean of 4.7±2.6; out of them 70 mild, 95 moderate and 68 severe representing 30%, 40.8% and 29.2%, respectively. Patients in group I had significantly less hypothyroidism as regards number of patients, number of symptoms and their severity compared to group II. Moreover, a significant positive correlation between number of hypothyroid symptoms and serum TSH level was detected in both groups. **Conclusion:** It is concluded to withdraw thyroxine for 3 weeks instead of 4 weeks for patients with well differentiated thyroid carcinoma prior to regular follow up I131 WBS to achieve the desired serum TSH level with significantly less hypothyroid symptoms and better quality of life.

Keywords: well differentiated thyroid carcinoma, hypothyroidism, T4 replacement therapy, serum TSH.

Corresponding Author: Kandeel, A **E-mail : ahmedkandeel@yahoo.com**

INTRODUCTION:

I131 whole body scan (WBS) is used in follow–up of patients with well differentiated thyroid cancer (WDTC) post total thyroidectomy and I131 ablation therapy. Traditionally, I131 WBS is performed after withdrawal of T4 for at least 4-6 weeks, as recommended by most guidelines, to stimulate endogenous TSH to a level more than 30mIU/L[1-4]. This is mandatory before WBS[5] and considered a prerequisite to guarantee optimal uptake of I131 by any functioning thyroid tissue[2-4]. T4 withdrawal is associated with significant symptoms of hypothyroidism, which is especially debilitating for young working adults and can compromise the patients' quality of life (QOL) and result in hypercholesterolemia and myopathy accompanied by a rise in creatine kinase (CK) [6,7]. In a study of T4 withdrawal prior to WBS, 92% of patients had symptomatic hypothyroidism and 85% had multi- symptomatic hypothyroidism with a median absence from salaried work equals 11 days per withdrawal [8]. In a trial to decrease morbidity, T3 was used and is withdrawn for only 2 weeks; the latter approach did not prevent development of profound hypothyroidism without significant difference in quality of life between T4 and T3 withdrawal[4]. These data goes with that reported by Serhal et al, their results cast doubt about the value and benefits of using T3 in preparing patients for radioactive iodine therapy [9]. The use of recombinant human thyroid stimulating hormone (rhTSH) has comparable rise in serum TSH level with significantly more preserved quality of life, Schroeder et al confirmed that short term hypothyroidism after T4 withdrawal is associated with significant decline in quality of life that is abolished by rhTSH use [10]. Yet, due to its high cost it is not provided routinely by many hospitals authorities. In clinical practice, after T4 withdrawal for 4 weeks, TSH level rises evidently more than 30 mIU/L. In agreement, several studies report that serum TSH rapidly reaches the level of >30 mIU/L at a mean of 17 to 18.1 days after T4 withdrawal. Therefore, a simple reduction of withdrawal time can be adopted, reducing the duration of

hypothyroidism and improving acceptance of scanning with I131 [9,11,12]. In a trial to decrease hypothyroidism and preserve better QOL, withdrawal of T4 was done for 3 weeks instead of 4 weeks. Chow et al reported a rise of TSH level >30 mIU/L in 96.2% of patients after 3 weeks of T4 withdrawal and concluded that to minimize impact of health related QOL, duration of T4 withdrawal can be reduced to 3 weeks [13].

AIM OF THE STUDY:

The aim of the current study was to compare effect of T4 withdrawal for 3 weeks versus withdrawal for 4 weeks on serum TSH level and hypothyroid symptoms in patients with well differentiated thyroid carcinoma presenting for follow up I131 whole body scan post total thyroidectomy and successful I131 ablation therapy.

PATIENTS AND METHODS:

The current study was approved by the institutional local ethical committee. It was performed prospectively on 100 patients with well differentiated thyroid carcinoma referred from June 2010 to January 2012 for routine follow up I131 WBS after being treated by total thyroidectomy and subsequently received postoperative I131 ablation. They were free on last I131 WBS with no residual, recurrent or metastatic functioning thyroid tissue. All patients were on regular replacement/ suppressive hormonal T4 therapy (125, 150 or 200 microgram/day). Baseline serum TSH level was done for all patients while on treatment. Patients were then randomly divided into two equal groups. Patients in group I were instructed to stop T4 for 3 weeks and present for I131 WBS. Patients in group II were instructed to stop T4 for 4 weeks prior to I131 WBS. Blood sample was withdrawn for estimation of serum TSH level for each patient prior to oral administration of the diagnostic I131 dose. Main twelve hypothyroid symptoms predominated in our patients in the current study were assessed by written questionnaire based on the study done by Canaries et al 1997[14]. The questionnaire was given to each patient for presence or absence of the symptom and if present, patients marked it as mild, moderate and severe.

