Article focus

There are no previous studies investigating the possibility that the single nucleotide polymorphism (SNP) in the adiponectin (ADIPOQ) gene may predispose patients to osteoarthritis (OA) development in an Asian population.

We investigated the association between the SNP rs182052 in the ADIPOQ gene and OA in the Chinese population.

Key messages

- The SNP rs182052 in the ADIPOQ gene may potentially modify individual susceptibility to knee OA in the Chinese population.
- Further studies are warranted to investigate our findings.

Strengths and limitations

- This is the first report of several polymorphisms in the ADIPOQ gene and knee OA disease in a Chinese population.
- Our findings showed that rs182052 is potentially associated with knee OA.
- Analysis has also shown a borderline association regarding rs182052 SNP, body mass index and risk of OA in our study population.
- Further studies need to be conducted with larger sample sizes and using different ethnic groups to validate and further investigate our findings.

Introduction

Osteoarthritis (OA) is the most common chronic joint disease in the elderly, and it is
predicted that it will be the single greatest cause of disabil-
ity in the general population by 2030.\textsuperscript{1} Similar increas-
ing trends in the prevalence of OA are found in China.
With ageing populations and a worldwide obesity epide-
demic, OA is regarded as a global public health issue.
Studies show that OA is a multifactorial disease that is
influenced by ageing, the environment, genetic predis-
position and the interactions between them.\textsuperscript{2,6}

There is substantial evidence highlighting the relation-
ship between obesity and OA.\textsuperscript{7-9} However, mechanical
loading cannot explain the incidence and progression of
OA in non-weight-bearing joints such as fingers and
wrists.\textsuperscript{4,10-12} This suggests probable complex mechanisms
linking obesity and OA, including biomechanical, physi-
ological and inflammatory.\textsuperscript{13,14} Adipose tissue is well rec-
ognized as an active endocrine organ, releasing various
adipokines such as adiponectin (ADIPOQ), leptin and vis-
fatin, which are involved in complex biological interac-
tions between fat and other tissues, and play a significant
role in bone formation and bone absorption.\textsuperscript{15,16} Obesity
is one of the strongest predictive and prognostic factors
for OA, particularly in knee joints, and, to a lesser extent,
the hip.\textsuperscript{17} Adiponectin, encoded by the ADIPQ gene, is
a specific protein secreted by adipose tissue.\textsuperscript{18} First
described in 1995, it has a modular structure consisting of
a collagen-like N-terminal domain and a C-terminal
globular domain that is similar to tumour necrosis factor-
alpha (TNF-\alpha).\textsuperscript{19,20} Adiponectin is a complex molecule
that plays an important role in the regulation of insulin
sensitivity and glucose homeostasis, as well as lipid and
fatty acid oxidation.\textsuperscript{21} ADIPQ gene expression has been
shown to reduce the production of pro-inflammatory
cytokines such as interleukin-6, interleukin-8 and TNF-\alpha,
and induce the release of anti-inflammatory cytokines.
This suggests a contribution to the low-grade inflamma-
tory state that exists in obesity.\textsuperscript{22-24} Recently, ADIPQ has
been found to participate in the inflammatory process,
and may trigger articular cartilage injury through the
upregulation of cytokines, matrix-degrading enzymes
and chemokines in both chondrocytes and synovial fibro-
blasts.\textsuperscript{25-27} A recent case-controlled study reported that
the ADIPQ level positively correlated with disease sever-
ity in patients with knee OA.\textsuperscript{28} ADIPQ might be consid-
ered as a potentially effective biomarker for joint damage
in OA.\textsuperscript{29}

The human ADIPQ gene is located on chromosome
3q27 and spans approximately 17 kb, consisting of three
exons and two introns.\textsuperscript{30} Previous studies have indicated
that the ADIPQ gene may be identified as a genetic
region for phenotypes associated with various diseases,
such as obesity, rheumatoid arthritis, diabetes and coro-
nary heart disease.\textsuperscript{31-34} However, the study of the rela-
tionship between ADIPQ polymorphisms and OA has
been limited.\textsuperscript{35}

Obesity may have a shared genetic background with
OA based on the well-established epidemiological link.
Given the role of ADIPQ in the inflammatory pathophysi-
ology of obesity and its link to OA, we hypothesized that
the ADIPQ gene expression could modulate the level of
ADIPQ and might potentially be a candidate gene, as a
marker for the susceptibility to OA. To the best of our
knowledge, no studies on the north east Chinese popula-
tion about the relationship between ADIPQ gene vari-
ants and the risk of OA have been conducted. The objective
of this study was to explore several ADIPQ polymor-
phisms and investigate their genetic association with the
susceptibility to OA among a Chinese population.

