Research Article

Association of MATN-3 and ADIPOQ Polymorphisms with Susceptibility to Knee Osteoarthritis

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Abstract

Objectives: The associations of Matrilin-3 (MATN3) and Adiponectin (ADIPOQ) polymorphisms with knee osteoarthritis (OA) risk have been reported, but it is currently the conclusions have been divergent. Thus, this study was performed to evaluate the association of MATN3 and ADIPOQ polymorphisms with susceptibility to knee OA.

Methods: We carried out this case-control study involving 105 cases with knee OA and 120 healthy subjects to evaluate the association of MATN3 rs8176070, ADI POQ rs1501299, rs822396, and rs2241766 polymorphisms with knee OA using RFLP-PCR assay.

Results: There was a significant association between MATN3 rs8176070 polymorphism and KOA risk. However, there was no significant association between rs1501299, rs822396, and rs2241766 polymorphisms at ADIPOQ gene and knee OA risk.

Conclusion: This piece of evidence revealed that the MATN3 rs8176070 polymorphism was serving as risk factor for development of knee OA, but not ADI POQ rs1501299, rs822396, and rs2241766 polymorphisms. However, well-designed and large-scale clinical studies are necessary to further validate our results.

Keywords: Adiponectin, Knee, MATN3, Osteoarthritis, Polymorphism.

O steoarthritis (OA) is a degenerative disorder of the articular cartilage, with activity of pro-inflammatory cytokines in the synovia, upregulation of synovial macrophages and osteoclasts, progressive destruction of joint cartilage, and narrowing of the joint space.[1, 2] OA is one of the most common causes of chronic pain which is defined as pain for more than three to six months.[3, 4] In western countries, radiographic evidence of OA is present in the majority of persons who are at least 65 years old, and in about 80 percent of persons more than 75 years of age.[5, 6] OA is usually classified as primary, or idiopathic with unknown etiology, and secondary when it follows a clearly defined pathology such as post-traumatic, congenital or metabolic events.[7, 8] Osteoarthritis of knee is most common type of degenerative disease and second most common form of disability worldwide.[1, 9, 10] Current clinical management of

knee OA aims to manage pain and maintain independent physical function through a combination of pharmacologic and nonpharmacologic interventions based on evidence of effectiveness in clinical trials.[11–13] Risk factors for primary knee OA include genetic factors, age, gender, ethnicity, obesity and diet. knee OA is associated with older age with 6% of adults aged greater than 30 years and 13% of persons aged 60 years and greater having symptomatic knee OA and being female.[8, 14] A study revealed that the prevalence of OA in the knee joint was 19.34%, in hand joins was 2.66% and in the neck was 2.21% in Iran. Moreover, OA in rural areas of Iran was more frequent in comparison with urban areas of Iran.[15]

The exact mechanism behind the knee OA is not fully known, but many interacting factors have been identified. Some studies reported that overweight produces oxidative stress on the articular cartilage, with the subsequent risk of OA.[16] Adiponectin (ADIPOQ) is one of the most abundantly secreted adipose tissue proteins and also is the only adipokine identified thus far that is negatively correlated with obesity.[17, 18] Thus, ADIPOQ gene might be candidate gene in the mechanism of OA since it has been shown to regulates energy and material metabolism.[19, 20] ADIPOQ has both anti-atherogenic and anti-inflammatory properties and implicated in the development of some metabolic disorders such as insulin resistance, obesity, and Type 2 diabetes (T2D).[21, 22] Moreover, matrilin-3 (MATN-3) is a member of family of extracellular matrix proteins and expressed in chondroblasts and osteoblasts but not in hypertrophic chondrocytes. Recently, several epidemiological studies indicated that the MATN-3 gene plays an important role in the synthesis of cartilage.[23]

Human ADIPOQ gene is located in the chromosomal region 3q27, contains three exons and two introns, and spans 16 kb.[24] The three common SNPs of ADIPOQ T45G (rs2241766), G276T (rs1501299) and -3964A>G (rs822396) were most widely studied.[25] In 2017, Cuzdan-Coskun et al., found a positive correlation between adiponectin concentration and the Kellgren-Lawrence (KL) grading scores (A scoring system describes the degree of joint degeneration via X-ray image system).[26] Moreover, the human Matrilin-3 (MATN3) gene to chromosome 2p24-p23 spans 23.4 kb, comprises 8 exons and the rs8176070 (SNP6) polymorphism has been widely studies in association with carpometacarpal joint of the hand osteoarthritis susceptibility.[27–32] So far, some studies already tried to evaluate associations of MATN-3 and ADIPOQ polymorphisms with risk of OA, but the results of these studies were controversial, especially when they were conducted in Mexican, Finnish and Chinese populations.[16, 33–36] Thus, we have conducted this cross-sectional study to assess the association of ADIPOQ rs1501299 (+276G>T), rs822396 (-3964A>G) and rs2241766 (+45T>G) polymorphisms with susceptibility to knee OA.

