The Journal of Physical Therapy Science

S P T S

Original Article

Relationship between atherosclerosis and knee osteoarthritis as graded by radiography and ultrasonography in females

Ayşe Aydemir Ekim[1]*, Esra Erkol İnal[2], Dilek Serin Kaya[1], Şebnem Yilmazer[1], Selen Kuzgun[1], Gamze Mumcu[1], Alper Yurdasiper[3], Ahmet Musmul[4]

[1] Department of Physical Medicine and Rehabilitation, Zübeyde Hanım Campus, Eskişehir State Hospital: Eskişehir, Turkey
[2] Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Süleyman Demirel University, Turkey
[3] Department of Radiology, Eskişehir State Hospital, Turkey
[4] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Osmangazi University, Turkey

Abstract. [Purpose] The aim of this study was to assess the relationship between atherosclerosis and knee osteoarthritis grade in women as assessed by both ultrasonography and radiography. [Subjects and Methods] Seventy women diagnosed with knee osteoarthritis were classified into two groups according to cartilage grading/radiographic grading. Patients with Kellgren-Lawrence grades 1 and 2 were included in group 1, while those with Kellgren-Lawrence grades 3 and 4 were included in group 2. Patients with cartilage grades 1–3 were included in group 1, while those with cartilage grades 4–6 were included in group 2. Patients were clinically assessed using a visual analog scale and the Western Ontario and McMaster Universities Arthritis Index. Radiographic osteoarthritis grade was scored using the Kellgren and Lawrence grading system. Using ultrasonography, symptomatic knees were graded and evaluated for distal femoral cartilage thickness. Carotid intima-media thickness and serum lipid levels were measured to assess atherosclerosis. [Results] Carotid intima-media thickness measurements were higher in group 2 than in group 1 as determined by the Kellgren-Lawrence and cartilage grading systems. Carotid intima-media thickness measurements were positively correlated with both the ultrasonographic cartilage grade and Kellgren-Lawrence. [Conclusion] The results of this study suggest that osteoarthritis as assessed by ultrasonography was successful and comparable to assessment with radiography. We showed a correlation between atherosclerosis and ultrasonographic knee osteoarthritis grade.
Key words: Knee osteoarthritis, Ultrasonography, Atherosclerosis

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent joint disorder with a great pain and disability burden[1]. It is characterized by the loss of cartilage structure, subchondral bone sclerosis, synovial inflammation, and osteophyte formation with involvement of the whole joint (i.e., joint failure)[2]. Different risk factors have been suggested for OA, such as age, female sex, and obesity. However, other potential risk factors have also been suggested, such as the presence of diabetes mellitus (DM), menopause, and high cholesterol levels[3–6].

Atherosclerosis is also a highly prevalent chronic disorder that has a substantial impact on quality of life and leads to ever-

increasing costs to society[1, 7]. Several observational studies have reported an association between subclinical measures of atherosclerosis and OA of the hands and knees, predominantly among women[8–10]. Similarly, a greater risk of cardiovascular death has been reported for patients with knee and/or hip OA[11]. However, it is unclear whether atherosclerosis and OA are associated as concurrent diseases due to a common etiology or whether they are causally related. The purpose of this study was to investigate the relationship between atherosclerosis and the progression of OA using ultrasonography (US) and plain radiography.

SUBJECTS AND METHODS

A total of 70 female patients who visited a physical medicine and rehabilitation outpatient clinic were recruited for this study. All patients with a diagnosis of knee OA according to the American College of Rheumatology criteria were enrolled[12]. The local ethics committee approved the study, and all participants provided written informed consent.

Patients with a history of myocardial infarction, percutaneous transluminal coronary angioplasty, surgery for ischemic heart disease, stroke, transient ischemic attack, carotid endarterectomy, inflammatory/infectious arthritis, knee surgery, or intra-articular injection within the previous month were excluded.

Patients were examined by a research physician. None of the patients had redness, swelling, or joint instability upon physical examination. Some had DM and/or arterial hypertension (AH); they did not use any drugs other than those specifically related to DM and AH. All of the patients participating in the study were postmenopausal.