RESULTS:

The current study included 100 patients with well differentiated thyroid carcinoma. Their age ranged from 17-64 years (mean=40.7±11.4 years). They were 95 females and 5 males (48 and 2 in group I; 47 and 3 in group II, respectively). The mean serum TSH level was 0.9±0.9 mIU/L at baseline and 98.2±41.2 mIU/L after T4 withdrawal. There was a homogenous distribution of the studied parameters between both groups regarding sex, means of age and baseline serum TSH level as shown in table 1. Serum TSH level after T4 withdrawal reached more than 30 mIU/L in all studied patients in both groups (mean=98.2±41.2 mIU/L) except for one female patient in group I (her serum TSH level was 26.4 mIU/L). Yet, a highly significant statistical difference was elicited between the two groups ($p<0.001$, table1). The number of hypothyroid symptoms was significantly higher in group II compared to that in group I (mean=4.7±2.6 versus 2.0±1.5, respectively) ($p<0.001$, table 1).

Table 1: Distribution of the studied parameters among the two groups with comparison.

Parameter	Group I (3 wk after T4 withdrawal) (N=50)			Group II (4 wk after T4 withdrawal) (N=50)			p value
	Mean±SD	Range	Median	Mean±SD	Range	Median	
Age (yr)	39.7±11.6	18-63	39	41.7±11.1	17-64	43	**NS**
Serum TSH (mIU/L)	0.9±0.9	0.01-3.4	0.7	0.9±1.0	0.01-3.7	0.7	**NS**
Base line	77.4±27.9	26.4-171	76	119.1±42.1	51.7-273	100	**< 0.001**
After T4 withdrawal							
Number of Hypo-thyroid Symptoms	2.0±1.5	0-5	2	4.7±2.6	0-9	5	**< 0.001**

In group I, eleven patients (22%) were asymptomatic, 8 patients (16%) complained of only one symptom (all reported general weakness) and the remaining 31 patients (62%) were multiple symptoms (range 2-5 symptoms). Likewise, in group II, four patients (8%) were asymptomatic, 3 patients (6%) complained of one symptom and the remaining 43 patients (86%) had a range of 2-9 symptoms. The total number of hypothyroid symptoms reported by symptomatic patients was 100 and 233 in group I and II respectively, a high significant statistical difference between both groups was elicited ($p < 0.001$). The commonest symptoms in both groups were fatigue, muscle pains, cold sensitivity, sleepiness, puffy eyes and dry skin (table 2).

Table 2: Frequency of main 12 hypothyroid symptoms in the studied patients.

Hypothyroid Symptom	Group I	Group II
Fatigue	21	34
Muscle pains	18	32
Cold sensitive	14	31
Sleepiness	11	29
Dry skin	8	24
Puffy eyes	7	21
Hair affection	7	19
Weight gain	6	15
Constipation	3	13
Lack of concentration	3	7
Dyspepsia	1	5
Memory changes	1	3
Total number *	**100**	**233**

* Indicates statistical significance ($p < 0.001$)

The QOL of the patients was objectively assessed by reporting the severity of hypothyroid symptoms into mild, moderate and severe. Figure 1 demonstrates the frequency of hypothyroid symptoms severity among the 100 symptoms recorded by 39 patients (78%) in group I compared to the severity of the 233 symptoms reported by 46 patients (92%) in group II. A high statistically significant difference was obtained on comparing the moderate and severe symptoms between both groups ($p<0.001$).

Pearson test for numerical correlation revealed a high significant positive correlation between the number of reported hypothyroid symptoms and late serum TSH level (after T4 withdrawal) in each group (r 0.5, $p <0.001$). Serum TSH level after T4 withdrawal showed non-significant correlation with the age of the studied patients (r 0.06, p 0.5).

