Analyses of the Genetic Polymorphisms rs3740199 and rs1871054 of the *ADAM12* Gene and the Alleles at the rs2073508 Loci of the *TGFB1* Gene and Their Contribution to Susceptibility to Primary Knee Osteoarthritis

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Abstract

Aims: To analyze the association of polymorphisms in the *ADAM12* (rs3740199 and rs1871054) and *TGFB1* (rs2073508) genes with knee osteoarthritis (KOA) in a population from northern Mexico.

Methods: A total of 296 individuals were included in the study. Primary KOA was confirmed according to the criteria established by the American College of Rheumatology. A real-time PCR-based DNA genotyping method was used to evaluate the rs3740199, rs1871054, and rs2073508 polymorphisms in 132 cases and 164 controls.

Results: Our results demonstrate that the *ADAM12* rs3740199 polymorphism was significantly associated with primary KOA under the recessive model ($p = 0.036$). However, after performing a multinomial logistic regression model, no significant association was found ($p = 0.722$). Furthermore, no associations for the rs1871054 and rs2073508 polymorphisms were observed in this study.

Conclusion: These findings suggest that polymorphisms within the *ADAM12* and *TGFB1* genes may not have a significant influence on primary KOA susceptibility in the Mexican Mestizo population; however, inclusion of other ethnic groups and a larger sample size are needed to more fully analyze the role of these polymorphisms with KOA risk.

Keywords: knee osteoarthritis, ADAM12, TGFB1, polymorphism

Introduction

Osteoarthritis (OA) is a complex chronic degenerative disease, which is developed as a result of the interaction of multiple risk factors, involving molecular disorders, followed by anatomical and physiological alterations, whose symptoms, signs, and grades of severity may differ among patients (Kraus *et al*., 2015).

The prevalence of knee osteoarthritis (KOA) worldwide is ~ 3.8% (Cross *et al*., 2014), affecting more than 200 million people (Collaborators., 2016). In Mexico, the prevalence of KOA was estimated at 17.6% (Macias-Hernandez *et al*., 2018).

Some studies have shown that the role of the genetic component in the risk of OA ranges from 40% to 80% (Su *et al*., 2015; Van Meurs, 2017). For instance, Genome-Wide Association Studies (GWAS) have identified that several single nucleotide polymorphisms (SNPs) were associated with decreased articular cartilage thickness in patients with OA, hip OA, total hip replacement (Styrkarsdottir *et al*., 2017), and KOA (Casalone *et al*., 2018).

Disintegrin and metalloproteinase domain-containing protein family (ADAMs) is encoded by the ADAM genes (Giebeler and Zigrino, 2016). *ADAM12* is a polymorphic gene located at 10q26.2 position (OMIM: 602714) and encodes ADAM metallopeptidase domain 12 protein (*ADAM12*), which plays an important role in synovitis (Lv *et al*., 2017). *ADAM12* also participates in chondrocyte proliferation and it has been found overexpressed in serum and cartilage from KOA subjects (Okada *et al*., 2008). However, there are still contradictory results

about the association between the *ADAM12* gene and susceptibility to KOA in different ethnic groups (Kerna *et al*., 2013; Lou *et al.*, 2014; Wang *et al*., 2015; Poonpet *et al*., 2016; Hao *et al*., 2017; Hu *et al*., 2017; Lv *et al*., 2017; Ren *et al*., 2017; Wu *et al*., 2017; Chen *et al*., 2018).

The transforming growth factor-beta (TGF-β) is a super-family of growth factors (Shen *et al*., 2014 Hinck, 2012), well known for the maintenance of articular cartilage (Van den Berg, 2000; Grimaud *et al*., 2002; Su *et al*., 2015). TGF-β1 is overexpressed in the serum of patients with OA (He *et al*., 2017), in which an association between TGF-β polymorphisms and OA has been previously described in some populations (Yamada *et al*., 2000; Blanco *et al*., 2015).

This study aimed to analyze the association between *ADAM12* (rs3740199 and rs1871054) and the *TGFB1* (rs2073508) gene polymorphisms in a northern Mexican population with knee OA.

