

Receipt of thyroid hormone deficiency treatment and risk of herpes zoster



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SUMMARY

Objective: Thyroid hormone (TH) has been suggested to control herpes virus gene expression and replication in neurons via epigenetics through its nuclear receptors. It has previously been shown that patients with hypothyroidism are predisposed to herpes zoster (HZ), suggesting that the TH deficiency may be a risk factor for varicella zoster virus (VZV) reactivation. The aim of this study was to test the hypothesis that TH treatment will ameliorate the complication of HZ.

Methods: This study investigated the hypothesis by enquiring into a comprehensive medical database at Kaiser Permanente Southern California (KPSC) to verify whether patients taking TH medication experience a reduction in HZ occurrence.

Results: It was shown by Kaplan–Meier analysis that hypothyroidism patients taking TH medicines had a lower risk of HZ. The fully adjusted analysis indicated that patients receiving medication for the treatment of TH deficiency exhibited a reduced risk of HZ (hazard ratio 0.60, 95% confidence interval 0.51–0.71). This lower risk of HZ was significant in all age groups except the 18–39 years cohort. In addition, female patients taking TH treatment exhibited a lower risk than their male counterparts.

Conclusions: Together these findings support the hypothesis that a constant level of TH will provide a degree of protection from contracting HZ. More studies are underway to evaluate the laboratory data for an analysis of hormonal effects on individuals.

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Introduction

Following the primary assault, varicella zoster virus (VZV) may establish a dormant state of infection within the dorsal root ganglia. Reactivation may occur decades later as herpes zoster (HZ, shingles), after the patient's initial exposure (varicella, chickenpox) (Dworkin et al., 2007). While usually a self-limited painful skin rash, shingles can be serious, with complications such as post-herpetic neuralgia (PHN), and the disease results in a significant economic burden (Blein et al., 2015). Common risk factors that may increase the chance of shingles are age older than 50 years, having a weakened immune system due to diabetes or HIV infection,

suffering stress or trauma, and undergoing cancer treatment, etc (Shafraan, 2016; Ogunjimi et al., 2015; Iglar et al., 2013; Forbes et al., 2016; Guignard et al., 2014). The relationship between thyroid hormone disruption and the pathophysiology of shingles has been mentioned previously, but this is not well-studied (Ajavon et al., 2015).

There are two forms of thyroid hormone (TH), depending on the number of iodine atoms per molecule: tri-iodothyronine (T_3) and thyroxine (T_4). These hormones are composed of two tyrosine molecules and are produced in the thyroid gland. They play significant roles in the regulation of metabolism, development, and immune responses. Common clinical complications due to TH disruptions are hyperthyroidism (caused by excess T_3 and T_4) and hypothyroidism (resulting from a hormone deficiency). Patients diagnosed with low thyroid hormones can be treated with levothyroxine, a synthetic thyroid hormone that is chemically identical to T_4 and is prescribed widely. Levothyroxine is included in the World Health Organization List of Essential Medicines, as it is one of the most important medications needed in a basic health

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system (WHO Expert Committee on the Selection and Use of Essential Medicines (19th: 2013: Geneva Switzerland) and World Health Organization, 2014).

It has been reported that thyroid hormones contribute, at least in part, to the replication and reactivation of herpes simplex virus type 1 (HSV-1), an alpha-herpes virus (Bedadala et al., 2010; Hsia et al., 2010; Hsia et al., 2011; Chen et al., 2014; Figliozzi et al., 2014; Hsia and Hsia, 2014; Chen et al., 2016). An epidemiology study at a rural medical center showed that patients with hypothyroidism were prone to shingles (Ajavon et al., 2015). The observation was based on a pilot cross-sectional analysis of existing medical records. This was the first report linking low TH to VZV reactivation and suggested that the hormone may protect patients from VZV reactivation. However, limitations impeded further discussions. For example, the National Drug Codes were not available, so it was not known whether/when the patients received TH medication. Furthermore, the cross-sectional study design was not able to disentangle the temporal relationship between TH treatment and the development of HZ.

This study was performed to test the hypothesis that TH treatment will ameliorate the complication of HZ. This was done by querying a large comprehensive database to determine whether patients taking TH medication exhibit a decreased occurrence of HZ.