None were smokers. Age, height, weight, and duration of symptoms were evaluated. Patients were clinically assessed for pain and functional status using a visual analog scale (VAS) at rest and at motion and the Western Ontario and McMaster Universities Arthritis Index (WOMAC), respectively. The WOMAC is a three-dimensional, disease-specific, self-administered health status measure that evaluates pain, joint stiffness, and physical function in patients with knee OA. The Turkish version of the WOMAC was used in this study[13].

Laboratory measures were determined using blood samples obtained after at least a 6-hour fast and included tests for glucose, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and renal/liver function, as well as lipid profiles for total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG).

Knee radiographs were evaluated using the Kellgren-Lawrence (K-L) grading system (range 1–4), the most widely used method for diagnosing knee OA, focusing on osteophytes and/or joint space narrowing[14, 15], and higher grades reflect greater severity of OA. Patients with K-L grades 1 and 2 were included in group 1, while those with K-L grades 3 and 4 were included in group 2.

All ultrasonographic measurements were performed by the same physiatrist using a 5–10-MHz linear probe (Diagnostic Ultrasound System, Shimadzu, Kyoto, Japan). All knees were graded and evaluated for distal femoral cartilage thickness. Distal femoral cartilage assessment was performed as patients lay in a supine position with their knees at maximum flexion. The transducer was placed axially above the outer patellar edge[16]. Cartilage thickness measurements were taken from the midpoints of the medial femoral condyle (MFC), intercondylar area (ICA), and the lateral femoral condyle (LFC). Cartilage thickness was measured as the distance between the thin hyperechoic line at the synovial space–cartilage interface and the sharp hyperechoic line at the cartilage–bone interface[17]. Cartilage grading (range, 0–6) was performed by evaluating the sharpness, clarity, and thickness of the cartilage band[16], and higher grades reflect greater severity of the disease. Patients with cartilage 1–3 were included in group 1, while those with cartilage grades 4–6 were included in group 2.

Carotid intima-media thickness (CIMT) measurements were obtained for both groups. All measurements were made by the same examiner in a quiet room in which the patient had been resting for 15 minutes. Participants were in the supine position with the neck extended. Ultrasound analysis of both common carotid arteries was performed by the same radiologist, who was not informed of the participants' histories or clinical/laboratory measurements. Measurements were performed using a B-mode high-resolution HD 15 ultrasound (Philips Healthcare, Bothell, WA, USA) with a 5–12 MHz linear probe. The distance between the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall was taken to represent the intima-media thickness. After localization of the common carotid artery, cross-sectional measurements were performed 10 mm proximal to the carotid bulb. Areas with mural atherosclerotic plaque were excluded from measurement. Three measurements were performed on each side. The mean for each side (right and left) was calculated and recorded. Focal widening of the vessel walls by 50% relative to adjacent segments with protrusion into the lumen or an intima-media thickness of >1.5 mm was defined as plaques. None of the patients had atherosclerotic plaque.

Statistical analyses were performed with IBM SPSS Statistics version 21. Data were expressed as the mean ± standard deviation for nominal variables and as the median (minimum-maximum) for ordinal variables. The normal distribution and homogeneity of each parameter was tested with independent samples t-tests. The Mann-Whitney U-test was used for data with non-normal distributions. Correlations among CIMT and disease measures were assessed by Spearman's correlation coefficients. Categorical variables (i.e., the presence of DM and/or AH) were evaluated with the χ^2 test. Statistical significance was set at $p < 0.05$.

Table 1. The clinical and demographic characteristics of the patients with OA

	Patients with OA (n=70)
Age (years)	61.6 ± 8.2
Height (m)	1.58 ± 0.1
Weight (kg)	78.1 ± 14
DM, n (%)	19 (27.1)
AH, n (%)	44 (62.9)
Duration of symptoms (years)	8.87 ± 4.5
WOMAC	
Pain	11.4 ± 2.9
Stiffness	4.64 ± 1.5
Function	42.9 ± 6.8
VAS	
At rest	4.47 ± 0.9
At motion	7.5 ± 0.9
ESR (mm/h)	19.9 ± 11.5
CRP (mg/l)	0.53 ± 0.5
TC (mg/dl)	230.6 ± 40.7
TG (mg/dl)	183.4 ± 82.2
HDL (mg/dl)	50.9 ± 11
LDL (mg/dl)	134.2 ± 34.5
CIMT (mm)	0.81 ± 0.2

Values are shown as the mean ± standard deviation or median (25–75 interquartile range).
OA: osteoarthritis; DM: diabetes mellitus; AH: arterial hypertension; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TC: total cholesterol; TG: trygliseride; HDL: high-density lipoprotein; LDL: low-density lipoprotein

RESULTS

Measurements of the 70 patients' symptomatic knees were analyzed. The demographic characteristics of the patients are presented in Table 1.

