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Total Serum Testosterone and Western Ontario and McMaster Universities Osteoarthritis Index Pain and Function Among Older Men and Women With Severe Knee Osteoarthritis

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Objective. To investigate whether serum total testosterone level is associated with knee pain and function in men and women with severe knee osteoarthritis (OA).

Methods. We enrolled 272 adults age ≥60 years (mean ± SD age 70.4 ± 4.4 years, 53% women) who underwent unilateral total knee replacement (TKR) due to severe knee OA. Serum testosterone levels and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function of the operated and contralateral knee were measured at 6–8 weeks after surgery. At the nonoperated knee, 56% of participants had radiographic knee OA with a Kellgren/Lawrence grade ≥2. Cross-sectional analyses were performed by sex and body mass index (BMI) subgroups, using multivariable regression adjusted for age, physical activity, and BMI.

Results. At the operated knee, higher testosterone levels were associated with less WOMAC pain in men (B = –0.62, $P = 0.046$) and women (B = –3.79, $P = 0.02$), and less WOMAC disability scores in women (B = –3.62, $P = 0.02$) and obese men (B = –1.99, $P = 0.02$). At the nonoperated knee, testosterone levels were not associated with WOMAC pain in men or women, but higher testosterone levels were associated with less disability in women (B = –0.95, $P = 0.02$). Testosterone levels were inconsistently associated with pain and disability in BMI subgroups among men. Only among obese women, testosterone levels were inversely associated with radiographic knee OA (odds ratio = 0.10, $P = 0.003$).

Conclusion. Higher total testosterone levels were associated with less pain in the operated knee in men and women undergoing TKR and less disability in women. At the nonoperated knee, higher testosterone levels were inconsistently associated with less pain and disability.

INTRODUCTION

Knee osteoarthritis (OA) is the most common cause of difficulty walking in older adults (1). Thirty percent of adults will develop symptomatic knee OA by the age of 65 years and nearly 50 percent of adults will develop symptomatic knee OA by the age of 85 years, with the highest risk among those who were overweight during extended periods of their lifetime (2).

The prevalence of symptomatic knee OA increases similarly with age in women and men until age 50 years. In the second half of life, women have a significantly higher prevalence of symptomatic knee OA (3) and greater disability from knee OA than men (4,5). The sex difference in knee OA prevalence and severity in the second half of life has not been well understood (4,6). However, given that cells in knee articular cartilage, underlying bone, and surrounding muscles in men and women express receptors for both estrogen and testosterone (7,8), hormonal factors are probably involved (4,6) with a potential benefit of a greater physiologic testosterone exposure (7,9–11).

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SIGNIFICANCE & INNOVATIONS

- Among both men and women with severe knee osteoarthritis who underwent unilateral total knee replacement, higher serum testosterone levels were associated with less Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain in the operated knee, independent of age, body mass index (BMI), and physical activity.
- Among women but not men, higher serum testosterone levels were also associated with less WOMAC disability in the operated and the nonoperated knee, independent of age, BMI, and physical activity.

With regard to changes in testosterone exposure with age, testosterone levels have been shown to decrease by ~1% per year in men starting at age 40 years (12). Clinical signs of testosterone deficiency in older men are a decrease in muscle mass and strength, a decrease in bone mass, and an increase in central body fat (13). Women have 20-fold lower testosterone levels compared to men (14), and their testosterone levels also decline with age, reaching a nadir after menopause, with a decline close to 15% of their premenopausal stage (15). Although the biologic role of testosterone in women remains unclear, the sharp and rapid decline after menopause may contribute to the age-related decline in physical function among women (7,9–11,16).

With regard to studies that link testosterone levels to OA, lower serum testosterone levels have been associated with a higher prevalence of hand but not knee OA in 1 study (17). Further, a small cross-sectional study among 45 healthy middle-aged men suggested a positive association between higher serum testosterone levels and medial tibial cartilage thickness (9). In 1 larger study of 309 overweight adults age ≥60 years with knee OA, higher testosterone levels were found to be associated with less Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness among men and better WOMAC function among women (18).

