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" Assessment of Carotid Atherosclerosis in Patients with Knee Osteoarthritis "

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Abstract:

Background: Atherosclerosis is a highly prevalent chronic disorder that substantially impacts quality of life and leads to significant morbidity and mortality. Atherosclerosis is an important feature associated with increased cardio-metabolic risk. Several factors may account for relationship between Knee osteoarthritis (KOA) and cardiovascular diseases (CVD)

Aim: The aim of this study is to assess the association between the severity of KOA and carotid atherosclerosis.

Subjects and Methods: A total of 100 consecutive patients with primary symptomatic KOA were invited to participate in this study. Patients were recruited from the Outpatient Rheumatology Clinic at Mansoura University Hospitals. The study included also 100 consecutive non-KOA subjects matched for age, sex and BMI with KOA patients. All patients met the 2010 EULAR criteria for diagnosis of KOA and patients had to show evidence of radiological changes of KOA by plain radiography and Knee Ultrasonography. Blood samples were collected from all participants to test for ESR, CRP, fasting blood sugar and lipid profile. Assessment of carotid atherosclerosis is made by measurements of Carotid intima media thickness (cIMT).

Results: Comparison between KOA group and non-KOA group. The mean Waist hip ratio was significantly higher in KOA group than non-KOA group ($p<0.001$). KOA patients had significantly more frequent HTN ($p=0.034$), T2DM ($p=0.025$) and Met syndrome ($p=0.002$). The mean FBS level, serum total cholesterol level of the KOA group was significantly higher than non-KOA group ($p=0.021$, $p=0.039$). KOA group had higher cIMT the non-KOA group ($p=0.003$) and more frequently had carotid plaques that non-KOA group ($p=0.005$). the rate of presence of HTN, T2DM and MetS differed significantly among the KOA subgroups ($p=0.032$, $p=0.013$ and $p=0.020$ respectively) with the KOA-KL4 subgroup had the highest rate of the three co-morbidities. The cIMT differed significantly among the KOA subgroups based on KL grading being thickest in the KOA-KL4 subgroup of patients ($p<0.001$). The rate of presence of carotid plaques differed among the groups, with rate being highest in KOA-KL4 subgroup (79.2%), followed by KOA-KL3 subgroup (35.7%) and is lowest in KOA-KL2 subgroup (8.3%). These differences were significant ($p<0.001$).

Conclusion: Carotid Atherosclerosis is associated with KOA, therefore, a diagnosis of OA may serve as a red flag for warning to evaluate CVD. The presence of the MetS, serum TC, radiological KL grade and higher US cartilage thickness grading were the strongest factors that predict the higher cIMT and higher prevalence of carotid plaques in patients with KOA. The presence of the MetS, serum TC and radiological KL grade were the strongest factors that predict the higher cIMT in patients with KOA ($p=0.026$, $p=0.006$, $p=0.004$ and $p=0.015$ respectively)

Keywords: Knee osteoarthritis, Carotid atherosclerosis, Carotid plaques, Carotid intima media thickness, Metabolic syndrome.

Introduction

Osteoarthritis (OA) is a highly prevalent chronic disease among elderly [1]. Atherosclerosis is a highly prevalent chronic disorder that leads to significant morbidity and mortality. There is an increasing evidence that suggests a potential link between OA and atherosclerosis [2]. For example, it had been suggested that the presence of diabetes mellitus (DM), hypertension (HTN), and high serum cholesterol level, all of which are well-established risk factors for CVD, are associated with increased risk of OA [3].

In addition, despite that OA had been traditionally referred to as a degenerative non-inflammatory disease; evolving data indicated that chronic low-grade inflammation is a major driver of ongoing joint degenerative process [4]. The chronic inflammatory state can be a crucial key factor that represent a link between OA and CVD [5]. Moreover, Immobility, due to arthritis, is a risk factor that increases CVDs risk among the patients [6]. Furthermore, nonsteroidal anti-inflammatory drugs, commonly used to treat OA-related pain, are associated with increased risk of CVD [7]**.**

Previous observational studies had reported an association between the subclinical measures of atherosclerosis and knee OA (KOA) as well as OA of the hands, predominantly in the females [8-9]. An elevated risk of cardiovascular death had been reported in patients with knee and/or hip OA [10]. Yet, despite OA being the most common articular disease, little is known regarding the exact relationship between CVD and OA. The aim of this study is to assess the association between the severity of KOA and carotid atherosclerosis.

Subjects and Methods

Subjects: A total of 100 consecutive patients with primary symptomatic KOA were invited to participate in this study. Patients were recruited from the Outpatient Rheumatology Clinic at Mansoura University Hospitals. The study included also 100 consecutive non-KOA subjects matched for age, sex and BMI with KOA patients.

