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Permalink

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Journal

European radiology, 28(3)

ISSN

0938-7994

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Publication Date

2018-03-01

DOI

10.1007/s00330-017-5054-y

Peer reviewed

Association of weight change with progression of meniscal intrasubstance degeneration over 48 months: Data from the Osteoarthritis Initiative

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Received: 13 March 2017 / Revised: 11 July 2017 / Accepted: 30 August 2017
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Abstract

Objectives To investigate the association of weight change over 48 months with progression of meniscal intrasubstance degeneration (MID).

Methods We studied 487 subjects with MID at baseline and after 48 months using 3-T MRI with the same protocol (FSE sequences with and without fat suppression). These participants lost weight ($\geq 3\%$, $n = 141$), had moderate weight gain (3–10%, $n = 77$), substantial weight gain ($>10\%$, $n = 15$) or maintained stable weight ($n = 254$). Progression of MID to a meniscal tear was assessed using the WOMS grading system and compared among weight change groups using logistic re-

gression. ANOVA and chi-square tests were used to study the differences in subjects' characteristics.

Results Progression of MID increased from weight loss to substantial weight gain ($p < 0.001$) and was significantly more likely with both moderate weight gain (odds ratio [OR], 4.9; 95% confidence interval [CI] 2.4–8.9) and substantial weight gain (OR, 9.5; 95% CI 3.2–28.5) compared to stable weight. Results were similar in both menisci for moderate weight gain (medial: OR, 6.8; 95% CI 3.5–11.3; lateral: OR, 2.6; 95% CI 1.1–6.6) and substantial weight gain (medial: OR, 21.0; 95% CI 5.1–80.7; lateral: OR, 9.7; 95% CI 0.95–100.2).

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Conclusion Weight gain is associated with an increased likelihood that meniscal intrasubstance degeneration will progress with the risk increasing with greater weight gain.

Key Points

- *Subjects who gained weight were more likely to develop meniscal tears.*
- *Greater amount of weight gain was associated with an increasing likelihood of progression.*
- *Prevention of weight gain has health benefits for the meniscus.*

Keywords Magnetic resonance imaging · Meniscal intrasubstance degeneration · Meniscal tears · Weight change · Meniscal lesion · BMI

Abbreviations

BMI	Body mass index
HKA	Angle hip-knee-ankle angle
KL	Kellgren–Lawrence
MID	Meniscal intrasubstance degeneration
MRI	Magnetic resonance imaging
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
RMSE	Root mean square error
WORMS	Whole-Organ Magnetic Resonance Imaging Score

Introduction

The human menisci are C-shaped or semicircular fibrocartilaginous structures with bony attachments on the tibial plateau, and they are essential for joint stability, shock absorption, distribution of contact forces, joint lubrication and proprioception [1]. Meniscal tears expose the adjacent articular cartilage to increased axial and shear stress, greatly increasing the risk of development and progression of knee osteoarthritis (OA) [2, 3] and may be a marker of early pre-radiographic disease [3–5].

Magnetic resonance (MR) imaging is the preferred noninvasive imaging modality for the evaluation of the meniscus. Using determination by arthroscopy as the standard of reference, MRI demonstrates a high sensitivity and specificity for the detection of meniscal tears [6]. Meniscal intrasubstance degeneration (MID), defined by increased intrameniscal signal on MRI that does not fulfil the criteria for a meniscal tear, is a frequent finding on MRI knee examination of older adults without radiographic OA or meniscal tears [7], and it may play a role in the development of knee OA [8, 9]. Histologically, this finding represents foci of mucoid degeneration [10, 11], and these meniscal changes may weaken the meniscal

structure and serve as a precursor and risk factor for degenerative meniscal tears [10, 12].

A recent study by Kumm et al. [7] of knees from the Osteoarthritis Initiative (OAI) cohort that had neither radiographic OA nor frank meniscal tears found that 26% had increased linear intrameniscal signal intensity, and that regression of this finding rarely occurred over 6 years. Knees with increased intrameniscal signal at baseline had a much higher risk of developing degenerative meniscal tears during follow-up when compared with knees without an elevated intrameniscal signal intensity.

