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Running head: Serum testosterone, WOMAC pain and function in knee OA

Total serum testosterone and WOMAC pain and function among older men and women with severe knee OA

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ABSTRACT

Objectives: We investigated if serum total testosterone (T)-level is associated with knee pain and function in men and women with severe knee osteoarthritis (OA).

Methods: We enrolled 272 adults ≥60 years (70.4±4.4 years, 53% women) who underwent unilateral total knee replacement (TKR) due to severe knee OA. Serum T-levels and WOMAC pain and function of the operated and contra-lateral knee were measured at 6-8 weeks after surgery. At the non-operated knee, 56% participants had radiographic knee OA with a Kellgren-Lawrence grade ≥2. Cross-sectional analyses were performed by gender and BMI subgroups using multivariable regression adjusted for age, physical activity and BMI.

Results: At the operated knee, higher T-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 non-operated knee, T-levels were not associated with WOMAC pain in men or women, but higher T-levels were associated with less disability in women (B = -0.95; P = 0.02). T-levels were inconsistently associated with pain and disability in BMI subgroups among men. Only among obese women, T-levels were inversely associated with radiographic knee OA (OR = 0.10; P = 0.003).

Conclusions: Higher total T-levels were associated with less pain in the operated knee in men and women undergoing TKR and less disability in women. At the non-operated knee, higher T-levels were inconsistently associated with less pain and disability.

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Significance & Innovation

- Among both men and women with severe knee osteoarthritis who underwent unilateral total knee replacement, higher serum testosterone levels were associated with less WOMAC pain in the operated knee, independent of age, 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 non-operated knee, independent of age, BMI and physical activity.

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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 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).

Prevalence of symptomatic knee OA increases similarly with age in women and men until the age of 50. 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 gender 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 (T) (7, 8), it is likely that hormonal factors are involved (4, 6) with a potential benefit of a greater physiological T-exposure (7, 9-11).

With regard to changes in T-exposure with age, T-levels have been shown to decrease by approximately 1% per year in men starting at age 40 (12). Clinical signs of T-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 T-levels compared to men (14), and their T-levels also decline with age reaching a nadir after menopause with a decline close to 15% of their premenopausal stage (15). Although the biological role of T 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 T-levels to OA, lower serum T-levels have been associated with a higher prevalence of hand but not knee OA in one study (17). Further, a small cross-sectional study among 45 healthy middle-aged men suggested a positive association between higher serum T-levels and medial tibial cartilage thickness (9). In one larger study of 309 overweight adults age 60 years and older with knee OA, higher T-levels were found to be associated with less 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 gender-specific differences for both pain sensitivity and

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threshold (19). Although the underlying mechanisms for these differences are not well understood, an influence of T on nociceptive processing is well established (19, 20). In fact, it has been suggested that T protects 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 two clinical trials with T-treatment among frail and hypogonadal older men (22, 23). Further potential benefits of higher physiological T-levels on OA pain and function may be explained by prior data that linked higher T-exposure to a decrease in fat mass and inflammatory response among men (7, 9-11). Further, preoperative supra-physiological T-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 T-levels and symptoms of knee OA with regard to pain and disability in the operated and non-operated knee among men and women age 60 years and older, who underwent unilateral total knee replacement (TKR) due to severe knee OA 6 to 8 weeks earlier. We chose this target population given their high risk of OA at the contra-lateral non-operated knee (25, 26) as well as the potential shared benefits of higher physiological T-levels on pain and disability at the operated and non-operated knee.

PATIENTS AND METHODS

Study design and Participants

The present study is a cross-sectional analysis of the baseline data from the Zurich Multiple Endpoint Vitamin D Trial in Knee OA Patients (NCT00599807; clinicaltrials.gov) (27). The original study was a 2-year double blind randomized controlled trial that investigated the effect of Vitamin D (2000 vs. 800 IU/d cholecalciferol) on pain and disability related to the rehabilitation of the operated knee and contra-lateral knee among 273 seniors age 60 years and older (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

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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, one male participant was excluded due to missing data on serum T-concentration reducing the analytical sample size for this study to 272 (for the radiologic assessment data was only available for 270 participants). Exclusion criteria of the original trial were history of inflammatory arthritis, chronic corticosteroid use, history of malabsorption disorder, kidney disease (estimated creatinine clearance <30 mL/min), current cancer, treatment with bisphosphonate, PTH hormone therapy, calcitonin therapy in the 6 months prior to enrolment, severe cognitive/visual/hearing impairments, 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 T-concentration

Fasting blood samples were taken between 8:00 and 9:30 am. Serum concentration of total T was measured by an electrochemoluminesence immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) with an inter-assay coefficient of variation (CV) of 3.9% at a level of 7.3 nmol/L and 3.5% at a level of 18.8 nmol/L.