Materials and Methods
Study design and participants. A population-based case-
controlled study was carried out to evaluate whether the
polymorphism of ADIPQ was associated with knee OA
in Harbin City in Heilongjiang Province, northern China.
With the assistance of the local community councils,
residents who lived at their registered address during
the study period, having permanent living records with
Chinese Han nationality, were recruited. The participants
were 40 years and over, and residents of the Hongqi com-
munity in the Xiangfan metropolitan district, and were
recruited using stage-stratified sampling methods, and
representing the middle standard of life in Harbin city.
A total of 1636 participants completed a questionnaire
and underwent clinical and radiological examination. Of
these, 110 participants were excluded for the following
reasons: no blood sample available (n = 36); no physi-
ological examination available (n = 29); and no radiological
images available (n = 45). The remaining 1526 partici-
ants were classified into four groups based on their cli-
cal and radiological knee status: Group 1) knee pain with
radiologically defined OA (n = 196); Group 2) the control
group having neither knee pain nor radiological evidence
of knee OA (n = 442); Group 3) knee pain without OA,
i.e. participants with knee pain but without radiologically
defined knee OA (n = 195); and Group 4) radiologically
defined knee OA but without knee pain (n = 693). The
OA patients in Group 1 had definite symptomatic OA and
radiological evidence in at least one knee joint.

The questionnaire was designed to collect data from
all participants regarding basic demographics, occupa-
tion and sporting activities, previous knee injury, family
history of OA and rheumatological manifestations.
Clinical symptoms were defined as significant when
signs and symptoms of knee pain were present for at
least one month’s duration during the previous 12
months. The radiological assessment of OA was made
using the Kellgren-Lawrence grading system.\textsuperscript{36} Knee
radiological images were evaluated independently by
two experienced radiologists (JR and SW) who were
blinded to patient presentation. Consensus was reached
whenever results were divergent. Cases where there was
uncertainty were recalled and re-examined by a specialist
to ensure the validity. The control group had no signs or
symptoms of arthritis or joint disease. Patients with a previous knee injury and secondary OA, and patients with inflammatory disease or rheumatoid arthritis and developmental dysplasia, were excluded. All participants underwent a physical examination, and body mass index (BMI) (weight/height²) was recorded. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body weight was measured with a digital scale to the nearest 0.1 kg. The classification of obesity status was defined according to the criteria of the Working Group on Obesity in China, based on the analysis of data collected from 239,972 Chinese adults in the 1990s:37 underweight and normal (BMI = 24.0); overweight (BMI 24.0 to 28.0); and obese (BMI ≥ 28.0).

The project protocol was reviewed and approved by the Ethics Committee of Harbin Medical University, and written informed consent was obtained from each participant.

**Single nucleotide polymorphism (SNP) selection.** Public databases of the National Center for Biotechnology Information (NCBI) were used to collect information about SNPs and genes.38 Based on the HapMap SNP database (phase II + III Feb 09, on NCBI B36 assembly, dbSNP b126) and Haploview 4.2 software,39 common SNPs (minor allele frequency (MAF) ≥ 5% in the Chinese Han population) were screened in ADIPOQ gene regions. The context sequences of SNPs with low linkage disequilibrium (LD) analysis (r² < 0.8) were retained. As a result, three targeting SNPs (rs182052, rs2082940, rs6773957) were finally selected and further determined to perform genotyping assays.

**Genotyping assays.** Peripheral blood was collected from each subject following informed consent, and genomic DNA from cases and controls was isolated from peripheral blood lymphocytes. Genomic DNA was extracted from the samples with a DNA extraction kit (Qiagen Inc, Valencia, California). Further DNA concentration measures were obtained using a Nanodrop 2000 spectrophotometer (ThermoFisher Scientific, Waltham, Massachusetts). Polymerase chain reaction (PCR) was performed in a total reaction volume of 4 μl containing about 10 ng of genomic DNA. The PCR conditions depended on the requirements of each probe according to the manufacturer’s indications. The genotype of each sample at this stage was performed using the iPLEX Sequenom MassARRAY platform (Sequenom Inc, San Diego, California).