Patients were divided into two group based on K-L grade. The duration of symptoms (p=0.012), WOMAC pain (p=0.049), WOMAC stiffness (p=0.002), WOMAC function (p<0.001), VAS at rest (p=0.036), and VAS at motion (p=0.005) values were found to be higher in group 2 than in group 1. Cartilage thicknesses for the MFC, ICA, and LFC (p<0.001) and height (p=0.004) were found to be higher in group 1 than group 2 (Table 2).

Patients were also divided into two groups based on the ultrasonographic cartilage grading system. The duration of symptoms (p=0.002), WOMAC pain (p=0.007), WOMAC stiffness (p=0.001), WOMAC function (p<0.001), VAS at rest (p=0.002), and VAS at motion (p=0.001) values were found to be higher in group 2 than in group 1. Cartilage thicknesses for the MFC, ICA, and LFC were found to be higher in group 1 than group 2 (p<0.001) (Table 3).

CIMT measurements were higher in group 2 than in group 1 according to both the K–L and the cartilage grading systems (p=0.001 and p=0.002, respectively) (Table 4).

There were positive correlations between CIMT measurements and WOMAC stiffness (r=0.265, p=0.026), WOMAC function (r=0.265, p=0.027), VAS at motion (r=0.309, p=0.009), LDL cholesterol (r=0.260, p=0.029), cartilage grade (r=0.369, p=0.02), and K–L grade (r=0.387, p=0.01) (Table 5).

There were negative correlations between CIMT measurements and HDL cholesterol (r=−0.299, p=0.012) and the following measures of cartilage thickness as assessed by ultrasonography: MFC (r=−0.339, p=0.004), ICA (r=−0.375, p=0.001), and LFC (r=−0.347, p=0.003) (Table 5).

Table 2. Radiographic evaluation of patients' knees of according to the K-L grading system

	Group 1 (n=39) (grades 1–2)	Group 2 (n=31) (grades 3–4)
Age (years)	60.5 ± 7.8	63.0 ± 8.6
Height (m)	1.60 ± 0.05	1.56 ± 0.05*
Weight (kg)	78.9 ± 9.8	77.0 ± 18.2
DM, n (%)	9 (23.1)	10 (32.3)
AH, n (%)	21 (53.8)	23 (74.2)
Duration of symptoms (years)	7.7 ± 4.4	10.4 ± 4.3*
WOMAC		
Pain	10.8 ± 3.1	12.2 ± 2.5*
Stiffness	4.18 ± 1.5	5.22 ± 1.3*
Function	40.5 ± 6.6	46.0 ± 5.8*
VAS		
At rest	4.28 ± 0.9	4.71 ± 0.8*
At motion	7.21 ± 0.9	7.87 ± 0.8*
Cartilage thickness (mm)		
MFC	2.24 ± 0.5	1.52 ± 0.2*
ICA	2.48 ± 0.4	1.89 ± 0.3*
LFC	2.41 ± 0.4	1.7 ± 0.3*
ESR (mm/h)	19.97 ± 11.4	19.8 ± 11.9
CRP (mg/l)	0.54 ± 0.4	0.53 ± 0.5
TC (mg/dl)	229.2 ± 38.3	232.5 ± 44.1
TG (mg/dl)	171.5 ± 85.9	198.2 ± 76
HDL (mg/dl)	51.4 ± 10.9	50.3 ± 11.2
LDL (mg/dl)	131.9 ± 32.8	137.1 ± 36.8

*$p < 0.05$. Values are shown as the mean ± standard deviation or median (25–75 interquartile range).
OA: osteoarthritis; K-L: Kellgren-Lawrence; DM: diabetes mellitus, AH: arterial hypertension; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analog scale; MFC: medial femoral condyle; ICA: intercondylar area; LFC: lateral femoral condyle; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TC: total cholesterol; TG: trygliseride; HDL: high-density lipoprotein; LDL: low-density lipoprotein

DISCUSSION

This study evaluated the association between CIMT and radiographic and ultrasonographic knee OA grades. The results showed that CIMT measurements were positively correlated with both the K-L grade and cartilage grade. Additionally, WOMAC stiffness, WOMAC function, and VAS scores at motion were also found to be positively correlated with CIMT measurements.