Assessment of covariates

Body mass index (BMI, in kg/m^2) was calculated as weight divided by height squared. BMI categories were defined according to WHO guidelines as underweight (BMI < 18.5 kg/m^2), normal weight (BMI ≥ 18.5 and < 25 kg/m^2), overweight (BMI ≥ 25 and < 30 kg/m^2), and obese (≥ 30 kg/m^2).

Physical activity levels were measured by an ankle-worn ambulatory activity monitor (StepWatch™ Step Activity Monitor, Cyma, Seattle, WA), 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 seven consecutive days. A measurement was considered as valid if at least three days with ≥10

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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 (MVPA) were defined as the average minutes per day with ≥30 steps/min according to the manufacturer's software manual (StepWatch^{TM} 3.1 Software Manual).

Outcome measurements

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function score

Knee pain and function (disability) of the operated and the non-operated 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 (0 = no symptoms, 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 osteoarthritis at the non-operated knee

To rate knee OA at the non-operated knee, we performed a plain x-ray of the contra-lateral knee in a semi-flexed weight-bearing position (we used the Multicentre Osteoarthritis Study (MOST) study centre standardized X-ray assessment procedures (33)). Kellgren-Lawrence (KL) grades were classified by a blinded knee OA radiology expert (0 = no radiographic features of osteoarthritis; 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; 4 = large osteophytes, marked joint space narrowing, severe sclerosis and definite bone deformity) (34).

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Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA). Distributions of continuous variables were examined for normality.–Differences in baseline characteristics between men and women were analyzed by using a χ^2 test for categorical variables and a Student's *t* test for continuous variables.

Associations between serum T-concentration and WOMAC pain and function (disability) score were analyzed by using multivariable robust linear regression models. For these analyses, among women only, T-levels were natural logarithmically (ln) transformed to approach normality. At the non-operated knee only, we also assessed the association between T-levels and KL 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 subgroup analysis by BMI (normal weight, overweight, and obese) to investigate whether specific BMI subgroups of seniors are more sensitive with regard to the relation between T and WOMAC scores or KL 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 T-levels are inversely associated with BMI (37, 38).

Statistical significance was set at $P \leq 0.05$; reported *P* values are two-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 KL grades. Women were significantly less physically active and had lower serum T-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 non-operated knee compared with men. At the non-operated knee, 48.4% (61/126) of men and 61.6% (90/144) of women had KL grade 2 or higher consistent with radiographic knee OA.

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In multivariable-adjusted analyses, at the operated knee (Table 2, Model 2), higher T-levels were associated with less WOMAC pain in both men (*B* = -0.62; 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 T-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 non-operated knee (Table 2), higher T-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 non-operated knee, higher T-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 T-level and KL-grade, only among obese women (Table 3), per one nmol/L increase in T-level, the odds of a higher KL-grade was reduced 10-fold (*OR* = 0.10; 95% CI: 0.02, 0.45; *P* = 0.003).

DISCUSSION

In this cross-sectional study among 272 men and women with severe knee OA who underwent unilateral TKR 6 to 8 weeks prior to enrolment, we found an association of T-level with symptoms of OA in the operated and the non-operated knee. Specifically, among both men and women, higher serum T-levels were associated with less WOMAC pain in the operated knee. Further, among women but not men, higher serum T-levels were also associated with less WOMAC disability in the operated and the non-operated 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 non-operated knee. Further, only among obese women, higher T-levels were associated with less radiographic changes due to knee OA. Consistent with the literature (25, 26),

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48% of men and 42% of women had radiographic knee OA at the non-operated knee according to standardized x-rays performed in all participants.

Our findings are consistent with an earlier study describing a non-significant inverse association between T-level and WOMAC disability among women and WOMAC stiffness among men with symptomatic knee OA age 60 years and older (18). As outlined in the introduction of this manuscript, a potential benefit of T-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 T-levels with better muscle strength (39, 40) and better muscle function (41) in patients with knee OA. Further, an influence of T on nociceptive processing (19, 20) and inflammatory response has been suggested in several studies (7, 9-11), all of which are considered important pathways in the development of OA (42, 43).

