Original Article

Randomised controlled trial of one week strict low-iodine diet versus one week non-specified low iodine diet in differentiated thyroid carcinoma

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ABSTRACT

Introduction: A low iodine diet (LID) is recommended prior to the Radioactive Iodine-131 (RAI) treatment or scanning in differentiated thyroid carcinoma (DTC) post total thyroidectomy. However, recommended strictness of LID is varying among major guidelines. This study was aim to investigate the patient's compliance to LID by measuring the urinary iodine level post LID.

Methods: A total of one hundred and four patients of DTC post total thyroidectomy patients that were planned for treatment or scanning were enrolled into the study. 55 patients are subjected to 1-week strict LID while the other 49 patients are subjected to 1-week non-specified LID before RAI administration. Baseline urinary iodine level were obtained prior to the LID and second urinary iodine level were measured at day-8 or prior to RAI administration.

Results: The compliance rate of patients that achieved urinary iodine level less than 100ug/L following 1-week strict LID was 89.1% as for the 1-weeks non-specified LID was 91.8% which did not show any significant difference between the two LID group (p=0.746). After 7 days institution of non-specified LID, the mean urinary iodine level was significantly reduced about 40.8% compared to strict LID (36.3%).

Conclusion: The 1 week of non-specified LID is effective enough to decrease the urinary iodine level in low iodine intake area and the longer duration of LID is more hindrance for the patient to comply.

Key words: Differentiated thyroid carcinoma; Low iodine diet; Urinary iodine level

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INTRODUCTION

A temporary low-iodine diet (LID) prior to radioactive iodine (RAI) ablation or diagnostic whole-body scan (WBS) is generally recommended [1]. Study by Pluijmen et al. recommended a low iodine diets with dietary iodine uptake of less than 50 μg/day and as well as simple recommendation to avoid iodine exposure like iodine containing medication prior to RAI therapy in order to increase the effective radiation dose [2].

Without LID, the iodine pool in the thyroid and body may interfere with the radioiodine uptake and it may reduce the effectiveness of radioiodine ablation. Other strategies to improve radioiodine uptake are by withdrawal of thyrotropin suppressant (Levothyroxine or Liothyronine) or by using recombinant human thyroid-stimulating hormone (TSH) by establishing higher TSH value [3].

The theory behind low-iodine diet is based on the simple fact that by reducing the plasma iodide concentration, it will increases the expression of the sodium iodide symporter (NIS) on both the normal and malignant thyroid [4], resulting in higher radioiodine uptake [2].

Strictness of LID prior to RAI ablation and diagnostic WBS are not well mentioned among major guidelines as described below.

I. The American Thyroid Association (ATA) Guideline 2015 recommends an LID of less than 50 mcg per day for 1 to 2 weeks before RAI ablation [3].
II. The British Thyroid Association (BTA) recommends an LID for 2 weeks before RAI ablation or therapy without mentioning the amount of daily iodine intake [5].
III. The European Thyroid Cancer Taskforce recommends an LID for 3 weeks before RAI administration without mentioning the amount of daily iodine intake [1].
IV. The American Association of Clinical Endocrinologists recommends an LID for 2–4 weeks before radioiodine scanning without mentioning the amount of daily iodine intake before I-131 treatment [1].

A variety of food listing on iodine diet restriction to achieve LID has been used. In a meta-analysis by Sawka et al. [1], they concluded that LID reduced the urinary iodine measurement, enhanced radioactive iodine uptake and possibly improved RAI treatment efficacy.

The European Association of Nuclear Medicine (EANM) Therapy Committee in 2008 recommended urinary iodine concentration less than 150-200 ug/L prior to the RAI ablation or scanning [6]. Otherwise, they suggest for postponement of RAI therapy if the reading of urinary simple iodine concentration is higher.

Factors that plays a major role in determining the duration and strictness of LID are the locality (whether in an iodine-sufficient or iodine- deficient areas) and the patients' lifestyle [7].

This study is aimed to assess the effectiveness of LID of different strictness in reducing urinary iodine level less than 100ug/L in the preparation of RAI ablation or diagnostic WBS in DTC.

