Clinical Significance of Diffuse Hepatic Uptake on Post-Therapeutic ^{131}I-Whole Body Scan in Differentiated Thyroid Cancer

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ABSTRACT

Background: Differentiated thyroid cancers (DTC) are among the most curable cancers, with a 10-year survival rate of 80–95%. These patients are treated by radio-iodine ablation (RAIA). Post-therapy whole body scan (Rx WBS) is done 5-7 days after RAIA. Diffuse hepatic uptake (DHU) in RxWBS after radioiodine remnant ablation might indicate metabolization of radioiodine-marked thyroglobulin fragments.

Objective: To analyze the diffuse hepatic uptake of ^{131}I on a post-ablative ^{131}I whole body scan by grading diffuse hepatic uptake and evaluating its clinical significance in the outcome of differentiated thyroid cancer (DTC).

Patients and Methods: This is a prospective cohort study conducted in the thyroid division of the National Institute of Nuclear Medicine and Allied Sciences (NINMAS). A total of 67 low- and intermediate-risk groups of differentiated thyroid carcinoma (DTC) patients who were referred to the thyroid division for radio-iodine ablation after thyroidectomy were chosen for the study. Analysis of Rx WBS images was done. DTC patients were divided according to visually graded diffuse hepatic uptake or no hepatic uptake and followed up for one year. Follow-ups were done by measuring Tg and TgAb and doing high-resolution ultrasound (HRUS) of the neck. One year later, a diagnostic whole-body scan was done. Outcomes were disease-free (DF) conditions, persistent disease (PD), or recurrence.

Results: Out of 67 patients, low-risk DTC was diagnosed in 32 and intermediate-risk in 35 patients. No high-risk group was included in this study. Two groups of patients were created: DHU and those with no hepatic uptake. Out of them, 48 patients had DHU. These findings and clinical data were compared and analyzed using SPSS, and a significant association (P = 0.40) was found between different doses of ^{131}I administered for ablation and DHU. Age, histopathological type, lymph node involvement, ALT level, thyroid bed uptake, and fatty liver were found to be insignificant when compared with DHU. After 1 year of follow-up, 52 (76.6%) patients were disease-free (DF), and persistence disease (PD) and recurrence were present in 10 (14.9%) and 5 (7.5%) patients, respectively. Among DF patients, DHU was present in 79.2% of patients. The comparison of DHU and the outcome of the DTC showed an insignificant p value of 0.640.

Conclusion: The ablative dose of ^{131}I greater than 100 mCi had a positive relationship with DHU, which might be due to radiolabeled hormones. There was no significant association between DHU and the uptake in the thyroid bed, Tg values, age, stage of the disease, presence of local or distant metastases, recurrence, or survival.

Keywords: Diffuse Hepatic Uptake, Post-therapeutic ^{131}I Whole Body Scan, Differentiated Thyroid Cancer

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INTRODUCTION

Thyroid cancer is one of the most common endocrine malignancies around the world. Differentiated thyroid carcinoma (DTC), arising from thyroid follicular epithelial cells, accounts for around 90% of all thyroid cancers. Papillary thyroid cancer accounts for around 85% of all differentiated thyroid carcinomas (1).

In DTC, the prognosis is usually very good, although the outcome depends on the stage of the disease, the time of onset, as well as factors such as age, grade, size, extension, distant metastasis, and low recurrence versus high-risk groups (2). About 5–23% of DTC patients suffer from persistent or recurrent disease, which is a leading cause of death in these cases (3).

DTC patients of different risk groups are treated by thyroidectomy followed by radioactive iodine ablation (RAIA) with TSH suppressive therapy and lifelong follow-up (4). Doctors use serial thyroglobulin (TG) monitoring to check for the recurrence of thyroid cancer following surgery. An initial and exact way to determine the outcome of DTC patients is still lacking.

Post-therapy whole body scan (RxWBS) is usually 5-7 days after RAIA (3). RxWBS detects remnant thyroid tissue, occult metastatic foci (if any), and also evaluates the avidity of known lesions (5). Diffuse hepatic uptake (DHU) is commonly seen in RxWBS but not in diagnostic whole-body scans (DxWBS) (6, 7). DHU in RxWBS has been an interesting research topic for many years. However, a higher administered dose of radioiodine inducing the metabolism of radiolabeled hormones in the liver and allowing visualization might be a possible explanation (8).