Methods

Subjects

This retrospective cohort study included censored data from January 1, 2011 through December 31, 2014, followed up to June 2015. The hypothyroidism medication cohort consisted of Kaiser Permanente Southern California (KPSC) members who were age 18 years or older and diagnosed with hypothyroidism (International Classification of Diseases, Ninth Revision (ICD-9) codes 244), who received TH disorder treatment, between January 1, 2011 and June 30, 2014; the first date of diagnosis was termed the index date. The non-hypothyroidism medication cohort consisted of randomly sampled KPSC members who were free of hypothyroidism and thyroid hormone disorder treatment. The non-hypothyroidism medication cohort patients were matched for age and sex to the hypothyroidism medication patients and recruited at a ratio of 3:1. The non-hypothyroidism medication individuals were assigned the same index dates as the matching hypothyroidism medication group individuals. The subjects in both cohorts were limited to individuals with continuous membership for 1 year before their index date. Individuals with the HZ vaccine code and who had been diagnosed with HZ prior to the index date were excluded from the analysis.

Exposure

The exposed cohort was the hypothyroidism medication patients who were diagnosed with hypothyroidism and had received orders of TH disorder treatment to treat hypothyroidism (Thyroid Disorder National Drug Codes) within 30 days of the diagnosis, between January 1, 2011 and December 31, 2014.

Outcomes

The incidence of HZ was defined by ICD-9 codes 053 from the hospital, outpatient, and emergency department settings during the study period (index date to June 2015). The subjects were followed passively by medical records until the diagnosis of HZ, vaccination with the HZ vaccine, or disenrollment from the health plan, whichever came first.

Covariates

Baseline demographic characteristics recorded included age, sex, race, health care utilization, and comorbid chronic diseases. Health care utilization was defined as the number of hospitalizations, outpatient or emergency department visits within 1 year before the index date. Chronic comorbid diseases were defined as one or more diagnoses for diabetes or for heart, lung, kidney, or liver disease within 1 year before the index date. Patients could be assigned multiple conditions.

Statistical analysis

Incidence was calculated by dividing the number of HZ cases by the total number of person-years. The 95% confidence intervals (CI) were estimated assuming that the occurrence of HZ follows a Poisson distribution. The hazard ratio (HR) is the chance of having shingles occurring in the hypothyroidism patients divided by the chance of the event occurring in the individuals without a history of hypothyroidism; the HRs and 95% CI were estimated for age, sex, race, and chronic comorbid diseases using Cox proportional hazards regression models (Spruance et al., 2004). Significance was set at 0.05 based on a two-sided test. The cumulative risk was measured by the Kaplan–Meier plot (Singh and Mukhopadhyay, 2011). SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Demographic analyses

A total 13 915 hypothyroidism medication patients and 41 745 non-hypothyroidism medication individuals were included in the study, with approximately 74% women in both groups (Table 1). Compared to the non-hypothyroidism medication cohort, the individuals in the hypothyroidism medication cohort were more likely to be white and to have attended more outpatient, inpatient, and emergency department visits in the 12 months prior to the index date. The hypothyroidism medication cohort had a higher prevalence of chronic conditions/diseases such as diabetes, kidney disease, and heart disease (Table 1).

Herpes zoster incidence

There were 884 cases of HZ identified in the study. Among the hypothyroidism medication and non-hypothyroidism medication cohorts, follow-up averaged 1.4 years; the HZ incidence yielded was 8.5 (95% CI, 7.3–9.9) per 1000 person-years in the hypothyroidism medication cohort and 12.4 (95% CI, 11.5–13.3) per 1000 person-years in the non-hypothyroidism medication cohort, by univariable analysis (Table 2). Among the non-hypothyroidism medication individuals, the HZ incidence varied by several factors.

Measurement of the hazard ratio and cumulative risk

In the fully adjusted analysis, taking medication to treat a TH deficiency was associated with a reduced risk of HZ (HR 0.60, 95% CI 0.51–0.71). The reduction in risk varied according to age at the index date, sex, race, and the presence of chronic diseases (e.g., diabetes). In general, patients taking medications, regardless of their sex, exhibited a significantly lower risk of HZ in all age groups except the 18–39 years group (Table 3). Of all the chronic conditions studied, diabetic patients received the greater protection from contracting HZ while using TH medication (HR 0.59, 95% CI 0.42–0.84, $p < 0.05$; Table 3).