With regard to pain sensitivity and potential relevance to OA, clinical and experimental investigations have consistently shown sex-specific differences for both pain sensitivity and threshold (19). Although the underlying mechanisms for these differences are not well understood, an influence of testosterone on nociceptive processing is well established (19,20). In fact, testosterone has been suggested as protecting men from chronic musculoskeletal pain conditions (21), either by a direct effect on nociceptive processing (19,20), or indirectly by an increase in muscle mass, strength, and function, as suggested by 2 clinical trials with testosterone treatment among frail and hypogonadal older men (22,23). Further potential benefits of higher physiologic testosterone levels on OA pain and function may be explained by prior data that linked higher testosterone exposure to a decrease in fat mass and inflammatory response among men (7,9–11). Further, preoperative supraphysiologic testosterone administration has been suggested to confer some early functional benefit among older men undergoing knee replacement in a small study of 25 men (24).

The aim of this cross-sectional study was to investigate a possible association between total serum testosterone levels and symptoms of knee OA with regard to pain and disability in the operated and nonoperated knee among men and women age ≥60 years who underwent unilateral total knee replacement (TKR) due to severe knee OA 6–8 weeks earlier. We chose this target population given their high risk of OA at the contralateral nonoperated knee (25,26) as well as the potential shared benefits of higher physiologic testosterone levels on pain and disability at the operated and nonoperated knee.

PATIENTS AND METHODS

Study design and participants. The current study is a cross-sectional analysis of the baseline data from the Zurich Multiple Endpoint Vitamin D Trial in Knee OA Patients (27). The original study was a 2-year, double-blind, randomized controlled trial that investigated the effect of vitamin D (2,000 versus 800 IU/day cholecalciferol) on pain and disability related to the rehabilitation of the operated knee and contralateral knee among 273 seniors age ≥60 years (mean age 70.3 years, 53% women) who underwent elective surgery for unilateral TKR due to severe knee OA. The baseline assessment took place 6–8 weeks after surgery at the Centre on Aging and Mobility at the University of Zurich, Switzerland, from October 2007 to February 2013. In the original trial, participants were not selected based on their vitamin D status, and 31.4% of participants were vitamin D deficient at baseline (27). Of 273 participants enrolled, 1 male participant was excluded due to missing data on serum testosterone concentration, reducing the analytical sample size for this study to 272 (the radiologic assessment data were only available for 270 participants). Exclusion criteria of the original trial were a history of inflammatory arthritis, chronic glucocorticoid use, a history of malabsorption disorder, kidney disease (estimated creatinine clearance <30 ml/minute), current cancer, treatment with bisphosphonate, parathyroid hormone therapy, calcitonin therapy in the 6 months prior to enrollment, severe cognitive/visual/hearing impairments, and inability to walk at least 3 meters with or without a walking aid (27). All participants gave their written informed consent, and the study was approved by the Cantonal Ethical Commission of Zurich (protocol identifier STZ 20/07), Switzerland.

Measurement of serum testosterone concentration. Fasting blood samples were taken between 8:00 and 9:30 AM. Serum concentration of total testosterone was measured by an electrochemiluminescence immunoassay (Roche Diagnostics) with an interassay coefficient of variation of 3.9% at a level of 7.3 nmoles/liter and 3.5% at a level of 18.8 nmoles/liter.

Assessment of covariates. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). BMI categories were defined according to World Health Organization guidelines as underweight (<18.5), normal weight (≥18.5 to <25), overweight (≥25 to <30), and obese (≥30). Physical activity levels were measured by an ankle-worn ambulatory activity monitor (StepWatch Step Activity Monitor), which records the number of steps taken every minute. The StepWatch monitor has been validated for use in older adults (28) and has been used to monitor physical activity in several patient groups, including patients with knee OA (29). In the current study, participants were instructed to wear the monitor during the day for 7 consecutive days. A measurement was considered valid if at least 3 days with ≥10 hours of recording were available, omitting blocks of >180 minutes of consecutive zeros, which was interpreted as device not worn. Minutes spent on moderate-to-vigorous physical activity were defined as the average minutes per day with ≥30 steps/minute according to the manufacturer's software manual (StepWatch 3.1 software manual).

Outcome measurements. *WOMAC pain and function score.* Knee pain and function (disability) of the operated and the nonoperated knee were assessed by the respective subscales of the WOMAC questionnaire. The WOMAC is a broadly validated and commonly used self-reported outcome tool for knee OA (30), including patients undergoing knee replacement (31). It consists of 24 items divided into 3 subscales: pain (5 items), stiffness (2 items), and physical function (17 items), with each item scoring on a 5-point Likert scale (none, mild, moderate, severe, and extreme). For the pain and physical function subscale, these scores were transformed to a 0 to 100 score (where 0 = no symptoms and 100 = extreme symptoms), with higher scores indicating more pain and more disability. We used a knee-specific paper-version of the German WOMAC 3.1 (32).