The following series of methods were used to control the quality of genotyping: 1) case and control samples were mixed on each plate; 2) genotyping was performed blinded to case or control status for the clinical personnel; 3) 5% of the samples were randomly selected for repeat genotyping as blind duplicates and the reproducibility was 100%. As a quality control measure, we included one sample with no template, and one sample duplicate per 96-well plate (a total of four per 384-well plate used). SDS 2.3 Allelic Discrimination Software (Applied Biosystems, Foster City, California) was employed to determine genotypes. Genotypes were provided manually by two different people in the laboratory.

**Statistical analysis.** The chi-squared test for categorical variables and Student’s t-test for continuous variables were used to analyze for differences in demographic characteristics, the selected variables and genotypes between cases and controls. The Hardy-Weinberg equilibrium (HWE) for the distribution of each SNP was evaluated using the goodness-of-fit χ² test, by comparing the observed genotype frequencies with the expected ones. Genotype-related odds ratios (ORs), their corresponding 95% confidence intervals (CIs) and associated p-values were estimated via unconditional logistic regression. This was calculated for an additive model (minor allele homozygotes versus heterozygotes versus major allele homozygotes) with adjustment for age, gender, BMI, occupation and physical activity. An association study is designed specifically to reveal associations that depend additively upon the minor allele. That is, the genotype of the individual that has two minor alleles (variant homozygote), rather than having no minor alleles (wild-type homozygote), is twice as likely to affect the outcome in a certain direction as just one minor allele (heterozygote) rather than no minor alleles (wild-type homozygote). The Bonferroni correction was used for multiple comparisons, which was a safeguard against multiple tests of statistical significance on the same data. For this study, three tagging SNPs on the ADIPOQ gene were genotyped, thus the associations between ADIPOQ SNPs and OA risk with p-values < 0.017 (0.05/3) were considered significant after correction for multiple testing. To examine the differences between subgroups, the chi-squared (χ²)-based Q-test was used to test the heterogeneity of effect sizes (ORs and 95% CIs) derived from corresponding subgroups. All p-values were two-sided, and those less than 0.05 were considered statistically significant. STATA (version 13.1; StataCorp, College Station, Texas) was used for all the statistical analyses.

**Results**

The basic demographic data of the 196 cases in group 1 with symptoms and radiological changes of OA and the 442 controls in group 2 are summarized in Table I. There was no significant difference detected in gender between OA cases and controls (χ² = 3.173, p = 0.090). The mean age of cases was significantly higher than that of controls (t = 6.486, p < 0.001). The distribution of BMI among cases and control is significantly different (χ² = 8.465, p = 0.015), and OA cases possessed a higher frequency of being overweight (39.29%) and obese (26.02%) compared with the control group (34.84% overweight and 18.78% obese). In terms of smoking and drinking status,
no significant difference was detected between the cases and the control group ($\chi^2 = 0.994, p = 0.330$ for smoking; $\chi^2 = 0.1379, p = 0.254$ for drinking). Also, no significant difference was checked for occupation or for physical activity between the cases group and the control group ($\chi^2 = 1.479, p = 0.224$ for occupation; $\chi^2 = 3.286, p = 0.090$ for physical activity).

The results for the three SNPs are shown in Supplementary table i. Genotyping success rates for all polymorphisms were greater than 98%, and the observed genotype frequencies for these SNPs in the control group were all in agreement with HWE ($p > 0.05$). Logistic regression analyses were performed for the three SNPs (Table II). It showed that the variant ADIPQ rs182052 was potentially associated with OA risk. Those individuals with the genotype GA versus GG and those with genotype AA compared with GA in rs182052 tended to present a higher risk of OA, and the allele A could increase the OA risk (additive model: OR = 1.38; 95% CI 1.07 to 1.76; $p = 0.012$). The associations of rs182052 and risk of OA remained significant after correction for multiple testing ($n = 3$) with $p < 0.017$. We found no evidence of any significant association between the remaining two SNPs and OA. That is, no statistical difference was found between the association of SNP rs2082940 and OA (additive model: OR = 1.16; 95% CI 0.87 to 1.55; $p = 0.303$), nor SNP rs6773957 and OA (additive model: OR = 1.03; 95% CI 0.80 to 1.33; $p = 0.819$) (Supplementary table i).