Table 1

Baseline characteristics of the study cohorts: hypothyroidism medication (HM) and non-hypothyroidism medication (NM)—Kaiser Permanente Southern California, 2011–2014.

Characteristic	HM (n = 13 915)	NM (n = 41 745)
Age of participants, years		
18–39	2039 (14.7%)	6116 (14.7%)
40–49	2185 (15.7%)	6553 (15.7%)
50–59	3578 (25.7%)	10 731 (25.7%)
60–69	2859 (20.5%)	8590 (20.6%)
≥70	3254 (23.4%)	9755 (23.4%)
Mean (SD)	58.1 (16.61)	58.1 (16.61)
Sex		
Female	10 344 (74.3%)	31 032 (74.3%)
Male	3571 (25.7%)	10 713 (25.7%)
Race		
White	8930 (64.2%)	21 702 (52.0%)
Black	920 (6.6%)	4584 (11.0%)
Asian Pacific Island	1195 (8.6%)	4966 (11.9%)
Native American/multiple	116 (0.8%)	420 (1.0%)
Other	520 (3.7%)	1580 (3.8%)
Unknown	2234 (16.1%)	8493 (20.3%)
Number of outpatient visits ^a		
0	1555 (11.2%)	7318 (17.5%)
1–4	6044 (43.4%)	20 663 (49.5%)
5–10	4015 (28.9%)	10 043 (24.1%)
≥11	2301 (16.5%)	3721 (8.9%)
Mean (SD)	5.7 (5.90)	4.1 (4.65)
Median (25th–75th percentile)	4 (2.0–8.0)	3 (1.0–6.0)
Number of emergency visits ^a		
0	10 377 (74.6%)	34 279 (82.1%)
1	1992 (14.3%)	5030 (12.1%)
≥2	1546 (11.1%)	2436 (5.8%)
Mean (SD)	0.6 (1.74)	0.3 (0.93)
Number of hospitalizations ^a		
0	11 786 (84.7%)	38 223 (91.6%)
1	1263 (9.1%)	2605 (6.2%)
≥2	866 (6.2%)	917 (2.2%)
Mean (SD)	0.3 (0.96)	0.1 (0.52)
Chronic conditions/diseases		
Diabetes	2562 (18.4%)	6259 (15%)
Kidney	1710 (12.3%)	3553 (8.5%)
Heart	1249 (9.0%)	2383 (5.7%)
Lung	188 (1.4%)	366 (0.9%)
Liver	452 (3.2%)	761 (1.8%)
Years of follow-up		
Mean (SD)	1.4 (0.86)	1.4 (0.85)
Median (25th–75th percentile)	1.1 (0.7–1.9)	1.1 (0.8–1.9)

SD, standard deviation. Values are presented as the number (%) of persons, unless indicated otherwise. $p < 0.001$ for all variables except age and sex, which were the matching factors.

^a Data relate to the 1-year period prior to the index date. The index date is the date the thyroid hormone was dispensed in the hypothyroidism medication cohort; this was matched for the non-hypothyroidism medication cohort.

The Kaplan–Meier plot depicting the cumulative risk of HZ in the hypothyroidism medication and non-hypothyroidism medication cohorts is given in [Figure 1](#). The number at the bottom of the figure is the number of patients at risk at the beginning of each interval for each group. The plot suggests a lower incidence of HZ in the hypothyroidism medication cohort in which the patients received TH medications than in the non-hypothyroidism medication cohort ([Figure 1](#)).

Discussion

The association between VZV reactivation and TH is unclear. The hypothesis of TH participation in viral reactivation was first

suggested in studies of HSV-1 ([Bedadala et al., 2010](#); [Hsia et al., 2010](#)). So far, there has been no comprehensive clinical study investigating the effect of TH on HSV or VZV reactivation. The study of HZ provided an opportunity to investigate the hypothesis, because the diagnosis of HZ is more accurate and inclusive, and the medical records are readily available.

The present study attempted to address the question by creating a cohort study using comprehensive health records from KPSC, which has approximately 4.2 million members. The hypothesis was that low TH increases the reactivation of VZV and that hypothyroidism patients taking TH medication maintain a better-controlled TH level, leading to a lower risk of HZ. It was anticipated that the HR comparing the risk of HZ between patients with TH medication and individuals without medicine would be close to unity. Surprisingly, the results revealed a significantly lower risk of HZ in the patients taking TH medication. In addition, this decrease was extended to hypothyroidism patients with other chronic conditions such as diabetes, an important risk factor for HZ.