Inclusion Criteria: All patients met the 2010 EULAR criteria for diagnosis of KOA [11] and patients had to show evidence of radiological changes of KOA by plain radiography. Control group (non-KOA group) had no knee pain and no radiological evidence of KOA They are matched for age, sex and BMI with KOA patients. All participants had provided a written informed consent for participation in the study prior to inclusion in the study.

Exclusion Criteria: Patients older than 60 years to minimize impact of age on cIMT, Patients with BMI >33.0 kg/m2 to minimize the impact of obesity on cIMT.

Patients with clinical evidence of atherosclerosis, history of myocardial infarction, CHF, cerebro-vascular disease including transient ischemic attacks or stroke.

Patients with history of cardiac procedures (e.g. surgery for IHD, percutaneous trans-luminal coronary angioplasty). Current or previous smoking habits. Patients with secondary KOA (inflammatory or infectious arthritis). Patients with recent knee trauma.

Patients with history of prior knee surgery.

Patients with knee IA injection in the past 3 months. Crystal induced arthropathy as gout or Calcium pyrophosphate dihydrate crystal deposition disease (CPPD)

All the studied patients will be subjected to thorough history taking and clinical examination. Obesity parameters including BMI, waist circumference, waist-hip ratio were measured. All patients completed the WOMAC questionnaire [12]**.** Met.S was defined according to the updated third report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP/ATPIII) criteria [13].

Blood samples were collected from all participants on the same day of history taking and clinical and radiological examination to test for ESR, CRP, fasting blood sugar and lipid profile.

Radiological Assessment

Anteroposterior and lateral weight-bearing radiographs with knee in semi-flexed position were obtained for right and left knees in each patient. Severity of KOA is evaluated using the KL grading system (range 1–4), and higher grades reflect greater severity of OA [14]. The clinical and radiological data of knee joint with the higher radiological KL grade (index knee) were included in the data analysis and statistical interpretation.

Ultrasonographic measurement of the cartilage thickness was performed with a linear probe (7 –12 MHz) of the medial femoral condyle. Cartilage thickness was measured, in millimeters, as the distance extending from the thin hyper echoic line at cartilage–synovial space interface to the sharp hyper echoic line at cartilage–bone interface [15]. Cartilage US evaluation include three parameters; sharpness, clarity, and thickness of the cartilage band that were graded ranging from 0 to 6. Higher grades indicate higher KOA severity [16].

Carotid Intima-Media Thickness Measurements

Measurements of cIMT were performed for all participants. A segment ~1.5 cm proximal to carotid artery bifurcation was identified and the cIMT of the far wall was measured as the distance from luminal–intimal layer to medial–adventitial layer [17]. One transverse measurement plus two longitudinal measurements of the cIMT were obtained from 10 adjacent spots at one mm interval. The mean of the 10 cIMT measurements on each side was calculated, and the average of both readings was recorded and used in the data analysis. Presence of carotid plaque was diagnosed according to Mannheim cIMT consensus report [18].

Statistical Analysis

All statistical procedures were done using SPSS version 20.0 statistic software. All variables containing continuous were normally distributed and were presented in mean ±SD. Categorical variables were demonstrated in number and percent. Comparisons were performed using independent sample Student's t test or one-way ANOVA test as appropriate. Categorical variables were compared using Chi-square test. OR were calculated for qualitative variables for presence of KOA or MetS. The *95% CI* was used to estimate precision of OR. Univariate regression analysis and multivariate regression analysis for factors associated with increased cIMT and with presence of carotid plaques in patients with KOA. The significance of p value was set at <0.05.

Results

All radiological images were performed and interpreted by the same experienced musculoskeletal radiologist who was blinded to the clinical and laboratory findings of the patients. The radiological findings of the patients were scored and interpreted two times with a 3-month interval. The kappa value for intra-rater agreement was 0.89 and 0.82 for KL grading on plain radiography and for US findings respectively.

Comparison of KOA group with non-KOA group

Table 1 demonstrates the comparison between KOA group and non-KOA group. The mean WHR was significantly higher in KOA group than non-KOA group (p<0.001). KOA patients had significantly more frequent HTN (p=0.034), T2DM (p=0.025) and MetS (p=0.002). The mean FBS level, serum total cholesterol level of the KOA group was significantly higher than non-KOA group (p=0.021, p=0.039). KOA group had higher cIMT the non-KOA group (p=0.003) and more frequently had carotid plaques that non-KOA group (p=0.005).