Further evaluation of the association between rs182052 and knee OA was performed using stratification of age and BMI (Table III). Significant associations between rs182052 and knee OA were found in subjects aged $\geq 57$ years (OR = 1.44; 95% CI 1.07 to 1.93; $p = 0.015$). Significant associations between rs182052 and knee OA were also detected in subjects with a BMI $< 24$ (OR = 1.69; 95% CI 1.14 to 2.50; $p = 0.009$). In addition, no significant heterogeneity was observed among the stratified subgroups of age and BMI ($p = 0.666$ and 0.321, respectively).

As well as the above stratification, we further explored gene-factor interaction in the identified SNP rs182052. Considering the significant differences in distribution of age and BMI between case and control groups, we further investigated whether the effect of rs182052 on OA risk was modified by age and BMI. Collectively, interaction analyses failed to detect any significant association between rs182052 and BMI on OA risk (multiple interaction $p = 0.063$) (Table IV). That is, among those individuals with BMI $< 24$, a combination with GA/AA genotype had a higher chance of developing OA (OR = 2.69; 95% CI 1.33 5.42; $p = 0.006$). Whereas, among those individuals with BMI $= 24$, a combination with the GG genotype presented a higher chance of developing OA (OR = 3.01; 95% CI 1.43 6.34; $p = 0.004$), and a combination with GA/AA genotype also tended to be more likely to develop OA (OR = 3.59; 95% CI 1.82 7.07; $p < 0.001$). As for the interaction of identified SNP

### Table 1. Distribution of selected variables in group 1 osteoarthritis cases and group 2 controls

| Variables                        | Cases (n = 196) | Control (n = 442) | Test  | p-value |
|----------------------------------|----------------|------------------|-------|---------|
| Mean age, yrs (so)               | 62.19 (8.76)   | 57.17 (9.19)     | $t = 6.486$ | < 0.001 |
| < 57, n (%)                      | 56 (28.57)     | 213 (48.19)      | $\chi^2 = 21.432$ | < 0.001 |
| $\geq$ 57, n (%)                 | 140 (71.43)    | 229 (51.81)      | $\chi^2 = 3.173$ | 0.090   |
| Gender, n (%)                    |                |                  |       |         |
| Male                             | 48 (24.49)     | 139 (31.45)      | $\chi^2 = 8.465$ | 0.015   |
| Female                           | 148 (75.51)    | 303 (68.55)      |       |         |
| Body mass index (BMI), n (%)     |                |                  |       |         |
| $< 24$ kg/m²                     | 68 (34.69)     | 205 (46.38)      |       |         |
| $24$ kg/m² $<$ BMI $< 28$ kg/m²  | 77 (39.29)     | 154 (34.84)      |       |         |
| $\geq 28$ kg/m²                  | 51 (26.02)     | 83 (18.78)       |       |         |
| Smoking status, n (%)            |                |                  |       |         |
| Ever                             | 46 (23.47)     | 119 (27.23)      | $\chi^2 = 0.994$ | 0.330   |
| Never                            | 150 (76.53)    | 318 (72.77)      | $\chi^2 = 1.379$ | 0.254   |
| Drinking status, n (%)           |                |                  |       |         |
| Ever                             | 52 (27.81)     | 134 (32.60)      | $\chi^2 = 1.479$ | 0.224   |
| Never                            | 135 (72.19)    | 277 (67.40)      |       |         |
| Occupation, n (%) €              |                |                  |       |         |
| Managerial                       | 85 (44.50)     | 218 (49.77)      | $\chi^2 = 3.286$ | 0.090   |
| Non-managerial                   | 106 (55.50)    | 220 (50.22)      |       |         |
| Physical activity, n (%)         |                |                  |       |         |
| Inactive                         | 68 (34.69)     | 177 (40.04)      |       |         |
| Less active                      | 78 (39.80)     | 185 (41.86)      |       |         |
| More active                      | 50 (25.51)     | 80 (18.10)       |       |         |

*Median age in control group
€The non-managerial occupations: Service; Farming, Forestry and Fishing; Precision Production, Craft and Repair; Operators, Fabricators and Labourers. The managerial occupations: Managerial and Professional; Technical, Sales and Administrative Support
†Inactive, no reported activity per week; less active, one to four times per week; more active, five or more times per week
$\chi^2$, chi-squared
rs182052 and age on OA risk, the similar pattern of non-significant interaction was also detected (multiple interaction \( p = 0.614 \)) (Supplementary table ii).