It is not entirely understood why TH medications confer this advantage. Physiological studies have indicated that the TH level often fluctuates, even in healthy individuals, but is still well regulated by the hypothalamic–pituitary–thyroid axis ([Warner and Mittag, 2012](#); [Leppaluoto et al., 1998](#); [Azukizawa et al., 1976](#); [Takeuchi et al., 1974](#)). It has been postulated that a temporary hormone reduction may be sufficient to relieve the TH-mediated suppression of herpes virus gene expression, thus initiating the scenario of reactivation ([Ajavon et al., 2015](#); [Hsia et al., 2011](#); [Chen et al., 2016](#)). It is likely that TH medicines, as an external source, maintain the serum TH level at a more stable baseline, thus decreasing the influence of hormone fluctuations inside the body. The individuals not taking TH medication are more vulnerable to HZ since their TH levels are often affected by internal/external stress stimuli. It was not possible to confirm the hypothesis in this study, as laboratory data were not readily available due to the retrospective study design. The measurement of TH levels was not performed routinely for the non-hypothyroidism patients included in this study. For the hypothyroidism patients, TH levels were usually tested every 3–6 months. Therefore it was challenging to obtain the data before the onset of shingles for confirmation. A prospective investigation with regular testing of TH levels would be appropriate to answer this question.

Hypothyroidism and its treatment are very complex. Patients very often have the condition before their first diagnosis, so it is difficult to verify the time of initial complication. Furthermore, some patients suffer secondary hypothyroidism. Sometimes individuals have normal T_4/T_3 , but thyroid stimulating hormone (TSH) is high due to congenital defects or peripheral hormone resistance ([Faust and Krone, 2014](#); [Nakajima et al., 2010](#); [Maniatis et al., 2006](#); [Davy et al., 1985](#); [Brescia et al., 2014](#); [Aoki et al., 2007](#); [Khandaria et al., 1993](#)). Occasionally the recipients of TH medicine display normal laboratory values for T_4/T_3 /TSH, but still complain of symptoms related to TH deficiency. Nonetheless, the present study provided evidence that, regardless of the therapeutic phenotype/outcome of hypothyroidism, the use of TH medication was associated with a lower risk of HZ, to some extent.

This study has limitations. For example, it is not known whether the T_4/T_3 values decreased before HZ incidence. Also, the data revealed that hypothyroidism patients were associated with more chronic disorders; hence, although the differences were controlled for in the analyses, the possibility that other treatments may have had an influence on the reduced risk of HZ cannot be excluded. In addition, this study was based on the presumption that the exposed group was on appropriate replacement. It is not impossible that the exposed group may have had lower TH levels than the control group due to non-adherence or sub-optimal replacement conditions.

Table 2

Comparison of herpes zoster incidence in the study cohorts by hypothyroidism medication status, 2011–2014.