Table 1. Comparison of the sociodemographic, laboratory and carotid artery US examination between the KOA group and non-KOA group and clinical features of KOA group

	KOA group	Non-KOA group	Mean difference or OR [95% CI]	Student's t test	
	Mean ±SD	Mean ±SD		t	p
Age (years) (Mean ±SD)	54.1 ±4.2	53.9 ±4.5		0.292	0.770
Sex (%)					
Females	71%	65%			
Males	29%	35%		0.827	0.363
Educational level (%)					
Basic	10%	8%			
Secondary	49%	58%			
University	41%	34%		1.633	0.442
Residence (%)					
Rural	54%	49%			
Urban	46%	51%		0.500	0.480
Obesity Parameters					
BMI (kg/m^2)	29.9 ±2.3	29.4 ±2.4	0.50 [-0.16, 1.16]	1.504	0.134
Waist circumference (cm)	110.9 ±13.9	107.9 ±10.6	3.00 [-0.45, 6.45]	1.716	0.088

W/H ratio	0.98 ±0.08	0.92 ±0.07	0.06 [0.04, 0.08]	4.983	<0.001
Co-morbidities (n, %)					
HTN	57%	42%	1.83 [1.04, 3.21]	4.500	0.034
T2DM	41%	26%	1.98 [1.09, 3.60]	5.050	0.025
Metabolic syndrome	46%	25%	2.56 [1.4, 4.65]	9.630	0.002
Clinical Features					
Duration of KOA (years)	8.6 ±2.8				
WOMAC scale					
Pain subscale	11.0 ±2.7				
Stiffness subscale	5.5 ±1.3				
Physical functioning subscale	51.7 ±6.8				
Total WOMAC score	68.3 ±10.2				
Laboratory findings					
ESR 1st hour (mm)	23.9 ±8.1	22.7 ±7.5	1.20 [-0.98, 3.38]	1.087	0.278
CRP (mg/dl)	1.49 ±0.68	1.38 ±0.55	0.11 [-0.07, 0.28]	1.258	0.210
FBS (mg/dl)	131.7 ±49.3	115.8 ±47.6	15.90 [2.39, 29.41]	2.320	0.021
Total cholesterol (mg/dl)	268.5 ±61.5	251.7 ±52.4	16.80 [2.13, 29.73]	1.990	0.039
TGs (mg/dl)	208.2 ±57.5	197.8 ±49.9	10.40 [-4.61, 25.41]	1.366	0.174
HDL-C (mg/dl)	43.9 ±5.3	45.2 ±7.1	-1.30 [-3.05, 0.45]	1.467	0.144
LDL-C (mg/dl)	183.3 ±58.2	169.0 ±64.1	14.30 [-2.77, 31.37]	1.652	0.100
KL grade					
Grade 2	48%				
Grade 3	28%				
Grade 4	24%				
Grade 5	-				
Grade 6	-				
Mean ±SD	2.8 ±0.8				
Cartilage US grading					
Grade 2	27%				
Grade 3	45%				
Grade 4	15%				
Grade 5	11%				
Grade 6	2%				
Mean ±SD	3.2 ±1.0				
Carotid artery US examination					
cIMT (mm)	0.89 ±0.25	0.78 ±0.27	0.11 [0.04, 0.18]	2.989	0.003
Plaques (%)	33%	16%	2.59 [1.31, 5.09]	7.812	0.005

Comparison among KOA-KL2, KOA-KL3 and KOA-KL4 subgroups

As shown in Table 2, despite that the BMI did not differ significantly among the KOA subgroups based on KL grading, significant differences had been found among the three subgroups as regards the WC (p<0.001) and WHR (p<0.001) being highest in KOA-KL4 subgroup. Moreover, the rate of presence of HTN, T2DM and MetS differed significantly among the KOA subgroups (p=0.032, p=0.013 and p=0.020 respectively) with the KOA-KL4 subgroup had the highest rate of the three co-morbidities. The duration of KOA showed significant difference among the KOA subgroups with the KOA-KL4 subgroup had the longest disease duration (p=0.011). Total WOMAC and subscales scores showed significant difference among the KOA subgroups (p<0.001) with the highest scores seen in KOA-KL subgroup. FBS, total cholesterol and TGs showed significant difference among the KOA subgroups based on KL grades (p<0.001, p=0.014 and p=0.003 respectively). The cIMT differed significantly among the KOA

subgroups based on KL grading being thickest in the KOA-KL4 subgroup of patients (p<0.001). The rate of presence of carotid plaques differed among the groups, with rate being highest in KOA-KL4 subgroup (79.2%), followed by KOA-KL3 subgroup (35.7%) and is lowest in KOA-KL2 subgroup (8.3%). These differences were significant (p<0.001).

Table 2. Comparison of the sociodemographic characteristics among KOA-KL4, KOA-KL3 and KOA-KL2 subgroups