**Discussion**

Osteoarthritis is a complex disease, arising from the interaction of multiple factors including individual genetic factors and environmental factors. Epidemiological studies have shown a strong genetic component to the susceptibility to OA.\(^2\) Growing evidence indicates that the release of additional adipokines may be responsible for the increase of OA observed among obese people.\(^27,28\)

Obesity might play a critical role in the development and progression of OA.\(^40\) From a pathophysiological perspective, there is increasing evidence to suggest that ADIPoQ plays an important role in the onset and progression of OA.\(^29\) In our study, we systematically evaluated the association of three tagging polymorphisms in the ADIPoQ gene with OA risk in a case-controlled study of 196 OA cases and 442 controls in a northern Chinese population. The SNP rs182052 was identified to be significantly associated with knee OA susceptibility. However, we found no evidence of significant association between SNP rs2082940, rs6773957 and knee OA risk.

To the best of our knowledge, this is the first study to evaluate the association of several polymorphisms in the ADIPoQ gene and the risk of symptomatic knee OA in an Asian population. For rs182052, the A allele appeared to be one of the risk factors for knee OA in our study. Zhan et al\(^35\) found no statistically significant difference between

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**Table II.** Associations between rs182052 in the adiponectin gene and knee osteoarthritis risk

| SNPs     | Genotypes | Case | Control | Crude OR (95% CI) | p-value | Adjusted OR (95% CI)* | p-value* |
|----------|-----------|------|---------|------------------|---------|----------------------|---------|
| rs182052 | GG        | 49   | 150     | 1                | 1       | 1                    | 1       |
|          | GA        | 95   | 204     | 1.43 (0.95 to 2.14) | 0.085   | 1.46 (0.95 to 2.23)  | 0.081   |
|          | AA        | 50   | 84      | 1.82 (1.13 to 2.93) | 0.013   | 1.88 (1.14 to 3.10)  | 0.013   |
|          | GA/AA     | 145  | 288     | 1.54 (1.05 to 2.25) | 0.025   | 1.58 (1.06 to 2.36)  | 0.023   |
|          | Additive  | 1.35 (1.07 to 1.71) | 0.012 | 1.38 (1.07 to 1.76) | 0.012   |

**Table III.** Stratified analysis on the associations of ADIPoQ rs182052 in osteoarthritis risk

| Characteristics | Case* | Control* | OR (95% CI)† | p-value† | p-value het‡ |
|----------------|-------|----------|--------------|----------|--------------|
| Age, yrs       |       |          |              |          |              |
| < 57           | 13/28/13 | 65/106/40 | 1.28 (0.82 to 2.00) | 0.275    | 0.666       |
| ≥ 57           | 36/67/37 | 85/98/44 | 1.44 (1.07 to 1.93) | 0.015    |              |
| Body mass index (BMI), kg/m²  |       |          |              |          |              |
| < 24           | 12/36/20 | 72/89/43 | 1.69 (1.14 to 2.50) | 0.009    | 0.321       |
| 24 ≤ BMI < 28  | 21/36/18 | 50/70/31 | 1.09 (0.72 to 1.65) | 0.675    |              |
| ≥ 28           | 16/23/12 | 28/45/10 | 1.40 (0.82 to 2.39) | 0.214    |              |

*Wild-type homozygote/heterozygote/variant homozygote
†Adjusted for age, gender, BMI, occupation and physical activity where appropriate in additive model
‡p for heterogeneity

**Table IV.** The interaction between rs182052 genotypes and body mass index (BMI) on knee osteoarthritis (OA) risk

| BMI (kg/m²) | Genotype | Case | Control | OR (95% CI) | p-value* |
|------------|----------|------|---------|-------------|----------|
| < 24       | GG       | 12   | 72      | 1           | 1        |
|            | GA/AA    | 56   | 132     | 2.69 (1.33 to 5.42) | 0.006    |
| ≥ 24       | GG       | 37   | 78      | 3.01 (1.43 to 6.34) | 0.004    |
|            | GA/AA    | 89   | 156     | 3.59 (1.82 to 7.07) | < 0.001  |

*p-value of interaction analysis between rs182052 and BMI on knee OA risk with adjustment for age, gender, occupation and physical activity

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VOL. 7, NO. 7, JULY 2018

**Obesity, Osteoarthritis and Genetic Risk**

498
ADIPQ rs1501299 expression and knee OA. In a further study, the same authors showed that rs1501299 and rs2241766 of the ADIPQ gene were not responsible for OA susceptibility among a Thai population.41 The different results between the Thai studies and our own study population may be due to genetic backgrounds, gender ratios, population substructure and environmental effects. The sample size in our study was larger than in those previous studies. Furthermore, other factors such as age, gender, BMI, occupation and physical activity were adjusted for in our study, in order to detect the association between ADIPQ and knee OA.