Previous research has linked hepatic uptake to the metabolism of thyroglobulin (Tg) produced by differentiated thyroid cancer cells. The clinical importance of DHU in ^{131}I is still uncertain (9). Liver metastases do not resemble this diffuse pattern of liver uptake; these lesions are typically discrete in nature (10, 11). Some studies reported that DHU is related to ^{131}I-labeleded thyroid hormones, especially Thyroxin (11). It has been suggested that tissue binding of ^{131}I-labeled iodoprotein causes diffuse hepatic uptake of Rx WBS. Large protein molecules and their complement of bound hormones can pass through the hepatic sinusoids, which are seen as huge gaps. These results suggest that diffuse liver activity could be caused by products originating from thyroid tissue remnants. Iodoprotein will be generated as a byproduct of ^{131}I radiation-induced tumor cell destruction. This suggests that high grades of thyroid bed uptake and liver bed uptake could indicate a successful ablation (12, 13). The degree of DHU may be a good indicator of the prognosis and survival without recurrence for the patient.

The aim of this study was to determine the frequency of DHU in DTC patients attending NINMAS and its clinical significance.

PATIENTS AND METHODS

A prospective cohort study was carried out in the thyroid division of the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), BSMMU campus, Shahbag, Dhaka, from September 2020 to December 2021 as an accomplishment of an MD (residency) degree in nuclear medicine at Bangladesh Sheikh Mujib Medical University (BSMMU). Ethical approval was obtained from the Medical Ethical Committee (MREC) of NINMAS. The objectives and procedure of the study were informed to the study subjects, and informed written consent was collected from each of the participants chosen for the study.

Study procedure:

1. Total of 67 DTC patients of low and intermediate risk groups (according to AJCC 8th edition, 2017) were included as study subjects who were referred to NINMAS for RAIA after total or near total thyroidectomy.
2. All patients underwent initial post-operative and pre-therapeutic evaluations (liver function tests, postoperative serum thyroglobulin (Tg), anti-thyroglobulin antibody (TgAb), and high-resolution ultrasound (HRUS) of the neck), including thorough counseling and detail.
3. A post-therapy whole-body scan was done on the 5th day after therapeutic administration of ^{131}I. The scans were obtained with a large field of view (LFOV) dual-head gamma camera. Anterior and posterior whole-body images were acquired with a high-energy parallel-hole collimator. A 20% window was centered on the principle photopeak of ^{131}I.
4. Image analysis: patients were divided into two groups: DHU and no hepatic uptake. DHU can be graded into 3 groups: mild uptake, moderate uptake, and marked uptake (14).

Follow up:

1. Patients were followed up for a period of one year. Disease status was updated during clinical follow-up visits with meticulous clinical examination, serum levels of FT3 and TSH, serum Tg, anti-Tg Ab, HRUS of the neck, and an abdominal ultrasound scan of patients.
2. Finally, different grades of DHU were compared with serum Tg and other related parameters.
3. The outcome of the patients was considered disease-free, persistent, or recurrent according to established DTC treatment guidelines.