	KOA patients subgroups			ANOVA test	
	KOA-KL2	KOA-KL3	KOA-KL4	F	p
Age (years) (mean ±SD)	53.3 ±4.5	54.4 ±4.3	55.3 ±3.5	1.897	0.155
Sex (n, %)					
Females	37, 77.1%	19, 67.9%	15, 62.5%		
Males	11, 22.9%	9, 32.1%	9, 37.5%	1.839	0.399
Educational level (n, %)					
Basic	3, 6.2%	4, 14.3%	3, 12.5%		
Secondary	23, 47.9%	14, 50.0%	12, 50.0%		
University	22, 45.8%	10, 35.7%	9, 37.5%	1.897	0.755
Residence (n, %)					
Rural	24, 50.0%	17, 60.7%	13, 54.2%		
Urban	24, 50.0%	11, 39.3%	11, 45.8%	0.818	0.664
BMI (kg/m^2)	29.6 ±2.3	30.0 ±2.6	30.1 ±1.7	0.497	0.610
Waist circumference (cm)	107.5 ±12.4	112.9 ±5.7	115.8 ±4.1	7.095	<0.001
W/H ratio	0.95 ±0.08	0.99 ±0.09	1.04 ±0.07	10.097	<0.001
HTN	23, 47.9%	14, 50.0%	19, 79.2%	6.909	0.032
T2DM	15, 31.3%	10, 35.7%	16, 66.7%	8.746	0.013
Metabolic syndrome	18, 37.5%	11, 39.3%	17, 70.8%	7.863	0.020
Duration of KOA (years)	7.9 ±2.8	8.5 ±2.6	10.0 ±2.7	4.775	0.011
WOMAC scale					
Pain subscale	9.4 ±1.9	11.0±1.8	14.3 ±2.0	51.628	<0.001
Stiffness subscale	4.8 ±0.9	5.5 ±0.8	7.0 ±1.0	45.649	<0.001
Physical functioning subscale	47.8 ±6.0	52.8 ±5.3	58.3 ±3.5	32.444	<0.001
Total WOMAC score	62.0 ±8.2	69.3 ±7.3	79.6 ±5.5	45.800	<0.001
ESR 1^{st} hour (mm)	22.8 ±8.6	24.3 ±7.9	25.5 ±7.4	0.895	0.412
CRP (mg/dl)	1.42 ±0.72	1.52 ±0.66	1.62 ±0.61	0.916	0.404
FBS (mg/dl)	122.4 ±31.1	137.7 ±29.7	153.6 ±24.8	9.337	<0.001
Total cholesterol (mg/dl)	264.9 ±41.1	271.2 ±39.8	295.0 ±40.6	4.477	0.014
TGs (mg/dl)	201.3 ±42.3	211.1 ±35.1	232.3 ±37.1	6.191	0.003

HDL-C (mg/dl)	42.8 ±5.5	43.8 ±4.8	45.9 ±5.0	2.822	0.064
LDL-C (mg/dl)	170.7 ±56.9	187.6 ±59.6	203.4 ±55.1	2.723	0.071
cIMT (mm)	0.76 ±0.07	0.89 ±0.22	1.16 ±0.31	33.747	<0.001
Presence of plaques	4, 8.3%	10, 35.7%	19, 79.2%	36.348	<0.001

As shown in Table 3, KOA patients with MetS had significantly higher WC and WHR than KOA patients without MetS (p=0.009 and p=0.027 respectively). Regarding the co-morbidities, HTN and T2DM were significantly more frequent in KOA patients with MetS than KOA patients without MetS (p<0.001 for both). WOMAC pain, stiffness and physical functioning subscales were significantly higher in KOA patients with MetS than patients without MetS (p=0.026, p=0.048 and p=0.022 respectively). Similarly, KOA patients with MetS had significantly higher total WOMAC score than patients without MetS (p=0.018). FBS was significantly higher in KOA patients with MetS than patients without MetS (p=0.010). Similarly, serum cholesterol, TGs and LDL-c were significantly higher in KOA patients with MetS in comparison to the patients without MetS (p=0.023, p=0.021 and 0.038 respectively) while KOA patients with MetS had significantly lower HDL-C than patients without MetS (p=0.010). KOA-MetS subgroup had significantly thicker cIMT than KOA-no-MetS subgroup (p=0.004). KOA-MetS subgroup had significantly more frequent carotid plaques than KOA-no-MetS subgroup (p=0.004). KOA-MetS subgroup had significantly higher US cartilage thickness grade than KOA-no-MetS subgroup (p=0.007).

Table 3. Comparison of the obesity parameters, co-morbidities and clinical features between KOA patients without and with MetS

	KOA-no-MetS	KOA-MetS	Mean difference	Student' t test	
	Mean ±SD	Mean ±SD	Or OR [95% CI]	t	P
Age (years) (mean ±SD)	53.6 ±4.2	54.6 ±4.2		1.187	0.238
Sex (n, %)					
Females	40, 74.1%	31, 67.4%			
Males	14, 25.9%	15, 32.6%		0.539	0.463
Educational level (n, %)					
Basic	4, 7.4%	6, 13.0%			
Secondary	28, 51.9%	21, 45.7%			
University	22, 40.7%	19, 41.3%		0.986	0.611
Residence (n, %)					
Rural	32, 59.3%	22, 47.8%			
Urban	22, 40.7%	24, 52.2%		1.307	0.253
BMI (kg/m^2)	29.8 ±2.3	30.0 ±2.2	0.21 [-1.12, 0.69]	0.469	0.640
Waist circumference (cm)	107.7 ±13.2	114.9 ±13.9	7.2 [1.81, 12.56]	2.653	0.009
W/H ratio	0.96 ±0.08	1.00 ±0.08	0.03 [0.004, 0.07]	2.252	0.027
Co-morbidities					
HTN	17, 31.5%	40, 87.0%	14.51 [5.17, 40.7]	31.189	<0.001
T2DM	11, 20.4%	30, 65.2%	14.07 [5.37, 36.9]	20.653	<0.001
Duration of KOA (years)	8.2 ±2.8	9.1 ±2.8	0.90 [-2.02, 0.22]	1.591	0.115

