ORIGINAL RESEARCH

Age-Related Macular Degeneration in Primary Osteoarthritis Egyptian Patients

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Introduction: Both primary osteoarthritis (OA) and age-related macular degeneration (AMD) cause disability in old people. This study aimed to detect the relation between primary osteoarthritis and age-related macular degeneration in a sample of geriatric Egyptian population.

Methods: This cross-sectional study included 222 primary OA patients. Medical history, musculoskeletal examination, body mass index (BMI) calculation, and ophthalmological examination, radiographs of anteroposterior view and weight-bearing position for both hips and both knees and posteroanterior view for hands, Kellgren and Lawrence grading score for radiological severity of OA, optical coherence tomography (OCT), and fundus fluorescence angiography FFA for evaluation of the macula were done. AMD was classified into early, intermediate, and late. The collected data were analyzed using SPSS version 25.0.

Results: Forty-six OA patients had AMD [19 cases had early, 15 cases had intermediate and 12 cases with late (7 neovascular (NV) and 5 geographic atrophy (GA))]. There was a significant correlation between AMD stages and OA grading score. There were significant differences between OA patient with AMD and those without AMD regarding age, disease duration, disease severity, family history of OA, daily mild exercise and calcium, and vitamin D intake. Multivariable analysis revealed that older age, more severe OA, low exercise and less calcium and vitamin D intake were considered independent risk factors for AMD development in primary OA.

Conclusion: Primary OA patients are more liable to AMD due to common risk factors and related pathogenesis. Ophthalmological follow up of those patients is recommended.

Keywords: primary osteoarthritis, age-related macular degeneration, age-related diseases

Introduction

Ageing is a process of molecular, cellular, and organ damage that increase the susceptibility to morbidity and mortality.[1] Although there is a controversy about considering ageing as a risk factor in age-related diseases, but there is an evident consensus that ageing and age-related diseases share the same basic molecular and cellular mechanisms.[2] Inflammaging, chronic sterile low-grade inflammation during ageing, contributes to the pathogenesis of age-related diseases.[3]

Primary osteoarthritis (OA) is one of the age-related diseases that causes disability in people aged >65 years. OA is not considered an inflammatory form of arthritis, but subclinical low-grade inflammation plays a key role in the disease pathogenesis.[3] Alterations in cell signaling promote a pro-inflammatory, catabolic state with augmented cell death that lead to increased joint tissue destruction and defective repair of damaged matrix.[4]

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Age-related macular degeneration (AMD) is a multifactorial retinal degenerative disease and one of the leading causes of visual impairment and even blindness. An estimated prevalence of 196 million people worldwide who suffer from AMD. Inflammation and immune system have a prevailing role in AMD pathogenesis.[5]

Inflammaging was proposed to give a crucial contribution in the onset of AMD and OA that may give the clue of their relationship.[6] Recent researches approved the coincidence of AMD and inflammatory diseases like gout[7] and OA.[8] We aimed to detect this relation in a sample of geriatric Egyptian population. Furthermore, we aimed to correlate their disease grading and severity. This may affect our policy for screening of AMD in Egyptian OA patients leading to early diagnosis.

Patients and Methods

This study was conducted from June 2018 to October 2019 as a collaborative study between the Rheumatology, Rehabilitation & Physical Medicine and the Ophthalmology Departments, Faculty of Medicine, in Benha University, Egypt.

The patients were collected from the outpatients' clinic of the Rheumatology, Rehabilitation & Physical Medicine Department, Benha University. All ophthalmological examination and imaging were done in Ophthalmology Department, Benha University. The study was approved by local Research Ethics Committee at Benha University (20-02-18) and was done in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki and its revisions. A written informed consent in Arabic language was obtained from every participant before being enrolled in the study.

Patients diagnosed as primary OA according to American College of Rheumatology Subcommittee on Osteoarthritis Guidelines[8] and aged ≥45 years old (45–80) were included in this study. Risk factors of AMD other than OA were excluded by a face to face questionnaire. Patients with history of alcohol consumption, smoking, hypertension, diabetes, 2ry OA, arthritis of diseases other than OA, chronic inflammatory diseases, chronic infection as tuberculosis were excluded.