METHODS

This randomized controlled trial study was conducted in the Department of Nuclear Medicine, Radiotherapy and Oncology, Hospital Universiti Sains Malaysia (USM). The study participants included patients who has DTC and preparing for RAI ablation or diagnostic WBS. The inclusion criteria for the study are all DTC patients including newly diagnosed with DTC and those who had prior RAI ablation or with residual disease for the RAI ablation or diagnostic WBS. They had undergone total thyroidectomy or near total thyroidectomy and withdrawal Levothyroxine (LT4) for 4 weeks prior to the therapeutic RAI or scanning. Patients who were pregnant, underlying renal impairment, recent history of intravenous contrast (about 6-8 weeks prior) or on iodine-containing drugs (eg : cough medicine, vitamin supplements containing iodine, amiodarone) were excluded from the study.

Sample size was calculated using repeated measure ANOVA formula using STATA software. The type 1 error (α) was set as 0.05 and power as 80%. The mean difference of urinary iodine level post 1-week LID was 26.7ug/L (SD 19.5) based on previous study [7].

Based on calculation, minimum sample size required for this study was 39 respondents. With additional of 30% drop out, total respondent become 57 respondents for each group. A total of 110 patients were included in the study. Six patients were excluded from the study due to default in treatment.

Simple random sampling of differentiated thyroid cancer patients who fulfills the inclusion criteria was used for the sampling method. We selected a group of samples/subjects from a larger group of differentiated thyroid carcinoma patients, preparing for RAI ablation or diagnostic WBS. Selected subjects were randomly grouped to 1-week strict LID or 1 week's non-specified LID group.

Random allocation of the recruited subjects was attempted using random numbers generated by the computer generated software. A written consent form was signed voluntarily for participation in this study without obligation. Our research was approved by the Human Research Ethics Committee of Universiti Sains Malaysia, serial number USM/JEPeM/15030097.

For strict LID, patients are given a 7-days sample menu of estimated iodine contain less than 50mcg per day which specifically prepared by dietician. They are also given list of foods that are not allowed to take. For non-specified LID, patients are informed about foods that are allowed and not allowed, and are given list of foods that not allowed to take and written instruction for LID 7 days prior to RAI ablation or diagnostic WBS. The iodine contains are not specified as long as patient's compliance to the list given.

RESULTS

A total of 104 patients fulfilling the inclusion criteria were included in this study. 55 patients had undergone 1-week strict LID and 49 patients undergone 1-week non-specified LID. Patient characteristics involved in the study were summarized in Table 1.

Majority of differentiated thyroid carcinoma patients in this study were female 91.3% and 8.7% were male (Table 1). The mean age was 43.2±13.6 years old with minimum age of 9 and maximum age of 77 years old. Malay ethnicity comprises majority of the cases at 92.3% in comparison to other races 7.7%.

In this study, most of the patients had papillary thyroid carcinoma. It is the main histology type comprises 80.8% of the cases and the remaining are of follicular histology type 19.2% (Table 1). 48 out of 104 cases were newly diagnosed differentiated while the rest were either case with residual or recurrent disease. Those patients that received the radioiodine are either for diagnostic WBS (67.3%) or RAI ablation on therapy (32.7%).

Three quarter of the patients (76.9%) have baseline urinary iodine level less than 100 ug/L (80) and 24 (23.1%) of them showed urinary iodine level greater than 100 ug/L (Table 2).

Table 3 showed that there was no significant association between the socio demographic factors (including gender, age, histology and stage) with urinary iodine level among the two iodine restricted diet groups (ρ-value > 0.05).

Table 4 showed that there is no significant difference in effect of LID in achieving urinary iodine level less than 100ug/L between 1-week strict LID or 1-week non-specified LID. In general, 91.8% of patients on 1-week non-specified LID has no difference in compliance compared to the 1-week strict LID (89.1%) in achieving urinary iodine level less than 100ug/L.

Table 1: Demographic data (n=104).