WOMAC scale					
Pain subscale	10.3 ±2.3	11.7 ±3.0	1.4 [0.35, -2.44]	2.262	0.026
Stiffness subscale	5.3 ±1.1	5.8 ±1.4	0.5 [0.15, 1.14]	1.999	0.048
Physical functioning subscale	50.3 ±6.4	53.4 ±6.9	3.05 [0.41, 5.69]	2.329	0.022
Total WOMAC score	66.1 ±9.3	70.9 ±10.6	4.80 [1.15, 9.04]	2.412	0.018
ESR 1st hour (mm)	22.8 ±7.9	25.1 ±8.3	2.3 [-5.58, 0.87]	1.407	0.162
CRP (mg/dl)	1.39 ±0.66	1.60 ±0.69	0.21 [-0.47, 0.06]	1.544	0.126
FBS (mg/dl)	120.0 ±40.6	145.5 ±55.2	25.5 [6.46, 44.6]	2.644	0.010
Total cholesterol (mg/dl)	255.7 ±56.8	283.5 ±63.9	27.8 [3.8, 51.78]	2.303	0.023
TGs (mg/dl)	196.0 ±53.0	222.5 ±59.7	26.5 [4.11, 48.86]	2.349	0.021
HDL-C (mg/dl)	42.6 ±4.5	45.3 ±5.8	2.69 [0.65, 4.74]	2.613	0.010
LDL-C (mg/dl)	172.8 ±50.2	196.4 ±62.1	23.6 [11.3, 55.92]	2.101	0.038
cIMT (mm)	0.83 ±0.18	0.97 ±0.30	0.14 [0.05, 0.24]	2.923	0.004
Presence of plaques	11, 20.4%	22, 47.8%	3.58 [1.49, 8.63]	8.469	0.004
US cartilage thickness grade	3.4 ±1.0	2.9 ±0.9	0.54 [0.15, 0.93]	2.733	0.007

On the univariate linear regression analysis, the variables that are associated with the cIMT in patients with KOA include WC, WHR, presence of HTN, presence of T2DM, presence of MetS, FBS, serum cholesterol, KL grade and US cartilage thickness grade. The multivariate regression analysis showed that presence of the MetS, serum TC, radiological KL grade and US cartilage thickness grade were the strongest factors that predict the higher cIMT in patients with KOA (p=0.005, p=0.039, p=0.012 and p=0.048 respectively) (Table 4).

Table 4. Univariate regression analysis for factors associated with increased cIMT in patients with KOA

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	P
Age	0.002	0.002	0.127	1.268	0.208
Sex	0.077	0.053	0.145	1.447	0.151
BMI	0.450	0.318	0.142	1.415	0.160
WC	0.110	0.045	1.191	2.443	0.016
WHR	0.015	0.007	0.198	2.002	0.048
HTN	0.084	0.039	0.153	2.148	0.034
T2DM	0.011	0.005	0.187	2.351	0.021
MetS	0.041	0.015	0.446	2.720	0.008
Duration of KOA	0.008	0.004	0.306	1.833	0.070
ESR	0.001	0.001	0.045	0.596	0.552
CRP	0.004	0.007	0.045	0.568	0.571
FBS	0.086	0.039	0.156	2.217	0.029
TC	0.011	0.005	0.187	2.360	0.020
TG	0.007	0.004	0.303	1.878	0.063

HDL	-0.005	0.007	-0.053	-0.709	0.480
LDL	0.018	0.016	0.194	1.140	0.257
Radiological KL grade	0.258	0.099	0.249	2.606	0.011
US cartilage thickness grade	0.135	0.052	0.218	2.483	0.016

On the univariate binary logistic regression analysis, the variables that are associated with the presence of carotid plaques in patients with KOA include WC, WHR, presence of HTN, presence of T2DM, presence of MetS, FBS, serum cholesterol, KL radiological grade and US cartilage thickness grade. The multivariate binary logistic regression analysis showed that presence of the MetS, serum TC and radiological KL grade were the strongest factors that predict the higher cIMT in patients with KOA (p=0.026, p=0.006, p=0.004 and p=0.015 respectively) (Table 5).