Materials and Methods

From February 2010 to February 2012, 296 subjects were included for this study. All participants, cases, and controls, were of Mexican Mestizo ethnicity, living in the city of Torreon, in the State of Coahuila, Mexico. All individuals received clinical and radiographic examinations by orthopedic specialists.

A group of 132 patients diagnosed with primary KOA, according to the criteria of the American College of Rheumatology (ACR) (Altman *et al*., 1986) and Kellgren/Lawrence (K/L) radiological assessment (Kellgren and Lawrence, 1957), were included for analysis. Secondary KOA due to congenital, traumatic, infectious, metabolic, or inflammatory disease, previous injuries or knee surgery, and undergoing treatment for KOA were established as exclusión criteria. In addition, 164 randomly selected healthy subjects were included as controls. All X-ray films for healthy controls showed a K/L score ≤ 1.

This protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine at the Autonomous University of Coahuila in Torreon (CB/04-10-17). Written and informed consent was obtained from all participants.

DNA samples

Blood samples (5 mL of venous blood) from cases and controls were obtained in tubes with EDTA. The methodology for DNA extraction and determination of the *ADAM12* polymorphisms has been described previously (Miller *et al*., 1988). DNA samples were stored at -80°C. DNA concentration was measured by spectrophotometry with the NanoDrop® equipment ND-1000 (NanoDrop, Berlin, Germany).

Genotyping

Reagents used were purchased from Applied Biosystems, CA, and the materials from Scientific Specialties, Inc. The allelic frequencies for rs3740199, rs1871054, and rs2073508 were detected by TaqMan™ probes (ACTGGGATCCAGAGGTCCCCACTCC[C/G] AACAGAGGCACTGACAACTTCATCA; GGCTCTCCAGAGTAGCACAGGCCAC[C/T] CTTGCTAGTGA; and TGCCTCCCCTGGAAAGGTCAGTGGT[A/G] TGTGGCTGCAG CAGCACAGTGTCCT, respectively). PCR plates with controls were included in the genotyping; 5 µL of TaqMan Genotyping Master Mix, 0.5 µL of the probe (20 x) labeled with VIC and FAM dyes for allele detection, and 3 µL of DNA (1–20 ng) were added to each well/mL and adjusted with nuclease-free water to a final volume of 11 µL, controls were included in this analysis. The reaction was subjected under the following conditions: 1 cycle at 95°C for 10 min for polymerase activation, and then, 40 cycles of denaturation at 95°C for 15 s and annealing/extension at 60°C for 1 min in an Applied real-time PCR system Biosystems

7300. The data were analyzed with 7300 system SDS version 1.3.1.21 software. Genotyping accuracy of the samples was confirmed by the genotyping of 10% randomly chosen samples.

Statistical analysis

Statistical Package for Social Sciences (SPSS) v22.0 (IBM Corp, Chicago, IL) software was used for the analysis. Quantitative variables were represented as means and standard deviations, while categorical variables as percentages. Mann–Whitney U and chi-squared tests were applied for bivariate analysis. Allelic and genotypic frequencies were calculated using the Hardy–Weinberg equilibrium (HWE) (Rodriguez *et al*., 2009). The association between *ADAM12* SNPs and the risk of KOA was estimated using inheritance models. Odds ratios along with their 95% confidence intervals (CIs 95%) were calculated. Besides, a multivariate logistic regression model adjusted for age, body mass index (BMI), and menopause was included in the analysis. In all cases, a *p*-value <0.05 was considered significant.

Results

This study included 132 (44.59%) cases and 164 (55.41%) controls. The clinical characteristics of the study population are shown in Table 1. The mean age was significantly higher in KOA cases than in healthy controls (63.53 ± 14.52; 55.98 ± 13.13; respectively, $p \leq 0.0001$). Also, BMI was significantly higher in cases compared with controls (28.39 ± 4.47; 27.38 ≤ 4.25; $p = 0.049$). In addition, age, menopause, and nutritional status were significantly associated with KOA ($p \leq 0.004$, $p \leq 0.0001$, and $p = 0.045$, respectively). On the contrary, gender, smoking, and type 2 diabetes were not associated with KOA after the analysis ($p = 0.245$, $p = 0.715$, and $p = 0.086$, respectively).

