Table
Relation of incident bisphosphonate use to risk of incident KR among older women with incident knee OA

Analytic Approach	Incident Bisphosphonate User	Non-Bisphosphonate User	Crude HR (95% CI)	Adjusted HR* (95% CI)
PS*-matched				
N	1964	1964		
Mean OA duration	4.4 ± 3.5years	4,5 ± 3,5 years		
Crude incidence rate per 1000 person-years	21.45	28.94	0.75 (0.59-0.94)	0.76 (0.61-0.96)
BMI-and age-matched				
N	1869	5017		
Mean OA duration	4.6 ± 3.5 years	3.1 ± 2,9 years		
Crude incidence rate per 1000 person-years	24.37	60.62	0.40 (0.33-0,49)	0.40 (0.30-0.53)

*Variables included in PS model and included in the "Adjusted HR" model: 1) OA severity and duration 2) General (age, gender, BMI, socioeconomic status); 3) Comorbidities (osteoporosis-related (osteoporosis, hip fracture, vertebral fracture, number of bone mineral density measurements), hypertension, diabetes (including severity), hyperlipemia, ischemic heart disease (including severity), heart failure, atrial fibrillation, stroke, dementia/cognitive impairment, depression, seizure disorder, venous thromboembolism, chronic obstructive lung disease, pneumonia, renal disease, liver disease, cancers except skin cancer, cellulitis, falls, inflammatory arthritis, arid peptic ulcer disease); 4) Habits (smoking status and alcohol use); 51 Health status (number of GP visits and hospitalization, albumin level); and 6) Medication use (Non-steroidal anti-inflammatory medications, opioid or non-opioid analgesics, anti-hypertensive, cholesterol lowering, insulin/oral hypoglycemic, glucocorticoids (systemic and inhaled), estrogens, and anti-epileptics)

or DMARD or biologic therapy), and those who had prior bisphosphonate or bone-modulating therapy. We identified women who had incident (first) prescription of a bisphosphonate (i.e., alendronate, etidronate-calcitonin, ibandronate, pamidronate, risedronate, zolendronate) after their incident (new onset) knee OA diagnosis. We computed propensity scores (PS) using logistic regression, with incident bisphosphonate use as the dependent variable and potential confounders that reflect indication for bisphosphonate use and for KR (Table) as the independent variables. Each incident bisphosphonate user was matched 1:1 with an unexposed subject with greedy matching using the PS within 1-year cohort accrual blocks. Follow-up started from the index date (date of 1st bisphosphonate prescription for the exposed, and randomly assigned to the unexposed within the one-year accrual block), and continued until KR, death, censoring, or end of study. The relation of incident bisphosphonate use to KR among women with incident knee OA was assessed using Cox proportional hazard models. Because body mass index (BMI) is an important confounder, we conducted separate analyses in which incident bisphosphonate users were matched by BMI (±0.5kg/m^2) and age (same birth year) to up to 4 unexposed subjects, and variables used in the PS model were additionally adjusted for in this model.

Results: In the PS-matched approach, we identified 1964 incident bisphosphonate users who were matched to 1964 non-users (mean age 76, mean BMI 27.4), with mean follow-up time of 3 years. The mean (SD) age at incident knee OA diagnosis was 72 (8), at incident bisphosphonate prescription was 76 (8), and at KR was 75 (7). Overall, covariates were well-balanced in the two groups. The crude incidence rate of KR among incident bisphosphonate users was 21.45 per 1000 person-years, and 28.94 per 1000 person-years among the non-users. The PS-matched model hazards ratio (HR) was 0.75 (95% CI 0.59-0.94). When additionally adjusted for the potential confounders included in the original PS model, the effect estimate remained unchanged (Table). In the BMI- and age-matched cohort approach (N=1869 incident users; 5017 matched non-users), the effect estimates remained protective (Table).

Conclusions: In this large cohort of older women with incident knee OA, those with incident bisphosphonate use had a lower risk of KR than non-users. While we cannot rule-out potential for residual confounding (e.g., confounding by indication) or possible depletion of susceptibles (i.e., women who had a KR prior to incident bisphosphonate use were excluded), these results suggest that bisphosphonates may have beneficial effects on knee OA.

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THE ATROPHIC PHENOTYPE OF KNEE OSTEOARTHRITIS (OA) IS NOT ASSOCIATED WITH MORE RAPID PROGRESSION OF DISEASE WHEN COMPARED WITH THE NON-ATROPHIC PHENOTYPE: THE MOST STUDY

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Purpose: In knees exhibiting fast progression of cartilage loss over time, osteophyte formation may lag behind cartilage loss, which might then manifest as an atrophic phenotype of knee osteoarthritis (OA). Cases of rapidly progressive OA were observed as a potential adverse event in studies evaluating efficacy of nerve growth factor inhibitors (aNGF). The atrophic phenotype of OA is believed to be a predisposing entity to more rapid progression of OA. To support the hypothesis that atrophic OA is associated with faster progression of disease, we assessed the associations of the presence of the atrophic phenotype of tibiofemoral OA at baseline with progression of radiographic JSN and MRI progression of cartilage loss over 30 months.