Also studies have reported that weight gain is associated with accelerated molecular cartilage deterioration in obese and overweight subjects [13], and that substantial weight loss over 48 months may have a protective effect on articular knee cartilage [14]. Weight changes may have similar effects on the development of degenerative meniscal tears, which could help explain the effects of weight loss and gain on cartilage integrity. However, to the best of our knowledge (as of March 2017, PubMed search), the impact of weight change on the risk of developing meniscal tears has not been studied.

The purpose of our study was to investigate the association of weight loss and weight gain with the risk of progression over 48 months to meniscal tear or maceration in the high-risk group of menisci with a finding of increased intrameniscal signal intensity at baseline.

Materials and methods

Subjects

The study was compliant with the Health Insurance Portability and Accountability Act and was approved by the institutional review board of all participating centres. All subjects provided written informed consent. Subjects were selected from the OAI (<http://www.oai.ucsf.edu>), a prospective multicentre cohort study, including a total of 4796 participants.

From 4796 OAI participants, we excluded those with missing BMI data at more than one time point from baseline, 12, 24 and 48 months ($n = 1813$), a baseline Kellgren–Lawrence (KL) score of the right knee greater than 3 representing advanced OA ($n = 93$), rheumatoid arthritis developed during study follow-up ($n = 18$), subjects who cycled through weight loss and weight gain periods during the 48 months (see below) ($n = 155$), incomplete right knee MR examinations at either baseline or 48 months ($n = 253$) and missing hip-knee-ankle angle (HKA angle) data ($n = 168$).

Of the remaining 2296 subjects, baseline and 48-month follow-up Whole-Organ Magnetic Resonance Imaging Score (WORMS) readings for the right knee obtained for previously published studies by our group were available for 1383 subjects

[13–19]. All pre-read studies were individually and independently reviewed by two radiologists, as detailed below.

We used these readings to identify 487 right knees with an increased intrameniscal signal intensity (WORMS meniscus score = 1) in the medial and/or lateral meniscus at baseline and no evidence of a meniscal tear or maceration anywhere in the knee (WORMS score = 2–4). None of the selected subjects in this study received arthroscopic treatment prior to or during the follow-up. A flowchart illustrating the patient selection is shown in Fig. 1.

Weight change

We grouped subjects by the amount of weight change from baseline to 48 months: weight loss (BMI decrease $>3\%$; $n = 141$), stable weight (BMI increase or decrease $\leq 3\%$; $n = 254$) and weight gain (BMI increase $>3\%$; $n = 92$). In order to analyse the effect of different amounts of weight gain in these subjects, we also defined subgroups with substantial weight gain (BMI increase $>10\%$; $n = 15$), moderate weight gain (BMI increase 3–10%; $n = 77$). As noted above, we excluded subjects who cycled between weight gain and loss. For this we calculated the annual rate of change in BMI over 48 months for each subject with a linear regression model and excluded those with a root mean square error (RMSE) of the weight change regression line above the 95th percentile.

Covariates

Knee alignment was assessed using the HKA angle measured from full limb radiographs [20–22]. History of trauma of the

right knee was assessed at baseline and at all annual follow-up by asking participants if they ever had a knee injury that caused a limited ability to walk for at least 2 days. KL grades were obtained from the central OAI reading of fixed flexion radiographs [23].

MR imaging

MR images were obtained using identical 3.0-Tesla scanners (Trio, Siemens) and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) at four sites (Ohio State University, Columbus, OH; University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; and Memorial Hospital of Rhode Island, Pawtucket, RI). The following sequences were used for the meniscal assessment: (i) 2D intermediate-weighted fast spin echo (FSE) sequences with fat suppression in the sagittal plane [repetition time (TR)/echo time (TE), 3200/30] and (ii) 2D intermediate-weighted FSE sequences with fat suppression in the coronal plane (TR/TE, 3700/29). More details are available in the OAI MR protocol [24].