Radiologic assessment of knee OA at the nonoperated knee. To rate knee OA at the nonoperated knee, we performed a plain radiograph of the contralateral knee in a semiflexed weight-bearing position (we used Multicenter Osteoarthritis Study standardized radiograph assessment procedures [33]). Kellgren/Lawrence (K/L) grades were classified by a blinded knee OA radiology expert (0 = no radiographic features of OA; 1 = possible joint space narrowing and osteophyte formation; 2 = definite osteophyte formation with possible joint space narrowing; 3 = multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity; and 4 = large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone deformity) (34).

Statistical analysis. Statistical analysis was performed using SAS software, version 9.4. Distributions of continuous variables were examined for normality. Differences in baseline characteristics between men and women were analyzed using a chi-square test for categorical variables and a Student's *t*-test for continuous variables.

Associations between serum testosterone concentration and the WOMAC pain and function (disability) score were analyzed by using multivariable robust linear regression models. For

Table 1. Characteristics of participants of the Zurich Knee Osteoarthritis Trial by sex*

Characteristic	Men	Women	Sex difference *P*	Total
Subjects, no. (%)	126 (47)	146 (53)	0.25	272
Age, years	70.3 ± 6.9	70.4 ± 6.0	0.83	70.4 ± 6.4
Body mass index, kg/m^2	27.6 ± 3.8	26.9 ± 4.1	0.11	27.2 ± 3.9
MVPA, minutes/day	45.3 ± 23.4	37.9 ± 21.6	0.009†	42.3 ± 22.6
Total testosterone, nmoles/liter	13.0 ± 4.6	0.4 ± 0.4	<0.0001†	6.3 ± 7.0
Kellgren/Lawrence grade, no. (%)‡				
0	32 (56)	25 (44)	0.11	57 (21)
1	33 (53)	29 (47)	–	62 (23)
2	18 (33)	36 (67)	–	54 (20)
3	31 (42)	42 (58)	–	73 (27)
4	12 (50)	12 (50)	–	24 (9)
WOMAC pain score (0–100)				
Operated knee	23.9 ± 14.4	32.6 ± 14.4	<0.0001†	28.5 ± 15.0
Nonoperated knee	4.2 ± 8.1	5.2 ± 8.2	0.32	4.7 ± 8.1
WOMAC functional score (0–100)				
Operated knee	21.8 ± 12.6	29.2 ± 13.9	<0.0001†	25.8 ± 13.8
Nonoperated knee	2.9 ± 6.6	5.4 ± 8.9	0.01†	4.3 ± 8.0

* Data are the crude mean ± SD unless indicated otherwise. Differences between men and women were assessed by using Student's *t*-test for continuous variables and a chi-square test for categorical variables. *P* values are 2-sided; statistical significance is set at $P < 0.05$. MVPA = moderate-to-vigorous physical activity; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Statistically significant.
‡ Values refer to the nonoperated knee (n = 270).

Table 2. Cross-sectional association between blood total testosterone concentration and WOMAC postoperative pain and functional scores in seniors age ≥60 years with knee osteoarthritis by sex*