Table 5. Binary logistic regression analysis for factors associated with presence of carotid plaques in patients with KOA

	B	Std. Error	Wald	Significance	Exp(B)
Age	0.803	0.451	3.174	0.075	2.232
Sex	0.216	0.744	0.084	0.772	1.241
BMI	0.186	0.170	1.194	0.274	1.204
WC	0.260	0.110	5.618	0.018	1.297
WHR	0.135	0.058	5.405	0.020	1.144
HTN	0.831	0.434	3.665	0.046	2.296
T2DM	0.061	0.028	4.809	0.028	1.063
MetS	0.175	0.057	9.535	0.002	1.192
Duration of KOA	0.128	0.077	2.729	0.099	1.137
ESR	0.011	0.372	0.001	0.977	1.011
CRP	1.473	4.490	0.108	0.743	4.361
FBS	0.043	0.019	5.359	0.021	1.044
TC	0.057	0.019	8.767	0.003	1.058
TG	0.082	0.046	3.233	0.072	1.086
HDL	-1.123	0.723	2.410	0.121	0.325
LDL	0.084	0.332	0.065	0.799	1.088
Radiological KL grade	1.363	0.466	8.576	0.003	3.910
US cartilage thickness grade	0.052	0.024	5.084	0.025	1.054

Discussion

In the first step of the statistical analysis of the present study, we compared the KOA patients with non-KOA participants regarding the potential factors associated with the disease. The major findings of this comparison were: (a) KOA patients had significantly higher frequency of MetS, (b) the individual components of MetS, including T2DM and HTN were more prevalent in KOA patients than non-KOA subjects, and KOA patients had significantly higher WHR, FBS and serum cholesterol than non KOA subjects and (c) KOA patients had more prevalent carotid plaques and thicker cIMT than non KOA subjects.

Our results showed that MetS were significantly more frequent among KOA patients than non-KOA participants. Regarding the individual components of MetS, our results also demonstrated that HTN and T2DM were significantly more prevalent in KOA patients compared to non-KOA participants. In addition, KOA had significantly higher WHR, FBS and serum cholesterol level than non-KOA patients.

In agreement with our findings, evidence from several cross-sectional studies had provided the support for the relationship between MetS or its individual components and OA. For example, a population-based cohort study reported a higher rate of MetS among the KOA patients (39%) than in non-OA participants (18%) [19].

Results from a longitudinal cohort study that explored the association between systolic and diastolic blood pressure or treatment with anti-hypertensives and KOA incidence indicated that KOA patients had significantly higher systolic blood pressure than controls. Moreover, the longitudinal follow up of the patients for 48 months revealed that HTN was associated with higher frequency of radiological KOA whereas treatment using ≥3 anti-hypertensive agents was associated with reduction of incidence [20].

Moreover, a case control study found that T2DM increases the risk of occurrence of KOA [21]. A systematic meta-analysis review of literature that analyzed data from 49 studies reported that the risk of KOA was significantly higher in T2DM than non-T2DM counterparts (OR=1.5), as was T2DM in KOA than non-OA counterparts (OR=1.4). The results of this meta-analysis highlight the higher prevalence of KOA among T2DM patients [22].

T2DM has been evidenced as an independent factor that predict development of OA in a population-based cohort study with follow up of participants over a period of 20 years [23]. Along this line, T2DM and hyperglycemia are likely to be associated with OA [24].

Li et al. [25] found that HTN, obesity, dyslipidemia and MetS was significantly more prevalent among the KOA patients than matched controls. In addition, the study found

a significant correlation between the degree of HTN, dyslipidemia or hyperglycemia and the severity of KOA symptoms. These findings are consistent our findings.

A large cross-sectional study that quantified the effect of dyslipidemia on KOA, showed that dyslipidemia was associated with knee joint pain (OR= 1.3) and clinical KOA (OR=1.34). Moreover, each one-unit increase in serum TGs level was associated with 9% increased risk of clinical KOA [26].

A systemic review reported that in radiological studies, radiological evidence of KOA was directly associated with MetS, HTN and T2DM. In addition, the symptomatic KOA was associated with MetS, HTN but not with T2DM [27].

A meta-analysis by ***Xiong et al.*** [28] that included large sample size (22 754 OA patients and 53 955 non-OA participants) proved that the OA risk was evidently higher among patients with dyslipidemia than those without dyslipidemia.

After adjustment for obesity, a link between MetS and OA was proven in several epidemiological studies that also suggest that the components of MetS, including T2DM, HTN or dyslipidemia either in cluster or independently participate in the OA pathogenesis [29]. The findings of the aforementioned studies together come in support for the association of MetS and its individual components with OA, in support to the findings of the present study.

The results of our study showed that cIMT was significantly thicker and plaques were significantly more frequent in KOA group than the non-KOA group. In agreement with our finding, a previous Egyptian study reported that KOA patients had significantly thicker cIMT than matched controls [30]. These findings are also in agreement that of with ***Martocchia et al.*** [31] that come in support for the associations between OA in many joints and atherosclerosis indicated by increased cIMT in female patients.