Two hundred and twenty-two [222] patients were involved in this study and asked about medical history, family history of OA, exercise type and duration/week, calcium intake and vitamin D supplement intake. They were subjected to clinical examination especially Musculoskeletal examination, body mass index (BMI) calculation, and Ophthalmological examination (fundus examination, slit lamp examination, intraocular pressure (IOP) measurement and visual acuity). Patients demographic details are presented in Table 1.

Radiographs of anteroposterior view and weight-bearing position for both hips and both knees and posteroanterior view for hands were done for all subjects. Kellgren and Lawrence grading score[9] was used to evaluate the radiological severity of OA.

Table 1 The Characteristics of the Patients

		Patients Without AMD (n= 176)		Patients with AMD (n = 46)		P-value
Males	N, %	48	27.3%	10	21.7%	0.447
Females	N, %	128	72.7%	36	78.3%	
Age (years)	Mean±SD	61.7	5.9	67.4	5.7	<0.001*
Disease duration (years)	Median, range	5	0–10	7	0–17	<0.001*
BMI (kg/m^2)	Mean±SD	31.9	4.5	33.7	4.7	0.021*
Family history of OA	N, %	48	27.3%	28	60.9%	<0.001*
Symptomatic OA	N, %	136	77.3%	42	91.3%	0.034*
OA severity (mean KL score)	Mean ±SD	2	0.6	2.4	0.8	0.001*
Exercise (15 min walking/day)	N, %	120	68.2%	4	8.7%	<0.001*
Calcium 1200 mg/day and vitamin D 600 IU/day intake	N, %	136	77.3%	9	19.6%	<0.001*

Note: *Statistically significant.
Abbreviations: OA, osteoarthritis; AMD, age-related macular degeneration; KL, Kellgren and Lawrence; BMI, body mass index; IU, International unit.

Optical Coherence Tomography (OCT), Fundus Fluorescein Angiography (FFA) were used for evaluation of the macula. AMD was classified as: -

Early AMD
Cases with drusen from 63 to 124 um with no pigmentary changes

Intermediate
Cases with drusen 125 um or larger and cases with drusen from 63 to 124 um with pigmentary changes

Late AMD
Neovascular AMD (NV) or geographic atrophy (GA)

NV is serous/hemorrhagic retinal pigment epithelial detachment and/or subretinal neovascular membrane and/or subretinal fibrosis with no retinal vasculopathy.

GA is retinal pigment epithelium depigmentation in area of 175 um or larger.[10,11]

Statistical Methods
The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Kolmogorov–Smirnov test was done to test the normality of data distribution. Significant data were nonparametric. Mean, Standard deviation (±SD) were used to describe parametric numerical data, while Median and range were used for non-parametric numerical data. Frequency and percentage were used for non-numerical data. Student's T-test was used to assess the statistical significance of the difference between two study group means. Mann Whitney Test (U-test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Correlation analysis was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. Logistic regression analysis was used for prediction of risk factors, using generalized linear models. N.B: p is significant if <0.05 at confidence interval 95%.

Results
Our study included 222 OA patients (58 males (26.1%) and 164 females (73.9%)), 18% of them (40 patients) were asymptomatic and diagnosed radiologically as primary OA and 82% of them (182 patients) were symptomatic. There was overlapping in the affected joints with knee OA was detected in 206 persons, hip OA in 45 and hand OA in 26 persons.

AMD was detected in 46 OA patients (10 males (21.7%), 36 females (78.3%)), 19 cases (41.3%) had early AMD (6 males, 13 females), 15 cases (32.6%) had intermediate AMD (3 males, 12 females) and 12 cases (26.1%) with late AMD (1 male, 11 females). Cases with late AMD were seven cases of NV and 5 cases with GA. (Figure 1)