Our study has several strengths. First, we recruited knee OA cases and selected controls from a community which might better represent the whole population and reduce potential selection bias. Second, the focus on well-defined radiological and clinical features allows for a stringent definition of OA in the study group and may allow differences in gene expression to be observed with more certainty. Osteoarthritis phenotype definitions, reflecting different subsets of OA, have been shown to influence the ability to detect genetic associations.42 Third, with our detailed investigation into whether the ADIPQ gene is associated with OA, we systematically evaluated three different tagging polymorphisms in both knee OA cases and controls; the SNP 182052 polymorphism was identified as being associated with knee OA.

However, our study does have limitations. First, OA is a multifactorial disease with a strong genetic component, with various different estimates of influence of genetic factors depending on the joint involved. We only evaluated the SNP rs182052, rs2082940 and rs6773957 in the ADIPQ gene and the risk of knee OA. Our results cannot be generalized to OA affecting other joints. Second, we only demonstrated an association. We are unable to show causation in terms of how this gene expression influences the process of OA. Third, due to the small sample size (a total of 196 OA cases and 442 control subjects), the statistical power is about 46.5% when detecting an effect size of 1.50 with an α level of 0.05 in relation to risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Ossteoarthrits Cartilage 2015;23:507-515.

Supplementary material

Tables showing a summary of the three single nucleotide polymorphisms and interaction between rs182052 genotypes and age on knee osteoarthritis risk.

References

1. Lotz M, Martel-Pelletier J, Christiansen C, et al. Value of biomarkers in osteoarthritis: current status and perspectives. Ann Rheum Dis 2013;72:1756-1763.
2. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Ossteoarthrits Cartilage 2015;23:507-515.
3. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Ossteoarthrits Cartilage 2010;18:24-33.
4. Leung GJ, Rainford KD, Kean WF. Osteoarthritis of the hand I: aetiology and pathogenesis, risk factors, investigation and diagnosis. J Pharm Pharmacol 2014;66:339-346.
5. Yin CM, Suen WC, Lin S, et al. Dysregulation of both mI1-40-3p and mI1-40-5p in synovial fluid correlate with osteoarthritis severity. Bone Joint Res 2017;6:612-618.
6. Nishioka H, Nakamura E, Hirose J, et al. MRI T1ρ and T2 mapping for the assessment of articular cartilage changes in patients with medial knee osteoarthritis after hemicapitellar osteotomy. Bone Joint Res 2016;5:294-300.
7. Harasymowicz NS, Clement ND, Azfer A, et al. Regional differences between perisynovial and infrapatellar adipose tissue deposits and their response to class II and class III obesity in patients with osteoarthritis. Arthritis Rheumatol 2017;69:1396-1406.
8. Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. Int J Obes 2008;32:211-222.
9. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis 1994;53:565-568.
10. Visser AW, Ioan-Facsinay A, de Mutsert R, et al. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. Arthritis Res Ther 2014;16:R19.
11. Yusuf E, Nelissen RG, Ioan-Facsinay A, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761-765.
12. Joo SD, Lee KB. Comparison of the outcome of total ankle arthroplasty for osteoarthritis with moderate and severe varus malalignment and that with neutral alignment. Bone Joint J 2017;99-B:1335-1342.
13. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. Curr Opin Rheumatol 2013;25:114-118.
14. Pottie P, Presle N, Terlain B, et al. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-1405.
15. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes 2006;55:1357-1345.
16. Smítková L, Mareschová D, Adipose tissue as an endocrine organ: an update on pro-inflammatory and anti-inflammatory microenvironment. Praga Med Rep 2015;116:1-11.
17. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. Lancet 2015;386:376-387.
18. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-783.
19. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746-26749.
20. Chandran M, Phillips SA, Ciarelli T, Henry RR. Adiponectin: more than just another fat cell hormone? Diabetes Care 2003;26:2442-2450.
21. Ahima RS. Metabolic actions of adipocyte hormones: focus on adiponectin. Obesity (Silver Spring) 2006;14(Suppl 1):S9-S15.
22. Toussirot E, Streit G, Wendling D. The contribution of adipose tissue and adipoceptors to inflammation in joint diseases. Curr Med Chem 2007;14:1090-1100.
23. Wulster-Radcliffe MC, Ajyoun KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. Biochem Biophys Res Commun 2004;316:924-929.
24. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 2004;323:630-635.