Previous studies had reported a higher odd of CVD including atherosclerosis, angina and CHF among OA patients than non-OA controls [32-33]. In addition, it is evidenced that OA patients are at an increased risk of mortality due to CVD [10].

Jonsson et al suggested that atherosclerotic vessels may play a triggering event in pathogenesis of OA is via producing micro-circulatory impairments in the synovial membrane and sub-chondral bone with subsequent cartilage degeneration.

In the second step of the present study, we had investigated the relationship between the KOA radiological severity (in terms of KL grade and US cartilage thickness grades) with the co-morbidities and the findings of carotid US examination. The major findings in this regard were (a) higher radiological severity is associated with higher WC and WHR, FBS serum cholesterol level in KOA patients; (b) T2DM, HTN and MetS were significantly

more prevalent in patients with higher KL grades and higher US cartilage thickness grades; (c) higher radiological severity is associated with higher cIMT and more prevalent plaques on KOA patients and (d) higher radiological severity is associated with longer disease duration and more severe WOMAC scores.

In agreement with our findings, ***Ekim et al.*** [34] found that the duration of knee symptoms, WOMAC total and subscales scores were significantly higher in group 2 (KOA patients with KL grade of 3 and 4) than in group 1 (KOA patients with grade 1 and 2). ***Ekim et al.*** also divided the KOA patients into two groups based on the US cartilage thickness grading; group with US grades 1–3 and the other group with US grades 4–6. Also, in agreement with the findings of the present study, ***Ekim et al.*** found that the duration of knee symptoms, WOMAC total and subscales scores were significantly higher in group with higher US grades than in group with lower US grades. Moreover, in agreement with our findings, the results of ***Ekim et al.*** revealed that cIMT was directly correlated with the K-L grades and also with US cartilage thickness grades in patients with KOA [34].

Similarly, ***Fouda et al.*** [30] recorded a statistically significant correlation between cIMT and KL radiological grading for OA severity. The study also divided the KOA patients into two groups based on the presence of carotid plaques and revealed that patients with carotid plaques had significantly higher KL grades than KOA patients without plaques.

These findings were also in line with the findings of a large prospective population-based study [2]. The study examined whether vascular alterations are associated with the presence and progression of OA. The study found that, after full adjustment of confounding factors, prevalence of KOA is associated with the cIMT and with presence of plaques. In addition, the results of that study showed a fully adjusted association between cIMT and prevalence of plaques with the radiological severity of KOA.

In the third step of our study, the patients with KOA were classified into two groups: KOA-MetS group and KOA-no-MetS group to recognize factors associated with MetS in KOA patients and to determine the effect of MetS on radiological severity of KOA. The major findings of this step revealed that: (a) Patient in KOA-MetS group had significantly higher WC, higher WHR, longer disease duration, higher WOMAC scores, more prevalent T2DM and HTN, higher serum cholesterol level than KOA-no-MetS and (b) Patient in KOA-MetS group had significantly thicket cIMT and more prevalent carotid plaques than KOA-no-MetS group.

MetS was diagnosed in 46% of the KOA patients participated in the study. In agreement with our findings, it is reported

that MetS is detected in 59% of OA patients compared to 23% of non-OA adults, in a population-based cohort study that included 7 714 adults [35].

A previous cross-sectional study analyzed data from 1,549 female KOA patients to identify the association between KOA (with a KL grade of ≥ 2) with the presence or absence of metabolic abnormality and obesity. Metabolically abnormal state was defined as presence of at least two abnormality of the five metabolic risk factors. The study found that prevalence of symptomatic KOA was higher in metabolically abnormal but normal weight than in metabolically healthy normal weight (51.6% versus 36.2% respectively) [36]. This finding indicates a potent association between KOA and metabolic abnormalities.

A prospective study found that the prevalence of MetS among KOA patients was 53.1% [37]. Another evidence for the association between MetS and KOA comes from the study of ***Yoshimura et al.*** [38], who found elevated risk for development and progression of KOA over a 3-years period associated with increased number of MetS components. On the other hand, an Egyptian study included population from Dakahlia government found that the prevalence of OA among patients with MetS was 83.3% [39].

In support to these finding, obese females with cardiometabolic clustering is at nearly 2-fold increased risk to have KOA than those without cardiometabolic clustering [40]. In the same study, the KOA prevalence in non-obese females with no cardio metabolic clustering was 4.7%, compared with 12.8% in obese females with no cardio metabolic clustering and 23.2% in obese females having cardio metabolic clustering.

The results of the current study showed that HTN and T2DM were significantly more frequent in KOA patients with MetS than KOA patients without MetS. In agreement with our findings, ***Afifi et al.*** [39] observed that HTN and T2DM were significantly more frequent in KOA patients with MetS than KOA patients without MetS.