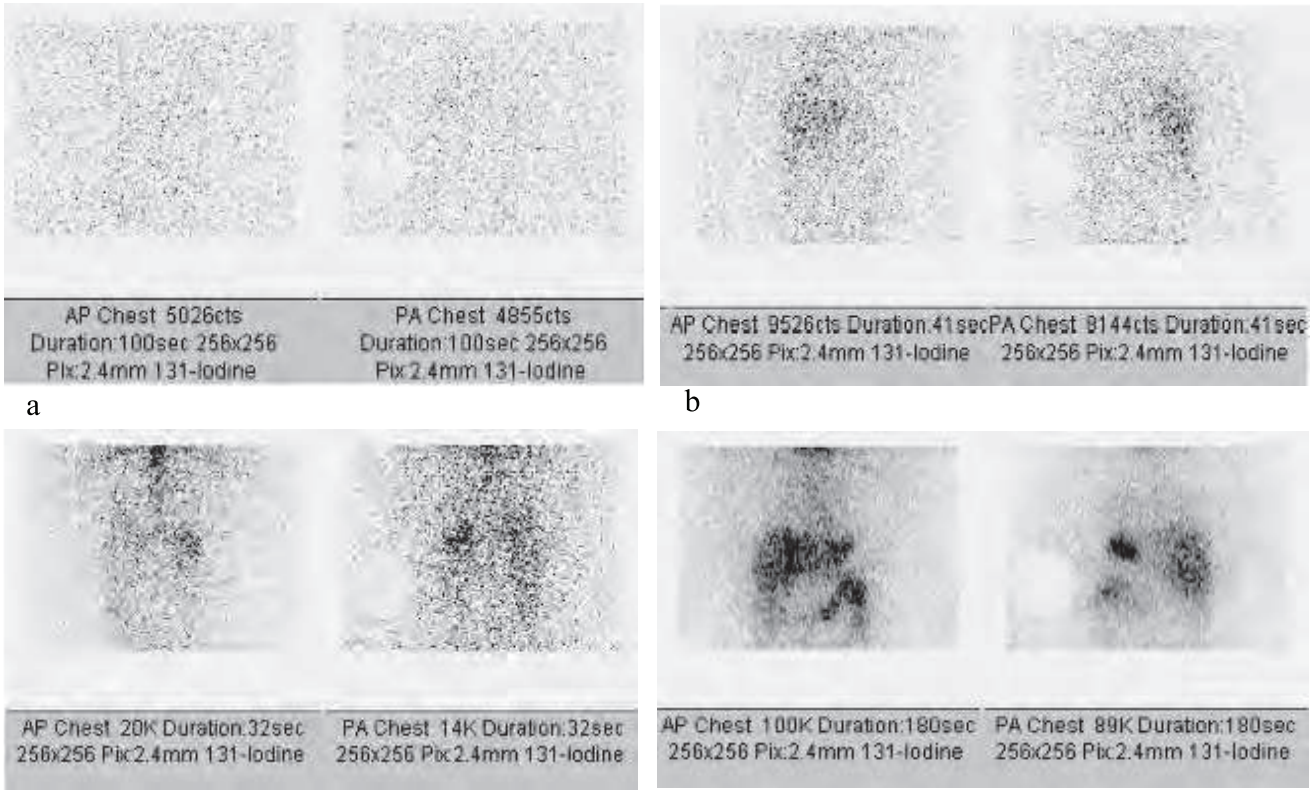

Figure 1: Different grades of Diffuse Hepatic Uptake, a) No Hepatic Uptake, b) Mild Hepatic Uptake, c) Moderate Hepatic Uptake, d) Marked Hepatic Uptake

Statistical analysis:

Statistical Package for Social Sciences version 26.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used to analyze the collected data. Frequencies and percentages were used to express the qualitative data, and means and ± deviations were used for continuous data. The chi-square test and unpaired t test are done for analysis. Fisher 's exact test was also used for qualitative data. A p-value of less than 0.05 was deemed statistically significant for all statistical tests.

RESULT

A total of 67 patients in this study, of which 89.6% were female. The mean age of DTC patients was 36.44 ± 13.14 years. 64.2% of patients were in the intermediate risk group. Lymph node involvement was present in 26.9% of patients. Out of 67 DTC patients, 56 had papillary thyroid cancer (PTC), and only one patient had follicular carcinoma.

Diffuse hepatic uptake was observed in 48 patients, while the rest of the 19 patients showed no hepatic uptake in the post-therapy whole-body scan. According to the grading of DHU, grade 1 "faint" uptake was observed in 14 patients, grade 2 "moderate" uptake in 17 patients, and grade 3 "marked" uptake in 17 patients.