Methods

Study Population

A total of 105 patients with knee OA fulfilled radiographic criteria of OA and American College of Rheumatology (ACR) was recruited to this study between December 2016 and March 2018 by non-random simple sampling method. Moreover, the control group was composed of 120 matched healthy individuals with no symptoms or signs on clinical examination or radiographic. The mean age of cases and controls was 55.6±7.4 and 56.9±6.4, respectively. Ethics approval of this study was issued by the Ethics Committee of Tehran Azad University (IR.AZ.SPH.REC.1397.087) and every participants enrolled in this study signed a consent form.

Inclusion criteria were as: 1: volunteered to participate in the study and aged between 40 and 70 years old, 2: body mass index <30 Kg/m^2, 3: corresponding to the diagnostic criteria of osteoarthritis of the knee. Exclusion criteria were as: participants with less than 20 years; 2: body mass index ≥30 Kg/m^2; 3: incompatible diagnostic criteria of knee joint osteoarthritis, 4: participants with secondary OA, inflammatory arthritis (rheumatoid arthritis, systemic lupus erythematosus, hemophilic arthritis, etc.) and 5: diabetes, hyperuricemia, heart disease, and infectious diseases.

DNA Extraction and Genotyping Method

Genomic DNA was extracted from whole blood and extracted using the QIAamp DNA blood mini kit (Qiagen, Hilden, Germany) according the manufacturer's protocol. DNA concentration and purity were determined by the NanoDrop ND1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). In this study we selected three SNPs including MATN-3 rs8176070 (SNP6), rs1501299 (+276G>T), rs822396 (-3964A>G) and rs2241766 (+45T>G) polymorphisms at ADIPOQ gene using the Restriction Fragment Length Polymorphism of PCR products (PCR-RFLP) method as previously reported.[37, 38] After amplification, the products were digested with 5 U of restriction enzymes AvaI for rs2241766, MseI for rs822396, and BsmI for rs1501299 for 15 hr at 37° C. The restriction products were resolved by agarose gel electrophoresis with 3.0% and stained with EtBr against a 100-bp ladder as standard and visualized under a UV transilluminator.

Statistical Analysis

The Court software was applied to assess Hardy-Weinberg equilibrium (HWE) of ADIPOQ rs1501299, rs822396, and

rs2241766 polymorphisms among controls. The associations of ADIPOQ polymorphisms with knee OA were tested using Chi-square. Odds ratio (ORs) and their corresponding 95% confidence intervals (CIs) were calculated for estimating ROP risk corresponding to ADIPOQ polymorphisms. All statistical analyses and procedures were analyzed using the Statistical Package for Social Science (SPSS) version 21 (IBM Corp., Armonk, N.Y., USA). Statistical significance was established at p<0.05.

Results

Table 1 showed the demographic characteristics of the KOA cases and controls. The mean age in cases with knee OA and controls was 55.6±7.4 and 56.9±6.4 years, respectively. The genotype frequencies of the ADIPOQ rs1501299, rs822396, and rs2241766 polymorphisms are shown in Table 2. The genotype frequencies of MATN-3 rs8176070, ADIPOQ rs1501299, rs822396, and rs2241766 polymorphisms for the control group were in accordance to Hardy-Weinberg equilibrium (HWE: p=0.465, p=0.826, and p=0.337, respectively).

For MATN3 rs8176070 polymorphism, BB, Bb, and bb genotypes were found in 40.9%, 38.1%, and 21.0% in cases with knee OA, respectively. In controls, BB, Bb, and bb genotypes were seen in 49.2%, 40.0%, and 10.8%, respectively. Frequency of mutant allele (b) was 40.0% in cases with knee OA and 30.8% in controls. There was a significant association between MATN3 rs8176070 polymorphism and an increased risk of knee OA (Table 2). The rs1501299 G>T genotypes in cases with knee OA were 27.6% GG, 56.2% GT and 16.2% TT, while in healthy subjects consisted of 30.0% GG, 52.5% GT and 17.5% TT. Frequency of mutant allele (T) was 44.2% in cases and 43.7% in healthy subjects. There was no significant association between rs1501299 G>T polymorphism at ADIPOQ gene and an increased risk of knee OA (Table 2). For rs822396 A>G, the genotypes in cases with knee OA were 30.4% AA, 51.5% AG and 18.1% GG, while in healthy subjects consisted of 35.0% AA, 47.5% AG and 17.5% GG. Frequency of mutant allele (G) was 43.8% in cases and 41.2% in controls. There was no significant association between rs822396 A>G polymorphism at ADI-