Imaging analysis

Baseline and 48-month follow-up images were reviewed by two radiologists (J.B.G. with 6 years, A.S.G. with 5 years of experience), blinded to patient information. In case of divergent findings, a consensus reading was performed with a third musculoskeletal radiologist (T.M.L., with 23 years of experience). The images were evaluated using the semiquantitative

Fig. 1 Flowchart illustrating subject selection from OAI database

WORMS grading system [25], modified as previously described [26, 27], and meniscal abnormalities were assessed in the medial and lateral meniscus. Meniscal lesions were graded from 0 to 4 in each of the three subcompartments of the medial and lateral meniscus (anterior horn/body/posterior horn). In the modified WORMS, subscales for meniscal pathologies range from 0 to 4 and encompass a grade (grade 1) describing intrasubstance meniscal changes without an actual tear (0 = normal, 1 = intrasubstance abnormalities, 2 = non-displaced tear, 3 = displaced or complex tear, and 4 = complete destruction or maceration of the meniscus) [28, 29]. Meniscus WORMS grade 1 (Fig. 2) was defined as abnormally high intrasubstance signal on fluid-sensitive sequences that does not reach the articular surface or the free margin of the meniscus, and was seen on two or more consecutive images or in two or more different planes.

High meniscal signal intensity was classified as a meniscal tear if it communicated with the superior, inferior or free edge of the meniscal surface on at least two consecutive images or two different planes [11] (Figs. 2 and 3). High meniscal signal that reached the meniscus surface on just a single slice section was considered indeterminate and the knee was excluded, as this is frequently diagnosed as a meniscal tear in arthroscopy [28, 30]. Progression to a meniscal tear or maceration meniscal pathology (WORMS ≥ 2) at 48 months required that the change occur in the same subcompartment (anterior horn, body and/or posterior horn of the medial or lateral menisci) as

Fig. 2 Longitudinal series of sagittal intermediate-weighted fat-saturated MR images from a study subjects exemplify **a, b** no progression of meniscal intrasubstance degeneration (arrow) over 48 months in the weight loss group and **c, d** progression of meniscal intrasubstance degeneration (arrow) into a medial meniscal tear (arrowhead) over 48 months in the moderate weight gain group

Fig. 3 Longitudinal series (baseline and 48 months) of sagittal intermediate-weighted fat-saturated MR images from a 60-year-old woman that gained more than 10% weight over 48 months, showing progression of meniscal intrasubstance degeneration (arrow) at baseline (**a**) into a horizontal meniscal degenerative type of tear (**b**) in the posterior horn of the medial meniscus over 48 months

the preceding high intrameniscal signal intensity. Tears in other subcompartments were not included as an outcome. Progression was determined separately for the medial and lateral menisci.

Statistical analysis

Statistical analysis was performed with SPSS (Version 23.0; IBM, Armonk, NY, USA) using a two-sided 0.05 level of significance. Reproducibility of WORMS meniscus scoring was assessed with intraclass correlation coefficients (ICC). Differences in subject characteristics between subjects with stable weight and those with weight loss and weight gain, respectively, were evaluated separately using one-way analysis of variance (ANOVA; numeric variables) and chi-square tests (categorical variables).

Logistic regression models were used to estimate odds ratios for progression of MID to meniscal tear/maceration comparing the weight change groups to the stable weight group. Tests for trend across the four weight change categories were obtained by including a 0–3 numeric variable corresponding to the weight change groups in the logistic model. We used generalised estimating equations to account for intraindividual effects in the analyses of both menisci combined. Progression of medial and lateral menisci was also analysed separately. All models were adjusted for age, sex, history of knee trauma or trauma up to 48-months follow-up, knee alignment, baseline BMI and KL score.

Reproducibility of meniscus scoring

The intra- and inter-reader reproducibility of the WORMS meniscus 0–4 grading was assessed in baseline using 20 subjects that were randomly selected, separately evaluated by both radiologists (J.B.G. and A.S.G.). ICCs for intraobserver agreement were 0.85 (0.79–0.93) and 0.87 (0.81–0.94), and

ICC for interobserver agreement was 0.83 (0.76–0.91). ICCs for intraobserver agreement for progression were 0.83 (0.77–0.93) and 0.84 (0.79–0.92), and ICC for interobserver agreement was 0.80 (0.69–0.90). These results are similar to those from previous studies [15, 18].

Results

Subject characteristics

Baseline characteristics of all subjects and for each group are described in Table 1. Over 48 months, weight loss subjects lost on average $7.3 \pm 2.9 \text{ kg/m}^2$, weight gain subjects on average gained $6.8 \pm 3.0 \text{ kg/m}^2$, while BMI of the stable weight group remained almost unchanged with an mean increase of $0.19 \pm 1.54 \text{ kg/m}^2$.