Both OA and atherosclerosis are common causes of morbidity and mortality. Arterial wall thickening has a strong prognostic value for cardiovascular diseases, and CIMT assessment allows easy identification of patients at risk, as shown in a recent systematic review and meta-analysis[18]. Today, there is widespread acceptance of CIMT as a reliable and easily reproducible noninvasive marker of preclinical atherosclerosis and future cardiovascular disease risk[19]. Early detection of atherosclerosis with a simple CIMT measurement and the use of related precautions can be life-saving for most patients. The relationship between OA and increased cardiovascular risk is not fully understood.

Different mechanisms have been postulated to explain the potential association between atherosclerosis and OA. One hypothesis is that they are concurrent diseases that share etiological features and risk factors[8, 20, 21]. Systemic inflammation caused by visceral adipose tissue could explain a shared pathogenesis and may consequently highlight a target for the prevention and treatment of atherosclerosis and OA[22, 23]. Another hypothesis is that atherosclerotic disease plays an initiating role by causing microcirculatory disturbances in the synovial membrane and subchondral bone that contribute to the cartilage destruction and pathophysiological processes of OA[9, 24, 29]. This hypothesis was put forth by Johnsson et al., who demonstrated an association between hand OA and atherosclerosis in older women[9, 24]. However, several genes, including the Klotho gene, have been found to be associated with both conditions, and a variety of other mechanisms may be involved, including inflammation and the accumulation of advanced glycation end-products[25–28].

Table 3. Ultrasonographic evaluation of patients' knees of according to the cartilage grading system

	Group 1 (n=30) (grades 1–3)	Group 2 (n=40) (grades 4–6)
Age (years)	60.3 ± 8.3	62.6 ± 8.1
Height (m)	1.60 ± 0.1	1.57 ± 0.1
Weight (kg)	79.0 ± 10.2	77.4 ± 16.4
DM, n (%)	6 (20)	13 (32.5)
AH, n (%)	19 (63.3)	25 (62.5)
Duration of symptoms (years)	7.0 ± 4.3	10.3 ± 4.2*
WOMAC		
Pain	10.5 ± 2.6	12.1 ± 2.9*
Stiffness	4.0 ± 1.5	5.12 ± 1.3*
Function	38.9 ± 6.3	46.0 ± 5.6*
VAS		
At rest	4.1 ± 0.9	4.75 ± 0.8*
At motion	7.03 ± 0.9	7.85 ± 0.8*
Cartilage thickness (mm)		
MFC	2.38 ± 0.4	1.58 ± 0.2*
ICA	2.58 ± 0.4	1.95 ± 0.3*
LFC	2.55 ± 0.3	1.75 ± 0.3*
ESR (mm/h)	22.2 ± 11	18.2 ± 11.7
CRP (mg/L)	0.59 ± 0.4	0.49 ± 0.4
TC (mg/dl)	229.3 ± 35.7	231.7 ± 44.5
TG (mg/dl)	164.7 ± 79.4	197.3 ± 82.5
HDL (mg/dl)	52.65 ± 10.9	49.6 ± 11
LDL (mg/dl)	131.7 ± 30.9	136.2 ± 37.2

*$p<0.05$. Values are shown as the mean ± standard deviation or median (25–75 interquartile range).
OA: osteoarthritis; K-L: Kellgren-Lawrence; DM: diabetes mellitus; AH: arterial hypertension; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analog scale; MFC: medial femoral condyle; ICA: intercondylar area; LFC: lateral femoral condyle; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TC, total cholesterol; TG: trygliseride; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 4. Carotid intima-media thickness according to K-L and cartilage grading system in patients with OA