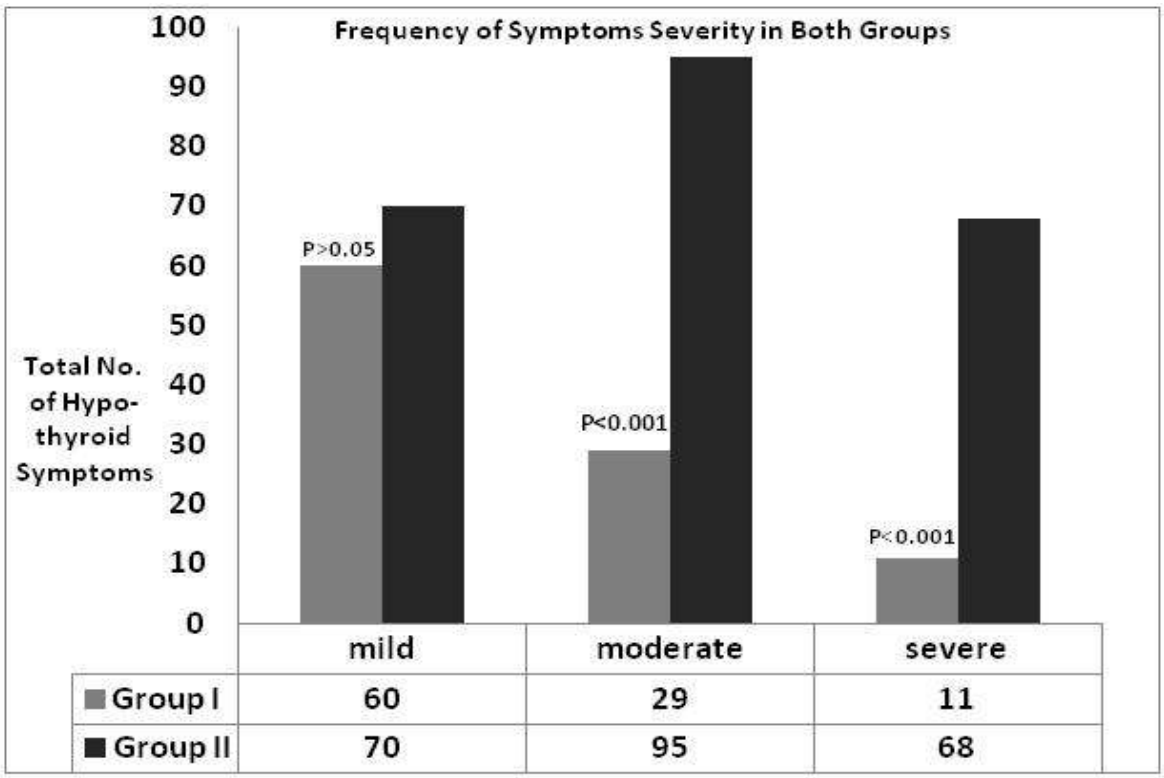

Figure 1: Frequency of hypothyroid symptoms severity in both groups with comparison.

DISCUSSION

A TSH value of 30mIU/L is the level known to be ideal prior to estimation of serum Tg level as well as prior to I131 WBS or I131 ablation to ensure best I131 uptake by residual thyroid tissue in patients with well differentiated thyroid cancer (WDTC) **(15-18).** Above this level no more I131 uptake was detected, as stated by Goldman et al, 1980 who concluded that exaggerated TSH rises had no additional benefits on I131 uptake at median TSH level of 68 mIU/L (2 weeks T3-off) versus 96 mIU/L (4 weeks T3-off) **(2)**. To achieve TSH elevation to the desired level (> 30 mIU/L) after thyroidectomy which is necessary to facilitate the uptake of radioiodine into thyroid remnants, a 4-6 weeks interval between thyroidectomy and radioiodine administration has been established **(1-4)**. Also, this is the traditional way used prior to follow up I131 whole body scan postoperatively to reach the desired TSH level**(5).** During this period of 4-6 weeks withdrawal of hormonal therapy, most patients have experienced overt symptoms of hypothyroidism. These symptoms make patients uncomfortable with inconveniency to receive ablative dose and/or perform the I131 WBS**(10).** The impact of this long period of T4 withdrawal on health related quality of life of patients with WDTC presented for regular follow up I131 WBS was behind the rational of our study to compare effect of T4 withdrawal for 3 weeks versus traditional withdrawal for 4 weeks on serum TSH level and hypothyroid symptoms. The striking finding in the current study was the profound elevation of serum TSH level after 3 weeks of T4 withdrawal much more than the desired 30 mIU/L (mean=77.4±27.9) in 98% of patients in group I. Our findings are keeping with the results of Rosario et al who stated that serum TSH levels > 30 mIU/L were reached in 78.4 and 100% of patients in the absence of thyroid hormone within 2 and 3 weeks, respectively **(19)**. Similarly, Grigsby et al reported that in most patients with cancer thyroid being prepared for I131 imaging or therapy, a TSH level > 30 mIU/L can be achieved by withdrawal of thyroid hormone therapy for 1-3 weeks**(20).** Serum Tg test is currently considered an essential investigation in the follow up of patients with WDTC, Golger et al on a trial to assess efficacy of shortening the time of withdrawal of T4 to only three weeks as a sufficient TSH stimulus, they concluded that a stimulated serum Tg test performed 3 weeks after T4 withdrawal is a simple and cost effective first line screening test with minimal morbidity which is sufficient to evaluate low risk WDTC patients for recurrent/residual carcinoma**(21).**