	Men: model 1		Men: model 2		Women: model 1†		Women: model 2†	
	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*
WOMAC pain score (0–100)								
Operated knee								
Total subjects (M/F)	−0.51 (−1.11, 0.09)	0.09	−0.62 (−1.23, −0.01)	0.05‡	−2.76 (−5.75, 0.23)	0.07	−3.79 (−6.90, −0.69)	0.02‡
BMI, kg/m^2§								
Normal weight	−1.25 (−2.23, −0.27)	0.013	−1.16 (−2.17, −0.15)	0.02‡	−5.67 (−11.81, 0.48)	0.07	−9.27 (−15.56, −2.98)	0.004‡
Overweight	−0.08 (−0.87, 0.72)	0.85	−0.01 (−0.81, 0.80)	0.99	−3.54 (−7.75, 0.68)	0.10	−3.88 (−8.20, 0.43)	0.08
Obese	−1.12 (−3.06, 0.82)	0.26	−1.36 (−3.54, 0.82)	0.22	0.28 (−5.07, 5.63)	0.92	1.30 (−3.62, 6.22)	0.60
$P_{interaction}$	–	0.29	–	0.38	–	0.09	–	0.01‡
Nonoperated knee								
Total subjects (M/F)	−0.01 (−0.11, 0.08)	0.77	−0.07 (−0.17, 0.03)	0.20	0.52 (−0.23, 1.28)	0.18	0.42 (−0.55, 1.38)	0.39
BMI, kg/m^2§								
Normal weight	−0.27 (−0.54, 0.00)	0.050	−0.39 (−0.68, −0.10)	0.009‡	−0.08 (−1.10, 0.94)	0.88	0.05 (−1.43, 1.54)	0.94
Overweight	0.0007 (−0.10, 0.10)	0.99	0.003 (−0.12, 0.13)	0.97	0.73 (−0.45, 1.91)	0.22	0.73 (−0.70, 2.16)	0.32
Obese	−0.63 (−1.29, 0.03)	0.06	−0.33 (−0.90, 0.24)	0.25	−0.73 (−4.98, 3.53)	0.74	0.69 (−3.51, 4.90)	0.75
$P_{interaction}$	–	0.18	–	0.14	–	0.51	–	0.88
WOMAC functional score (0–100)								
Operated knee								
Total subjects (M/F)	−0.01 (−0.53, 0.51)	0.97	−0.11 (−0.66, 0.44)	0.70	−3.57 (−6.53, −0.61)	0.02‡	−3.62 (−6.65, −0.58)	0.02‡
BMI, kg/m^2§								
Normal weight	−0.62 (−1.67, 0.44)	0.25	−0.60 (−1.77, 0.56)	0.31	−6.51 (−12.34, −0.68)	0.03‡	−6.54 (−12.81, −0.28)	0.04‡
Overweight	0.31 (−0.34, 0.95)	0.35	0.31 (−0.39, 1.00)	0.39	−3.41 (−7.29, 0.47)	0.09	−4.04 (−8.12, 0.04)	0.052
Obese	-0.96 (−2.53, 0.61)	0.23	−1.99 (−3.62, −0.37)	0.02‡	−0.48 (−7.15, 6.20)	0.89	1.26 (−4.57, 7.08)	0.67
$P_{interaction}$	–	0.95	–	0.71	–	0.13	–	0.11
Nonoperated knee								
Total subjects (M/F)	−0.0005 (−0.04, 0.03)	0.98	−0.0006 (−0.03, 0.03)	0.97	−0.66 (−1.33, 0.01)	0.05	−0.95 (−1.73, -0.17)	0.02‡
BMI, kg/m^2§								
Normal weight	0.04 (−0.32, 0.39)	0.83	0.02 (0.25, 0.30)	0.88	0.07 (−0.62, 0.76)	0.85	0.05 (−0.82, 0.92)	0.91
Overweight	0.004 (−0.01, 0.02)	0.64	−0.0006 (−0.20, 0.20)	0.87	−1.02 (−2.09, 0.04)	0.06	−1.24 (−2.49, 0.02)	0.054
Obese	−0.07 (−0.28, 0.15)	0.55	0.001 (−0.02, 0.02)	0.99	−2.89 (−5.25, −0.53)	0.02	−2.50 (−5.14, 0.14)	0.06
$P_{interaction}$	–	0.35	–	0.16	–	0.17	–	0.13

* Values (n = 272), unless indicated otherwise, are unstandardized regression coefficients (B) and 95% confidence intervals (95% CIs) for the association between blood total testosterone concentration (nmoles/liter) and Western Ontario and McMaster Universities Osteoarthrits Index (WOMAC) pain and functional scores derived from multivariable linear robust regression models unadjusted (model 1) or adjusted for age, body mass index (BMI) status (normal weight, overweight, and obese, except BMI strata) and moderate-to-vigorous physical activity (model 2) for men and women separately. *P* values are 2-sided and uncorrected; statistical significance was set at $P \leq 0.05$. M/F = male/female.
† In women, the blood concentration of total testosterone was natural logarithmically (ln) transformed to approach normality.
‡ Statistically significant.
§ Normal weight: BMI 18.5–24.9; overweight: 25.0–29.9; obese: ≥30.0. One female senior was marginally underweight with BMI 18.2.

these analyses, among women only, testosterone levels were natural logarithmically (ln) transformed to approach normality. At the nonoperated knee only, we also assessed the association between testosterone levels and K/L grades based on ordinal logistic regression models. All analyses were performed in an unadjusted way (model 1) and adjusted for age, BMI status (normal weight, overweight, obese, except in BMI strata), and physical activity (model 2), and for men and women separately. For all analyses, model 2 was considered the main model. Moreover, we performed a subgroup analysis by BMI (normal weight, overweight, and obese) to investigate whether specific BMI subgroups of seniors are more sensitive with regard to the relationship between testosterone and WOMAC scores or K/L grades. These analyses were performed because obesity is a very well documented risk factor for knee OA (35,36), and several studies have shown that testosterone levels are inversely associated with BMI (37,38). Statistical significance was set at a *P* value less than or equal to 0.05; reported *P* values are 2-sided.