At baseline, MID was present in the medial meniscus of 386 knees (193 in stable weight, 113 in weight loss and 80 in weight gain groups) and in the lateral meniscus of 279 knees (158 in stable weight, 86 in weight loss and 35 in weight gain groups). By design, there were no grade 2 or higher meniscal abnormalities in either compartment.

Progression of meniscal intrasubstance degeneration over 48 months

None of the menisci with intrasubstance degeneration at baseline showed regression to a normal meniscus signal (from WORMS grade 1 to 0) over 48 months. Overall, 25% of menisci with intrasubstance degeneration progressed to a tear or maceration. Of the 386 medial menisci with baseline intrasubstance degeneration, 110 (28%) progressed to tear/maceration (meniscal WORMS grade 1 to ≥ 2) over 48 months; 76 (69%) of these to WORMS grade 2 (nondisplaced tear), 16 (15%) to grade 3 (displaced or complex tear) and 18 (16%) to grade 4 (maceration). Of 279 lateral menisci with intrasubstance degeneration at baseline, 56 (20%) progressed to a tear or maceration; 36 of these (64%) to WORMS grade 2, 13 (23%) to grade 3 and 7 (13%) to grade 4. Progression was significantly more frequent in the medial than in the lateral meniscus ($p = 0.014$). Overall, of 665 menisci (medial and lateral) with intrasubstance degeneration at baseline, 166 (25%) progressed to a tear or maceration. Of these, 111 (67%) progressed to WORMS grade 2, 33 (20%) to grade 3 and 22 (13%) to grade 4.

Subjects with and without knee trauma during the study did not show significant differences regarding the rate of progression of intrasubstance degeneration to a tear over 48 months ($p = 0.56$). The knee alignment (HKA angle) did not show any significant ($p > 0.05$) association with progression of intrasubstance degeneration to a tear over 48 months; subgroup analysis in the different subcohorts showed that neither

varus nor valgus alignment or HKA angle was significantly associated with progression.

Weight change and progression of meniscus degeneration

Progression of MID to meniscal tears/maceration in both menisci combined increased from 17% in the weight loss group to 64% in the group with substantial weight gain ($p < 0.001$ for trend) (Fig. 4). Those with any weight gain, as well as the subgroup with moderate weight gain, had a significant 5-fold increase in the odds of progression, and the substantial weight gain group had a 10-fold increase in progression, compared to the stable weight group (Table 2).

Progression in the medial meniscus

In the medial menisci with intrasubstance degeneration, progression to tear/maceration increased from 17% in the weight loss group to 69% in those with substantial weight gain ($p < 0.001$ for trend) (Fig. 4). The group with any weight gain and those with moderate weight gain both had a significant 7-fold increase in the odds of progression, while the group with substantial weight gain had a 21-fold increase in progression compared to the stable weight group (Table 2).

Among subjects losing weight there was a nonsignificant trend towards lower odds for progression of MID to meniscal tears in the medial meniscus when comparing these to subjects with stable weight (OR, 0.5; 95% CI 0.30–1.10; $p = 0.09$).

Progression in the lateral meniscus

In lateral menisci with intrasubstance degeneration, progression to tear/maceration increased from 17% in the weight loss group to 63% in those with substantial weight gain ($p < 0.001$ for trend) (Fig. 4). The group with any weight gain and the subgroup with moderate weight gain both had a significant 2- to 3-fold increase in the odds of progression to meniscal tear/maceration, while the substantial weight gain subgroup had a 10-fold increase in progression compared to the stable weight group (Table 2). There was no difference in the odds of lateral meniscus progression in the weight loss group compared to the stable weight group.

Discussion

Our study showed that among subjects with meniscal intrasubstance degeneration those who gained weight over 48 months were substantially more likely to develop meniscal tears or maceration over the same time period compared to subjects with stable weight. A greater amount of weight gain was significantly associated with an increasing likelihood of progression of meniscal degeneration, with well over 60% of menisci