Table 1: Clinical characteristics of study subjects (N=67) and its relationship with diffuse uptake of ^{131}I in post therapy whole body scan:

Patient Demography	No hepatic uptake	Diffuse hepatic uptake	p-value
Gender			
Male (10.4%)	0 (0.0)	7 (14.6)	0.079
Female (89.6%)	19 (100.0)	41 (85.4)	
Age (years)			
≤20(10.4%)	0 (0.0)	7 (14.6)	
21 – 30 (29.9%)	6 (31.6)	14 (29.2)	
31 – 40 (29.9%)	7 (36.8)	13 (27.1)	
41 – 50 (13.4%)	1 (5.3)	8 (16.7)	
>50 (16.4)	5 (26.3)	6 (12.5)	
Mean ± SD	38.95 ± 12.78	35.45 ± 13.28	0.331
Risk group			
Intermediate (64.2%)	6 (31.6)	29 (60.4)	0.033
Low (35.8%)	13 (68.4)	19 (39.6)	
Tumor histology			
Papillary Carcinoma of Thyroid (83.6%)	13 (68.4)	42 (87.5)	0.095
Follicular variant of papillary thyroid carcinoma (14.9%)	5 (26.3)	6 (12.5)	
Follicular carcinoma (1.5%)	1 (5.3)	0 (0.0)	
Focality			
Unifocal (59.3%)	14 (73.7)	26 (54.2)	0.142
Multifocal (40.7%)	5 (26.3)	22 (45.8)	
Lymph node involvement			
Present (26.9 %)	3 (15.8)	15 (31.3)	0.198
Absent (73.1 %)	16 (84.2)	33 (68.7)	

Chi-Square test and unpaired t test was done

Table 1 shows, Clinical characteristics of the patients did not show any association with diffuse hepatic uptake. Only the comparison between intermediate & low risk group showed significant p value (0.033). Total 29 patients of intermediate risk group out of 35 showed DHU.

Table 2: Association of therapeutic dose of ^{131}I with diffuse hepatic uptake (N=67)

^{131}-I (mci)	No hepatic uptake (n=19)	Diffuse hepatic uptake (n=48)	p-value
<100	13 (68.4%)	19 (39.6%)	
≥100	6 (31.6%)	29 (60.4%)	
Mean ± SD	83.7 ± 37.0	103.8 ± 34.9	0.040^{s}

Unpaired t test was done S=significant

Table 2 shows, Among the 67 patients, 35 (52.2%) patients received more than 100mCi of radio-iodine as their therapeutic dose. Out of these 35, DHU was found in 29 (60.4%) patients. Unpaired t test was done. Test showed significant p value (0.040). So, ablative dose had an association with DHU.

Table 3: Relationship of ALT level before radioactive iodine ablation and hepatic uptake of ^{131}I on post therapy whole body scan

ALT level	No hepatic uptake	Diffuse hepatic uptake	p-value
High (>35 U/L)	3 (15.8%)	13 (27.1%)	0.328^{ns}
Normal (≤35 U/L)	16 (84.2%)	35 (72.9%)	

Chi-Square test was done
ns=not significant

Table-3 Shows the study evaluated the relationship with ALT level. Total 16 patients showed raised ALT level. Among them 13 (27.1%) patients showed DHU on Rx WBS. Table -3, shows DHU does not have any relationship with ALT level.

Table 4: Relationship of hepatic uptake of ^{131}I on post therapy whole body scan with thyroid bed uptake and ultrasonography (USG) of liver during 1st follow up (N=67):

Thyroid bed uptake	No hepatic uptake	Diffuse hepatic uptake	p-value
No uptake	2 (10.5)	2 (4.2)	0.680 *
Positive Uptake	17 (89.5)	46 (95.8)	
Liver Ultrasound			
Normal Study	16 (84.2%)	34 (70.8%)	0.257**
Fatty Liver	3 (15.8%)	14 (29.2%)	

*** Fisher' Exact test was Done**
**** Chi square test was Done**

Out of 67 patients, 5.9% patients with DTC showed no uptake of ^{131}I in thyroid bed in post therapy whole body scan (Table 4) with a P value of 0.680, suggesting no association of thyroid bed uptake of ^{131}I. However, different grades of fatty infiltration of liver was observed in 17 out of 67 patients. Among them DHU was detected in 14 patients. There was insignificant relationship of DHU with fatty liver.

Table 5: Association of thyroid bed uptake on post therapy whole body scan with outcome of the differentiated thyroid carcinoma patients (n =67)

	No uptake in thyroid bed	Thyroid bed uptake	p-value
Disease free	3 (75.0%)	49 (77.8%)	0.737
Persistence disease	1 (25.0%)	9 (14.3%)	
Recurrence	0 (0.0%)	5 (7.9%)	

Chi-Square test was done

Table-6: Serum Thyroglobulin level in follow up visits of study subjects (n=67) at different time intervals.