RESULTS

The characteristics of the 272 study participants (127 men and 145 women) are shown in Table 1. There were no significant differences between men and women with regard to mean age, BMI, and K/L grades. Women were significantly less physically active and had lower serum testosterone levels than men. Moreover, women had significantly worse (higher) WOMAC pain and more disability (higher WOMAC function scores) at the operated knee and worse disability (higher WOMAC function scores) at the nonoperated knee compared with men. At the nonoperated knee, 48.4% of men (61 of 126) and 61.6% of women (90 of 144) had K/L grade ≥2, consistent with radiographic knee OA.

In multivariable-adjusted analyses, at the operated knee (Table 2, model 2), higher testosterone levels were associated with less WOMAC pain in both men (B = –0.62 [95% confidence interval (95% CI) –1.23, –0.01]; *P* = 0.05) and women (B = –3.79 [95% CI –6.90, –0.69]; *P* = 0.02). This association was most pronounced in the subgroup of normal-weight men (B = –1.16 [95% CI –2.17, –0.15]; *P* = 0.02) as well as in the subgroup of normal-weight women (B = –9.27 [95% CI –15.56, –2.98]; *P* = 0.004). At the operated knee, higher testosterone levels were also associated with less disability among obese men (B = –1.99 [95% CI –3.62, –0.37]; *P* = 0.02) and less disability among all women (B = –3.62 [95% CI –6.65, –0.58]; *P* = 0.02), and most pronounced among normal-weight women (B = –6.54 [95% CI –12.81, –0.28]; *P* = 0.04).

At the nonoperated knee (Table 2), higher testosterone levels were associated with less WOMAC pain only in normal-weight men (B = –0.39 [95% CI –0.68, –0.10]; *P* = 0.009). Further, at the nonoperated knee, higher testosterone levels were associated with less disability (better WOMAC function), among all women (B = –0.95 [95% CI –1.73, –0.17]; *P* = 0.02). With regard to the association between testosterone level and K/L grade, only among obese women (Table 3), per 1 nmole/liter increase in testosterone level, the odds of a higher K/L grade was reduced 10-fold (odds ratio = 0.10 [95% CI 0.02, 0.45]; *P* = 0.003).

DISCUSSION

In this cross-sectional study of 272 men and women with severe knee OA who underwent unilateral TKR 6–8 weeks prior to enrollment, we found an association of testosterone level with symptoms of OA in the operated and the nonoperated knee. Specifically, among both men and women, higher serum testosterone levels were associated with less WOMAC pain in the operated knee. Further, among women but not men, higher serum testosterone levels were also associated with less WOMAC disability in the operated and the nonoperated knee. Notably, these associations were independent of age, BMI, and physical activity. With regard to subgroups by BMI, there were inconsistent signals for men in the nonoperated knee. Further, only among obese women, higher testosterone levels were associated with fewer

Table 3. Cross-sectional association between blood total testosterone concentration and K/L grade in participants of the Zurich Knee Osteoarthritis Trial stratified by sex*

	Men: model 1		Men: model 2		Women: model 1		Women: model 2	
K/L grade (0–4)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Total subjects (M/F)	1.01 (0.94, 1.08)	0.84	1.00 (0.93, 1.08)	0.90	0.54 (0.25, 1.19)	0.13	0.66 (0.29, 1.50)	0.32
BMI, kg/m^2†								
Normal weight	1.03 (0.90, 1.19)	0.67	0.99 (0.85, 1.15)	0.89	1.63 (0.23, 11.53)	0.62	2.85 (0.31, 26.32)	0.35
Overweight	0.98 (0.89, 1.07)	0.59	0.99 (0.90, 1.08)	0.75	1.01 (0.30, 3.39)	0.99	0.94 (0.27, 3.26)	0.93
Obese	1.10 (0.89, 1.38)	0.38	1.11 (0.87, 1.41)	0.39	0.21 (0.05, 0.87)	0.03	0.10 (0.02, 0.45)	0.003‡
$P_{interaction}$	–	0.54	–	0.72	–	0.11	–	0.06