Table 1 Baseline subject characteristics

	All subjects	Weight loss ^b	Stable weight ^b	Moderate weight gain ^b	Substantial weight gain ^b	<i>P</i> value Weight loss vs. stable weight group	<i>P</i> value Moderate weight gain vs. stable weight group	<i>P</i> value Substantial weight gain vs. stable weight group
<i>n</i>	487 (100%)	141 (29%)	254 (52.0%)	77 (16%)	15 (3%)			
(% of all subjects)								
Age	61.8 ± 8.9	64.2 ± 9.2	61.7 ± 8.9	58.7 ± 7.1	64.6 ± 6.2	0.05 ^c	0.07 ^c	0.1 ^c
(years; mean ± SD)								
Sex	302 (62.0%)	82 (58.2%)	154 (60.6%)	66 (71.7%)	9 (60%)	0.63 ^d	0.06 ^d	0.9 ^d
(female; <i>n</i> (%))								
Baseline BMI	27.9 ± 3.6	28.7 ± 3.2	27.5 ± 3.7	27.4 ± 3.9	29.2 ± 3.8	0.02 ^c	0.76 ^c	0.04 ^c
(kg/m ² ; mean ± SD)								
HKA angle	−0.721 ± 3.6	−0.37 ± 3.1	−0.67 ± 3.8	−1.3 ± 3.6	−0.38 ± 3.3	0.42	0.11 ^c	0.45 ^c
						0.13 ^c	0.4 ^c	0.01 ^c
Baseline KL score								
KL = 0 (<i>n</i> (%))	140 (28.7%)	43 (30.4%)	67 (26.4%)	26 (34.60%)	4 (26.20%)			
KL = 1 (<i>n</i> (%))	121 (24.8%)	24 (17.1%)	69 (27.6%)	21 (26.90%)	1 (9.80%)			
KL = 2 (<i>n</i> (%))	157 (32.2%)	52 (36.9%)	81 (32.2%)	21 (26.90%)	7 (47.70%)			
KL = 3 (<i>n</i> (%))	69 (14.1%)	22 (15.6%)	35 (13.8%)	9 (11.60%)	3 (16.30%)			
Knee trauma ^a								
Prior to the baseline	109 (22%)	19	64	25	1	0.02 ^c	0.5 ^c	0.04 ^c
Between baseline and 48 months	41 (8%)	12	25	3	1	0.7 ^c	0.08 ^c	0.5 ^c

^a History of trauma of the right knee was assessed by asking participants if they ever had a knee injury that caused a limited ability to walk for at least 2 days^b Subjects in the three different groups adjusted for age, sex, baseline BMI, KL score, knee trauma and HKA angle^c ANOVA^d Pearson's chi-squared test

Fig. 4 Percentage of meniscal intrasubstance degeneration progression in the different weights groups, in the medial meniscus (**a**), lateral meniscus (**b**) and both (medial and lateral menisci combined) (**c**). *Tests for trend across the four weight change categories were obtained by including a 0–3 numeric variable corresponding to the weight change groups in the logistic model

showing progression in subjects having substantial weight gain (BMI change >10%). Of note, menisci with intrasubstance degeneration at baseline in subjects who lost weight over this time period did not have a significantly decreased likelihood of progression to tear/maceration compared to stable weight individuals, although there was a nonsignificant trend for a protective effect of weight loss in the medial meniscus.

Table 2 Odds ratio for progression to tear/maceration in menisci with intrasubstance degeneration at baseline in weight change groups compared to the subjects with stable weight

	Weight loss (<3%) OR (95% CI)	Weight gain (>3%)	Moderate weight gain (3–10%)	Substantial weight gain (>10%)
Medial meniscus ^a	0.5; 0.30, 1.10; $p = 0.09$	OR, 7.0; 95% CI 3.72–13.34; $p < 0.001$	OR, 6.8; 95% CI 3.5–11.3; $p < 0.001$	OR, 21.0; 95% CI 5.1–80.7; $p < 0.001$
Lateral meniscus ^a	OR, 0.9; 95% CI 0.41–2.06; $p = 0.9$	OR, 2.9; 95% CI 1.23–6.85; $p = 0.01$	OR, 2.6; 95% CI 1.1–6.6; $p = 0.01$	OR, 9.7; 95% CI 0.95–100.2; $p = 0.04$
Both menisci ^b	OR 0.6; 95% CI 0.33–1.26; $p = 0.2$	OR, 5.1; 95% CI 2.75–9.59; $p < 0.001$	OR, 4.9; 95% CI 2.4–8.9; $p < 0.001$	OR, 9.5; 95% CI 3.2–28.5; $p < 0.001$

^a Logistic regression analyses adjusting for age, sex, baseline BMI, baseline KL score, knee trauma and knee alignment. Significant results ($p < 0.05$) are in bold