IPOQ gene and an increased risk of knee OA (Table 2). For rs2241766 T>G polymorphism, TT, TG, and GG genotypes were found in 43.8%, 48.6%, and 7.6% in cases with knee OA, respectively. In controls, TT, TG, and GG genotypes were seen in 42.5%, 48.3%, and 9.2%, respectively. Frequency of mutant allele (G) was 31.9% in cases with knee OA and 33.3% in healthy subjects. There was no significant association between rs2241766 T>G polymorphism at ADIPOQ gene and an increased risk of knee OA (Table 2).

Discussion

Our results showed that the MATN-3 rs8176070 (SNP6) polymorphism was significantly associated with an increased risk of knee OA in our population. Gu et al., in a study with 420 OA cases and 312 healthy controls suggested that the MATN3 rs8176070 was associated with OA risk in the Chinese Han population.[39] In another study, Diab et al., showed that the MATN-3 rs8176070 might be associated with the risk and severity of knee OA in Egyptian patients, particularly the heterozygote genotype.[36] However, García-Alvarado et al., in a study indicated that there was no a significant relationship between the MATN3 gene and KOA susceptibility in Mexican mestizos.[40] Moreover, Shah et al., in a cohort of 50 patients with primary knee OA and 50 demographically matched healthy controls reported that the MATN-3 gene polymorphism was not associated with knee OA in the Indian population.[41]

Adiponectin is a novel adipocyte-derived hormone with various biological functions.[42] It is the fact that some reported SNPs in ADIPOQ gene are correlative with obesity, metabolic syndrome, T2DM and Gestational diabetes (GDM).[43, 44] It has been reported that ADIPOQ rs1501299 and rs2241766 were connected with the alteration of serum concentrations of ADP either by increasing (G276T SNP) or decreasing (T45G SNP) its levels.[45] Therefore, functional ADIPOQ genetic polymorphisms, which may alter the expression level of adiponectin, may also affect individual susceptibility to knee OA.[33, 34] Some studies have reported that circulating adiponectin levels have been found to be decreased in patients with OA.[16, 33, 35] Some of those studies revealed that ADIPOQ level has a protective effect on the progression of OA.[46, 47] However, the results have been inconsistent and inconclusive. Because of relatively small sample sizes, these studies provide limited evidence and might be underpowered to evaluate the risk. In the current study we have evaluated the association of ADIPOQ rs1501299, rs822396, and rs2241766 polymorphisms with risk of knee OA. Our results showed that these three rs1501299 (+276G>T), rs822396 (-3964A>G) and rs2241766 (+45T>G) polymorphisms at ADIPOQ were not associated with an increased risk of knee OA.

Table 1. Clinical characteristics of the KOA cases and controls		
Variables	KOA (n=105)	Controls (n=120)
Age (years)	55.6±7.4	56.9±6.4
Number female/male	54/51	61/59
BMI (kg/m²)	20.2±6.1	20.1±7.4
Kellgren-Lawrence grade	8/45/38/14	
Lequesne's index	11.9± 2.4	

Table 2. Distribution of MATN3 and ADIPOQ polymorphisms in KOA cases and controls.