Hamad et al. [37] found that 32% of the KOA patients were diabetic, 44.9% were hypertensive and 24.5% had dyslipidemia. The study also found that 63.2% of the KOA patients had advanced radiological grade (KL grade of 3 and 4). The prevalence of high TGs level, high cholesterol level and low HDL cholesterol level was 19.14%, 54.3% and 18.9% respectively. These findings are consistent the findings of the present study. The study of ***Zhang et al.*** [41] revealed that HTN was significantly associated with higher prevalence of radiological KOA (OR of 2.01) and symptomatic KOA (OR of 1.5).

Our results revealed that pain, stiffness and physical functioning subscales and total WOMAC score were significantly higher in KOA-MetS group of patients in comparison to KOA-no-MetS group of patients. This

finding comes in support to the findings of ***Afifi et al.*** [39] study who reported a significant difference in the WOMAC score between MetS patients with KOA compared to obese OA controls after adjustment for age, gender, body weight and BMI being worse in KOA patients with MetS. The same study also found a significant association between WOMAC score and MetS by linear regression analysis.

The study of ***Hamad et al.*** [37] reported a significant difference between KOA patients with than those without MetS in terms of Lequesne index and WOMAC pain score. In addition, ***Almeida et al.*** **[42]** found that KOA patients with MetS had significantly higher individual pain score and higher total WOMAC score and lower functional performance than KOA patients without KOA. ***Oliinyk*** **[43]** analyzed the impact of MetS on WOMAC index in patients with OA and found that concomitant OA with MetS exerted adverse effects on WMAC subscales as well as total score.

An American longitudinal, population-based study had assessed the effect of obesity and MetS with KOA (defined as a KL score $\geq$2), knee joint pain, and physical functioning performance found that female patients with KOA having cardio-metabolic clustering were more frequently to report limitations (in terms of pain and physical functioning) compared with females in cardiometabolic group [40]. One Korean population-based study found that the increase of self-reported knee pain intensity due to OA parallel the increase the number of MetS components, after adjustment for age, gender, body weight and BMI [44].

The multivariate regression analysis revealed that presence of the MetS, serum TC and radiological KL grade were the strongest factors that predict the higher cIMT in patients with KOA. The multivariate binary logistic regression analysis revealed that presence of the MetS, serum TC and radiological KL grade were the strongest factors that predict the higher cIMT in patients with KOA.

Afifi et al. [39] found that MetS and each of its individual components; WC, HTN, T2DM, high TG, and low HDL were significantly associated with OA in linear regression analysis. ***Fouda et al.*** [30] performed multi-regression analysis to determine variables associated with presence of carotid plaques in KOA patients and found that OA duration and radiological severity based on KL grading are the strongest predictors of presence carotid plaques among patients with KOA.

A previous Egyptian study observed a significant difference in the radiological grading of KOA between the MetS patients with KOA compared to obese OA patients without MetS independent of age, gender, body weight or BMI. In addition, the linear regression analysis revealed a significant

association between severity of radiological grading and MetS [39].

Clustering of MetS components was significantly correlated with higher risk of KOA severity on the KL scale in Japanese patients. Severity of K-L grades of KOA is significantly elevated with the increasing number of MetS components in the patient [38]. Hyperglycemia and HTN were associated with higher radiological KOA severity after adjustment for other confounding factors [35]. After adjustment for demographic and lifestyle confounding factors, a direct association was found between radiological KOA and MetS and each of its individual components in the Korean population [45].

It is generally agreed that medications have little effect on the prevention of OA progression rather than causing pathological improvement of the disease. If the OA risk factors are completely recognized, effective treatment strategy can be developed which may help to decrease OA prevalence. It had been suggested that MetS is emerged as a risk factor for OA, but there is insufficient evidence to support this proposition. Thus, our study provides another evidence to support the hypothesis that the individual components of MetS or clustering of these components forming complete picture of MetS are risk factors for KOA.

However, the study had several limitations. The study design was of cross-sectional type. Therefore, it is not possible to infer causality as this design precludes causal relationship. Larger longitudinal studies is warranted to explore the causal link between the two conditions and to identify the differential associations with other joints. Also, this study did not examine condition of vascularity in the bones directly. So, it is not possible to address the effect of this critical local factor on OA radiological grading, clinical manifestations or disease progression. The absence of analysis of other potential cofounding factors such as diet, physical activity, lifestyle behavior and smoking is another limitation in this study. It is possible that patients with OA experienced pain with movements and thus avoided participation in regular physical activity, which may explain in part the vascular pathology.

Conclusion

This study showed that atherosclerosis is associated with KOA, therefore, a diagnosis of OA may serve as a red flag for warning to evaluate CVD. The presence of the MetS, serum TC, radiological KL grade and higher US cartilage thickness grading were the strongest factors that predict the higher cIMT and higher prevalence of carotid plaques in patients with KOA.

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