25. Choi HM, Lee YA, Lee SH, et al. Adiponectin may contribute to synovitis and joint destruction in rheumatoid arthritis by stimulating vascular endothelial growth factor, matrix metalloproteinase-1, and matrix metalloproteinase-13 expression in fibroblast-like synoviocytes more than proinflammatory mediators. Arthritis Res Ther 2009;11:R161.

26. Frommer KW, Zimmermann B, Meier FMP, et al. Adiponectin-mediated changes in effector cells involved in the pathophysiology of rheumatoid arthritis. Arthritis Rheum 2010;62:2886-2899.

27. Koskinnen A, Justlin S, Nieminen R, et al. Adiponectin associates with markers of cartilage degradation in osteoarthritis and induces production of proinflammatory and catabolic factors through mitogen-activated protein kinase pathways. Arthritis Res Ther 2011;13:R184.

28. Francin PJ, Abot A, Guillaume C, et al. Association between adiponectin and cartilage degradation in human osteoarthritis. Osteoarthr Cartilage 2014;22:519-526.

29. Cuzdan CN, Ay S, EvciK FD, Oztuna D. Adiponectin: is it a biomarker for assessing the disease severity in knee osteoarthritis patients? Int J Rheum Dis 2017;20:142-149.

30. Takahashi M, Arita Y, Yamagata K, et al. Genomic structure and mutations in AdipoQ gene polymorphisms and anthropometric obesity in the Jackson Heart Study cohort. BMC Med Genet 2015;16:95.

31. Riestra P, Gebreab SY, Xu R, et al. Gender-specific associations between ADIPOQ gene polymorphisms and adiponectin levels and obesity in the Jackson Heart Study cohort. BMC Med Genet 2015;16:95.

32. Rodriguez-Rodriguez L, Garcia-Bermúdez M, González-Juanatey C, et al. Lack of association between ADIPOQ rs298729 and ADIPOQ rs1501289 polymorphisms and cardiovascular disease in rheumatoid arthritis patients. Tissue Antigens 2011;77:74-78.

33. Sun Y, Li DG, Li Q, et al. Relationship between adipocytokine gene polymorphism and lipid levels and diabetes. J Biol Regul Homeost Agents 2015;29:221-227.

34. Kanu JS, Gu Y, Zhi S, et al. Single nucleotide polymorphism rs3774261 in the AdipoQ gene is associated with the risk of coronary heart disease (CHD) in Northeast Han Chinese population: a case-control study. Lipids Health Dis 2016;15:6.

35. Zhan D, Yuktanandana P, Anomasiri W, Tanavalee A, Hon-sawvek S. Association of adiponectin +276G>T polymorphism with knee osteoarthritis. Biomed Rep 2014;2:229-232.

36. Keligren JH, Lawrence JS, Bier F. Genetic factors in generalized osteo-arthritis. Ann Rheum Dis 1962;22:237-255.

37. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 2002;15:83-96.

38. No authors listed. dbSNP Short Genetic Variations. NCBI. www.ncbi.nlm.nih.gov/projects/SNP (date last accessed 9 July 2018).

39. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263-265.

40. Payab M, Amoli MM, Dorbani M, Hasani-Ranjbar S. Adiponectin gene variants and abdominal obesity in an Iranian population. Eat Weight Disord 2017;22:85-90.

41. Zhan D, Thuntecho S, Tanavalee A, et al. Association of adiponectin gene polymorphisms with knee osteoarthritis. World J Orthop 2017;8:719-725.

42. Thysen S, Luyten FP, Lories RJU. Targets, models and challenges in osteoarthritis research. Dis Model Mech 2015;8:17–30.

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L. Jiang: Contribution to the research design and critical revisions, Review of the final version and approval for publication.
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Conflict of Interest Statement
None declared.

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