Association of ADAM12 genetic polymorphisms with primary KOA

Table 2 shows the allelic and genotypic distribution of rs3740199, rs1871054, and rs2073508 polymorphisms in healthy controls. Genotype frequencies were consistent with the Hardy–Weinberg equilibrium ($p = 0.939$, $p = 0.070$, and $p = 0.123$, respectively).

Table 3 shows that the *ADAM12* rs3740199 polymorphism was significantly associated with primary KOA for the recessive model ($p = 0.036$) in the bivariate analysis. However, after performing a multinomial logistic regression model, no significant association was found in the recessive model ($p = 0.722$). Moreover, no association was found for rs1871054 and rs2073508 in both adjusted and nonadjusted models.

Discussion

Over the last years, different genetic studies have been performed to identify genes that encode for proteins associated with OA susceptibility. From these, the rs3740199 (c.142G> C) polymorphism of *ADAM12* gene had been previously associated with KOA in a Thai male population (Poonpet *et al*., 2016); likewise, several meta-analyses have reported this association (Hu *et al*., 2017; Ren *et al*., 2017; Wu *et al*., 2017). However, we did not find any association for rs3740199 *ADAM12* polymorphism in our study, in agreement with other authors (Limer *et al*., 2009; Kerna *et al*., 2013; Lou *et al*., 2014; Wang *et al*., 2015).

On the contrary, the CC genotype of rs1871054 polymorphism of *ADAM12* gene had also been associated with an increased risk for susceptibility to KOA in a Chinese Han population (Lou *et al*., 2014; Wang *et al*., 2015). Several meta-analysis studies have also found an association with this polymorphism (Hu *et al*., 2017; Lv *et al*., 2017; Ren *et al*., 2017; Chen *et al*., 2018). Also, in an Estonian population, the C allele was associated with advanced grades of KOA (Kerna *et al*., 2013). This polymorphism (rs1871054) is in linkage disequilibrium with

rs1044122, belonging to the same haplotype (Lou *et al*., 2014). However, in the present study, we did not find any association for rs1871054 *ADAM12* polymorphism.

Moreover, it has been suggested that the rs3740199 polymorphism may affect the proteolytic activity of ADAM12. ADAM12 performs the cleavage of the insulin-like growth factor-binding protein system 3 and 5 (IGFBP-3 and IGFBP-5) releasing insulin-like growth factor type 1 (IGF-1), and when the excision is absent, there is an insufficiency of IGF-1. It is important to note that when bioavailability of IGF-1 is present, chondrocyte proliferation is carried out. Due to the insufficiency of IGF-1, there is no proliferation of chondrocytes causing the loss of articular cartilage, this leads to the development of the disease (Okada et al., 2008; Poonpet *et al*., 2016). Therefore, this polymorphism may be important in the progression of KOA (Lv *et al*., 2017), since it has been associated with the progression of KOA (Wang *et al*., 2015).

In addition, it has been described that ADAM12-L can enhance the signaling of TGFβ by modulating TGF-β type II receptor traffic (TβIIR) (Kveiborg *et al*., 2008). Moreover, TGFβ selectively and positively regulates the expression of ADAM12-L in OA chondrocytes and promotes chondrocyte proliferation (Okada *et al*., 2008). In a study performed by Blanco *et al*. (2015), the rs2073508 *TGFB1* polymorphism was significantly associated with KOA progression in a European Caucasian population. That study described an association between rs2073508 TGF-β polymorphism and KOA progression in the European Caucasian population. Therefore, we also explored the rs2073508 *TGFB1* polymorphism, however, not the association with KOA susceptibility.

It is worth mentioning that our study may present some limitations; first, the relatively small sample size. Second, OA is a complex disease, and thus, the possible gene/gene and gene/environment interactions may have influenced our results. However, we tried to overcome these limitations. First, the diagnosis of KOA as well as healthy controls was validated by specialized personnel in osteoarthritis and radiological measures and not just self-reported. The

genotype frequencies of the *ADAM12* SNPs rs3740199 and rs1871054 and the TGFB1 SNP rs2073508, analyzed in this study, were consistent with the Hardy–Weinberg equilibrium ($p > 0.05$) as described in Table 2. Finally, aging, menopause, BMI, and gender were also accounted for when interpreting results.