^b Generalised estimating equation analyses adjusting for age, sex, baseline BMI, baseline KL score, knee trauma and knee alignment. Significant results ($p < 0.05$) are in bold

Given the greatly increased risk of developing OA in knees with meniscal tears [2–5], our findings have potentially important implications for prevention. Obesity and overweight are modifiable risk factors for knee OA [29, 31, 32] and clinical trials of weight loss show that it is moderately effective in improving pain and function in persons with symptomatic knee OA. Observational studies suggest that weight loss is associated with a reduced risk of developing knee OA [33, 34]. A more recent study found that weight loss over 48 months was associated with slowed biochemical knee cartilage degeneration, as measured with T2 mapping as well as with improved knee symptoms [14]. On the other hand, Teichtahl et al. [35] showed that weight gain was associated with increased cartilage volume loss in adults with meniscal tears, and Bucknor et al. [13] found that individuals with at least 5% weight gain had a significantly higher progression of cartilage and meniscal lesions compared to the control cohort with stable weight over 4 years. Given the known challenges of sustained weight loss in older adults with knee OA [36, 37], prevention of weight gain [38] may offer a feasible approach to prevention of knee OA in this population.

While weight gain was associated with a 7-fold higher odds for progression in the medial meniscus and a 3-fold higher odds for progression in the lateral meniscus, weight loss showed a trend for a reduced risk of progression in the medial meniscus only. A reason for this may be that the medial meniscus, which is associated with a higher risk of degenerative tears than the lateral meniscus [39, 40], is less mobile and absorbs higher forces during weight-bearing than the lateral meniscus.

The vast majority of meniscal intrasubstance signal abnormalities and incident meniscal tears and maceration observed in our study are likely to be degenerative in nature. As found previously [7] and confirmed in the present study, meniscal intrasubstance signal abnormalities indicating MID in older individuals are very unlikely to regress. When assessing meniscal intrasubstance signal abnormalities, one possible differential diagnosis for degeneration is meniscal contusion, frequently found in younger subjects and usually related to a distinct trauma mechanism. These “traumatic” high intrameniscal signal changes are likely to regress and have not proven to be associated with the development of meniscal tears overtime [41]. Also as shown previously [7] and confirmed in our study, intrasubstance meniscal signal abnormalities in older individuals have a high risk of progressing to a degenerative tear or maceration in the same meniscal segment. Moreover, the mean age of our study subjects was 61.8 years and none of our study subjects presented any high-grade ligament pathology or rupture during follow-up, suggesting that signal abnormalities assessed were caused by MID rather than posttraumatic intrameniscal contusions.

Our study has some limitations: Firstly, the results in the substantial weight gain group are based on a relatively small cohort. However, together with the moderate weight gain group

we were able to follow 92 subjects, who gained weight longitudinally over 48 months and results of the two groups are consistent though less pronounced in the moderate weight gain group. Secondly, we included knees with a history of trauma at baseline and that were reported to have suffered injury during follow-up. Therefore some of the meniscal lesions observed in our study may have been traumatic in origin rather than degenerative. Thirdly, the images were evaluated using the semiquantitative WORMS grading system [25–27] and meniscal extrusion is not included in these subscales for meniscal pathologies. Since meniscal extrusion is less frequently found in normal morphological menisci (without a tear or a higher-grade meniscal pathology) [42], the presence of this finding in our baseline studies is unlikely to be frequent. Finally, we assessed only subjects with an intrasubstance degeneration present at baseline, a group at very high risk for developing a frank meniscal tear, so our findings may not apply to the risk of developing a meniscal tear in knees with normal menisci.

In conclusion, our results demonstrated that weight gain is associated with a substantially increased likelihood of progression of meniscal intrasubstance degeneration to meniscal tear or maceration, with individuals having an increase of 10% or more in BMI over 48 months having a 10-fold increase in the odds of progression over the same time period. Prevention of weight gain in older persons may have substantial benefits for the health of the meniscus.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Thomas Link.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Funding The OAI is a public–private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer, Inc.; Novartis Pharmaceuticals Corporation; Merck Research Laboratories; and GlaxoSmithKline. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

Statistics and biometry Charles E. McCulloch, Ph.D. kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Written informed consent was waived by the institutional review board.

Ethical approval Institutional review board approval was obtained.

Methodology

- prospective

- diagnostic or prognostic study
- multicentre study

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