Serum Thyroglobulin	No hepatic uptake	Diffuse hepatic uptake	-value
1st follow up			
Tg<1ng/dl	5 (26.3)	19 (39.6)	0.307^{ns}
Tg>1ng/dl	14 (73.7)	29 (60.4)	
2nd follow up			
Tg<1ng/dl	15 (78.9)	42 (87.5)	0.376^{ns}
Tg>1ng/dl	4 (21.1)	6 (12.5)	
3rd follow up			
Tg<1ng/dl	14 (73.6)	38 (79.2)	0.862^{ns}
Tg>1ng/dl	5 (26.4)	10 (20.8)	

Chi square test was done
ns=not significant

The study subjects were followed up for one year. Serum Tg level did not have any association with DHU. First follow up was done after 3months of RAIA and 2nd follow after 6 months of RAIA.

Table 7: Diffuse hepatic uptake in post therapy whole body scan with outcomes (N=67)

	No hepatic uptake	Diffuse hepatic uptake	p-value
Disease free	14 (73.7%)	38 (79.2%)	0.640
Recurrence	1 (5.3%)	4 (8.3%)	
Persistent disease	4 (21.1%)	6 (12.5%)	

Chi-Square test was done

Patients with diffuse hepatic uptake in RxWBS were followed for 1 year. DxWBS was done after 1 year. With analysis of DxWBS, Tg level and other test modalities, total 5 patients showed recurrence. Among them, 4 patients showed DHU. Total 52 patients were disease free. Among 79.2% patients showed DHU. P value is insignificant. According to this, DHU did not have any role in the outcome of DTC.

DISCUSSION

Established DTC management guidelines recommend a ^{131}I whole body scan after every radioiodine therapy because of its high sensitivity in determining the extent of the thyroid remnant and detecting occult lesions (5).

The visualization of hepatic uptake on ^{131}I WBS has been reported by numerous laboratories to vary widely, from 44 to 97%. The significance of these findings has long been a source of controversy (7,15,16). However, in this study, a total of 48 (71.6%) patients showed DHU on RxWBS. This study was aimed at finding the clinical significance of diffuse liver activity with the prognosis of disease, though the time frame was short for an established statement.

Female preponderance was observed in this study with a ratio of 1:9 (M: F). A similar study reported the ratio as 1:3 (M: F) (17). This discrepancy may be explained by the fact that thyroid disease is more common in female populations, and female DTC patients met the criteria more and could participate in this study.

In this study, 83.5% of patients were below the 50-year-old age group, with a mean age of 36.44±13.14 years. Among 67 DTC patients, 64.2% were in the intermediate risk group, while 35.8% were in the low-risk category. Papillary thyroid carcinoma (PTC) was found in 83.6% of patients, and follicular variant of papillary thyroid cancer (FVPTC) was diagnosed in 14.9% of patients. Only one patient had follicular carcinoma (1.5%). Esther et al. reported that PTC represented 90% of all thyroid cancers in their study, and Lujiao et al. found 24–33% FVPTC in their study.

Patients in the high-risk group with distant metastases were not included in this study, but a number of patients (26.9%) in the intermediate-risk group had lymph node metastases. Age, sex, tumor histology, focality, and lymph node involvement were unremarkable features to play any role in the diffuse pattern of hepatic uptake of ^{131}I. However, AJCC (8th edition) risk groups had a positive correlation with DHU in RxWBS. An unpaired t test was done, and the P value was 0.033. Total of 60.4% of patients in the intermediate-risk group showed DHU. It might be due to the higher dose of ^{131}I administered to patients in the intermediate-risk group.

Statistically significant differences were found between the low-dose group (^{131}I <100 mci) and the high-dose (^{131}I >100 mci) group of DTC patients. Patients with a high ablative dose (>100 mci) showed DHU in 60.4% of patients. The ablative dose of ^{131}I had a positive correlation with DHU, showing a P value of 0.040. Some researchers found that DHU is related to the administered dose of ^{131}I (14,15). ^{131}I-labeled thyroid hormones, predominantly radiolabeled thyroxine. Thyroid hormones metabolized in the liver are excreted in the bile, and while excretion of these hormones occurs, the liver is visualized on both DxWBS and RxWBS (18).