Polymorphism	KOA (n=105)	Controls (n=120)	Odds Ratio		
			OR	90% CI	p
MATN3 rs8176070					
BB	43 (40.9)	59 (49.2)	Ref.		
Bb	40 (38.1)	48 (40.0)	0.923	0.539-1.579	0.770
bb	22 (21.0)	13 (10.8)	2.182	1.038-4.587	0.040
Alleles					
B	126 (60.0)	166 (69.2)	Ref.		
b	84 (40.0)	74 (30.8)	1.495	1.014-2.206	0.043
Genetic Mode					
Dominant	62 (59.0)	61 (50.8)	1.395	0.822-2.366	0.217
Recessive	83 (79.0)	107 (89.2)	0.458	0.218-0.964	0.040
ADIPOQ rs1501299					
Genotypes					
GG	29 (27.6)	36 (30.0)	Ref.		
GT	59 (56.2)	63 (52.5)	1.160	0.686-1.964	0.579
TT	17 (16.2)	21 (17.5)	0.911	0.452-1.836	0.794
Alleles					
G	117 (55.7)	135 (56.3)	Ref.		
T	93 (44.2)	105 (43.7)	1.022	0.704-1.484	0.909
Genetic Mode					
Dominant	76 (72.3)	84 (70.0)	1.123	0.629-2.004	0.694
Recessive	88 (83.8)	99 (82.5)	1.098	0.545-2.213	0.794
ADIPOQ rs822396					
Genotypes					
AA	32 (30.4)	42 (35.0)	Ref.		
AG	54 (51.5)	57 (47.5)	1.170	0.693-1.977	0.557
GG	19 (18.1)	21 (17.5)	1.042	0.525-2.065	0.907
Alleles					
A	118 (56.2)	141 (58.8)	Ref.		
G	94 (43.8)	99 (41.2)	1.154	0.794-1.678	0.453
Genetic Mode					
Dominant	73 (69.5)	78 (65.0)	1.228	0.702-2.150	0.471
Recessive	86 (82.0)	99 (825)	0.960	0.484-1.904	0.907
ADIPOQ rs2241766					
Genotypes					
TT	46 (43.8)	51 (42.5)	Ref.		
TG	51 (48.6)	58 (48.3)	1.010	0.598-1.705	0.972
GG	8 (7.6)	11 (9.2)	0.817	0.316-2.115	0.677
Alleles					
T	143 (68.1)	160 (66.7)	Ref.		
G	67 (31.9)	80 (33.3)	0.937	0.631-1.391	0.747
Genetic Mode					
Dominant	59 (56.2)	69 (57.5)	0.948	0.559-1.609	0.843
Recessive	97 (92.4)	109 (90.8)	1.224	0.473-3.167	0.677

OR: Odds Ratio; CI: Confidence Interval.

Similarly, two previous studies among Thais and Finnish women failed to show a significant association between ADIPOQ polymorphisms and knee OA risk. Zhan et al., reported that ADIPOQ +45T>G and +276G>T (rs1501299) polymorphisms did not contribute to susceptibility to OA among Thais. However, their results revealed that knee OA patients with ADIPOQ +276GG genotype have a higher potential risk in the severity of OA than those having the GT and TT genotypes. Moreover, Zhan et al., found that the GG genotypes at +45T>G and +276G>T were associated with

plasma adiponectin concentration in both healthy subjects and knee OA patients.[19] In 2018, Hämäläinen et al., in a well-designed study with 320 cases and 764 controls analyzed the association of 18 polymorphisms in nine adipokine and adipokine receptor genes including LEP, LEPR, ADIPOQ, RETN, NAMPT, SERPINA12, ITLN1, RARRES2, and APLN with radiographic hand OA in Finnish women. Their results did not show an association between the ADIPOQ polymorphisms and risk of hand OA.[33]

However, our results about the association between ADIPOQ rs266729 polymorphism and knee OA risk were inconsistent in the previously studies. Recently, two studies already evaluated associations of two common functional ADIPOQ polymorphisms, rs1501299 and rs2241766, with the susceptibility to knee OA among Chinese and Mexican populations. In 2019, Shang et al., in a study of 372 knee OA cases and 453 healthy subjects evaluated the association between ADIPOQ rs1501299 polymorphism and KOA in a Chinese population. Their results showed that ADIPOQ rs1501299 polymorphism was intensified the risk of knee OA in the Chinese Han population.[34] In the same year, Fernández-Torres et al., evaluated the role of nine polymorphism of six genes including PEPD, AGER, IL6, ADIPOQ, PON1, and CA6 in development of KOA by OpenArray system in a Mexican population. Their results revealed that ADIPOQ rs1501299 polymorphism may be play an important role in OA pathogenesis. Moreover, they analyzed epistasis with the multifactor dimensionality reduction (MDR) method and the results showed that the epistasis analysis may provide an excellent tool for identifying individuals at high risk of KOA development.[16] In 2018, Jiang et al., in other study among Chinese population found that ADIPOQ rs182052 may potentially modify individual susceptibility to knee OA in the population. No other studies of negative or null associations between knee OA and the other ADIPOQ variants were found.[35]

Conclusion

In summary, our results suggested that the MATN-3 rs8176070 (SNP6) polymorphism was associated with an increased risk of knee OA in our population. However, there was no a significant association between rs1501299, rs822396, and rs2241766 polymorphisms at ADIPOQ gene with risk of knee OA. The association between ADIPOQ polymorphisms and knee OA may also be modified by gene-gene and gene-environmental interactions. However, due to lack of raw data, we could not conduct relevant analyses. Thus, our results should be considered with caution until replicated in further well-designed studies in different ethnicities.

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