Methods: MOST study participants with available OARSI grading system scores of tibiofemoral JSN and osteophytes on radiographs (from 0 to 3), tibiofemoral WORMS grades on MRI for cartilage morphology (from 0 to 6) and osteophytes (from 0 to 7) for all ten subregions, as well as WORMS grades on MRI for meniscal morphology (from 0 to 4) and meniscal extrusion (from 0 to 3) bilaterally, performed at baseline and 30 months follow-up (FU), were included. Based on baseline radiographs, the atrophic phenotype of tibiofemoral OA was defined as OARSI grades 1 or 2 for JSN and grade 0 (absence) for osteophytes. Non-atrophic knee OA was defined as OARSI grades 1 or 2 with osteophytes grades 2 or 3. Based on baseline MRI, atrophic knee OA was defined as tibiofemoral severe cartilage damage (grades 5 or 6) in at least 1 of 10 subregions with absent or tiny osteophytes (grades 0 to 2) in all tibiofemoral subregions. Regarding progression of JSN on radiographs from baseline to FU, three groups were defined: no progression (no increase in OARSI grade in both tibiofemoral compartments), slow (an increase

Table 1
Differences between atrophic OA knees vs. non-atrophic OA knees regarding progression of JSN and progression of cartilage loss, using both (radiographic and MRI) definitions of atrophic vs. non-atrophic knee OA.

Progression of JSN (Radiographic definition)	Atrophic OA knees	Non-atrophic OA knees	p-vaiues
No progression	54/77 (70%)	224/373 (60%)	
Slow progression	22/77 (29%)	143/373 (38%)	0.25
Fast progression	1/77 (1%)	6/373 (2%)	
Progression of Cartilage Loss (Radiographic definition)	**Atrophic OA knees**	**Non-atrophic OA knees**	
No progression	45/77 (58%)	171/373 (46%)	0.12
Slow progression	13/77 (17%)	91/373 (24%)	
Fast progression	19/77 (25%)	111/373 (30%)	
Progression of JSN (MRI definition)	**Atrophic OA knees**	**Non-atrophic OA knees**	
No progression	30/50 (60%)	248/400 (62%)	
Slow progression	19/50 (38%)	146/400 (36%)	0.94
Fast progression	2/50 (1%)	6/400 (2%)	
Progression of cartilage loss (MRI definition)	**Atrophic OA knees**	**Non-atrophic OA knees**	
No Progression	29/50 (58%)	187/400 (47%)	
Slow Progression	12/50 (24%)	92/400 (23%)	0.17
Fast Progression	9/50 (18%)	121/400 (30%)	

Table 2
Association of atrophic knee OA with any progression of JSN and cartilage loss, compared to non-atrophic OA knees using both (radiographic and MRI) definitions of atrophic and non-atrophic OA.

OA phenotype (Radiographic definition)	Absence of progression of JSN	Any progression of JSN	Adjusted odds ratio	
			OR (95%CI)	p-value
Non-atrophic OA	224/373 (60%)	149/373 (40%)	1.0 (ref)	
Atrophic OA	54/77 (70%)	23/77 (3096)	0.6 (0.4, 1.0)	0.06
OA phenotype (Radiographic definition)	**Absence of progression of cartilage loss**	**Any progression of cartilage loss**	**Adjusted odds ratio**	
			OR (95%CI)	**p-value**
Non-atrophic OA	171/373 (46%)	202/373 (54%)	1.0 (ref)	–
Atrophic OA	45/77 (58%)	32/77 (42%)	0.6 (0.3, 1.0)	0.04
OA Phenotype (MRI Definition)	**Absence of Progression of JSN**	**Any Progression of JSN**	**Adjusted Odds Ratio**	
Non-atrophic OA			**OR (95%CI)**	**p-value**
	248/400 (62%)	152/450 (38%)	1.0 (ref)	–
Atrophic OA	30/50 (60%)	20/50 (40%)	1.2 (0.7, 2.3)	0.53
OA Phenotype (MRI Definition)	**Absence of Progression of Cartilage Loss**	**Any Progression of Cartilage Loss**	**Adjusted Odds Ratio**	
			OR (95%CI)	**p-value**
Non-atrophic OA	187/400 (47%)	213/400(53%)	1.0 (ref)	–
Atrophic OA	29/50 (58%)	21/50 (4296)	0.7 (0.4,1.3)	0.24

