LEVOTHYROXINE USE MAY BE ASSOCIATED WITH LONGITUDINAL QUADRICEPS ATROPHY AND SUBSEQUENT KNEE OA RISK: PRELIMINARY ANALYSIS FROM OAI COHORT

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Introduction and Objectives.

Levothyroxine, the primary treatment for hypothyroidism, is prescribed for more than 7% of Americans. Levothyroxine use, or the underlying hypothyroidism can be associated with musculoskeletal symptoms; however, no prior work has investigated this association using sensitive biomarkers.

We examined the association between levothyroxine use and longitudinal MRI biomarkers for thigh muscle mass and composition in participants at-risk of knee OA and their mediatory role in subsequent knee OA radiographic and symptomatic incidence.

Materials and Methods.

Thighs and knees of OAI participants without established radiographic knee OA were included. Levothyroxine users were defined as self-reported use at all annual follow-up visits until the 4th-year and were matched with nonusers for potential confounders using 1:2/3 propensity-score (PS) matching. We developed and validated a deep learning method for automated thigh segmentation and assessed the association between levothyroxine use and 4-year longitudinal changes in muscle mass, including cross-sectional area (CSA) and muscle composition biomarkers including intramuscular adipose tissue (intra-MAT), contractile percentage, and specific force (force per CSA). We further assessed whether levothyroxine use is associated with an 8-year risk of standard knee OA radiographic and symptomatic incidence. Finally, we assessed whether the association between levothyroxine use and knee OA incidence is mediated via muscle changes.

Results.

We included 1485 matched thighs/knees (387:1098 users:non-users; age: 62±9 years, female/male:3.1). Levothyroxine use was associated with decreased quadriceps CSAs (mean difference, 95%CI: -15.46mm2/year, -25.11– -5.82) but not thigh muscles' composition biomarkers. Levothyroxine use was also associated with an increased 8-year risk of radiographic (hazard ratio (HR):1.59, 1.15–2.20) and symptomatic knee OA incidence (HR:1.60, 1.12–2.29). A decrease in quadriceps CSA partially mediated the increased risk of knee OA incidence associated with levothyroxine use.

Conclusion.

Our exploratory analyses suggest that levothyroxine use is associated with loss of quadriceps muscle mass, which partially mediates increased risk of subsequent KOA incidence.

Clinical relevance.

Levothyroxine users might have increased risk of thigh muscle atrophy and subsequent KOA. Study interpretation should consider underlying thyroid function as a potential confounder or effect modifier and therefore, future studies are warranted to investigate the underlying thyroid function biomarkers for longitudinal thigh muscles atrophy and associated KOA incidence risk.

Table 1. Baseline characteristics of participants after matching according to levothyroxine use.

	Levothyroxine non-users	Levothyroxine users	
Variables in the PS-matching	N: 1098	N: 387	**SMD**
Demographic characteristics			
Age (year) [mean (SD)]	61.58 (8.97)	62.00 (8.48)	0.048
No. of women [N (%)]	850 (77.4)	302 (78.0)	0.015
Race, non-white [N (%)] †	93 (8.5)	29 (7.5)	0.036
Comorbidities and risk factors			
PASE score [mean (SD)]	158.67 (72.34)	155.99 (84.68)	0.034
BMI (kg/m^2) [mean (SD)]	27.02 (4.48)	27.20 (4.2)	0.040
Abdominal (central) obesity [N (%)] *	801 (73.0)	291 (75.2)	0.051
Waist circumference (cm) [mean (SD)]	99.11 (12.64)	99.71 (12.88)	0.047
Alcohol use, ≥1/week [N (%)]			0.081
None	176 (16.0)	64 (16.5)	
<1 drink/wk	390 (35.5)	141 (36.4)	
1-3 drinks/wk	188 (17.1)	61 (15.8)	
4-7 drinks/wk	183 (16.7)	65 (16.8)	
8-14 drinks/wk	101 (9.2)	40 (10.3)	
+15 drinks/wk	60 (5.5)	16 (4.1)	
Smoking, current or past [N (%)]	486 (44.3)	168 (43.4)	0.017
Diabetes [N (%)]	61 (5.6)	25 (6.5)	0.038
Malignancy [N (%)]	40 (3.6)	9 (2.3)	0.077
Charlson Comorbidity score [mean (SD)]	0.36 (0.87)	0.35 (0.70)	0.017
KL grade [N (%)]	338 (30.8)	116 (30.0)	0.018
Knee injury [N (%)]	185 (16.8)	76 (19.6)	0.072
Medications			
Lipid-lowering drug [N (%)]	310 (28.2)	116 (30.0)	0.038
NSAID [N (%)]	177 (16.1)	67 (17.3)	0.032
Aspirin [N (%)]	46 (4.2)	16 (4.1)	0.003
Systemic corticosteroid [N (%)]	137 (12.5)	55 (14.2)	0.051
Antineoplastic agents [N (%)]	33 (3.0)	8 (2.1)	0.060