Characteristics		Frequency (n)	Percentage (%)
Gender	Male	9	8.7
	Female	95	91.3
Age	Below 45	49	47.1
	45 and above	55	52.8
Ethnic	Malay	96	92.3
	Chinese	7	6.7
	Others	1	1.0
Histology	Papillary	84	80.8
	Follicular	20	19.2
Type of cases	New cases	48	46.2
	Old cases	56	53.8
Procedure	Therapeutic RAI	34	32.7
	Diagnostic WBS	70	68.3
Stage	Below 45		
	Stage I	34	32.7
	Stage II	15	14.4
	Above 45		
	Stage I	18	17.3
	Stage II	10	6.6
	Stage III	7	6.7
	Stage IVa	6	5.8
	Stage IVb	-	-
	Stage IVc	14	13.5

Table 2: Distribution of baseline urinary iodine level among the DTC patients in both group of LID (n=104).

Baseline urinary iodine level	1-week strict LID		1-week non-specified LID		Total
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)	n (%)
Below 100 ug/L	42	40.4	38	36.5	80 (76.9)
100 ug/L and above	13	12.5	11	10.6	24 (23.1)

Table 3: Association between socio demographic factors among the DTC patients on both group of LID (n=104).

Characteristics		Frequency (n)	Percentage (%)	p-value
Gender	Male	2 (3.6)	7 (14.3)	0.08 *
	Female	53 (96.4)	42 (85.7)	
Age	Mean (SD)	43.3 (13.73)	41.69 (16.74)	0.591**
Histology	Papillary	42 (76.4)	42 (85.7)	0.227***
	Follicular	13 (23.6)	7 (14.3)	
Stage	Below 45			0.84*
	Stage I	19 (70.4)	15(68.2)	
	Stage II	8 (29.6)	7 (31.8)	
	Above 45			
	Stage I	9 (32.1)	9 (33.3)	
	Stage II	6 (21.4)	4 (14.8)	
	Stage III	3 (10.7)	4 (14.8)	
	Stage IVa	4 (14.3)	2 (7.4)	
	Stage IVb	-	-	
	Stage IVc	6 (21.4)	8 (29.6)	

*Fisher's exact test; ** Independent T test; *** Pearson Chi-square

Table 4: The effect of LID on urinary iodine level in achieving <100ug/L between both groups (n=104).

Urinary iodine level <100ug/L	1-week strict LID n (%)	1-week non-specified LID n (%)	p-value
Yes	49 (89.1)	45 (91.8)	0.746*
No	5(10.9)	4(8.2)	

*Fisher's exact Test: significant when p<0.05

After 7 days post institution of non-specified LID, the mean urinary iodine was significantly reduced to 63.8 ug/L form the baseline of 107.8 ug/L which showed about 40.8% of reduction compared to strict LID with only 36.3% reduction after 1-week strict LID (Table 5).

As expected, there is significant difference in mean difference of urinary iodine level in baseline and after institution of LID in both groups (Table 6).

Table 7 showed no significant difference in mean difference of urinary iodine level post institution of LID between both groups (p-value 0.634).

DISCUSSION

Nuclear Medicine, Radiotherapy and Oncology Department of Hospital USM is the primary center that provides RAI treatment and diagnostic WBS for differentiated thyroid carcinoma in east coast part of Peninsular Malaysia. Hence, the data obtained from this study revealed the general overview of the socio demographic profile of DTC in east coast region. Malay ethnicity constituted majority of the number of patients recruited in this study as they form the majority of the citizens in Kelantan.

Table 5: Comparison of mean urinary level iodine between baseline and after institution of LID in both groups.

Urinary iodine sample	1-week strict LID	1-week non-specified LID
	Mean (SD) ug/L	Mean (SD) ug/L
Baseline	89.24 (69.2)	107.8 (69.04)
Second sample*	56.85 (50.07)	63.82(51.21)

* Second sample – taken on day -8 post institution of LID

Table 6: Mean difference of urinary iodine level in comparison to baseline and after institution of LID in both groups.