Characteristic	Hypothyroidism medication (n = 13 915)				Non-hypothyroidism medication (n = 41 745)				RR (95% CI)	p-Value
	No. of participants	No. of cases	Total No. of person-years	Incidence per 1000 person-years (95% CI)	No. of participants	No. of cases	Total No. of person-year	Incidence per 1000 person-years (95% CI)		
Age of participants, years										
18–39	2039	8	2961.19	2.7 (1.4–5.4)	6116	28	8953.5	3.1 (2.2–4.5)	0.86 (0.39–1.90)	0.716
40–49	2185	17	3243.75	5.2 (3.3–8.4)	6553	77	9872.95	7.8 (6.2–9.8)	0.67 (0.40–1.13)	0.134
50–59	3578	46	5129.1	9.0 (6.7–12.0)	10 731	203	15 193.91	13.4 (11.6–15.3)	0.67 (0.49–0.92)	0.013
60–69	2859	35	3923.2	8.9 (6.4–12.4)	8590	183	11 348.35	16.1 (14.0–18.6)	0.55 (0.39–0.79)	0.001
≥70	3254	56	3788.64	14.8 (11.4–19.2)	9755	231	13 045.97	17.7 (15.6–20.1)	0.83 (0.62–1.12)	0.225
Sex										
Female	10 344	123	14 194.04	8.7 (7.3–10.3)	31 032	565	42 814.15	13.2 (12.2–14.3)	0.66 (0.54–0.80)	<0.0001
Male	3571	39	4851.83	8.0 (5.9–11.0)	10 713	157	15 600.53	10.1 (8.6–11.8)	0.80 (0.56–1.14)	0.212
Race										
White	8930	118	12 181.63	9.7 (8.1–11.6)	21 702	437	30 054.81	14.5 (13.2–16.0)	0.67 (0.54–0.81)	<0.0001
Black	920	9	1207.95	7.5 (3.9–14.3)	4584	60	6521.45	9.2 (7.1–11.8)	0.81 (0.40–1.63)	0.555
Asian	1195	14	1647.49	8.5 (5.0–14.3)	4966	78	6867.89	11.4 (9.1–14.2)	0.75 (0.42–1.32)	0.320
Pacific Island										
Multiple	116	0	160.2	–	420	5	597.27	8.4 (3.5–20.1)	–	–
Other	520	3	704.59	4.3 (1.4–13.2)	1580	25	2285.14	10.9 (7.4–16.2)	0.39 (0.12–1.29)	0.122
Unknown	2234	18	3144.02	5.7 (3.6–9.1)	8493	117	12 088.11	9.7 (8.1–11.6)	0.59 (0.36–0.97)	0.037
Chronic conditions/diseases										
Diabetes	2562	41	3289.6	12.5 (9.2–16.9)	6259	169	8445.84	20.0 (17.2–23.3)	0.62 (0.44–0.87)	0.006
Kidney	1710	30	1924.93	15.6 (10.9–22.3)	3553	95	4645.95	20.4 (16.7–25.0)	0.76 (0.50–1.15)	0.197
Heart	1249	29	1337.22	21.7 (15.1–31.2)	2383	65	3089.84	21.0 (16.5–26.8)	1.03 (0.66–1.60)	0.892
Lung	188	6	211.98	28.3 (12.7–63.0)	366	16	453.13	35.3 (21.6–57.6)	0.80 (0.31–2.07)	0.647
Liver	452	11	545.82	20.2 (11.2–36.4)	761	21	978.19	21.5 (14.0–32.9)	0.94 (0.45–1.95)	0.865
Overall	13 915	162	19 045.87	8.5 (7.3–9.9)	41 745	722	58 414.67	12.4 (11.5–13.3)	0.69 (0.58–0.82)	<0.0001

RR, rate ratio; CI, confidence interval.

Table 3

Hazard ratio of herpes zoster in the study cohorts.

Subgroups	HR (95% CI)			
	Unadjusted	p-Value	Adjusted ^a	p-Value
All	0.69 (0.58–0.82)	<0.001	0.60 (0.51–0.71)	<0.001
Age of participants, years				
18–39	0.86 (0.39–1.89)	0.714	0.77 (0.35–1.73)	0.532
40–49	0.67 (0.40–1.13)	0.137	0.58 (0.34–0.99)	0.044
50–59	0.67 (0.49–0.93)	0.015	0.58 (0.42–0.80)	0.001
60–69	0.56 (0.39–0.80)	0.002	0.50 (0.34–0.72)	0.000
≥70	0.83 (0.62–1.12)	0.223	0.71 (0.53–0.95)	0.023
Sex				
Female	0.66 (0.54–0.80)	<0.001	0.59 (0.48–0.72)	<0.001
Male	0.80 (0.56–1.13)	0.204	0.69 (0.48–0.98)	0.040
Race				
White	0.67 (0.54–0.82)	<0.001	0.62 (0.50–0.76)	<0.001
Black	0.81 (0.40–1.64)	0.560	0.69 (0.34–1.41)	0.310
Asian Pacific Island	0.75 (0.42–1.32)	0.322	0.73 (0.41–1.30)	0.283
Native American/multiple	–	–	–	–
Other	0.39 (0.12–1.31)	0.128	0.29 (0.08–1.08)	0.064
Unknown	0.59 (0.36–0.97)	0.039	0.49 (0.29–0.80)	0.005
Chronic conditions/diseases				
Diabetes	0.62 (0.44–0.88)	0.007	0.59 (0.42–0.84)	0.003
Kidney	0.76 (0.51–1.15)	0.197	0.67 (0.44–1.03)	0.067
Heart	1.04 (0.67–1.62)	0.850	0.84 (0.53–1.32)	0.439
Lung	0.80 (0.31–2.04)	0.636	0.56 (0.20–1.54)	0.260
Liver	0.95 (0.46–1.96)	0.883	0.85 (0.40–1.82)	0.683

HR, hazard ratio; CI, confidence interval.