Data are presented in numbers of knees. BMI: Body Mass Index, KL: Kellgren-Lawrence grade, NSAIDs: Non-steroidal Anti-inflammatory Drugs, PASE: Physical Activity for Elderly Scale, PS: Propensity-score, SMD: Standardized Mean Difference, SD: Standard Deviation. † Race of participants was categorized as white and non-white considering the small number of participants in each non-white race group.
* Abdominal obesity was defined as a waist circumference of ≥94 cm in men and ≥80 cm in women on physical examination according to international diabetes foundation criteria

Table 2. The association between levothyroxine use and risk of KOA radiographic and symptomatic incidence.

Outcomes	Hazard ratio (95%CI), P
KOA radiographic Incidence	**1.59 (1.15-2.2), P:0.005**
KOA symptomatic Incidence	**1.60 (1.12-2.29), P:0.01**

CI: Confidence interval, JSN: Joint Space Narrowing, Knee osteoarthritis. Cox proportional hazard model was used for analysis. Levothyroxine use, as the independent variable, was associated with an increased risk of KOA incidence over the 8-year follow-up period.

Table 3. Longitudinal changes in thigh muscle markers between PS-matched levothyroxine users vs. non-users

	Average Difference/year (95% CI), P			
	CSA (mm2)	**Intra-MAT CSA (mm2)**	**Contractile %**	**Specific strength**
Total thigh	**-19.82 (-36.23 - -3.40), P:0.018**	2.89 (-0.93 - 6.71), P:0.138	-0.03 (-0.07 - 0.01), P:0.156	–
Quadriceps	**-15.46 (-25.11 - -5.82), P:0.002**	1.92 (-0.52 - 4.37), P:0.124	-0.04 (-0.10 - 0.01), P:0.145	0.00 (-0.05 - 0.05), P:0.899
Flexors	-1.14 (-7.10 - 4.82), P:0.708	1.32 (-0.79 - 3.42), P:0.220	-0.02 (-0.09 - 0.05), P:0.562	-0.01 (-0.05 - 0.04), P:0.741
Adductors	-2.69 (-8.66 - 3.28), P:0.377	-0.28 (-1.10 - 0.53), P:0.497	-0.02 (-0.11 - 0.07), P:0.706	–
Sartorius	-0.24 (-1.19 - 0.71), P:0.621	0.01 (-0.40 - 0.42), P:0.971	-0.03 (-0.15 - 0.10), P:0.692	–