Unfortunately, serum Tg was not assessed in the current study, however we could expect the same finding of Golger et al based on the resultant high mean serum TSH level after 3 weeks of T4 withdrawal in our patients. By shortening the period of T4 withdrawal to 3 weeks, patients in group I in the present study exhibited better QOL during the 3 weeks off-T4 and better tolerability to perform the procedure than patients in group II. Hypothyroidism was significantly lower in group I as regards number and severity of symptoms than that in group II.

Moreover, the number of reported hypothyroid symptoms was significantly correlated with elevation of serum TSH level in both groups; this allows us to advocate the unnecessary longer period of T4 withdrawal to attain high serum TSH level prior to routine follow up I131 WBS as this might exaggerate hypothyroid symptoms and intolerability of patients without additional benefits. Chow et al, 2007 stated the different factors that affect TSH rise, including duration of T4 withdrawal, age and degree of TSH suppression before T4 withdrawal. It was observed that there is a trend of lower endogenous TSH rise after thyroid hormone withdrawal in elderly patients mostly attributed to more sluggish hypothalamo- pituitary axis in response to the negative feedback system of serum T4 changes[22]**.** This was not the same in the present study where marked rise in TSH level had elicited, that may be attributed to the relatively younger ages of our studied patients (median age was 39 and 43 years in group I and II, respectively). However, the only patient that did not achieve desired serum TSH level in group I is an elderly female 63 years old. Patients with suppressed TSH level have a rapid rate of TSH elevation on withdrawal [22]. This particular issue was not evaluated in our patient population.

CONCLUSION:

Three weeks withdrawal of T4 has comparable effect to 4 weeks withdrawal on the rise of serum TSH level with significantly less hypothyroidism as regards number and severity of symptoms ensuring better quality of life. So, we recommend cessation T4 replacement for only 3 weeks instead of the traditional approach of 4 weeks withdrawal prior to regular follow up I131 whole body scan in patients with well differentiated thyroid carcinoma after successful complete ablation.

REFERENCES:

1. **Maxon HR, Smith HS.** Radioiodine 131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. Endocrinol Metab Clin North Am.;19:685-717; 1990.
2. **Goldman JM, Line BR, Aamodt RL, Robbins J.** Influence of triiodothyronine withdrawal time on 131I uptake post thyroidectomy for thyroid cancer. J Clin Endocrinol Metab.;50:734-9; 1980.
3. **Edmonds CJ, Hayes S, Kermode JC, Thompson BD.** Measurement of serum TSH and thyroid hormones in the management and treatment of thyroid carcinoma with radioiodine. Br J Radiol.;50:799; 1977.
4. **Hilts SV, Hellman D, Anderson J, Woolfenden J, Van Antwerp J, Patton D.** Serial TSH determination after T3 withdrawal or thyroidectomy in the therapy of thyroid carcinoma. J Nucl Med.; 20:928; 1979.