	K-L grading		Cartilage grading	
	Group 1 (n=39) (grades 1–2)	Group 2 (n=31) (grades 3–4)	Group 1 (n=30) (grades 1–3)	Group 2 (n=40) (grades 4–6)
CIMT (mm)	0.76 ± 0.2	0.88 ± 0.2*	0.75 ± 0.2	0.86 ± 0.2*

*$p<0.05$. Values are shown as the mean ± standard deviation or median (25–75 interquartile range).
OA: osteoarthritis; K-L: Kellgren-Lawrence; CIMT: carotid intima-media thickness

Johnsson et al. showed that when data were coupled to evidence of hand OA, there was clearly significant positive association in females, with those having total knee or hip replacements and hand OA exhibiting the highest level of atherosclerosis[30]. In another study, independent correlations were reported between measures of atherosclerosis and the prevalence of knee and/or hand OA in women after adjusting for cardiovascular risk factors[10]. In the present study, CIMT measurements were found to correlate positively with the presence and progression of knee OA in women.

Cigarette smoking, a poor-quality diet, physical inactivity, excessive alcohol consumption, and obesity are all recognized as major preventable causes of coronary heart disease and premature mortality[31–34]. The risk of atherosclerosis is higher in men than in women, but its prevalence in women increases rapidly with certain risk factors, such as menopause, obesity,

Table 5. Correlation with carotid intima-media thickness in OA patients

	Correlation coefficient
Age (years)	0.266
Height (m)	−0.088
Weight (kg)	−0.059
Duration of symptoms (years)	0.180
WOMAC	
Pain	0.141
Stiffness	0.265*
Function	0.265*
VAS	
At rest	0.099
At motion	0.309*
ESR (mm/h)	−0.103
CRP (mg/l)	0.028
TC (mg/dl)	0.140
TG (mg/dl)	0.210
HDL (mg/dl)	−0.299*
LDL (mg/dl)	0.260*
Cartilage thickness (mm)	
MFC	−0.339*
ICA	−0.375*
LFC	−0.347*
Cartilage grading (1–6)	0.369*
K-L grading (1–4)	0.387*

*$p<0.05$. Values are shown as the mean ± standard deviation or median (25–75 interquartile range).
OA: osteoarthritis; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TC: total cholesterol; TG: trygliseride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MFC: medial femoral condyle; ICA: intercondylar area; LFC: lateral femoral condyle; K-L: Kellgren-Lawrence

increasing age, and the presence of DM. In addition, knee pain, such as that caused by OA, can lead to a sedentary lifestyle, and cardiometabolic syndrome might also be present[10]. In our study, CIMT, as a marker of preclinical atherosclerosis, increased in menopausal women with severe knee OA. Notably, CIMT measurements were significantly higher in patients who experienced pain during motion and/or functional disability in daily life.

The imaging modalities most frequently used are conventional radiography and, within the last decade, ultrasonography[35]. Radiographically diagnosed OA is believed to be most commonly manifested in the knee joint[36].

Cartilage thickness is indirectly evaluated by measuring the joint space width. However, variability in knee positioning can lead to variations in these estimates[36]. Another major limitation of measuring the joint space width is that clinicians can only measure the sum of the two opposing cartilage layers and cannot measure the individual cartilage layer thicknesses[37, 38].

Ultrasonography is a noninvasive, widely available, and relatively inexpensive technique. It can be promptly performed, is easily accepted by patients, is a radiation-free diagnostic test, and does not have any contraindications[39]. A previous study reported good agreement between cartilage thickness measurements obtained by magnetic resonance imaging (MRI) and those obtained by ultrasonography[40–42]. The present study showed an association between radiographic and ultrasonographic grades for clinical features of knee OA. At the same time, in patients with knee OA, there was a correlation between CIMT and both radiographic and ultrasonographic grades.

Despite widespread interest in the community, few studies have addressed the relationship between atherosclerosis and OA. This is the first study to explore the relationship between subclinical atherosclerosis and ultrasonographic findings in patients with knee OA. This study showed that ultrasonography is a valid and reliable method for evaluating OA progression. Further research into the pathogenesis of increased cardiovascular risk in patients with OA should be a high priority, as many risk factors are likely to be modifiable.

REFERENCES

1) Woolf AD, Pfleger B: Burden of major musculoskeletal conditions. Bull World Health Organ, 2003, 81: 646–656. [Medline]

2) Hunter DJ, Felson DT: Osteoarthr BMJ, 2006, 332: 639–642.