There were significant differences between OA patient with AMD and those without AMD regarding age, disease duration, disease severity, family history of OA, daily mild exercise, and calcium and vitamin D intake. (Table 1)
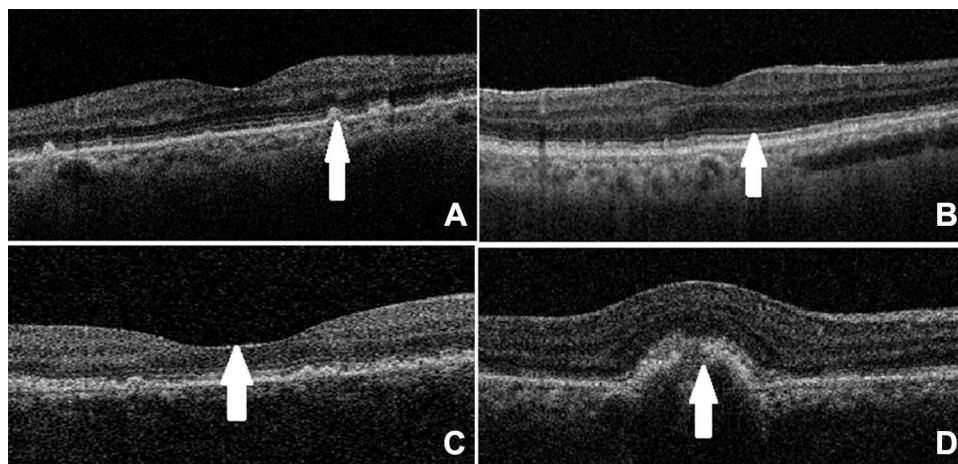

Figure 1 OCT images of some AMD cases: (**A**) Early AMD (white arrow: drusen, (**B**) Intermediate AMD (white arrow: pigmentary changes, (**C**) Late AMD with geographic atrophy (white arrow: macular atrophy), (**D**) Late AMD with CNV (white arrow: CNV).

Regression analysis was conducted for prediction of AMD using age, gender, duration, BMI, family history, symptoms, severity, exercise, calcium and vitamin D intake as covariates. (Table 2)

In univariable analysis older age, longer disease duration, higher BMI, positive family history, symptomatic OA, more severe OA, low exercise and less calcium and vitamin D intake were significantly associated with AMD occurrence in Primary OA patients.

Taking significant covariates in univariable into multivariable analysis revealed that only older age, more severe OA, low exercise and less calcium and vitamin D intake were considered independent risk factors for AMD development in Primary OA patients.

There was a significant correlation between AMD severity stages and OA severity grading score (r = 0.876, p<0.001) (Figure 2). The distribution of AMD stages in different OA grades is shown in Table 3.

Discussion

Both AMD and OA are degenerative diseases linked to aging and, in both diseases, the extracellular matrix is involved in pathogenesis.[8] The two diseases share some disease mechanisms, like implication of the complement pathway of the innate immune system.[9] Reliable biochemical and genetic evidences have verified that complement dysregulation is a mark of AMD vulnerability.[12,13] Also, evidence from biochemical studies and animal models has recommended a share for complement activation in OA.[14]

AMD is a degenerative disease of the photoreceptors and retinal pigment epithelium of the macula. Early detection is valued as it is the third worldwide cause of blindness in old age.[12] Previous studies pointed to the coincidence of AMD and inflammatory diseases as gout and OA.[7,8] We designed this study to assess the prevalence of AMD in a sample of Egyptian OA patient to highlight the association between the two diseases that may help in early detection of AMD.

We screened 222 Egyptian primary OA patients for presence of AMD. AMD was detected in 46 OA patients (20.7%). There was a significant correlation between the stage of AMD and the severity of OA. Our data pointed to older age, more severe OA, low exercise and less calcium and vitamin D intake as risk factors for AMD development in Primary OA patients.

In the current study, we founded that AMD in primary OA patients (20.7%) is significantly higher than in healthy population. Development of AMD in apparently healthy populations was previously reported in several studies. An Egyptian study screened 532 individuals and reported only 6.6% having AMD.[11] Also, in a metanalysis study, AMD was reported in 12.3% in Europeans, 7.4% in Asians and 7.5% in Africans of healthy populations.[16]

The results from former studies have reported little differing results for any possible association between AMD and OA. Zlateva et al, concluded that patients neovascular AMD patients were more liable to develop arthritis than controls; though, this finding related specifically to RA, and not OA.[17] The Age-Related Eye Disease Study (AREDS) detected a tendency toward increased prevalence of arthritis in individuals with neovascular AMD but this was insignificant; moreover, this category was described as "arthritis" and made no discrepancy between OA and RA.[18]

Regarding stages of AMD in our study, 41.3% of OA patients with AMD had early AMD and 26% had late