Comparison	1-week strict LID			1-week non-specified LID		
Baseline – 1 week	Mean difference	(95% CI)	p-value*	Mean difference	(95% CI)	p-value *
(day 8)	32.38	(12.37, 52.32)	0.002	43.98	(20.7, 67.3)	<0.001

*Repeated measured ANOVA: significant when p<0.05

Table 7: Mean difference of urinary iodine level post institution of LID in between 2 groups.

Comparison	Mean difference	(95% CI)	p-value*
1-week strict LID – 1-week non-specified LID	3.84	(12.10, 19.78)	0.634

*Repeated measured ANOVA: significant when p<0.05

For this study, majority of the cases recruited are female and older than 45 years old. 91.3% of patients were female and 52.8% of the patients were 45 years and above of age. All these findings show similar trend to the data obtained from the National Cancer Registry, 2006 as shown below (Figure 1) [8].

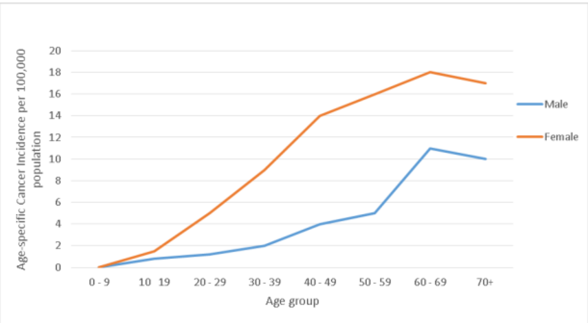

Fig 1. Thyroid Age Specific Cancer Incidence per 100,000 population by sex, Peninsular Malaysia 2006 [8].

Eighty percent of the patients had papillary thyroid carcinoma, which the most frequent type of DTC [9]. However, this study did not show significant association between socio demographic factors and urinary iodine level among DTC patients on LID.

Unlike the study done by Gilliland et al. [10], which shows that the demographic characteristics listed in this study has an important prognostic role in DTC patients. However, findings in one population can be generalized to other populations is not known. In general, findings have been inconsistent, possibly as a result of bias introduced by the use of institution-based patient series, the heterogeneous distributions of histologic types among the series and differences in follow-up measures and histologic classification of disease.

According to the World Health Organization (WHO), adequate iodine intake is defined by median urinary iodine concentration of 100-199 ug/L. A cross-sectional school-based study by Selamat et al. [11] among school children aged 8-10 years old on iodine status in states of Malaysia reported that low iodine intake area was more marked in six states of Peninsular Malaysia which includes Kelantan. Others were Kedah, Penang, Perak, Pahang and Terengganu where median urinary iodine level range between 68 to 88 ug/L. The finding is similar to our study finding of median urinary level ranging from 81 to 97 ug/L in the recruited patients which mainly from Kelantan. The study also stated overall prevalence of urinary iodine below 100ug/L in the six states were more than 50%. The finding is comparable with our study as about 70% of patients recruited into this study have baseline urinary iodine level of less than 100ug/L. And they are included in the study as no previous study on LID prior to RAI ablation and diagnostic WBS done in iodine-deficiency area.

American Thyroid Association (ATA) Guideline 2015 recommends iodine intake less than of <50 mcg/day for 1–2 weeks before RAI ablation, particularly for those patients in high iodine intake areas [3]. Iodine intake varies depending on the location and lifestyle or diet patterns of the patients [7]. The strictness of LID can have a significant impact on patients' quality of life and as a consequence, patients have difficulty to comply with.

As Kelantan and other East Coast states (Terengganu and Pahang) are considered as iodine-deficient area, it is assumed that the duration of 1-week LID is enough and sufficient to achieve low urinary iodine level. However, the strictness of LID is undetermined as no previous study done in the iodine-deficient area. 55 recruited patients underwent 1-week strict LID and 49 patients underwent 1-week non-specified LID.

For 1-week strict LID, our 7-day sample menu specifically designed by dietician with daily iodine intake of less than 50 mcg as recommended by the major guidelines [12]. The menu gives a rough estimate on how much amount can a patients consumed in a meal. The diet menu is quite strict for patient to follow and comply with. The sample menu was explained in detailed by nurses or dietician to the patients and they also were given a diet list of food that they should avoid during the preparation. While for the 1-week non-specified LID group of patients, they were given verbal instruction and list of food that should be avoid prior to the RAI therapy or scanning.