3) Berenbaum F: Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. Ann Rheum Dis, 2011, 70: 1354–1356. [Medline] [CrossRef]

4) Roman-Blas JA, Castañeda S, Largo R, et al.: Osteoarthritis associated with estrogen deficiency. Arthritis Res Ther, 2009, 11: 241. [Medline] [CrossRef]

5) Sniekers YH, Weinans H, Bierma-Zeinstra SM, et al.: Animal models for osteoarthritis: the effect of ovariectomy and estrogen treatment—a systematic approach. Osteoarthritis Cartilage, 2008, 16: 533–541. [Medline] [CrossRef]

6) Davies-Tuck ML, Hanna F, Davis SR, et al.: Total cholesterol and triglycerides are associated with the development of new bone marrow lesions in asymptomatic middle-aged women—a prospective cohort study. Arthritis Res Ther, 2009, 11: R181. [Medline] [CrossRef]

7) Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation, 2012, 125: e2–e220. [Medline] [CrossRef]

8) Saleh AS, Najjar SS, Muller DC, et al.: Arterial stiffness and hand osteoarthritis: a novel relationship? Osteoarthritis Cartilage, 2007, 15: 357–361. [Medline] [CrossRef]

9) Jonsson H, Helgadottir GP, Aspelund T, et al.: Hand osteoarthritis in older women is associated with carotid and coronary atherosclerosis: the AGES Reykjavik study. Ann Rheum Dis, 2009, 68: 1696–1700. [Medline] [CrossRef]

10) Hoeven TA, Kavousi M, Clockaerts S, et al.: Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. Ann Rheum Dis, 2013, 72: 646–651. [Medline] [CrossRef]

11) Nüesch E, Dieppe P, Reichenbach S, et al.: All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ, 2011, 342: d1165. [Medline] [CrossRef]

12) Altman R, Asch E, Bloch D, et al. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Arthritis Rheum, 1986, 29: 1039–1049. [Medline] [CrossRef]

13) Basaran S, Guzel R, Seydaoglu G, et al.: Validity, reliability, and comparison of the WOMAC osteoarthritis index and Lequesne algofunctional index in Turkish patients with hip or knee osteoarthritis. Clin Rheumatol, 2010, 29: 749–756. [Medline] [CrossRef]

14) Kellgren JH, Lawrence JS: Radiological assessment of osteo-arthrosis. Ann Rheum Dis, 1957, 16: 494–502. [Medline] [CrossRef]

15) Spector TD, Hart DJ, Byrne J, et al.: Definition of osteoarthritis of the knee for epidemiological studies. Ann Rheum Dis, 1993, 52: 790–794. [Medline] [CrossRef]

16) Lee CL, Huang MH, Chai CY, et al.: The validity of in vivo ultrasonographic grading of osteoarthritic femoral condylar cartilage: a comparison with in vitro ultrasonographic and histologic gradings. Osteoarthritis Cartilage, 2008, 16: 352–358. [Medline] [CrossRef]

17) Yoon CH, Kim HS, Ju JH, et al.: Validity of the sonographic longitudinal sagittal image for assessment of the cartilage thickness in the knee osteoarthritis. Clin Rheumatol, 2008, 27: 1507–1516. [Medline] [CrossRef]

18) Lorenz MW, Markus HS, Bots ML, et al.: Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation, 2007, 115: 459–467. [Medline] [CrossRef]

19) O'Leary DH, Polak JF, Kronmal RA, et al. Cardiovascular Health Study Collaborative Research Group: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med, 1999, 340: 14–22. [Medline] [CrossRef]

20) Wang Q, Rozelle AL, Lepus CM, et al.: Identification of a central role for complement in osteoarthritis. Nat Med, 2011, 17: 1674–1679. [Medline] [CrossRef]

21) Niculescu F, Rus H: Complement activation and atherosclerosis. Mol Immunol, 1999, 36: 949–955. [Medline] [CrossRef]

22) Grundy SM: Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab, 2007, 92: 399–404. [Medline] [CrossRef]

23) Katz JD, Agrawal S, Velasquez M: Getting to the heart of the matter: osteoarthritis takes its place as part of the metabolic syndrome. Curr Opin Rheumatol, 2010, 22: 512–519. [Medline] [CrossRef]