In conclusion, these findings suggest that polymorphisms within the *ADAM12* and *TGFB1* genes may not influence KOA susceptibility in the Mexican Mestizo population, however, the lack of associations should be confirmed by larger samples, independent studies, and performed in other ethnic groups to support the role of rs3740199, rs1871054, and rs2073508 in KOA risk.

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Author Disclosure Statement

No competing financial interests exist.

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Table 1. Comparison of Clinical Characteristics Between Knee Osteoarthritis and Healthy Control Subjects

Characteristics	KOA *N* = 132	Healthy controls *N* = 164	OR (95% CI)	*p*-value
Age (mean – SD)	63.53 ± 14.52	55.98 ± 13.13		<0.0001[*,a]
Age stratified *n* = 296				
≥ 56 years	88 (66.7)	82 (50.0)	2.000 (1.245–3.213)	0.004[*,b]
< 56 years	44 (33.3)	82 (50.0)		
Gender *n* = 296				
Male	46 (34.8)	68 (41.5)	0.755 (0.470–1.213)	0.245[b]
Female	86 (65.2)	96 (58.5)		
Smoking *n* = 296				
Smoker	22 (16.7)	30 (18.3)	0.893 (0.488–1.636)	0.715[b]
Nonsmoker	110 (83.3)	134 (81.7)		
Type 2 diabetes *n* = 296				
Diabetic	52 (39.4)	49 (29.9)	1.526 (0.941–2.474)	0.086[b]
Nondiabetic	80 (60.6)	115 (70.1)		
Menopause *n* = 182				
Menopausal	74 (86.0)	59 (61.5)	3.867 (1.853–8.069)	<0.0001[*,b]
Nonmenopausal	12 (14.0)	37 (38.5)		
BMI (mean – SD)	28.39 ± 4.47	27.38 ± 4.25		0.049[*,a]
Nutritional status *n* = 296				
Underweight	0 (0.0)	2 (1.2)		0.045[*,b]
Normal range	32 (24.2)	40 (24.4)		
Overweight	54 (40.9)	86 (52.4)		
Obesity	46 (34.8)	36 (22.0)		
Severity *n* = 132				
Grade I	23 (17.4)			
Grade II	45 (34.1)			
Grade III	57 (43.2)			
Grade IV	7 (5.3)			

[a] Mann–Whitney U test.

[b] Chi-squared test.

[*] $p < 0.05$ significant.

BMI, body mass index; OR, odds ratio; SD, standard deviation.

Table 2. Allelic and Genotypic Distribution of the rs3740199, rs1871054, and rs2073508 Polymorphisms Between Primary Knee Osteoarthritis and Healthy Controls

Polymorphisms	Wild type *n* (%)	Variant *n* (%)	Genotype *n* (%)			HWE *p*-value
	G	C	GG	CG	CC	
rs3740199 ADAM12	371 (62.7)	221 (37.3)	125 (42.2)	121 (40.9)	50 (16.9)	
KOA	161 (61.0)	103 (39.0)	58 (43.9)	45 (34.1)	29 (22.0)	
Healthy controls	210 (64.0)	118 (36.0)	67 (40.9)	76 (46.3)	21 (12.8)	0.939[*,a]
Frequency (MXL[b])	(57.8)	(42.2)	(35.9)	(43.8)	(20.3)	
	T	C	TT	CT	CC	
rs1871054 ADAM12	256 (43.2)	336 (56.8)	45 (15.2)	166 (56.1)	85 (28.7)	
KOA	124 (47.0)	140 (53.0)	24 (18.2)	76 (57.6)	32 (24.2)	
Healthy controls	132 (40.2)	196 (59.8)	21 (12.8)	90 (54.9)	53 (32.3)	0.070[*,a]
Frequency (MXL[b])	(44.5)	(55.5)	(20.3)	(48.4)	(31.2)	
	G	A	GG	AG	AA	
rs2073508 TGFB1	492 (83.1)	100 (16.9)	210 (70.9)	72 (24.3)	14 (4.7)	
KOA	222 (84.1)	42 (15.9)	96 (72.7)	30 (22.7)	6 (4.5)	
Healthy controls	270 (82.3)	58 (17.7)	114 (69.5)	42 (25.6)	8 (4.9)	0.123[*,a]
Frequency (MXL[b])	(89.8)	(10.2)	(81.2)	(17.2)	(0.16)	

[a] Hardy–Weinberg equilibrium (HWE).