* Values (n = 270), unless indicated otherwise, are odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between blood total testosterone concentration (nmoles/liter) and Kellgren/Lawrence (K/L) grade derived from ordinal logistic regression models unadjusted (model 1), or adjusted for age, body mass index (BMI) status (normal weight, overweight, obese, except BMI strata) and moderate-to-vigorous physical activity (model 2) for men and women separately. *P* values are 2-sided and uncorrected; statistical significance is set at $P \leq 0.05$. M/F = male/female.

† Normal weight: BMI 18.5–24.9; overweight: 25.0–29.9; obese: ≥30.0. One female senior was marginally underweight with BMI 18.2.

‡ Statistically significant.

radiographic changes due to knee OA. Consistent with the literature (25,26), 48% of men and 42% of women had radiographic knee OA at the nonoperated knee according to standardized radiographs performed in all participants.

Our findings are consistent with an earlier study describing a nonsignificant inverse association between testosterone level and WOMAC disability among women and WOMAC stiffness among men with symptomatic knee OA age ≥60 years (18). As outlined in the introduction of this article, a potential benefit of testosterone level with regard to pain and disability among patients with severe knee OA could be explained by prior findings supporting a positive association of higher testosterone levels with better muscle strength (39,40) and better muscle function (41) in patients with knee OA. Furthermore, an influence of testosterone on nociceptive processing (19,20) and inflammatory response has been suggested in several studies (7,9–11), all of which concern important pathways in the development of OA (42,43).

Except among obese women, we did not find an association between testosterone levels and radiographic changes of knee OA, despite the high prevalence of radiographic OA at the nonoperated knee in our study. On the one hand, this finding is in line with prior studies where symptoms and the extent of radiographic changes show discrepant findings (36,44). On the other hand, we may have missed such an association due to the sample selection, where the most severely affected knee had undergone surgery and could not be assessed radiographically with respect to K/L grade. Notably, however, symptoms are considered the patient-relevant feature of OA rather than the extent of radiographic changes (45).

Our study has several strengths. The results for the association of testosterone levels and pain are consistent for men and women at the operated knee and disability for women at the operated and nonoperated knee. Also, our study has a moderately large sample size, with 272 men and women age ≥60 years. Further, we used the WOMAC questionnaire, considered the gold standard for pain and disability measurement among patients with knee OA with and without TKR (31,46). Finally, WOMAC scores in our study are representative of those reported in the literature among similar patient groups (47,48).

Our study also has limitations. Its cross-sectional design does not allow the exploration of cause and effect. Also, our study is a secondary analysis of a randomized controlled trial not powered for the association of testosterone level and symptoms of knee OA. Therefore, the study was possibly underpowered to show significant results for all subgroups. Further, assessments were obtained 6–8 weeks after unilateral TKR. Thus, analgesic regimens, and especially the use of opioid pain medications (49), may have influenced the association between testosterone levels and WOMAC pain and disability. Notably, in 1 large cross-sectional study (National Health and Nutrition Examination Survey) (50), participants taking opioids had a higher odds of having low testosterone levels than those unexposed to opioids, which is consistent with further literature suggesting that opioids can suppress gonadal hormone production, possibly reducing testosterone levels (49). Unfortunately, we were not able to explore the potential confounding by use of pain medication (and specifically opioid use) on pain and disability in our study. However, all participants were recruited in a stable health state, 6–8 weeks after surgery, with rehabilitation efforts largely completed; thereby, there was a reduced likelihood of exposure to opioid pain medications.

In conclusion, the current study suggests a possible advantage of higher sex-specific physiologic testosterone levels among both men and women undergoing unilateral TKR due to severe knee OA. Additional studies with a prospective design are needed to further explore and clarify the role of higher physiologic testosterone levels in patients with symptomatic knee OA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bischoff-Ferrari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Orav, Egli, Theiler, Felson, Bischoff-Ferrari.

Acquisition of data. Orav, Egli, Theiler, Felson, Bischoff-Ferrari.

Analysis and interpretation of data. Freystaetter, Fischer, Orav, Egli, Theiler, Münzer, Felson, Bischoff-Ferrari.

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