Table 2 Regression Analysis for Prediction of AMD in Primary OA Patients

	Univariable				Multivariable			
	p	OR	95% CI		p	OR	95% CI	
Gender	0.443	1.186	0.766	1.836				
Age	<0.001	1.098	1.061	1.136	0.024*	1.083	1.011	1.160
Disease duration	<0.001	1.131	1.075	1.189	0.147	1.123	0.960	1.313
BMI	0.023	1.049	1.007	1.093	0.379	1.363	0.885	1.048
Family history of OA	<0.001	2.277	1.543	3.358	0.100	1.921	0.883	4.182
Symptomatic OA	0.030	1.851	1.060	3.232	0.239	1.961	0.639	6.014
OA severity	0.003	1.441	1.136	1.828	0.007*	1.471	1.272	1.815
Exercise	<0.001	0.189	0.115	0.310	<0.001*	0.106	0.046	0.245
Calcium and vitamin D intake	<0.001	0.226	0.147	0.346	<0.001*	0.119	0.053	0.266

Note: *Statistically significant.
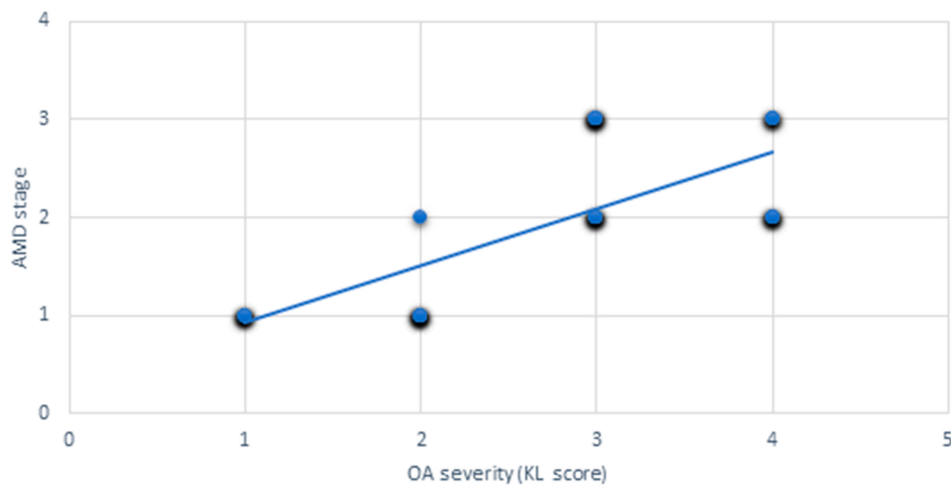**Abbreviations:** OR, odds ratio; CI, confidence interval.

Figure 2 Correlation between OA severity grading and AMD stages (r = 0.876, p<0.001).

AMD. That is clearly higher than reported ratios of both AMD stages in apparently healthy individuals (Europeans early: 11.2% and late: 0·5%, Asians early: 6.8% and late: 7.4%, Africans early: 7.1% and late: 0·3%[16] Egyptians early: 5.3% and late: 2.4%).[11]

This emphasizes the suggestion of the co-pathogenesis of both diseases. Inflammaging,[6,8] the complement activation,[19,20] and the involvement of the extracellular matrix are degenerative pathogenesis implicated in both. However, some previous researches reported the co-incidence of AMD in arthritis-suffering patients but not vice versa.[15] Treatments of OA[21,22] or/and profoundly systemic inflammatory process[23] may be of risk in developing AMD. Moreover, we found that older age, more severe OA, low exercise and less calcium and vitamin D intake were associated with higher incidence of AMD in OA patients.

The strength of this study is AMD screening in all OA stages even the asymptomatic stage that was provided by collecting the patients from outpatients' clinic in addition to the Elderly Care. Noting that the previous reports were based on hospital admissions and day specialist care representing the more severe end of OA.[15] On the other hand, our limitations were the relatively small sample number and neglecting the implications of the treatment lines.

We concluded that primary OA patients are more liable to develop AMD and early detection may be of great benefit in treatable stages that devoid these patients the blindness. Also, we found that less exercise, low calcium and vitamin D intake, older age, and more severe OA stage are risk factors of Primary OA patients to develop AMD.

Disclosure

The authors report no conflicts of interest in this work.

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Table 3 AMD in Different OA Grades

KL severity	No AMD	Early AMD	Intermediate AMD	Late AMD
Grade 1	58 patients	10 patients	–	–
Grade 2	66 patients	8 patients	3 patients	–
Grade 3	52 patients	1 patient	7 patients	6 patients
Grade 4	46 patients	–	5 patients	6 patients

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