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Fragility Fractures in Male Veterans on Thyroid Hormone Therapy

M Papaleontiou¹, D Reyes-Gastelum¹, MR Haymart¹

¹Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

To the Editor:

One in four men over the age of 50 sustain a fragility fracture during their lifetime, leading to higher mortality rates and worse functional outcomes than women (1). Specifically, one-third of men sustaining a hip fracture will die within the following year, at a rate twice as high as women, and another one-third will fracture again (2). Whether supraphysiologic dosages of exogenous thyroid hormone have adverse skeletal effects remains controversial. Despite numerous studies suggesting an association between serum thyroid stimulating hormone (TSH) level and fracture risk in post-menopausal women, studies in men yield conflicting results (3). To examine the association between serum TSH and fragility fractures in male thyroid hormone users, we conducted a population-based, retrospective cohort study using the Corporate Data Warehouse of the Veterans Health Administration between January 1, 2004 and December 31, 2013. This study was exempt from the University of Michigan Institutional Review Board (IRB) and approved by the Ann Arbor Veteran Affairs IRB.

We included men aged ≥ 18 years on thyroid hormone therapy [thyroxine (T4) alone or liothyronine (T3)-containing preparation], without thyroid cancer, who had at least two outpatient TSH measurements following the first recorded prescription of thyroid hormone therapy. The outcome measure was incident fragility fractures. We used inpatient and outpatient ICD-9 and CPT-4 codes to identify patients who had at least one fragility fracture of the hip, pelvis, vertebra or forearm/wrist. We excluded patients with traumatic or pathological fractures. Data were censored at last TSH measurement. Multivariable generalized mixed-effects regression was used to determine factors associated with incident fragility fractures. Serum TSH measurements were assembled into a longitudinal dataset. Serum TSH was log-transformed and used as a continuous, time-varying covariate.

Among 517,024 patients, 139,657 (27.0%) had at least one TSH ≥ 0.5 mIU/L following the first recorded prescription for thyroid hormone therapy. Overall, 12,397 (2.4%) of patients

Corresponding author and person to whom reprint requests should be addressed: Maria Papaleontiou, MD, Assistant Professor of Medicine, Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, North Campus Research Complex, 2800 Plymouth Rd. Bldg. 16, 453-S, Ann Arbor, MI 48109, Phone: (734) 764-9733, Fax: (734) 936-8944, mpapaleo@med.umich.edu.

AUTHOR DISCLOSURE STATEMENT

The authors have nothing to disclose.

sustained incident fragility fractures (median follow-up, 51 months). Serum TSH was not associated with incident fragility fractures (OR, 0.99, 95% CI 0.98–1.01). Age ≥ 65 years (e.g., ≥ 85 years: OR 2.31, 95% CI 2.12–2.53; compared to <50 years), more comorbidities (e.g., Charlson/Deyo comorbidity score ≥ 2: OR 3.66, 95% CI 3.52–3.81; compared to score zero), and steroid use for longer than 3 months (OR 1.11, 95% CI 1.02–1.21; compared to ≤ 3 months) were associated with incident fragility fractures. History of osteoporosis (untreated: OR 2.17, 95% CI 1.96–2.40; treated: OR 1.40, 95% CI 1.25–1.56), and previous fragility fracture (OR 6.71, 95% CI 6.19–7.28) were also associated with incident fragility fractures (Table 1).

In this large study of male Veterans, over-replacement with thyroid hormone was common. However, contrary to several studies in post-menopausal women(3), serum TSH was not associated with increased incident fragility fractures in this cohort. As expected, the strongest predictor for sustaining a fragility fracture was a previous fragility fracture. In conclusion, despite limitations of observational studies, the lack of an independent effect of exogenous hyperthyroidism on fragility fractures in this cohort is reassuring, and provides additional data towards developing an improved risk-stratified approach when managing thyroid hormone therapy.

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Table 1.

Patient characteristics associated with fragility fractures

Characteristics	Patients with fractures N (%)	OR (95% CI)	P value
Age (years)			
<50	835 (1.97)	1.00 (ref)	
50–64	3,943 (2.41)	0.93 (0.86 – 1.00)	0.056
65–74	2,457 (1.97)	0.92 (0.85 – 1.00)	0.037
75–84	3,872 (2.65)	1.44 (1.34 – 1.56)	<0.001
85	1,290 (3.24)	2.31 (2.12 – 2.53)	<0.001
Median Household Income ^c			
<\$35,000	1,832 (2.71)	1.00 (ref)	
\$35,000 – \$59,999	7,608 (2.34)	0.96 (0.92 – 1.01)	0.155
\$60,000	2,957 (2.38)	1.00 (0.95 – 1.06)	0.933
Charlson/Deyo Comorbidity Score			
0	4,245 (1.16)	1.00 (ref)	
1	2,059 (4.35)	2.89 (2.74 – 3.05)	<0.001
2	6,093 (5.87)	3.66 (3.52 – 3.81)	<0.001
Thyroid Stimulating Hormone (TSH) ^a	3.14 (0.001 – 125.0) ^b	0.99 (0.98 – 1.01)	0.192
Androgen Use			
No	11,826 (2.42)	1.00 (ref)	
Yes	571 (2.08)	0.97 (0.89 – 1.06)	0.491
Steroid Use			
3 months	11,804 (2.36)	1.00 (ref)	
> 3 months	593 (3.31)	1.11 (1.02 – 1.21)	0.022
Known History of Osteoporosis			
No	11,247 (2.27)	1.00 (ref)	
Yes (interaction effect with)			
Osteoporosis Medication Use ^d			
No	378 (5.14)	2.17 (1.96 – 2.40)	<0.001
Yes	772 (5.29)	1.40 (1.25 – 1.56)	<0.001
Previous Fragility Fracture			
No	11,722 (2.29)	1.00 (ref)	
Yes	675 (15.83)	6.71 (6.19 – 7.28)	<0.001

^aTSH was log transformed and analyzed as a continuous, time-varying covariate for the analysis.^bTSH median and range reported in mIU/L.^cMedian household income by geographic region.^dTwo-way interaction between known history of osteoporosis and osteoporosis medication use was included in the model due to reaching statistical significance (p<0.001)

Abbreviations: OR, odds ratio; CI, confidence interval; ref, reference