^a Adjusted for age, sex, race, health care utilization, and chronic disease in the model.

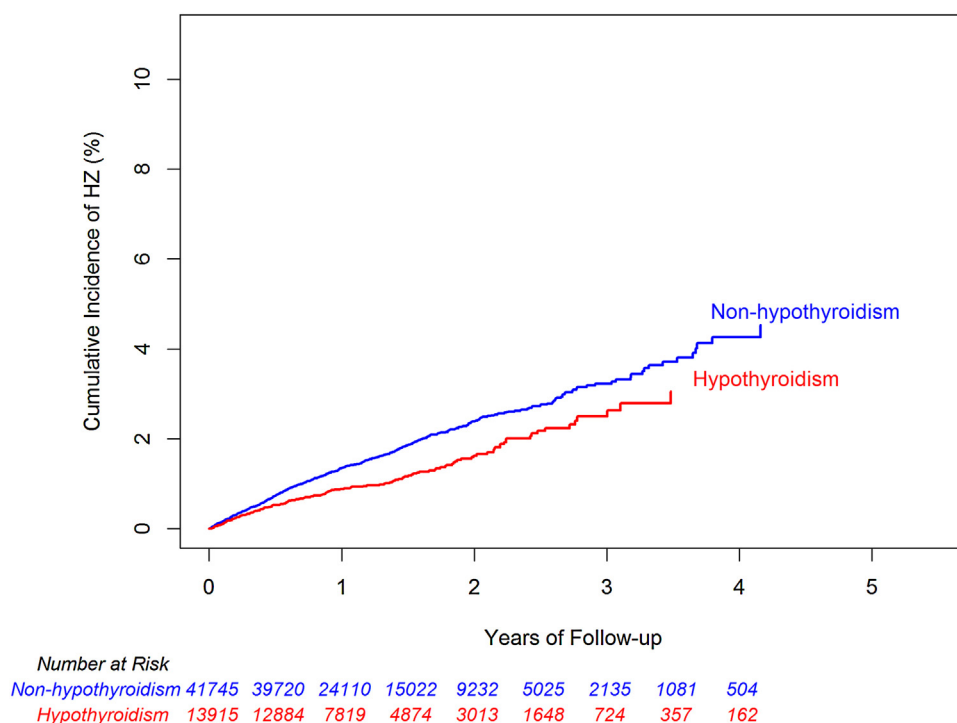


Figure 1. Kaplan–Meier estimates of the cumulative risk of herpes zoster (HZ) by hypothyroidism medication status. The cumulative risks of HZ in the hypothyroidism medication and non-hypothyroidism medication cohorts were measured by Kaplan–Meier plot analysis. This demonstrated that the hypothyroidism medication cohort, in which patients received thyroid hormone medications, exhibited a lower incidence of HZ. Non-hypothyroidism (blue line): this cohort of patients received no hypothyroidism medication. Hypothyroidism (red line): this cohort of patients received medication for the treatment of hypothyroidism. It was noted that the number at risk decreased over time; this was because the number at risk at interval ‘n’ equals the number at risk at interval ‘n – 1’ minus the occurrence of HZ and loss-to-follow up during the interval ‘n – 1’.

In conclusion, the present study evaluated the impact of TH medication on HZ occurrence through a retrospective cohort analysis examining the electronic health records from a managed care organization. The results suggest that medications usually taken for the treatment of hypothyroidism deliver an unforeseen benefit, protecting users from HZ. This may have implications for HZ prevention among individuals with hypothyroidism. The limitations of this study have been discussed and further investigations are underway to address the mechanisms of this intriguing observation.

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Ethics

This project has been reviewed by the University of Maryland Eastern Shore Institutional Review Board (IRB) and deemed exempt, category 4. Exempt studies do not require further review by the IRB.

Conflict of interest

The authors declare no conflicts of interest.

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