[b] Frequencies of individuals of Mexican ancestry living in Los Angeles according to 1K Genomes project.

*$p > 0.05$ significant.

Table 3. Evaluation of the Association Between rs3740199, rs1871054, and rs2073508 Polymorphisms and Primary Knee Osteoarthritis

Genetic model	Genotype	KOA *n* = 132	Healthy controls *n* = 164	OR (95%CI)[a]	*p*-value	Adjusted OR (95% CI)[b]	Adjusted [p]-value
RS3740199 ADAM12							
Codominant[1]	CG	45 (43.7)	76 (53.1)	0.684 (0.411–1.138)	0.143	0.581 (0.284–1.186)	0.136
	GG	58 (56.3)	67 (47.9)				
Codominant[2]	CC	29 (33.3)	21 (23.9)	1.595 (0.822–3.094)	0.166	1.028 (0.408–2.590)	0.954
	GG	58 (66.7)	67 (76.1)				
Dominant	CG+CC	74 (56.1)	97 (59.1)	0.881 (0.554–1.401)	0.593	0.664 (0.344–1.283)	0.223
	GG	58 (43.9)	67 (40.9)				
Recessive	CC	29 (22.0)	21 (12.8)	1.917 (1.035–3.550)	0.036*	1.169 (0.494–2.766)	0.722
	CG+GG	103 (78.0)	143 (87.2)				
RS1871054 ADAM12							
Codominant[1]	CT	76 (76.0)	90 (81.1)	0.739 (0.382–1.430)	0.368	1.830 (0.721–4.642)	0.203
	TT	24 (24.0)	21 (18.9)				
Codominant[2]	CC	32 (57.1)	53 (71.6)	0.528 (0.254–1.098)	0.086	1.256 (0.463–3.409)	0.655
	TT	24 (42.9)	21 (28.4)				
Dominant	CT+CC	108 (81.8)	143 (87.2)	0.661 (0.350–1.249)	0.200	1.539 (0.651–3.638)	0.326
	TT	24 (18.2)	21 (12.8)				
Recessive	CC	32 (24.2)	53 (32.3)	0.670 (0.400–1.122)	0.127	0.859 (0.425–1.738)	0.673
	CT+TT	100 (75.8)	111 (67.7)				
RS2073508 TGFB1							
Codominant[1]	AG	30 (23.8)	42 (26.9)	0.848 (0.494–1.458)	0.551	0.691 (0.321–1.488)	0.345
	GG	96 (76.2)	114 (73.1)				

Table 3. Evaluation of the Association Between rs3740199, rs1871054, and rs2073508 Polymorphisms and Primary Knee Osteoarthritis

Genetic model	Genotype	KOA *n* = 132	Healthy controls *n* = 164	OR (95%CI)[a]	*p*-value	Adjusted OR (95% CI)[b]	Adjusted [p]-value
Codominant[2]	AA	6 (5.9)	8 (6.6)	0.891 (0.299–2.656)	0.835	0.688 (0.193–2.456)	0.565
	GG	96 (94.1)	114 (93.4)				
Dominant	AG+AA	36 (27.3)	50 (30.5)	0.855 (0.515–1.420)	0.545	0.704 (0.352–1.407)	0.320
	GG	96 (72.7)	114 (69.5)				
Recessive	AA	6 (4.5)	8 (4.9)	0.929 (0.314–2.746)	0.893	0.735 (0.210–2.568)	0.630
	AG+GG	126 (95.5)	156 (95.1)				

[a] Binary logistic regression model.

[b] Multinomial logistic regression model adjusted by age, BMI, and menopause.

*$p < 0.05$ significant.