of up to one OARSI grade in at least one compartment), and fast progression (an increase of more than one OARSI grade in at least one compartment). Regarding progression of cartilage loss on MRI from baseline to FU, three groups were defined: no progression (same WORMS grade in all ten subregions), slow (an increase up to one WORMS grade, including within-grade increase, in at least one of the ten subregions), and fast progression (an increase of more than one WORMS grade in at least one of the ten subregions). Co-variance analysis was performed to test if there were differences between atrophic vs. non-atrophic knee OA phenotypes, using both (radiographs and MRI) definitions, regarding no progression, slow, and fast progression of JSN and cartilage loss. Logistic regression analysis with generalized estimated equations was performed to assess the association of atrophic knee OA with any progression of JSN and cartilage loss, compared to non-atrophic OA knees (reference group). The results were adjusted for age, gender, body mass index, tibiofemoral malalignment, progression of meniscal damage and extrusion.

Results: A total of 450 knees from 398 participants were included. Using the radiographic definition, there were 77 (17.1%) atrophic OA and 373 (82.9%) non-atrophic OA knees at baseline. Using the MRI definition, there were 50 (11.1%) atrophic OA and 400 (88.9%) non-atrophic OA knees. There were no significant differences between both groups (atrophic vs. non-atrophic) regarding fast progression of JSN or cartilage damage (Table 1). Logistic regression analysis using both definitions showed that the atrophic phenotype of knee OA was not at increased risk for progression of disease compared to the non-atrophic phenotype (Table 2). Using the radiographic definition, a modest protective effect against progression of MRI cartilage loss was demonstrated for atrophic OA knees when compared to the non-atrophic group (OR = 0.6 (95%CI 0.3, 1.0); p=0.04).

Conclusions: Based on these results, the atrophic phenotype of knee OA does not predispose OA joints to more rapid progression compared to non-atrophic OA. This finding might be of potential relevance for eligibility of participants with atrophic knee OA in aNGF programs who are commonly excluded due to potential increased risk for rapid progressive OA.

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CROSS-SECTINAL AND LONGITUDINAL ASSOCIATIONS BETWEEN SERUM LEVELS OF HIGH SENSITIVITY C-REACTIVE PROTEIN, RESISTIN AND KNEE BONE MARROW LESIONS IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Purpose: Low-grade inflammation may play a role in osteoarthritis (OA). Although some studies reported that inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) were increased in OA, the findings for associations between hs-CRP and OA are inconsistent. The link between serum levels of hs-CRP and bone marrow lesions (BMLs) in OA patientshas not been explored., Similarly, the findings for the associations between resistin and OA are controversial and little is known if resistin is associated with BMLs. The aims of this study were, therefore, to describe the association between serum levels of hs-CRP, resistin and BMLs cross sectionally and longitudinally in patients with knee OA.

Methods: A total of 188 patients (mean 63 years, range 50-79, female 53%) with symptomatic knee OA were selected from a randomised placebo controlled clinical trial studying the effect of vitamin D supplementation on OA. Serum levels of hs-CRP and resistin were tested at baseline and 24 months later using enzyme-linked immunosorbent assay (ELISA). T2 weighted fat-supressed fast spin echo magnetic resonance imaging (MRI) was performed at baseline and 24 months to assess compartmental and total knee BMLs scores and their changes using modified Whole-Organ MRI Score system (WORMS). Linear or logistic regression analyses were used to determine the association of baseline hs-CRP and resistin with total knee BMLs as well as changes or increases in BMLs before and after adjustment for age, sex, BMI, treatment (vitamin D / placebo) and CRP / resistin as appropriate.

Results: At baseline, quartiles of serum level of hs-CRP were associated with total knee bone marrow lesions in multivariable analyses (OR: 1.45 per quartile, 95% CI: 1.01, 2.09). Serum levels of resistin were associated with total knee BMLs (β:0.04 per ng/ml, 95% CI: 0.01, 0.08). Longitudinally, quartiles of serum levels of hs-CRP predicted increases in total knee BMLs (OR: 1.51 per quartile, 95% CI: 1.08, 2.12; Figure 1), and changes in serum levels of hs-CRP were associated with changes in total knee BMLs (β: 0.09, 95% CI: 0.04, 0.34). Baseline resistin levels were not significantly associated with change in total BMLs. Change in serum levels of resistin were only associated with changes in lateral tibiofemoral BMLs (β: 0.16, 95%CI: 0.01, 0.05) and not total knee BMLs (β: 1.01, 95%CI: 0.97, 1.04).

Conclusions: This is the first study to report that serum levels of hs-CRP are associated with total knee BMLs and predict worsening knee BMLs over 2 years in patients with knee OA, suggesting inflammatory involvement in the pathogenesis of BMLs. Serum resistin levels are associated with BMLs in knee OA, but the causal relationship is unknown.