5. **Schlumberger M, Baudin E.** Serum thyroglobulin determination in the follow-up of patients with differentiated carcinoma. Eur J Endocrinol.;138:249-52; 1998.
6. **Lien EA, Nedrebo BG, Varhaug JE, Nygard O, Aakvaag A, Ueland PM.** Plasma total homocysteine levels during short-term iatrogenic hypothyroidism. J Clin Endocrinol Metab.; 85:1049-53; 2001.
7. **Weissel M, Kainz H, Hofer R.** Changes in biochemical parameters during complete thyroid hormone deficiency of short duration in athyreotic patients. J Nucl Med.; 27: 1528-32; 1986.
8. **Markus L, Ralph F, Markus D, Christoph R.** Thyroid Hormone Withdrawal in Patients with Differentiated Thyroid Carcinoma: A One Hundred Thirty-Patient Pilot Survey on Consequences of Hypothyroidism and a Pharmaco-economic Comparison to Recombinant Thyrotropin Administration. Thyroid.; 15 (10): 1147-55; 2005.
9. **Serhal DI, Nasrallah MP, Arafah BM.** Rapid rise in serum thyrotropin concentrations after thyroidectomy or withdrawal of suppressive thyroxine therapy in preparation for radioactive iodine administration to patients with differentiated thyroid cancer. J Clin Endocrinol Metab. Jul;89 (7):3285-9; 2004.
10. **Schroeder PR, Haugen BR, Pacini F, Reiners C, Schlumberger M, Sherman SI, et al.** A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. J Clin Endocrinol Metab. ; 91 (3):878–84; 2006.
11. **Mazzaferri EL.** Radioiodine and other treatments and outcomes. In: Braverman LE, Utiger RD, Ingbar SH, Werner SC. Werner and Ingbar's the thyroid: a fundamental and clinical textbook, 8th ed. Philadelphia: Lippincott- Williams, Wilkins.; 904–929; 2000.
12. **Liel Y.** Preparation for radioactive iodine administration in differentiated thyroid cancer patients. Clin Endocrinol (Oxf).;57:523–527; 2002.
13. **Chow SM, Au KH, Choy TS, Lee SH, Yeung NY, Leung A, et al.** Health-related quality-of-life study in patients with carcinoma of the thyroid after thyroxine withdrawal for whole body scanning. Laryngoscope. Nov; 116 (11) :2060-6; 2006.
14. **Canaris GJ, Steiner JF, Chester Ridgway E.** Do Traditional Symptoms of Hypothyroidism Correlate with Biochemical Disease? J Gen Internal Med.;12:544-550; 1997.
15. **Schlumberger MJ.** Papillary and follicular thyroid carcinoma. N Engl J Med.; 29:297–306; 1998.
16. **Klain MRM, Leboulleux S, Baudin E, Schlumberger M.** Radioiodine therapy for papillary and follicular thyroid carcinoma. Eur J Nucl Med Mol Imaging.; 29(suppl 2):S479–S85; 2002.
17. **Meier DA, Brill DR, Becker DV, Clarke SE, Silberstein EB, Royal HD, et al.** Procedure guideline for therapy of thyroid disease with 131iodine. J Nucl Med.;43:856–861; 2002.

18. **Singer PA, Cooper DS, Daniels GH, Ladenson PW, Greenspan FS, Levy EG, et al.** Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch Intern Med.; 156:2165–2172; 1996.
19. **Rosário PWS, Vasconcelos FPJ, Cardoso LD, Lauria MW, Rezende LL, Padrão EL, et al.** Managing Thyroid Cancer Without Thyroxine Withdrawal. Arq Bras Endocrinol Metab.;50 (1):91-96; 2006.
20. **Grigsby PW, Siegel BA, Bekker S, Clutter WE, Moley JF.** Preparation of Patients with Thyroid Cancer for 131I Scintigraphy or Therapy by 1–3 Weeks of Thyroxine Discontinuation. J Nucl Med.; 45:567–570; 2004.
21. **Golger A, Fridman TR, Eski S, Witterick IJ, Freeman JL, Walfish PG.** Three-week thyroxine withdrawal thyroglobulin stimulation screening test to detect low-risk residual/ recurrent well-differentiated thyroid carcinoma. J Endocrinol Invest.; 26:1023–1031; 2003.
22. **Chow SM, Choy TS, Morris CG, Kwan CK, Poon PCM, Shek CC, et al.** Factors Affecting Endogenous Thyroid-stimulating Hormone Rise after Thyroxine. Withdrawal in Preparation for I-131 Whole-body Scan for Patients with Diferentiated Thyroid Carcinoma. J HK Coll Radiol.; 10:3-8; 2007.