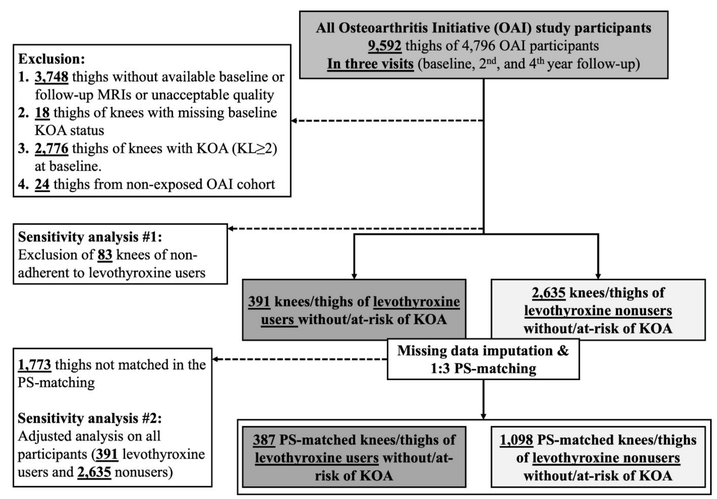
Longitudinal mixed-effect regressions were used to assess the difference in muscle biomarkers between PS-matched levothyroxine users and non-user participants. CI: Confidence interval, CSA: Cross-sectional Area, Intra-MAT: Intra-muscular Adipose Tissue.

Table 4. Mediatory role of thigh muscle MRI markers in the effect of levothyroxine use on KOA incidence.

	Mediatory variables†	Total association of levothyroxine use with KOA incidence (Through Equation 1 in Figure 2)	Direct association of levothyroxine use with KOA incidence† (Through Equation 2 in Figure 2)	Mediatory role of muscle markers in the levothyroxine KOA incidence association † (Through Equations 3a and 3b in Figure 2)
KOA incidence	**4-year changes in CSA**	**Estimate (95% CI), P**		
Radiographic	**Quadriceps**	10.908 (6.442 - 15.653), P<0.001	10.331 (5.558 - 15.108), P<0.001	**0.577 (0.210 - 1.084), P<0.001**
	Total thigh muscles	11.907 (7.110 - 16.518), P<0.001	11.845 (7.076 - 16.470), P<0.001	0.061 (-0.276 - 0.544), P:0.800
Symptomatic	**Quadriceps**	9.459 (5.285 - 13.539), P<0.001	9.217 (5.154 - 13.294), P<0.001	**0.242 (0.012 - 0.514), P:0.020**
	Total thigh muscles	9.053 (5.775 - 12.329), P<0.001	9.241 (5.860 - 12.714), P<0.001	-0.188 (-0.487 - 0.051), P:0.240

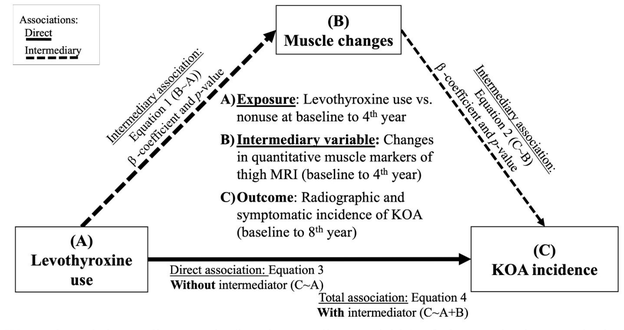
CI: Confidence interval, CSA: Cross-sectional Area, Intra-MAT: Intra-muscular Adipose Tissue, JSN: Joint space narrowing, KOA: Knee osteoarthritis.
* KOA incidence was found to be associated with levothyroxine use and were selected for causal mediation analysis. † Since mixed models could not be used in mediation analysis of R mediate package, here longitudinal changes in the muscle biomarkers were assessed as relative change index between baseline and 4th-year visits, i.e., (baseline - 4th-year)/baseline.

Figure 1. Flowchart of study selection criteria and cohorts.



KL: Kellgren-Lawrence grade, KOA: Knee osteoarthritis, PS: Propensity score.

Figure 2. Causal mediation analysis.



We evaluated the mediatory role (i.e., intermediary variable) of changes in the quantitative muscle markers of thigh (baseline to 4th year) for the association between levothyroxine use (i.e., exposure variable) and incidence of KOA (baseline to 8th year) (i.e., outcome variable).

KOA: Knee osteoarthritis

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