24) Conaghan PG, Vanharanta H, Dieppe PA: Is progressive osteoarthritis an atheromatous vascular disease? Ann Rheum Dis, 2005, 64: 1539–1541. [Medline] [CrossRef]

25) Zhang F, Zhai G, Kato BS, et al.: Association between KLOTHO gene and hand osteoarthritis in a female Caucasian population. Osteoarthritis Cartilage, 2007, 15: 624–629. [Medline] [CrossRef]

26) Rhee EJ, Oh KW, Lee WY, et al.: The differential effects of age on the association of KLOTHO gene polymorphisms with coronary artery disease. Metabolism, 2006, 55: 1344–1351. [Medline] [CrossRef]

27) Libby P: Role of inflammation in atherosclerosis associated with rheumatoid arthritis. Am J Med, 2008, 121: S21–S31. [Medline] [CrossRef]

28) Reddy VP, Beyaz A: Inhibitors of the Maillard reaction and AGE breakers as therapeutics for multiple diseases. Drug Discov Today, 2006, 11: 646–654. [Medline] [CrossRef]

29) Kornaat PR, Sharma R, van der Geest RJ, et al.: Positive association between increased popliteal artery vessel wall thickness and generalized osteoarthritis: is OA also part of the metabolic syndrome? Skeletal Radiol, 2009, 38: 1147–1151. [Medline] [CrossRef]

30) Jonsson H, Helgadottir GP, Aspelund T, et al.: The presence of total knee or hip replacements due to osteoarthritis enhances the positive association between hand osteoarthritis and atherosclerosis in women: the AGES-Reykjavik study. Ann Rheum Dis, 2011, 70: 1087–1090. [Medline] [CrossRef]

31) World Health Organization: Public Health Agency of Canada. Preventing chronic diseases: a vital investment. Ottawa: World Health Organization; Public Health Agency of Canada, 2005.

32) Danaei G, Ding EL, Mozaffarian D, et al.: The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med, 2009, 6: e1000058. [Medline] [CrossRef]

33) Folsom AR, Yatsuya H, Nettleton JA, et al. ARIC Study Investigators: Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol, 2011, 57: 1690–1696. [Medline] [CrossRef]

34) United States: Department of Health and Human Service Healthy people 2010: Understanding and improving health. Boston: Jones and Bartlett Publisher, 2001.

35) Babyn PS: Pediatric musculoskeletal imaging. Semin Musculoskelet Radiol, 2009, 13: 157. [CrossRef]

36) Mazzuca SA, Brandt KD, Katz BP: Is conventional radiography suitable for evaluation of a disease-modifying drug in patients with knee osteoarthritis? Osteoarthritis Cartilage, 1997, 5: 217–226. [Medline] [CrossRef]

37) Yao JQ, Seedhom BB: Ultrasonic measurement of the thickness of human articular cartilage in situ. Rheumatology (Oxford), 1999, 38: 1269–1271. [Medline] [CrossRef]

38) Kim K, Lee HY, Lim SJ: Effects of increased standing balance on pain in patients with knee osteoarthritis. J Phys Ther Sci, 2016, 28: 87–89. [Medline] [CrossRef]

39) Richardson ML, Selby B, Montana MA, et al.: Ultrasonography of the knee. Radiol Clin North Am, 1988, 26: 63–75. [Medline]

40) Spannow AH, Stenboeg E, Pfeiffer-Jensen M, et al.: Ultrasound and MRI measurements of joint cartilage in healthy children: a validation study. Ultraschall Med, 2011, 32: S110–S116. [Medline] [CrossRef]

41) Pradsgaard DØ, Fiirgaard B, Spannow AH, et al.: Cartilage thickness of the knee joint in juvenile idiopathic arthritis: comparative assessment by ultrasonography and magnetic resonance imaging. J Rheumatol, 2015, 42: 534–540. [Medline] [CrossRef]

42) Koca I, Boyaci A, Tutoglu A, et al.: The relationship between quadriceps thickness, radiological staging, and clinical parameters in knee osteoarthritis. J Phys Ther Sci, 2014, 26: 931–936. [Medline] [CrossRef]