Raised ALT levels were found in 16 patients (23.9%) out of 67, but DHU was present in 13 (27.1%) patients with no statistical significance.The relationship of DHU with different grades of fatty infiltration of the liver was assessed with abdominal ultrasound scans. Fatty liver was present in 17 (25.3%) patients. Among them, 14 patients showed DHU. An author described that DHU intensities were related to high ALT and AST levels along with fatty changes in the liver detected in USG (19). Previous authors suggested that the mechanism of DHU in patients with decreased liver function might be due to the delayed action of hepatic enzymes. A chi-square test was done to see the relationship, but the P value (0.257) was not significant. So, this study found no relationship between fatty liver and DHU in RxWBS.

Out of 67 patients, a total of four (5.9%) showed no uptake of ^{131}I in the thyroid bed on RxWBS, but two of these four showed DHU, and the P value is not significant (0.680). So, no relationship was found between DHU and thyroid bed uptake of ^{131}I. DHU and thyroid bed uptake grading was done visually, which might vary from person to person. In this study, about 49 (77.8%) patients with thyroid bed uptake were disease-free, while five patients showed recurrence. A total of three patients (75.0%) with no uptake

in the thyroid bed out of four were disease-free. Thyroid bed uptake did not have any significant relationship with the outcome of the disease.

Another author reported that DHU indicates a functioning thyroid remnant or a functioning distant metastasis (16, 20). Kim et al. stated in their studies that DHU and thyroid bed uptake of ^{131}I were significant prognostic factors. DHU suggested that thyroid tissue had been destroyed, while thyroid bed uptake of ^{131}I on RxWBS represented the remaining thyroid tissue. Thus, it implied effective therapy. Additionally, he said that a bad prognosis was predicted by increased residual ^{131}I in the thyroid bed and no hepatic absorption on RxWBS. It was reported that DHU on RxWBS without thyroid bed uptake of ^{131}I or without any evidence of metastasis might be for hidden metastasis (6). It was revealed that there is no correlation between DHU and thyroid remnants and distant metastatic foci (19).

Some research showed a significant correlation between hepatic uptake and serum Tg (15 and 21). Prasanta et al. found a weak connection with Tg by correlating with hepatic thigh ratio (HTR) and serum Tg. level.

After RAIA, patients were followed up with serum Tg level and other parameters for 1 year in this study. Tg level <1ng/ml with insignificant TgAb was thought to be disease-free for DTC patients. At first follow-up, Tg levels <1 ng/mL were found in 24 patients. Among them, DHU was present in 19 patients.

After the second follow-up, 57 patients showed a Tg level <1ng/ml, and 10 patients showed a Tg level >1ng/ml. DHU was present in 42 patients who showed a Tg level <1 ng/mL. At the end of the third follow-up, 52 patients showed a Tg level <1 ng/mL. We observed that Tg levels were decreasing, but at the end of the follow-up, five patients showed relapse. The mean Tg was increased in grade 3 patients. The serum Tg level did not have any significant p value. An author found that the intensity of DHU on RxWBS of patients with evident iodine-avid disease is correlated with a higher percentage of serum TG reduction and a subsequent better prognosis (21). In this study, at the end of one year, five out of 67 showed recurrence. Among them, four patients showed positive DxWBS, and one patient showed lymph node metastasis. PD was present in 10 patients. Among them, two patients showed a Tg level >100 ng/mL.

About 52 patients were DF at the end of one year. Among them, DHU was present in 38 patients, while no hepatic uptake was present in 14 patients. A chi-square test was done for comparison of both groups. The P value was 0.640, which was not significant. DHU did not have any significance in the outcome. DHU was a significant predictor of outcome found in several researches and some of them reported that more intense visualization of DHU might be considered as a better outcome (14), which seems contradictory to this study.

CONCLUSION

The higher ablative dose of ^{131}I may have contributed to the increased frequency and intensity of DHU in the post-therapy whole body scan. There was no correlation found between the diffuse pattern of hepatic uptake following ablative doses in patients with DTC following total thyroidectomy and the presence or absence of local or distant metastases, serum Tg levels, or uptake in the thyroid bed. This study found no connection between DHU and DTC's clinical outcome.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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