There are 2 main ways in which urine can be collected for iodine measurement which are; 24-hours urine collection and spot urinary sample. 24-hours urine collection is a highly accurate in measuring urine iodine intake and excretion [7]. Spot urine sample is quantified in relation to urinary creatinine excretion (iodine/creatinine ratio) [13]. Two main methods to determine urinary iodine level which are simple method using microplates on the basis of the Sandell-Kolthoff reaction or inductively-coupled plasma mass spectrometry. Inductively-coupled plasma mass spectrometry method considered the most accurate for measuring urinary iodine, and often taken as the reference method by the Centers for Disease Control and Prevention (CDC) [13]. For our study, spot urinary iodine were measured using urine iodine micromethod (UIMM) recommended by Hussain, Khalid [14]. UIMM is a combination of WHO (2001) reference method and method by Ohashi et al. [15] which using microplates by a modification of the Sandell-Kolthoff reaction.

Based on this study, 90% of patients had urinary iodine level less than 100ug/L after consuming the prescribed LID in both groups. The effectiveness of urinary iodine level reduction as slightly better in 1-week non-specified LID (40.8%). This could be due to the fact that a stringent diet menu may result in difficulty to follow and result in decline in compliance. However, there was no significant different in both groups. Based on this study, 90.4% (94) of patients instructed to follow LID prior to the RAI therapy and diagnostic WBS procedure, showed reduction of urinary iodine level below 100ug/L. The finding is comparable with systematic review by Sawka et al. [1]. The review reported that urinary levels were significantly reduced after LID (duration ranging from 5 days to 4 weeks) compared to baseline. From our study, after 7 days institution of non-specified LID, the mean urinary iodine level was significantly reduced to 63.8 ug/L from the baseline of 107.8 ug/L, which showed about 40.8% of reduction compared to strict LID with only 36.3% reduction. This shows that in an iodine-deficiency area, non-stringent LID is sufficient to achieve urinary iodine level less than 100 ug/L. A stringent diet menu is not the best solution to reduce the level of urinary iodine required in a patient as the process may be inconvenient for the patient to follow and further resulting decline in compliance. Hence, 1-week non-specified LID is sufficient to reduce urinary iodine level to less than 100ug/L.

Comparison of mean difference of urinary iodine level post institution of LID in between the 2 groups (1-week strict LID versus 1-week non-specified LID) showed no significant difference with p-value of 0.634. These signify that there is no difference in 1-week strict LID and 1-week non-specified LID in reducing the urinary iodine level to less than 100ug/L.

Since there was no significant difference in percentage in reducing urinary iodine level less than 100 ug/L in both groups and no significant difference in mean difference urinary iodine level before and after institution of LID in both group, a less strict LID is sufficient enough to achieve targeted urinary iodine level especially in low iodine intake areas. From the above result, we can conclude that even 1 week of non-specified LID is enough to reduce the urine iodine level less than 100ug/L.

For future study, we would like to suggest to study the effect of the two diet methods in the regions with sufficient iodine diets as the current study done only in iodine-deficient regions. It would be interesting to evaluate the post therapy images outcome of the two diet methods even though there is no significant difference in mean difference of urinary iodine level before and after institution of LID in both group.

CONCLUSION

In conclusion, 1-week duration of non-specified LID is sufficient enough prior to the RAI therapy or diagnostic WBS to achieve urinary iodine level less than 100ug/L in iodine deficiency area. As in our study, three quarter of patients have baseline urinary iodine level less than 100ug/l which showed regular low iodine consumption among the local population. There is no significant difference in percentage in reducing urinary iodine level less than 100 ug/L in both groups and no significant difference in mean difference urinary iodine level before and after institution of LID in both groups. The stricter of LID may cause greater inconvenience to patients, difficult to comply and hence reduce the compliance to the low iodine diet.

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