Except among obese women, we did not find an association between T-levels and radiographic changes of knee OA despite the high prevalence of radiographic OA at the non-operated knee in our study. On the one hand, this 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 KL 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 T levels and pain are consistent for men and women at the operated knee, and disability for women at the operated and non-operated knee. Also, our study has a moderately large sample size with 272 men and women age 60 years and older. 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 of 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 T-level and symptoms of knee OA. Therefore, it is possible that the study was underpowered to show significant results for all subgroups. Further, assessments were obtained 6

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to 8 weeks after unilateral TKR. Thus, it is possible that analgesic regimens, and especially the use of opioid pain medications (49), may have influenced the association between T-levels and WOMAC pain and disability. Notably, in one large cross-sectional study (NHANES) (50), participants on opioids had a higher odds of having low T-levels than those unexposed to opioids, which is consistent with further literature suggesting that opioids can suppress gonadal hormone production possibly reducing T-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 to 8 weeks after surgery with rehabilitation efforts largely completed, and thereby reduced likelihood of exposure to opioid pain medications.

In summary, the present study suggests a possible advantage of higher gender-specific physiological T-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 physiological T-levels in patients with symptomatic knee OA.

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TABLES

TABLE 1

Characteristics of participants of the Zurich Knee Osteoarthritis trial by gender

	Men	Women	Gender difference (*P*)	Total population
Subjects [n (%)]	126 (47)	146 (53)	0.25	272
Age a (y)	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)
Physical activity (min MVPA/day)	45.3 (23.4)	37.9 (21.6)	**0.009**	42.3 (22.6)
Total testosterone (nmol/L)	13.0 (4.6)	0.4 (0.4)	**<0.0001**	6.3 (7.0)
Kellgren-Lawrence grade [*n* (%)] [a]				
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)				

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Operated knee	23.9 (14.4)	32.6 (14.4)	**<0.0001**	28.5 (15.0)
Non-operated 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)
Non-operated knee	2.9 (6.6)	5.4 (8.9)	**0.01**	4.3 (8.0)

Data are crude means (± SD) or *n* (%). Differences between men and women were assessed by using Student's *t* test for continuous variables and a χ^2 test for categorical variables. *P* values are two-sided; statistical significance is set at $P < 0.05$. Abbreviations: MVPA, moderate to vigorous physical activity; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

[a] Values refer to the non-operated knee (n = 270).

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TABLE 2

Cross-sectional association between blood total testosterone concentration and Western Ontario and McMaster Universities Arthritis Index (WOMAC) post-operative pain and functional scores in seniors age 60 and older with knee osteoarthritis by gender

	Men				Women[a]			
	Model 1		Model 2		Model 1		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**
Body mass index (kg/m^2)								
Normal weight (18.5-24.9)[b]	-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 (25.0-29.9)	-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 (≥30.0)	-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**
Non-operated knee								

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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
Body mass index (kg/m²)								
Normal weight (18.5-24.9) [b]	-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 (25.0-29.9)	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 (≥30.0)	-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**
Body mass index (kg/m²)								
Normal weight (18.5-24.9) [b]	-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 (25.0-29.9)	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 (≥30.0)	-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
Non-operated 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**

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Body mass index (kg/m^2)								
Normal weight (18.5-24.9) [b]	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 (25.0-29.9)	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 (≥30.0)	-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

Data (n = 272) are unstandardized regression coefficients (*B*) and 95% confidence intervals (95% CIs) for the association between blood total testosterone concentration (nmol/L) and WOMAC pain and functional scores derived from multivariable linear robust regression models unadjusted (Model 1) or adjusted for age, 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 two-sided and uncorrected; statistical significance was set at $P \leq 0.05$. Abbreviations: BMI, body mass index; F, females; M, males; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

[a] In women, the blood concentration of total testosterone was natural logarithmically (ln) transformed to approach normality.

[b] One female senior was marginally underweight with BMI = 18.2.

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TABLE 3

Cross-sectional association between blood total testosterone concentration and Kellgren-Lawrence grade in participants of the Zurich Knee Osteoarthritis trial stratified by gender [a]

	Men				Women			
	Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*
Kellgren-Lawrence grade (0-4)								
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
Body mass index (kg/m^2)								
Normal weight (18.5-24.9) [a]	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 (25.0-29.9)	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 (≥30.0)	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**
$P_{\text{interaction}}$		0.54		0.72		0.11		0.06

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Data (n = 270) are odds ratios (OR) and 95% confidence intervals (95% CIs) for the association between blood total testosterone concentration (nmol/L) and Kellgren-Lawrence grade derived from ordinal logistic regression models unadjusted (Model 1) or adjusted for age, 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 two-sided and uncorrected; statistical significance is set at $P \leq 0.05$. Bolded *P* values indicate a statistical significance at $P < 0.05$ level. Abbreviations: BMI, body mass index; F, females; M, males.

[a] One female senior was marginally underweight with BMI = 18.2 kg/m^2.

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